TOXICOLOGICAL PROFILE FOR MERCURY

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

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Mercury–Draft for Public Comment was released in September 1997. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry
Division of Toxicology/Toxicology Information Branch
1600 Clifton Road NE, E-29
Atlanta, Georgia 30333

FOREWORD

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

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

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

Each profile includes the following:

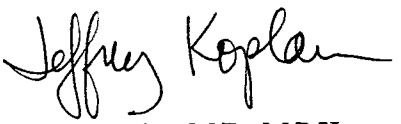
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

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

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

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

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Jeffrey P. Koplan, M.D., M.P.H.
Administrator
Agency for Toxic Substances and
Disease Registry

*Legislative Background

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

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

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

Section 1.6 How Can (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-447-1544 (to be replaced by 1-888-42-ATSDR in 1999)
or 404-639-6357 ***Fax:*** 404-639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://atsdr1.atsdr.cdc.gov:8080

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

CONTRIBUTORS

CHEMICAL MANAGER(S)/AUTHORS(S):

John Risher, Ph.D.
ATSDR, Division of Toxicology, Atlanta, GA

Rob DeWoskin, Ph.D.
Research Triangle Institute, Research Triangle Park, NC

THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

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

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

PEER REVIEW

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

1. Mr. Harvey Clewell, K.S. Crump Group, ICF Kaiser International, Inc., Ruston, LA

2. Dr. Ingeborg Harding-Barlow, Private Consultant, Environmental and Occupational Toxicology, 3717 Laguna Ave., Palo Alto, California;

3. Dr. Thomas Hinesly, Professor (Emeritus), Department of Natural Resources and Environmental Sciences, University of Illinois, Champaign-Urbana, Illinois;

4. Dr. Loren D. Koller, Professor, College of Veterinary Medicine, Oregon State University, Corvallis, Oregon; and

5. Dr. Kenneth Reuhl, Professor, Neurotoxicology Laboratory, Rutgers University, Piscataway, New York.

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

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

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

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about mercury and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Mercury has been found in at least 714 of the 1,467 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which mercury is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance or by skin contact.

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

1.1 WHAT IS MERCURY?

Mercury occurs naturally in the environment and exists in several forms. These forms can be organized under three headings: metallic mercury (also known as elemental mercury), inorganic mercury, and organic mercury. Metallic mercury is a shiny, silver-white metal that is a liquid at room temperature. Metallic mercury is the elemental or pure form of mercury (i.e., it is not combined with other elements). Metallic mercury metal is the familiar liquid metal used in thermometers and some electrical switches. At room temperature, some of the metallic mercury

will evaporate and form mercury vapors. Mercury vapors are colorless and odorless. The higher the temperature, the more vapors will be released from liquid metallic mercury. Some people who have breathed mercury vapors report a metallic taste in their mouths. Metallic mercury has been found at 714 hazardous waste sites nationwide.

Inorganic mercury compounds occur when mercury combines with elements such as chlorine, sulfur, or oxygen. These mercury compounds are also called mercury salts. Most inorganic mercury compounds are white powders or crystals, except for mercuric sulfide (also known as cinnabar) which is red and turns black after exposure to light.

When mercury combines with carbon, the compounds formed are called "organic" mercury compounds or organomercurials. There is a potentially large number of organic mercury compounds; however, by far the most common organic mercury compound in the environment is methylmercury (also known as monomethylmercury). In the past, an organic mercury compound called phenylmercury was used in some commercial products. Another organic mercury compound called dimethylmercury is also used in small amounts as a reference standard for some chemical tests. Dimethylmercury is the only organic mercury compound that has been identified at hazardous waste sites. It was only found in extremely small amounts at two hazardous waste sites nationwide, but it is very harmful to people and animals. Like the inorganic mercury compounds, both methylmercury and phenylmercury exist as "salts" (for example, methylmercuric chloride or phenylmercuric acetate). When pure, most forms of methylmercury and phenylmercury are white crystalline solids. Dimethylmercury, however, is a colorless liquid.

Several forms of mercury occur naturally in the environment. The most common natural forms of mercury found in the environment are metallic mercury, mercuric sulfide (cinnabar ore), mercuric chloride, and methylmercury. Some microorganisms (bacteria and fungi) and natural processes can change the mercury in the environment from one form to another. The most common organic mercury compound that microorganisms and natural processes generate from other forms is methylmercury. Methylmercury is of particular concern because it can build up in certain edible

freshwater and saltwater fish and marine mammals to levels that are many times greater than levels in the surrounding water (see Section 1.2).

Mercury is mined as cinnabar ore, which contains mercuric sulfide. The metallic form is refined from mercuric sulfide ore by heating the ore to temperatures above 1,000 degrees Fahrenheit. This vaporizes the mercury in the ore, and the vapors are then captured and cooled to form the liquid metal mercury. There are many different uses for liquid metallic mercury. It is used in producing of chlorine gas and caustic soda, and in extracting gold from ore or articles that contain gold. It is also used in thermometers, barometers, batteries, and electrical switches. Silver-colored dental fillings typically contain about 50% metallic mercury. Metallic mercury is still used in some herbal or religious remedies in Latin America and Asia, and in rituals or spiritual practices in some Latin American and Caribbean religions such as Voodoo, Santeria, and Espiritismo. These uses may pose a health risk from exposure to mercury both for the user and for others who may be exposed to mercury vapors in contaminated air.

Some inorganic mercury compounds are used as fungicides. Inorganic salts of mercury, including ammoniated mercuric chloride and mercuric iodide, have been used in skin-lightening creams. Mercuric chloride is a topical antiseptic or disinfectant agent. In the past, mercurous chloride was widely used in medicinal products including laxatives, worming medications, and teething powders. It has since been replaced by safer and more effective agents. Other chemicals containing mercury are still used as antibacterials. These products include mercurochrome (contains a small amount of mercury, 2%), and thimerosal and phenylmercuric nitrate, which are used in small amounts as preservatives in some prescription and over-the-counter medicines. Mercuric sulfide and mercuric oxide may be used to color paints, and mercuric sulfide is one of the red coloring agents used in tattoo dyes.

Methylmercury is produced primarily by microorganisms (bacteria and fungi) in the environment, rather than by human activity. Until the 1970s, methylmercury and ethylmercury compounds were used to protect seed grains from fungal infections. Once the adverse health effects of methylmercury were known, the use of methymercury- and ethylmercury as fungicides was

banned. Up until 1991, phenylmercuric compounds were used as antifungal agents in both interior and exterior paints, but this use was also banned because mercury vapors were released from these paints.

Chapter 3 contains more information on the physical and chemical properties of mercury.
Chapter 4 contains more information on the production and use of mercury.

1.2 WHAT HAPPENS TO MERCURY WHEN IT ENTERS THE ENVIRONMENT?

Mercury is a naturally occurring metal found throughout the environment. Mercury enters the environment as the result of the normal breakdown of minerals in rocks and soil from exposure to wind and water, and from volcanic activity. Mercury releases from natural sources have remained relatively constant in recent history, resulting in a steady rise in environmental mercury. Human activities since the start of the industrial age (e.g., mining, burning of fossil fuels) have resulted in additional release of mercury to the environment. Estimates of the total annual mercury releases that result from human activities range from one-third to two-thirds of the total mercury releases. A major uncertainty in these estimates is the amount of mercury that is released from water and soils that were previously contaminated by human activities as opposed to new natural releases. The levels of mercury in the atmosphere (i.e., the air you breathe in the general environment) are very, very low and do not pose a health risk; however, the steady release of mercury has resulted in current levels that are three to six times higher than the estimated levels in the preindustrial era atmosphere.

Approximately 80% of the mercury released from human activities is elemental mercury released to the air, primarily from fossil fuel combustion, mining, and smelting, and from solid waste incineration. About 15% of the total is released to the soil from fertilizers, fungicides, and municipal solid waste (for example, from waste that contains discarded batteries, electrical switches, or thermometers). An additional 5% is released from industrial wastewater to water in the environment.

With the exception of mercury ore deposits, the amount of mercury that naturally exists in any one place is usually very low. In contrast, the amount of mercury that may be found in soil at a particular hazardous waste site because of human activity can be high (over 200,000 times natural levels). The mercury in air, water, and soil at hazardous waste sites may come from both natural sources and human activity.

Most of the mercury found in the environment is in the form of metallic mercury and inorganic mercury compounds. Metallic and inorganic mercury enters the air from mining deposits of ores that contain mercury, from the emissions of coal-fired power plants, from burning municipal and medical waste, from the production of cement, and from uncontrolled releases in factories that use mercury. Metallic mercury is a liquid at room temperature, but some of the metal will evaporate into the air and can be carried long distances. In air, the mercury vapor can be changed into other forms of mercury, and can be further transported to water or soil in rain or snow. Inorganic mercury may also enter water or soil from the weathering of rocks that contain mercury, from factories or water treatment facilities that release water contaminated with mercury, and from incineration of municipal garbage that contains mercury (for example, in thermometers, electrical switches, or batteries that have been thrown away). Inorganic or organic compounds of mercury may be released to the water or soil if mercury-containing fungicides are used.

Microorganisms (bacteria, phytoplankton in the ocean, and fungi) convert inorganic mercury to methylmercury. Methylmercury released from microorganisms can enter the water or soil and remain there for a long time, particularly if the methylmercury becomes attached to small particles in the soil or water. Mercury usually stays on the surface of sediments or soil and does not move through the soil to underground water. If mercury enters the water in any form, it is likely to settle to the bottom where it can remain for a long time.

Mercury can enter and accumulate in the food chain. The form of mercury that accumulates in the food chain is methylmercury. Inorganic mercury does not accumulate up the food chain to any extent. When small fish eat the methylmercury in food, it goes into their tissues. When larger fish eat smaller fish or other organisms that contain methylmercury, most of the methylmercury

originally present in the small fish will then be stored in the bodies of the larger fish. As a result, the larger and older fish living in contaminated waters build up the highest amounts of methyl-mercury in their bodies. Saltwater fish (especially sharks and swordfish) that live a long time and can grow to a very large size tend to have the highest levels of mercury in their bodies. Plants (such as corn, wheat, and peas) have very low levels of mercury, even if grown in soils containing mercury at significantly higher than background levels. Mushrooms, however, can accumulate high levels if grown in contaminated soils. For further information on what happens to mercury in the environment, see Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO MERCURY?

Because mercury occurs naturally in the environment, everyone is exposed to very low levels of mercury in air, water, and food. Between 10 and 20 nanograms of mercury per cubic meter (ng/m^3) of air have been measured in urban outdoor air. These levels are hundreds of times lower than levels still considered to be "safe" to breathe. Background levels in nonurban settings are even lower, generally about 6 ng/m^3 or less. Mercury levels in surface water are generally less than 5 parts of mercury per trillion parts of water (5 ppt, or 5 ng per liter of water), about a thousand times lower than "safe" drinking water standards. Normal soil levels range from 20 to 625 parts of mercury per billion parts of soil (20–625 ppb; or 20,000–625,000 ng per kilogram of soil). A part per billion is one thousand times bigger than a part per trillion.

A potential source of exposure to metallic mercury for the general population is mercury released from dental amalgam fillings. An amalgam is a mixture of metals. The amalgam used in silver-colored dental fillings contains approximately 50% metallic mercury, 35% silver, 9% tin, 6% copper, and trace amounts of zinc. When the amalgam is first mixed, it is a soft paste which is inserted into the tooth surface. It hardens within 30 minutes. Once the amalgam is hard, the mercury is bound within the amalgam, but very small amounts are slowly released from the surface of the filling due to corrosion or chewing or grinding motions. Part of the mercury at the surface of the filling may enter the air as mercury vapor or be dissolved in the saliva. The total amount of mercury released from dental amalgam depends upon the total number of fillings and

surface areas of each filling, the chewing and eating habits of the person, and other chemical conditions in the mouth. Estimates of the amount of mercury released from dental amalgams range from 3 to 17 micrograms per day (μg/day). The mercury from dental amalgam may contribute from 0 to more than 75% of your total daily mercury exposure, depending on the number of amalgam fillings you have, the amount of fish consumed, the levels of mercury (mostly as methylmercury) in those fish, and exposure from other less common sources such as mercury spills, religious practices, or herbal remedies that contain mercury. However, it should be kept in mind that exposure to very small amounts of mercury, such as that from dental amalgam fillings, does not necessarily pose a health risk.

Whether the levels of exposure to mercury vapor from dental amalgam are sufficiently high to cause adverse health effects, and exactly what those effects are, continues to be researched and debated by scientists and health officials. U.S. government summaries on the effects of dental amalgam conclude that there is no apparent health hazard to the general population, but that further study is needed to determine the possibility of more subtle behavioral or immune system effects, and to determine the levels of exposure that may lead to adverse effects in sensitive populations. Sensitive populations may include pregnant women, children under the age of 6 (especially up to the age of 3), people with impaired kidney function, and people with hypersensitive immune responses to metals. If you belong to this group, you should discuss your medical condition with your dentist prior to any dental restoration work. Removal of dental amalgams in people who have no indication of adverse effects is not recommended and can put the person at greater risk, if performed improperly. Chelation therapy (used to remove metals from the body tissues) itself presents some health risks, and should be considered only when a licensed occupational or environmental health physician determines it necessary to reduce immediate and significant health risks due to high levels of mercury in the body. For additional information on health risks associated with mercury dental amalgam, see Section 2.5, "More on the Health Effects of Dental Amalgam."

Some religions have practices that may include the use of metallic mercury. Examples of these religions include Santeria (a Cuban-based religion whose followers worship both African deities

and Catholic saints), Voodoo (a Haitian-based set of beliefs and rituals), Palo Mayombe (a secret form of ancestor worship practiced mainly in the Caribbean), and Espiritismo (a spiritual belief system native to Puerto Rico). Not all people who observe these religions use mercury, but when mercury is used in religious, ethnic, or ritualistic practices, exposure to mercury may occur both at the time of the practice and afterwards from contaminated indoor air. Metallic mercury is sold under the name "azogue" (pronounced ah-SEW-gay) in stores called “botanicas.” Botanicas are common in Hispanic and Haitian communities, where azogue may be sold as an herbal remedy or for spiritual practices. The metallic mercury is often sold in capsules or in glass containers. It may be placed in a sealed pouch to be worn on a necklace or in a pocket, or it may be sprinkled in the home or car. Some people may mix azogue in bath water or perfume, or place azogue in devotional candles. Because metallic mercury evaporates into the air, these practices may put anyone breathing the air in the room at risk of exposure to mercury. The longer people breathe the contaminated air, the greater their risk will be. The use of metallic mercury in a home or an apartment not only threatens the health of the people who live there now, but also threatens the health of future residents who may unknowingly be exposed to further release of mercury vapors from contaminated floors or walls.

Metallic mercury is used in a variety of household products and industrial items, including thermostats, fluorescent light bulbs, barometers, glass thermometers, and some blood pressure devices. The mercury in these devices is contained in glass or metal, and generally does not pose a risk unless the item is damaged or broken, and mercury vapors are released. Spills of metallic mercury from broken thermometers or damaged electrical switches in the home may result in exposure to mercury vapors in indoor air. You must be careful when you handle and dispose of all items in the home that contain metallic mercury.

Very small amounts of metallic mercury (for example, a few drops) can raise air concentrations of mercury to levels that may be harmful to health. The longer people breathe the contaminated air, the greater the risk to their health. Metallic mercury and its vapors are extremely difficult to remove from clothes, furniture, carpet, floors, walls, and other such items. If these items are not

properly cleaned, the mercury can remain for months or years, and continue to be a source of exposure.

It is possible for you to be exposed to metallic mercury vapors from breathing contaminated air around hazardous waste sites, waste incinerators, or power plants that burn mercury-containing fuels (such as coal or other fossil fuels), but most outdoor air is not likely to contain levels that would be harmful. Exposure to mercury compounds at hazardous waste sites is much more likely to occur from handling contaminated soil (i.e., children playing in or eating contaminated surface soil), drinking well-water, or eating fish from contaminated waters near those sites. Not all hazardous sites contain mercury, and not all waste sites that do contain mercury have releases of mercury to the air, water, or surface soils.

You can be exposed to mercury vapors from the use of fungicides that contain mercury. Excess use of these products may result in higher-than-average exposures. You may also be exposed to mercury from swallowing or applying to your skin outdated medicinal products (laxatives, worming medications, and teething powders) that contain mercurous chloride. Exposure may also occur from the improper or excessive use of other chemicals containing mercury, such as skin-lightening creams and some topical antiseptic or disinfectant agents (mercurochrome and thimerosal).

Workers are mostly exposed from breathing air that contains mercury vapors, but may also be exposed to other inorganic mercury compounds in the workplace. Occupations that have a greater potential for mercury exposure include manufacturers of electrical equipment or automotive parts that contain mercury, chemical processing plants that use mercury, metal processing, construction where building parts contain mercury (e.g., electrical switches, thermometers), and the medical professions (medical, dental, or other health services) where equipment may contain mercury (e.g., some devices that measure blood pressure contain liquid mercury). Dentists and their assistants may be exposed to metallic mercury from breathing in mercury vapor released from amalgam fillings and to a much lesser extent from skin contact with

amalgam restorations. Family members of workers who have been exposed to mercury may also be exposed to mercury if the worker's clothes are contaminated with mercury particles or liquid.

Some people may be exposed to higher levels of mercury in the form of methylmercury if they have a diet high in fish, shellfish, or marine mammals (whales, seals, dolphins, and walruses) that come from mercury-contaminated waters. Methylmercury accumulates up the food chain, so that fish at the top of the food chain will have the most mercury in their flesh. Of these fish, the largest (i.e., the oldest) fish will have the highest levels. The Food and Drug Administration (FDA) estimates that most people are exposed, on average, to about 50 ng of mercury per kilogram of body weight per day (50 ng/kg/day) in the food they eat. This is about 3.5 micrograms (µg) of mercury per day for an adult of average weight. This level is not thought to result in any harmful effects. A large part of this mercury is in the form of methylmercury and probably comes from eating fish. Commercial fish sold through interstate commerce that are found to have levels of methylmercury above an "action level" of 1 ppm (established by the FDA) cannot be sold to the public. This level itself is below a level associated with adverse effects. However, if you fish in contaminated waters and eat the fish you catch, you may be exposed to higher levels of mercury. Public health advisories are issued by state and federal authorities for local waters that are thought to be contaminated with mercury. These advisories can help noncommercial (sport and subsistence) fishermen and their families to avoid eating fish contaminated with mercury. Foods other than fish that may contain higher than average levels of mercury include wild game, such as wild birds and mammals (bear) that eat large amounts of contaminated fish. People in the most northern climates may be exposed to high levels of mercury from eating meat or fat from marine mammals including whales, dolphins, walruses, and seals. These marine mammals are at or near the top of their marine food chain. Plants contain very little methylmercury or other forms of mercury. Mushrooms grown in mercury-contaminated soil may contain levels of mercury that could pose some risk to health, if large amounts were eaten.

See Chapter 5 for more information on how you might be exposed to mercury.

1.4 HOW CAN MERCURY ENTER AND LEAVE MY BODY?

A person can be exposed to mercury from breathing in contaminated air, from swallowing or eating contaminated water or food, or from having skin contact with mercury. Not all forms of mercury easily enter your body, even if they come in contact with it; so it is important to know which form of mercury you have been exposed to, and by which route (air, food, or skin).

When you swallow small amounts of metallic mercury, for example, from a broken oral thermometer, virtually none (less than 0.01%) of the mercury will enter your body through the stomach or intestines, unless they are diseased. Even when a larger amount of metal mercury (a half of a tablespoon, about 204 grams) was swallowed by one person, very little entered the body. When you breathe in mercury vapors, however, most (about 80%) of the mercury enters your bloodstream directly from your lungs, and then rapidly goes to other parts of your body, including the brain and kidneys. Once in your body, metallic mercury can stay for weeks or months. When metallic mercury enters the brain, it is readily converted to an inorganic form and is "trapped" in the brain for a long time. Metallic mercury in the blood of a pregnant woman can enter her developing child. Most of the metallic mercury will accumulate in your kidneys, but some metallic mercury can also accumulate in the brain. Most of the metallic mercury absorbed into the body eventually leaves in the urine and feces, while smaller amounts leave the body in the exhaled breath.

Inorganic mercury compounds like mercurous chloride and mercuric chloride are white powders and do not generally vaporize at room temperatures like elemental mercury will. If they are inhaled, they are not expected to enter your body as easily as inhaled metallic mercury vapor. When inorganic mercury compounds are swallowed, generally less than 10% is absorbed through the intestinal tract; however, up to 40% may enter the body through the stomach and intestines in some instances. Some inorganic mercury can enter your body through the skin, but only a small amount will pass through your skin compared to the amount that gets into your body from swallowing inorganic mercury.

Once inorganic mercury enters the body and gets into the bloodstream, it moves to many different tissues. Inorganic mercury leaves your body in the urine or feces over a period of several weeks or months. A small amount of the inorganic mercury can be changed in your body to metallic mercury and leave in the breath as a mercury vapor. Inorganic mercury accumulates mostly in the kidneys and does not enter the brain as easily as metallic mercury. Inorganic mercury compounds also do not move as easily from the blood of a pregnant woman to her developing child. In a nursing woman, some of the inorganic mercury in her body will pass into her breast milk.

Methylmercury is the form of mercury most easily absorbed through the gastrointestinal tract (about 95% absorbed). After you eat fish or other foods that are contaminated with methylmercury, the methylmercury enters your bloodstream easily and goes rapidly to other parts of your body. Only small amounts of methylmercury enter the bloodstream directly through the skin, but other forms of organic mercury (in particular dimethylmercury) can rapidly enter the body through the skin. Organic mercury compounds may evaporate slowly at room temperature and may enter your body easily if you breathe in the vapors. Once organic mercury is in the bloodstream, it moves easily to most tissues and readily enters the brain. Methylmercury that is in the blood of a pregnant woman will easily move into the blood of the developing child and then into the child's brain and other tissues. Like metallic mercury, methylmercury can be changed by your body to inorganic mercury. When this happens in the brain, the mercury can remain there for a long time. When methylmercury does leave your body after you have been exposed, it leaves slowly over a period of several months, mostly as inorganic mercury in the feces. As with inorganic mercury, some of the methylmercury in a nursing woman's body will pass into her breast milk.

For more information on how mercury can enter and leave your body, please see Chapter 2.

1.5 HOW CAN MERCURY AFFECT MY HEALTH?

The nervous system is very sensitive to mercury. In poisoning incidents that occurred in other countries, some people who ate fish contaminated with large amounts of methylmercury or seed grains treated with methylmercury or other organic mercury compounds developed permanent

damage to the brain and kidneys. Permanent damage to the brain has also been shown to occur from exposure to sufficiently high levels of metallic mercury. Whether exposure to inorganic mercury results in brain or nerve damage is not as certain, since it does not easily pass from the blood into the brain.

Metallic mercury vapors or organic mercury may affect many different areas of the brain and their associated functions, resulting in a variety of symptoms. These include personality changes (irritability, shyness, nervousness), tremors, changes in vision (constriction (or narrowing) of the visual field), deafness, muscle incoordination, loss of sensation, and difficulties with memory.

Different forms of mercury have different effects on the nervous system, because they do not all move through the body in the same way. When metallic mercury vapors are inhaled, they readily enter the bloodstream and are carried throughout the body and can move into the brain. Breathing in or swallowing large amounts of methylmercury also results in some of the mercury moving into the brain and affecting the nervous system. Inorganic mercury salts, such as mercuric chloride, do not enter the brain as readily as methylmercury or metallic mercury vapor.

The kidneys are also sensitive to the effects of mercury, because mercury accumulates in the kidneys and causes higher exposures to these tissues, and thus more damage. All forms of mercury can cause kidney damage if large enough amounts enter the body. If the damage caused by the mercury is not too great, the kidneys are likely to recover once the body clears itself of the contamination.

Short-term exposure (hours) to high levels of metallic mercury vapor in the air can damage the lining of the mouth and irritate the lungs and airways, causing tightness of the breath, a burning sensation in the lungs, and coughing. Other effects from exposure to mercury vapor include nausea, vomiting, diarrhea, increases in blood pressure or heart rate, skin rashes, and eye irritation. Damage to the lining of the mouth and lungs can also occur from exposure to lower levels of mercury vapor over longer periods (for example, in some occupations where workers were exposed to mercury for many years). Levels of metallic mercury in workplace air are generally much greater than the levels normally encountered by the general population. Current

levels of mercury in workplace air are low, due to increased awareness of mercury's toxic effects. Because of the reduction in the allowable amount of mercury in workplace air, fewer workers are expected to have symptoms of mercury toxicity. Most studies of humans who breathed metallic mercury for a long time indicate that mercury from this type of exposure does not affect the ability to have children. Studies in workers exposed to metallic mercury vapors have also not shown any mercury-related increase in cancer. Skin contact with metallic mercury has been shown to cause an allergic reaction (skin rashes) in some people.

In addition to effects on the kidneys, inorganic mercury can damage the stomach and intestines, producing symptoms of nausea, diarrhea, or severe ulcers if swallowed in large amounts. Effects on the heart have also been observed in children after they accidentally swallowed mercuric chloride. Symptoms included rapid heart rate and increased blood pressure. There is little information on the effects in humans from long-term, low-level exposure to inorganic mercury.

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.

Studies using animals indicate that long-term oral exposure to inorganic mercury salts causes kidney damage, effects on blood pressure and heart rate, and effects on the stomach. Study results also suggest that reactions involving the immune system may occur in sensitive populations after swallowing inorganic mercury salts. Some animal studies report that nervous system damage occurs after long-term exposure to high levels of inorganic mercury. Short-term, high-

level exposure of laboratory animals to inorganic mercury has been shown to affect the developing fetus and may cause termination of the pregnancy.

Animals exposed orally to long-term, high levels of methylmercury or phenylmercury in laboratory studies experienced damage to the kidneys, stomach, and large intestine; changes in blood pressure and heart rate; adverse effects on the developing fetus, sperm, and male reproductive organs; and increases in the number of spontaneous abortions and stillbirths. Adverse effects on the nervous system of animals occur at lower doses than do harmful effects to most other systems of the body. This difference indicates that the nervous system is more sensitive to methylmercury toxicity than are other organs in the body. Animal studies also provide evidence of damage to the nervous system from exposure to methylmercury during development, and evidence suggests that the effects worsen with age, even after the exposure stops.

Some rat and mice strains that are susceptible to autoimmune responses develop kidney damage as a result of an immune response when exposed to relatively low levels of mercury vapor or mercury chloride.

Animals given inorganic mercury salts by mouth for most of their lifetime had increases in some kinds of tumors at the highest dose tested. Rats and mice that received organic mercury (methyl-mercury or phenylmercury) in their drinking water or feed for most of their lives had an increased incidence of cancer of the kidney, but this affected only the males that received the highest amount of mercury given (not the females). Since the high doses caused severe damage to the kidneys prior to the cancer, these animal studies provide only limited information about whether mercury causes cancer in humans. As a result, the Department of Health and Human Services (DHHS) and the International Agency for Research on Cancer (IARC) have not classified mercury as to its human carcinogenicity. The Environmental Protection Agency has determined that mercury chloride and methylmercury are possible human carcinogens. Chapter 2 contains more information on the health effects of mercury in humans and animals.

1.6 HOW CAN MERCURY AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

Children are at risk of being exposed to metallic mercury that is not safely contained, to mercury that may be brought home on work clothes or tools, or to methylmercury-contaminated foods. Methylmercury eaten or swallowed by a pregnant woman or metallic mercury that enters her body from breathing contaminated air can also pass into the developing child. Inorganic mercury and methylmercury can also pass from a mother's body into breast milk and into a nursing infant. The amount of mercury in the milk will vary, depending on the degree of exposure and the amount of mercury that enter the nursing woman's body. There are significant benefits to breast feeding, so any concern that a nursing woman may have about mercury levels in her breast milk should be discussed with her doctor. Methylmercury can also accumulate in an unborn baby's blood to a concentration higher than the concentration in the mother.

For similar exposure routes and forms of mercury, the harmful health effects seen in children are similar to the effects seen in adults. High exposure to mercury vapor causes lung, stomach, and intestinal damage and death due to respiratory failure in severe cases. These effects are similar to those seen in adult groups exposed to inhaled metallic mercury vapors at work.

Children who had been exposed to excessive amounts of mercurous chloride tablets for worms or mercurous chloride-containing powders for teething discomfort had increased heart rates and elevated blood pressure. Abnormal heart rhythms were also seen in children who had eaten grains contaminated with very high levels of methylmercury.

Other symptoms of poisonings in children who were treated with mercurous chloride for constipation, worms, or teething discomfort included swollen red gums, excessive salivation, weight loss, diarrhea and/or abdominal pain, and muscle twitching or cramping in the legs and/or arms. Kidney damage is very common after exposure to toxic levels of inorganic mercury.

Metallic mercury or methylmercury that enters the body can also be converted to inorganic mercury and result in kidney damage.

Children who breathe metallic/elemental mercury vapors, eat foods or other substances containing phenylmercury or inorganic mercury salts, or use mercury-containing skin ointments for an extended period may develop a disorder known as acrodynia, or pink disease. Acrodynia can result in severe leg cramps; irritability; and abnormal redness of the skin, followed by peeling of the hands, nose, and soles of the feet. Itching, swelling, fever, fast heart rate, elevated blood pressure, excessive salivation or sweating, rashes, fretfulness, sleeplessness, and/or weakness may also be present. It was once believed that this syndrome occurred only in children, but recent reported cases in teenagers and adults have shown that they can also develop acrodynia.

In critical periods of development before they are born, and in the early months after birth, children and fetuses are particularly sensitive to the harmful effects of metallic mercury and methylmercury on the nervous system. Harmful developmental effects may occur when a pregnant woman is exposed to metallic mercury and some of the mercury is transferred into her developing child. Thus, women who are normally exposed to mercury vapors in the workplace (such as those working in thermometer/barometer or fluorescent light manufacturing or the chlor-alkali industry) should take measures to avoid mercury vapor exposures during pregnancy. Exposures to mercury vapors are relatively rare outside of the workplace, unless metallic mercury is present in the home.

As with mercury vapors, exposure to methylmercury is more dangerous for young children than for adults, because more methylmercury easily passes into the developing brain of young children and may interfere with the development process.

Methylmercury is the form of mercury most commonly associated with a risk for developmental effects. Exposure can come from foods contaminated with mercury on the surface (for example, from seed grain treated with methylmercury to kill fungus) or from foods that contain toxic levels of methylmercury (as in some fish, wild game, and marine mammals). Mothers who are exposed to methylmercury and breast-feed their infant may also expose the child through the milk. The

effects on the infant may be subtle or more pronounced, depending on the amount to which the fetus or young child was exposed. In cases in which the exposure was very small, some effects might not be apparent, such as small decreases in IQ or effects on the brain that may only be determined by the use of very sensitive neuropsychological testing. In instances in which the exposure is great, the effects may be more serious. In some such cases of mercury exposure involving serious exposure to the developing fetus, the effects are delayed. In such cases, the infant may be born apparently normal, but later show effects that may range from the infant being slower to reach developmental milestones, such as the age of first walking and talking, to more severe effects including brain damage with mental retardation, incoordination, and inability to move. Other severe effects observed in children whose mothers were exposed to very toxic levels of mercury during pregnancy include eventual blindness, involuntary muscle contractions and seizures, muscle weakness, and inability to speak. It is important to remember, however, that the severity of these effects depends upon the level of mercury exposure and the time of exposure. The very severe effects just mentioned were reported in large-scale poisoning instances in which pregnant and nursing women were exposed to extremely high levels of methylmercury in contaminated grain used to make bread (in Iraq) or seafood (in Japan) sold to the general population.

Researchers are currently studying the potential for less serious developmental effects, including effects on a child's behavior and ability to learn, think, and solve problems that may result from eating lower levels of methylmercury in foods. A main source of exposure to methylmercury for the pregnant woman and the young child is from eating fish. Most fish purchased in the market in the United States do not have mercury levels that pose a risk to anyone, including pregnant women. Since mercury accumulates in the muscles of fish, larger fish that feed on smaller fish and live for long periods usually have larger concentrations of methylmercury than fish that feed on plants. For example, shark and swordfish normally contain the highest levels of mercury out of all ocean fish. Scientists have an ongoing debate about the value of fish in the diet versus any risk from increased exposure of pregnant women to methylmercury that may be in the fish. The safety of most fish sold commercially in the United States is regulated by the FDA. These fish pose no health risk to those who purchase and eat them. Only fish or wildlife containing relatively high

levels of methylmercury are of concern, and these are discussed in Section 1.7 of this toxicological profile.

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

If your doctor finds that you have been exposed to significant amounts of mercury, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Children may be exposed to metallic mercury if they play with it. Metallic mercury is a heavy, shiny, silver liquid. When metallic mercury is spilled, it forms little balls or beads. Children are sometimes exposed to metallic mercury when they find it in abandoned warehouses or closed factories, and then play with it or pass it around to friends. Children have also taken metallic mercury from school chemistry and physics labs. Broken thermometers and some electrical switches are other sources of metallic mercury. Sometimes children find containers of metallic mercury that were improperly disposed of, or adults may bring home metallic mercury from work, not knowing that it is dangerous.

To protect your children from metallic mercury, teach them not to play with shiny, silver liquids. Schoolteachers (particularly science teachers) and school staff need to know about students' fascination with metallic mercury. Teachers and school staff should teach children about the dangers of getting sick from playing with mercury, and they should keep metallic mercury in a safe and secured area (such as a closed container in a locked storage room) so that children do not have access to it without the supervision of a teacher. Metallic mercury evaporates slowly, and if it is not stored in a closed container, children may breathe toxic mercury vapors.

In the past, mercurous chloride was widely used in medicinal products such as laxatives, worming medications, and teething powders. These older medicines should be properly disposed of and replaced with safer and more effective medicines. Other chemicals containing mercury, such as mercurochrome and thimerosal (sold as Merthiolate and other brands), are still used as antiseptics or as preservatives in eye drops, eye ointments, nasal sprays, and vaccines. Some skin-lightening

creams contain ammoniated mercuric chloride and mercuric iodide. These and all other mercury-containing medicines should be kept safely out of the reach of children to prevent an accidental poisoning. Nonmedicinal products, including some fungicides that contain mercury compounds and paints that contain mercuric sulfide or mercuric oxide, should also be safely stored out of the reach of children.

You should check to see if any medicines or herbal remedies that you or your child use contain mercury. Some traditional Chinese and Indian remedies for stomach disorders (for example, herbal balls) contain mercury, and if you give these remedies to your children, you may harm them. If you are pregnant or nursing a baby and you use mercury-containing ethnic or herbal remedies, you could pass some of the mercury to your unborn child or nursing infant.

If you use metallic mercury or azogue in religious practices, you may expose your children or unborn child to mercury or contaminate your home. Such practices in which mercury containing substances have traditionally been used include Santeria (a Cuban-based religion whose followers worship both African deities and Catholic saints), Voodoo (a Haitian-based set of beliefs and rituals), Palo Mayombe (a secret form of ancestor worship practiced mainly in the Caribbean), or Espiritismo (a spiritual belief system native to Puerto Rico).

Metallic mercury is used in a variety of household products and industrial items, including thermostats, fluorescent light bulbs, barometers, glass thermometers, and some blood pressure measuring devices. You must be careful when you handle and dispose of all items in the home that contain metallic mercury.

If small amounts of mercury are spilled, be very careful cleaning it up. Do not try to vacuum spilled metallic mercury. Using a vacuum cleaner to clean up the mercury causes the mercury to evaporate into the air, creating greater health risks. Trying to vacuum spilled metallic mercury also contaminates the vacuum cleaner. Also, take care not to step on the mercury and track it into other areas of the home. Metallic mercury vapors are very toxic and have no odor. Do not remain unnecessarily in that room, and try not to let metallic mercury contact your eyes, skin, or clothing. If you think you have been exposed directly to metallic mercury, wash yourself

thoroughly and discard contaminated clothing by placing them in a sealed plastic bag. Perhaps the most important thing to remember if you break a household thermometer is do not panic. The amount of mercury contained in an oral thermometer is small and does not present an immediate threat to human health. However, if it is not properly cleaned up and disposed of, it may present a health risk over time, particularly to infants, toddlers, and pregnant women.

If a thermometer breaks on a counter top or uncarpeted floor, remove children from the area. Mercury is not absorbent, so do not try to wipe or blot it up with a cloth or paper towel; that will only spread the mercury and break it up into smaller beads, making it more difficult to find and remove. Instead, clean up the beads of metallic mercury by using one sheet of paper to carefully roll them onto a second sheet of paper, or by sucking very small beads of mercury into an eye dropper. After picking up the metallic mercury in this manner, put it into a plastic bag or airtight container. The paper and eye dropper should also be bagged in a zip-lock plastic container. All plastic bags used in the cleanup should then be taken outside of the house or apartment and disposed of properly, according to instructions provided by your local health department or environmental officials. Try to ventilate the room with outside air, and close the room off from the rest of the home. Use fans (that direct the air to the outside and away from the inside of the house) for a minimum of one hour to speed the ventilation.

If a thermometer breaks and the liquid/metallic mercury spills onto a carpeted floor, try to collect the mercury beads in the manner described in the above paragraph. Depending on the cut or pile of the carpeting, however, it may not be possible to collect all of the spilled mercury. Regardless, do not vacuum. Instead, call your local (county, city, or state) health department and tell them of your situation. (You may also call the Agency for Toxic Substances and Disease Registry [ATSDR] toll-free at 1-888-42-ATSDR [1-888-422-8737] to obtain additional guidance, if local assistance cannot be obtained.)

If larger amounts of metallic mercury are found (for example, a jar of liquid mercury), it should be contained in an airtight container, and you should call your local health department for instructions on how to safely dispose of it. If the mercury is in an open container or the container does not have a lid, place a piece of plastic wrap around the top of the container to prevent

vapors from escaping; then wash your hands thoroughly. If a larger amount is spilled, leave the area and contact your local health department and fire department. Do not simply throw metallic mercury away, but instead seek professional help.

ATSDR and EPA strongly recommend against the use of metallic (liquid) mercury that is not properly enclosed in glass, as it is in thermometers. This form of mercury should not be used or stored in homes, automobiles, day-care centers, schools, offices, or other public buildings. If you notice a child with metallic mercury on his or her clothing, skin, or hair, call the fire department and let them know that the child needs to be decontaminated.

Metallic or inorganic mercury can be carried into the home from a workers' contaminated clothing and shoes. Increased exposure to mercury has been reported in children of workers who are exposed to mercury at work, and increased levels of mercury were measured in places where work clothes were stored and in some washing machines. The children most likely to be exposed to risky levels of mercury are those whose parents work in facilities that use mercury (for example, a scientific glassware manufacturing plant or a chlor-alkali chemical plant), but where no protective uniforms or footgear are used. In some reported cases in which children were exposed in this way, protective clothing was used in the workplace by the parent, but work gloves, clothes, and boots, which were contaminated with mercury, were taken home, thus exposing family members. If you have questions or concerns about exposure to mercury at work, you have a right to obtain information from your employer about your safety and health on the job without fear of punishment. The Occupational Safety and Health Administration (OSHA) requires employers to provide Material Safety Data Sheets (MSDSs) for many of the chemicals used at the workplace. Information on these sheets should include chemical names and hazardous ingredients, important properties (such as fire and explosion data), potential health effects, how you get the chemical(s) in your body, how to properly handle the materials, and what to do in an emergency. Your occupational health and safety officer at work can and should tell you whether chemicals you work with are dangerous and likely to be carried home on your clothes, body, or tools, and whether you should be showering and changing clothes before you leave work, storing your street clothes in a separate area of the workplace, or laundering your work clothes at home separately from other clothes.

Your employer is legally responsible for providing a safe workplace and should freely answer your questions about hazardous chemicals. Your OSHA-approved state occupational safety and health program or OSHA can also answer any further questions you might have, and help your employer identify and correct problems with hazardous substances. If you would like to make a formal complaint about health hazards in your workplace, your OSHA-approved state occupational safety and health program or OSHA office will listen to your complaint and inspect your workplace when necessary.

One way in which people are routinely exposed to extremely small amounts of mercury is through the gradual (but extremely slow) wearing-away process of dental amalgam fillings, which contain approximately 50% mercury. The amount of mercury to which a person might be exposed from dental amalgams would depend on the number of amalgams present and other factors. The Centers for Disease Control and Prevention (CDC) has determined that dental amalgam fillings do not pose a health risk, although they do account for some mercury exposure to those having such fillings. People who frequently grind their teeth or often chew gum can add to the small amount of mercury normally released from those fillings over time. If you are pregnant, the decision of whether to have dental amalgam or a nonmercury material used for fillings, or whether existing amalgam fillings should be repaired or replaced during pregnancy, should be made in consultation with your dentist. The practice of having all your dental amalgam fillings replaced with non-mercury filling materials just to remove the possibility of mercury exposure is not recommended by ATSDR. In fact, the removal of the mercury amalgam fillings would actually expose the patient to a greater amount of mercury for a while. Other sources of mercury may increase your overall exposure, such as the amount of fish consumed per week, especially if caught in local waters contaminated with mercury or of certain species known to be higher in mercury content (shark and swordfish), or an exposure to mercury from a nearby hazardous waste site or incinerator.

You or your children may be exposed to methylmercury when eating certain types of fish caught from contaminated waters, or when eating certain types of wildlife from mercury contaminated areas. Most states, Native American tribes, and U.S. Territories have issued fish and/or wildlife advisories to warn people about methylmercury contaminated fish and/or wildlife. Most of the

methylmercury advisories relate to specific types of freshwater or saltwater fish or shellfish, or freshwater turtles. Each state, Native American tribe, or U.S. Territory sets its own criteria for issuing fish and wildlife advisories. A fish or wildlife advisory will specify which bodies of water or hunting areas have restrictions. The advisory will tell you what types and sizes of fish or game are of concern. The advisory may completely ban eating fish or tell you to limit your meals of a certain type of fish. For example, an advisory may tell you to eat a certain type of fish no more than once a month; or an advisory may tell you only to eat certain parts of fish or game, or how to prepare it to decrease your exposure to methylmercury. The fish or wildlife advisory may be stricter to protect pregnant women, nursing women, and young children. To reduce your children's exposure to methylmercury, you should follow the instructions recommended in the fish or wildlife advisories. Information on Fish and Wildlife Advisories in your state is available from your state public health or natural resources department. Signs may also be posted in certain fishing and hunting areas with information about contaminated fish or wildlife.

FDA currently advises that pregnant women and women of childbearing age who may become pregnant limit their consumption of shark and swordfish to no more that one meal per month. This advice is given because methylmercury levels are relatively high in these fish species. Women of childbearing age are included in this advice because dietary practices immediately before the pregnancy could have a direct bearing on fetal exposure during pregnancy, particularly during the earlier months of pregnancy.

FDA further advises that persons other than pregnant women and women of childbearing age in the general population limit their regular consumption of shark and swordfish (which typically contains methylmercury around 1 ppm) to about 7 ounces per week (about one serving) to stay below the acceptable daily intake for methylmercury. For fish species with methylmercury levels averaging 0.5 ppm, regular consumption should be limited to 14 ounces per week. Recreational and subsistence fishers who eat larger amounts of fish than the general population and routinely fish the same waterbodies may have a higher exposure to methylmercury if these waters are contaminated. People who consume greater than 100 grams of fish (approximately 3.5 ounces) every day are considered high-end consumers. This is over 10 times more than the amount of fish consumed by members of the general population (6.5 g/day). No consumption advice is necessary

for the top ten seafood species that make up about 80% of the seafood sold in the United States: canned tuna, shrimp, pollock, salmon, cod, catfish, clams, flatfish, crabs, and scallops. The methylmercury in these species is generally less than 0.2 ppm, and few people eat more than the suggested weekly limit of fish (i.e., 2.2 pounds).

If you are concerned about a mercury exposure or think that you or your child are experiencing the adverse effects of mercury, you should consult with a doctor or public health official who is familiar with the health effects of mercury.

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

There are reliable and accurate ways to measure mercury levels in the body. These tests all involve taking blood, urine, or hair samples, and must be performed in a doctor's office or in a health clinic. Nursing women may have their breast milk tested for mercury levels, if any of the other samples tested are found to contain significant amounts of mercury. Most of these tests, however, do not determine the form of mercury to which you were exposed. Mercury levels found in blood, urine, breast milk, or hair may be used to determine if adverse health effects are likely to occur (see Section 2.5). Mercury in urine is used to test for exposure to metallic mercury vapor and to inorganic forms of mercury. Measurement of mercury in whole blood or scalp hair is used to monitor exposure to methylmercury. Urine is not useful for determining whether exposure has occurred to methylmercury. Levels found in blood, urine, and hair may be used together to predict possible health effects that may be caused by the different forms of mercury.

Blood and urine levels are used as markers to determine whether someone has been exposed to mercury. They are used to determine whether exposure to mercury has occurred and to give a rough idea of the extent of exposure, but they do not tell exactly how much exposure has occurred. Except for methylmercury exposures, blood is considered useful if samples are taken within a few days of exposure. This is because most forms of mercury in the blood decrease by one-half every three days if exposure has been stopped. Thus, mercury levels in the blood provide

more useful information after recent exposures than after long-term exposures. Several months after an exposure, mercury levels in the blood and urine are much lower. Hair, which is considered useful only for exposures to methylmercury, can be used to show exposures that occurred many months ago, or even more than a year ago if the hair is long enough and careful testing methods are used. After short-term exposures to metallic mercury, mercury vapor can be detected in the breath, but this occurs to a significant extent only within a few days after exposure, and is not a method normally used to determine if mercury exposure has occurred. For more information on testing for mercury levels in the body, see Chapters 2 and 6.

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

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

Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

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

EPA and FDA have set a limit of 2 parts inorganic mercury per billion (ppb) parts of water in drinking water. EPA is in the process of revising the Water Quality Criteria for mercury. EPA currently recommends that the level of inorganic mercury in rivers, lakes, and streams be no more than 144 parts mercury per trillion (ppt) parts of water to protect human health (1 ppt is a thousand times less than 1 part per billion, or ppb). EPA has determined that a daily exposure (for an adult of average weight) to inorganic mercury in drinking water at a level up to 2 ppb is not likely to cause any significant adverse health effects. FDA has set a maximum permissible level of 1 part of methylmercury in a million parts (ppm) of seafood products sold through interstate commerce (1 ppm is a thousand times more than 1 ppb). FDA may seize shipments of fish and shellfish containing more than 1 ppm of methylmercury, and may seize treated seed grain containing more than 1 ppm of mercury.

OSHA regulates levels of mercury in the workplace. It has set limits of 0.1 milligrams of mercury per cubic meter of air (mg/m^3)for organic mercury and 0.05 mg/m^3 for metallic mercury vapor in workplace air to protect workers during an 8-hour shift and a 40-hour work week. NIOSH recommends that the amount of metallic mercury vapor in workplace air be limited to an average level of 0.05 mg/m^3 during a 10-hour work shift.

1.10 WHERE CAN I GET MORE INFORMATION?

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry
Division of Toxicology
1600 Clifton Road NE, Mailstop E-29
Atlanta, GA 30333

* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)
Fax: (404) 639- 6315 or -6324

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

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 605-6000

2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

Mercury is a metal element that occurs naturally in the environment. Metallic or elemental mercury (Hg^0) is the main form of mercury released into the air by natural processes. Mercury bound to other chemicals may have valence states of either +1 (Hg^{+1}) or +2 (Hg^{+2}). Mercury with a valence state of +1 is referred to as mercurous mercury, and mercury with a valence state of +2 is referred to as mercuric mercury. Many inorganic and organic compounds of mercury can be formed from the mercuric (divalent) cation (Hg^{+2}). For information on the physical and chemical properties of mercury, refer to Chapter 3.

There are many similarities in the toxic effects of the various forms of mercury, but there are also significant differences. In the text, tables, and figures of this profile, the metallic mercury and the inorganic salts, including mercurous chloride, mercuric chloride, mercuric acetate, and mercuric sulfide, are organized under the general heading of inorganic mercury. The organic mercury compounds including methyl-mercuric chloride, dimethylmercury, and phenylmercuric acetate are addressed in this document under the heading of organic mercury. In most discussion in the text, the specific effects are attributable to a particular form, and the form is specified.

The general population is most commonly exposed to mercury primarily from two sources: (1) eating fish and marine mammals (e.g., whales, seals) that may contain some methylmercury in their tissues or (2) from the release of elemental mercury from the dental amalgam used in fillings. It is not known how much of the elemental mercury released from dental amalgam is inhaled as a mercury vapor, how much is breathed out, how much is swallowed in a liquid form, or how much is converted into a mercuric salt that is either swallowed of directly absorbed into the oral mucosa. Exposure to mercury, however, does not necessarily mean that adverse health effects will result. Health effects depend upon the amount of exposure, the form

of mercury, and the route of exposure. Each form and route leads to different effects, and these are discussed in detail in this chapter. The levels of mercury that the general population are exposed to from either fish or dental amalgam are discussed in Chapter 5. Hazard assessments combine the information in Chapter 5 on exposure levels with the dose-response information in this chapter to develop an estimate of the potential for adverse health effects from any given exposure.

In the environment, inorganic mercury can be methylated by microorganisms to methylmercury. Methylmercury will accumulate in the tissues of organisms. The animals at the top of the food chain tend to accumulate the most methylmercury in their bodies. Any source of mercury release to the environment may, therefore, lead to increased levels of methylmercury in tissues of large fish and mammals. Occupational exposures are primarily to metallic mercury vapor. Accidental exposures to mercury are more common than accidental exposures to many hazardous substances, because liquid mercury is shiny and interesting, and because liquid mercury has been used in many electrical and mechanical devices. Accidental exposures, even to small amounts of mercury, may be harmful. Liquid mercury is poorly absorbed by the skin and from the intestines, but vapors that are released from liquid mercury are readily absorbed through the lungs and are very harmful when inhaled. The text in this chapter provides considerable detail on a number of accidental exposures to all forms of mercury. This information is intended to inform the reader and help prevent accidental exposures in the future.

The literature on the health effects of mercury is extensive. However, the human and animal data are generally limited to inhalation exposure to metallic mercury vapors and oral exposure to inorganic and organic mercury compounds. There is limited dermal exposure information on adverse effects from ointments and creams that contain inorganic mercury compounds.

Once absorbed, metallic and inorganic mercury enter an oxidation-reduction cycle. Metallic mercury is oxidized to the divalent inorganic cation in the red blood cells and lungs of humans and animals. Evidence from animal studies suggests that the liver is an additional site of oxidation. Absorbed divalent cation from exposure to mercuric compounds can, in turn, be reduced to the metallic or monovalent form and released as exhaled metallic mercury vapor. In the presence of protein sulfhydryl groups, mercurous mercury (Hg^{+}) disproportionates to one divalent cation (Hg^{+2}) and one molecule at the zero oxidation state (Hg^{0}). The conversion of methylmercury or phenylmercury into divalent inorganic mercury can probably occur soon after absorption, also feeding into the oxidation-reduction pathway.

This profile contains a discussion of acrodynia under Relevance to Public Health (Section 2.5). Acrodynia is an idiosyncratic hypersensitivity response from exposure to mercury and is characterized by certain cardiovascular, dermal, and neurological effects, among others. In the section on health effects by route of exposure, the relevant symptoms are discussed under the appropriate headings without reference to the syndrome. This occurs, in part, because there is some overlap between symptoms characteristic of acrodynia and those seen in persons who are not hypersensitive and, in part, because not every report of a study in which the symptoms were observed states whether the authors considered the affected person to have suffered from acrodynia.

This profile also contains a general discussion of the human exposures to mercury associated with dental amalgam. This discussion is at the end of the Relevance to Public Health Section 2.5, under the heading More on Health Effects and Dental Amalgam.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

Levels of significant exposure (LSE) for each route and duration are presented in Tables 2-1, 2-2, and 2-3 and illustrated in Figures 2-1, 2-2, and 2-3. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end-points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less

serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of mercury are indicated in Tables 2-2 and 2-3 and Figures 2-2 and 2-3. Cancer effects could occur at lower exposure levels; however, a range for the upper bound of estimated excess risks (ranging from a risk of 1 in 10,000 to 1 in 10,000,000 [10^{-4} to 10^{-7}]) has not been developed by EPA.

Estimates of human Minimal Risk Levels (or MRLs) have been made for mercury. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. Although the term, MRL, may seem to imply a slight level of risk, MRLs are, in fact, considered to represent safe levels of exposure for all populations, including sensitive subgroups. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs may be revised.

2.2.1 Inhalation Exposure

Most of the studies on inhalation exposure concern exposure to metallic mercury vapor. For this reason, the term "metallic mercury" will be used in this section instead of "inorganic mercury." Other forms of inorganic mercury do not pose a risk by the inhalation pathway. Inhalation of sufficient levels of metallic mercury vapor has been associated with systemic toxicity in both humans and animals. The major target organs of metallic mercury-induced toxicity are the kidneys and the central nervous system. At high-exposure levels, respiratory, cardiovascular, and gastrointestinal effects also occur. Some metallic mercury vapor may condense (Milne et al. 1970), or in the case of vapors from dental amalgam, may dissolve in saliva and be ingested (WHO 1991). Condensed droplets are more likely to be ingested than inhaled (resulting in a lower absorbed dose than would be expected for a given concentration in air). Mercury vapor concentrations in the general work environment may also be lower than those in the micro-environment immediately surrounding workers (Bell et al. 1973; Stopford et al. 1978); therefore, estimates of air mercury values in occupational studies should be carefully evaluated for bias towards a level that may be lower than actual exposure levels.

No studies were located concerning effect levels following inhalation exposure to inorganic salts of mercury (e.g., mercuric or mercurous salts, oxides). Also, much of the information located regarding effects of metallic mercury vapors or volatile organic compounds (VOCs) comes from studies with significant limitations. Information on inhalation exposure to organic mercury compounds (e.g., alkyl mercury compounds) in humans is limited to case reports and includes only qualitative data on gastro-intestinal, renal, muscular, and neurological effects. In many cases, it is difficult to determine whether effects observed in exposed persons were directly attributable to mercury exposure. In addition, a great deal of the information on effects associated with inhalation exposure to metallic mercury vapor comes from studies conducted several decades ago, when methods for determining exposure levels were less precise than current methods.

2.2.1.1 Death

Metallic Mercury. Several studies have reported death in humans following accidental acute-duration exposure to high, but unspecified, concentrations of metallic mercury vapor (Campbell 1948; Kanluen and Gottlieb 1991; Matthes et al. 1958; Rowens et al. 1991; Soni et al. 1992; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961). Death in all cases was attributed to respiratory failure. In all of these cases, high levels of mercury vapors were generated by volatilizing metallic mercury by heating.

Available animal data on death from exposure to metallic mercury vapors were also limited to acute-duration exposures (Ashe et al. 1953; Christensen et al. 1937; Livardjani et al. 1991b). Rats, guinea pigs, and mice died from severe pulmonary edema following a 24–48-hour exposure to an unspecified concentration of metallic mercury vapor resulting from spillage of mercury droplets on the floor of a static exposure chamber (Christensen et al. 1937). Exposure of rats to 27 mg/m^3 of elemental mercury vapors for 2 hours, followed by observation for 15 days, resulted in substantial mortality (20 of 32 rats died prior to their scheduled sacrifice) (Livardjani et al. 1991b). Rabbits appeared to be less sensitive, with death occurring in 1 of 2 rabbits exposed to 28.8 mg/m^3 metallic mercury for 30 hours and no deaths in rabbits exposed to the same concentration for 20 hours or less (Ashe et al. 1953).

All reliable LOAEL values for death following exposure to inorganic mercury in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Organic Mercury. Case studies of occupational exposure to alkyl mercury compounds have reported deaths in humans following inhalation exposure to organic mercury vapors. The cause of death was not reported, but most subjects died after developing profound neurotoxicity (Hill 1943; Hook et al. 1954). Exposure to diethylmercury vapor (estimated exposure level = 1–1.1 mg/m^3) for 4–5 months resulted in the death of 2 women (Hill 1943). The cause of death was not reported; however, the symptoms experienced by the women were consistent with mercury toxicity, and autopsies revealed pronounced gastrointestinal disorder. It is unclear whether the gastrointestinal effects were directly attributable to the mercury exposure. A 41-year-old man with 3–4 years of exposure to alkyl mercury compounds used in seed dressing died within approximately 3 months after cleaning up a spill of liquid containing alkyl mercury (Hook et al. 1954). A 57-year-old male employed for 5 years treating lumber with an alkyl mercury preparation (unspecified) died soon after developing neurological toxicity (Lundgren and Swensson 1949).

Table 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Death							
1	Rat (Wistar)	1 or 2 hr				27 M (20/32 died prior to scheduled sacrifice)	Livardjani et al. 1991 ELEM
Systemic							
2	Rat (Wistar)	1 or 2 hr	Resp			27 M (death by asphyxiation; lung edema; hyaline membranes, necrosis of alveolar epithelium; and fibrosis)	Livardjani et al. 1991 ELEM
3	Rabbit	1-30 hr	Resp			28.8 (marked cellular degeneration and some necrosis)	Ashe et al. 1953 ELEM
			Cardio			28.8 (marked cellular degeneration and some necrosis)	
			Gastro			28.8 (marked cellular degeneration and some necrosis)	
			Hepatic			28.8 (widespread necrosis)	
			Renal			28.8 (widespread necrosis)	
Neurological							
4	Rabbit	1-30 hr				28.8 (brain necrosis)	Ashe et al. 1953 ELEM

Table 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Developmental							
5	Rat (Sprague-Dawley)	8 d 1 or 3 hr/d Gd 11-14 + 17-20				1.8 (offspring hypoactive at 3 mo of age, significant retardation in spatial learning, reduced ability to adapt to new environment)	Danielsson et al. 1993 ELEM
6	Rat (Sprague-Dawley)	7d 1,4 hr/d ppd 11-17				0.05 M (offspring hyperactive, significantly impaired spatial learning)	Fredriksson et al. 1992 ELEM
7	Rat (Sprague-Dawley)	6 d 1.5 hr/d Gd 14-19				1.8 (offspring hyperactive, significantly impaired spatial learning, deficits in adaptive behavior)	Fredriksson et al. 1996 ELEM
INTERMEDIATE EXPOSURE							
Systemic							
8	Rat	12-42 wk 5 d/wk 3 hr/d	Resp	3.0 M			Kishi et al. 1978 ELEM
			Hepatic	3.0 M			
			Renal		3.0 M (dense deposits in tubular cells; lysosomal inclusions)		

Table 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
9	Rabbit	1-11 wk 5 d/wk 7 hr/d	Resp		6.0 (unspecified histopathological changes in lungs)		Ashe et al. 1953 ELEM
			Cardio		6.0 (unspecified histopathological changes in heart)		
			Gastro		6.0 (unspecified histopathological changes in colon)		
			Hepatic			6.0 (marked cellular degeneration with mild necrosis in liver)	
			Renal			6.0 (marked cellular degeneration; widespread necrosis in kidneys)	
10	Rabbit	12 wk 5 d/wk	Cardio		0.86 (unspecified histopathological changes)		Ashe et al. 1953 ELEM
			Renal		0.86 (mild to moderate unspecified histopathological changes in the kidneys)		
Immunological/Lymphoreticular							
11	Mouse (SJL/N)	10 wk 5 d/wk 0.5-19 hr/d		0.075 F	0.17 F (serum antinucleolar antibodies)		Warfvinge et al. 1995 ELEM
Neurological							
12	Rat	12-41 wk 5 d/wk 3 hr/d				3.0 M (significant decline in conditioned avoidance response and increase in escape response latency)	Kishi et al. 1978 ELEM

Table 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL			Reference Chemical Form
					Less serious (mg/m3)	Serious (mg/m3)		
13	Rabbit	12 wk 5 d/wk 7 hr/d				0.86	(unspecified histopathological changes in the brain)	Ashe et al. 1953 ELEM
14	Rabbit	1-11 wk 5 d/wk 7 hr/d				6.0	(marked cellular degeneration with brain necrosis)	Ashe et al. 1953 ELEM
15	Rabbit	13 wk 4 d/wk 6 hr/d				4	(tremors)	Fukuda 1971 ELEM
	Developmental							
16	Monkey (Squirrel)	15-17 wk 5 d/wk 4 or 7 hr/d last 2/3 gestation				0.5	(increase in duration and variability in lever-press performance, aberrant transitions)	Newland et al. 1996 ELEM
CHRONIC EXPOSURE								
	Systemic							
17	Rat	72 wk 5 d/wk 7 hr/d	Renal	0.1				Ashe et al. 1953 ELEM
18	Dog	83 wk 5 d/wk 7 hr/d	Renal	0.1				Ashe et al. 1953 ELEM
19	Rabbit	83 wk 5 d/wk 7 hr/d	Renal	0.1				Ashe et al. 1953 ELEM

Table 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (continued)

Key to figure[a]	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
Neurological							
20	Human	1-5 yr			0.076 M (difficulty with heel-to-toe gait)		Ehrenberg et al. 1991 ELEM
21	Human	1-41 yr 15.3 yr mean			0.026[b] M (increased frequency of mild intention tremors with weight load)		Fawer et al. 1983 ELEM
22	Human	0.7-24 yr			0.014 (impaired performance on neurobehavioral tests)		Ngim et al. 1992 ELEM

[a]The number corresponds to entries in Figure 2-1.
[b]Used to derive a chronic inhalation Minimal Risk Level (MRL) of $2x10^{-4}$ mg/m^3; concentration corrected for intermittent exposure and divided by an uncertainty factor of 30 (3 for use of a minimal LOAEL and 10 for human variability).

ALT = alanine amino transferase; AST = aspartate aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); ELEM = elemental mercury; Endocr = endocrine; F = female; Gastro = gastrointestinal; Gd = gestational day; Hemato = hematological; hr = hour(s); IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; ppd = postpartum day (s); Resp = respiratory; wk = week(s); yr = year(s)

Figure 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation

Acute (≤14 days)

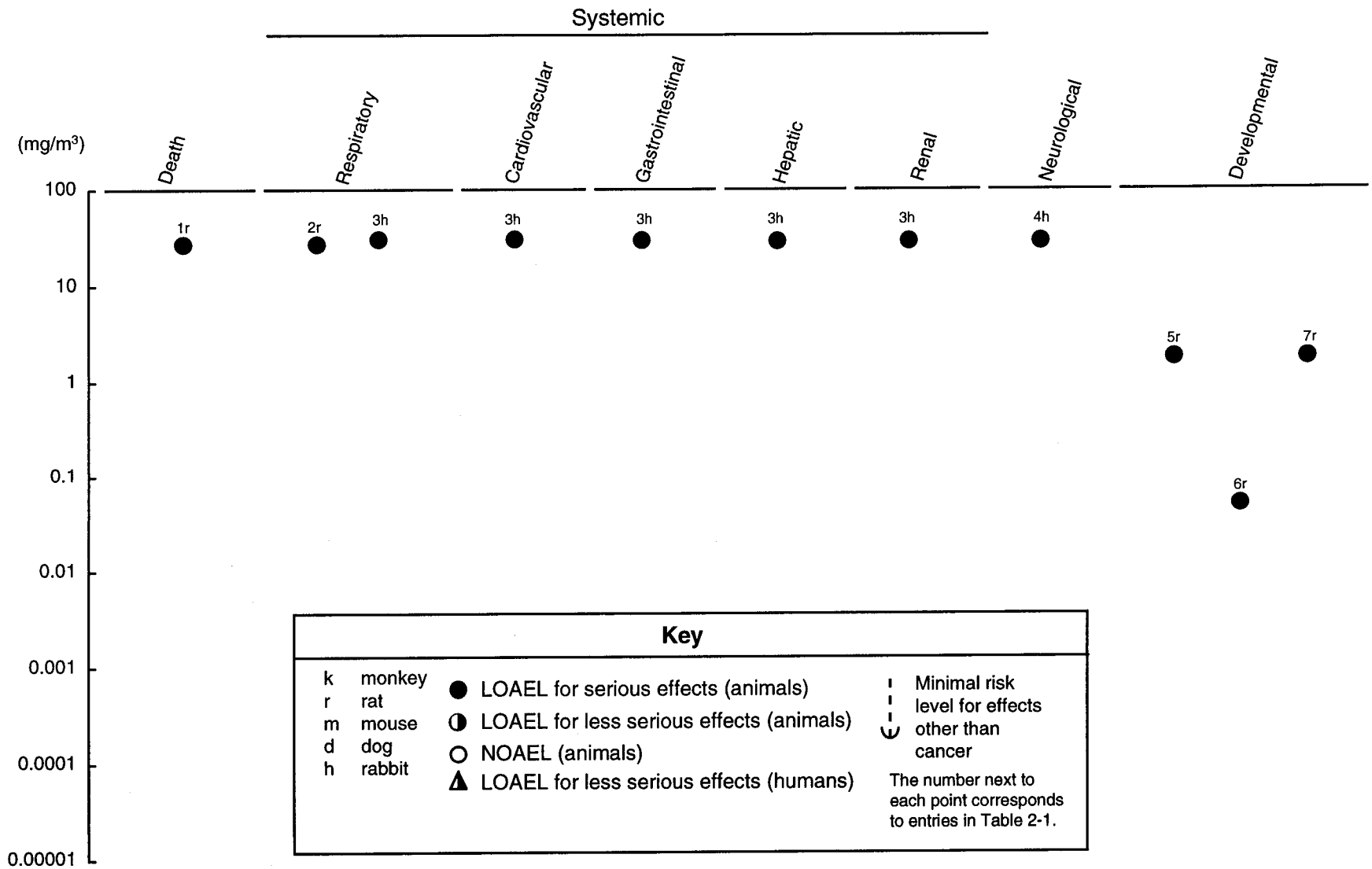


Figure 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (cont.)

Intermediate (15-364 days)

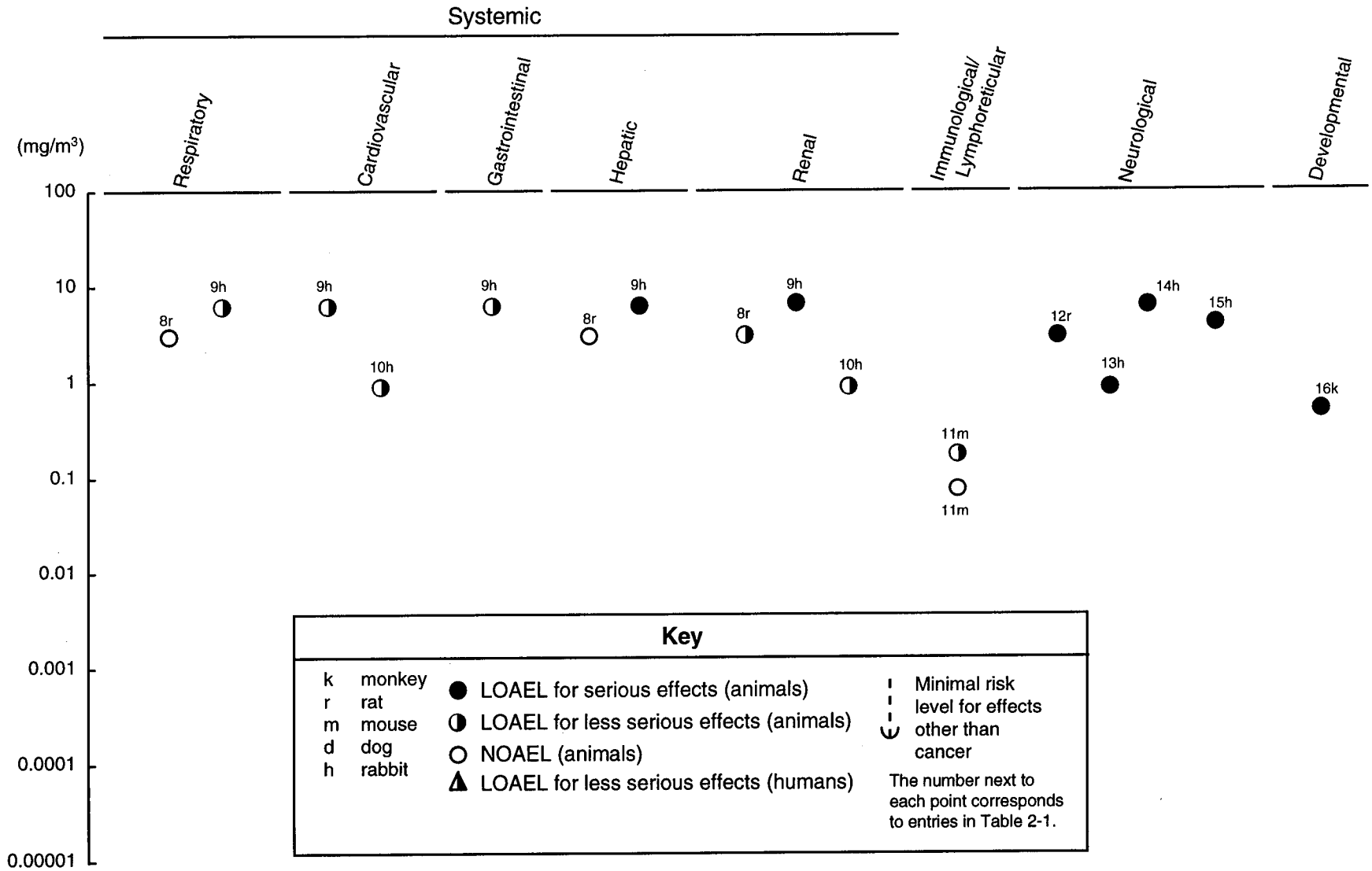
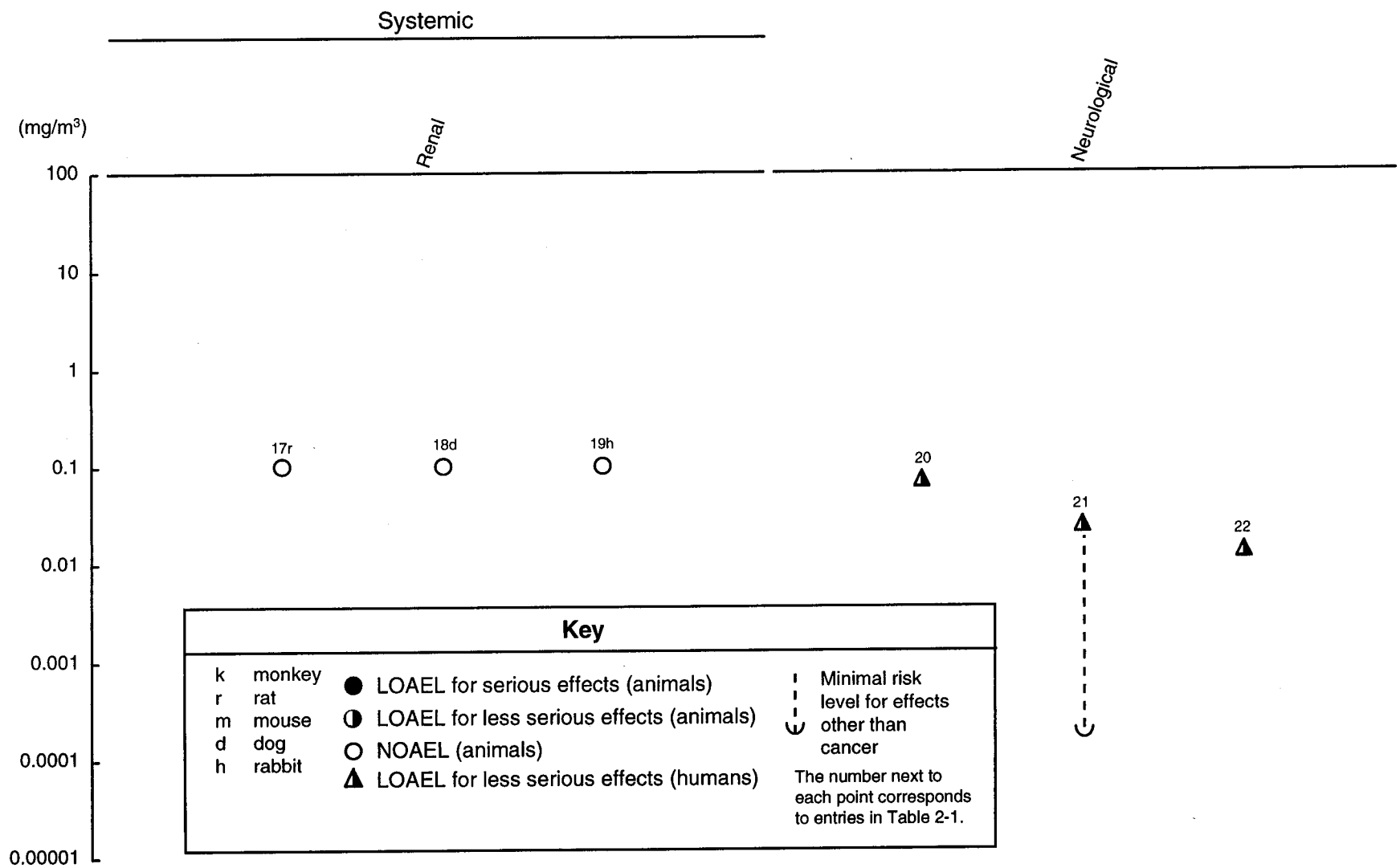


Figure 2-1. Levels of Significant Exposure to Inorganic Mercury - Inhalation (cont.)

Chronic (≥365 days)



A 39-year-old farmer who had treated seeds with phenylmercuric acetate for 6–7 seasons died within several months of developing severe neurological toxicity (Brown 1954).

Four rats died soon after developing severe ataxia following inhalation of unspecified concentrations of methylmercury iodide vapor for 22 days (Hunter et al. 1940).

2.2.1.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects

Metallic Mercury. In humans, respiratory symptoms are a prominent effect of acute-duration high-level exposure to metallic mercury vapors. The most commonly reported symptoms include cough, dyspnea, and tightness or burning pains in the chest (Bluhm et al. 1992a; Gore and Harding 1987; Haddad and Sternberg 1963; Hallee 1969; Kanluen and Gottlieb 1991; King 1954; Lilis et al. 1985; Matthes et al. 1958; McFarland and Reigel 1978; Milne et al. 1970; Rowens et al. 1991; Snodgrass et al. 1981; Soni et al. 1992; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961). X-ray analyses of the lungs have primarily shown diffuse infiltrates or pneumonitis (Bluhm et al. 1992a; Garnier et al. 1981; Gore and Harding 1987; Hallee 1969; King 1954; Soni et al. 1992; Tennant et al. 1961). Pulmonary function may also be impaired. Airway obstruction, restriction, hyperinflation (Snodgrass et al. 1981), and decreased vital capacity (Lilis et al. 1985; McFarland and Reigel 1978) have been reported. The decreased vital capacity observed by Lilis et al. (1985) persisted for 11 months after exposure. In the more severe cases, respiratory distress, pulmonary edema (alveolar and interstitial), lobar pneumonia, fibrosis, and desquamation of the bronchiolar epithelium have been observed. The ensuing bronchiolar obstruction by mucus and fluid results in alveolar dilation, emphysema, pneumothorax, and possibly death (Campbell 1948; Gore and Harding 1987; Jaffe et al. 1983; Kanluen and Gottlieb 1991; Matthes et al. 1958; Taueg et al. 1992; Teng and Brennan 1959; Tennant et al. 1961).

Little information is available regarding exposure levels resulting in the above symptoms. However, workers accidentally exposed to mercury vapors at an estimated concentration of up to 44.3 mg/m^3 for 4–8 hours exhibited chest pains, dyspnea, cough, hemoptysis, impairment of pulmonary function (i.e.,

reduced vital capacity), diffuse pulmonary infiltrates, and evidence of interstitial pneumonitis (McFarland and Reigel 1978).

Very little information was located regarding respiratory effects associated with intermediate-duration exposures. However, two studies noted chronic coughs in subjects exposed to metallic mercury vapor for several weeks (Schwartz et al. 1992; Sexton et al. 1976). No respiratory symptoms and no abnormalities were noted upon examining chest X-rays or the results of pulmonary function tests in a group of chloralkali workers exposed for an average of >6 years to levels of mercury ranging from near 0 to 0.27 mg/m^3 (85% of the group was exposed at or below 0.1 mg/m^3) (Smith et al. 1970).

Respiratory effects in animals have been observed following acute inhalation exposure of metallic mercury vapors. Rats exposed to 27 mg/m^3 of elemental mercury vapors for 2 hours then observed for 15 days displayed dyspnea and death due to asphyxiation (Livardjani et al. 1991b). Respiratory tract lesions included lung edema, necrosis of the alveolar epithelium and hyaline membranes, and occasional lung fibrosis.

Exposure to 28.8 mg/m^3 of mercury vapor lasting from 1 to 20 hours produced effects ranging from mild to moderate pathological changes (unspecified) (Ashe et al. 1953). For exposures lasting 30 hours, marked cellular degeneration and some necrosis were observed in the lungs of 1 rabbit. Less severe respiratory changes (unspecified mild-to-moderate pathological changes) were reported in rabbits following exposure to metallic mercury vapor at 6 mg/m^3 for 7 hours a day, 5 days a week for 1–11 weeks (Ashe et al. 1953). The usefulness of these results is limited because the study did not specify the pathological changes nor distinguish between primary and secondary effects (i.e., pathological changes secondary to induced shock).

Congested lungs were observed in rats exposed to 1 mg/m^3 metallic mercury vapors for 100 hours continuously per week for 6 weeks (Gage 1961). In rats exposed to 3 mg/m^3 mercury vapor for only 3 hours a day, 5 days a week for 12–42 weeks, pathological examination revealed no significant changes in the respiratory system (Kishi et al. 1978). The potential for oral exposure was not quantified in these studies; however, it is likely that most of the exposure was via inhalation.

Organic Mercury. Dyspnea, respiratory depression, and respirations frequently obstructed by mucus were observed in a farmer who had treated grain with phenylmercuric acetate for several seasons (Brown 1954). An autopsy revealed purulent bronchopneumonia. It is unclear whether the respiratory effects were direct

effects of the phenylmercuric acetate or secondary to the severe neurotoxicity also seen in this subject. A case study reported that no respiratory effects were observed in four men inhaling unspecified concentrations of methylmercury for several months (Hunter et al. 1940). Both of these studies are limited because exposure levels were unknown.

No studies were located regarding respiratory effects in animals after inhalation exposure to organic mercury.

Cardiovascular Effects

Metallic Mercury. Increases in heart rate and blood pressure have been reported following inhalation exposure to metallic mercury in humans. Acute inhalation exposure to high concentrations of metallic mercury vapor generated by heating metallic mercury resulted in increased blood pressure (Haddad and Sternberg 1963; Hallee 1969; Snodgrass et al. 1981) and heart rate/palpitations (Bluhm et al. 1992a; Haddad and Sternberg 1963; Hallee 1969; Jaffe et al. 1983; Snodgrass et al. 1981; Soni et al. 1992; Teng and Brennan 1959). In one of these cases, the increase in heart rate was characterized as a sinus tachycardia (Soni et al. 1992). Exposures of longer durations due to spills or occupational exposures have also been reported to result in increased blood pressure (Fagala and Wigg 1992; Foulds et al. 1987; Friberg et al. 1953; Karpathios et al. 1991; Taueg et al. 1992) and increased heart rate (Fagala and Wigg 1992; Foulds et al. 1987). A single case report was located regarding cardiovascular effects resulting from inhalation of mercury vapors released from a paint that contained a high level of phenylmercuric acetate (Aronow et al. 1990). The affected child was diagnosed with acrodynia and exhibited a rapid heart beat and hypertension.

Chronic-duration occupational exposures, however, have given mixed results regarding effects on blood pressure and heart rate. Two studies of workers exposed to relatively low levels of mercury (near 0–0.27 mg/m^3 in one study and an average of 0.075 mg/m^3 in the other) for an average of greater than 6 or 7 years showed no effects on blood pressure or electrocardiography (Schuckmann 1979; Smith et al. 1970). In contrast, workers exposed to an estimated 0.03 mg/m^3 of mercury vapor (estimate based on blood levels) for at least 5 years reported an increased incidence of palpitations, and cardiovascular reflex responses were slightly reduced compared to unexposed matched controls (Piikivi 1989). Also, workers in a thermometer plant had a high incidence of hypertension (5 of 9 workers) (Vroom and Greer 1972). A morbidity and mortality study of chloralkali workers showed an increased likelihood of death due to

ischemic heart and cerebrovascular disease (Barregard et al. 1990). These studies are limited, however, because exposure to other chemicals may have contributed to the effects observed, exposure levels may have been estimated from only a few actual determinations, and other risk factors were not consistently considered.

Significant increases in systolic blood pressure and diastolic blood pressure were found in volunteers with dental amalgam containing mercury when compared to a control group (matched for age and sex) that had no amalgam fillings (Siblerud 1990). However, the length of time that the individuals had the dental amalgams was not reported. Furthermore, the blood pressure levels of the amalgam group were closer than those of the nonamalgam group to "normal" blood pressure levels reported for the general population. The authors suggested that the populations from which such normal values are drawn are likely to include many people with amalgam dental fillings, but without additional data to determine which control group would best represent “normal,” these results have limited use.

In animals, cardiovascular effects were noted following inhalation exposure to mercury vapor. Marked cellular degeneration with some necrosis of heart tissue was observed in rabbits following acute intermittent exposure to 28.8 mg/m^3 metallic mercury vapor for periods ranging from 4 to 30 hours (Ashe et al. 1953). Mild-to-moderate pathological changes (unspecified) were seen for 1–4-hour exposures. Exposures to lower concentrations (0.86–6 mg/m^3) of mercury vapor for periods ranging from 2 to 12 weeks also resulted in mild-to-moderate pathological changes (unspecified) in the hearts of rabbits. The usefulness of these results is limited because the study did not specify the pathological changes nor distinguish between primary and secondary effects (i.e., pathological changes secondary to induced shock).

Organic Mercury. Only two case histories were located regarding cardiovascular effects in persons exposed by inhalation to organic mercury compounds. No cardiovascular effects were reported in four men hospitalized for neurological symptoms after inhaling an unspecified concentration of methylmercury dust for at least several months (Hunter et al. 1940). Elevated blood pressure was reported in two men exposed occupationally to methylmercury compounds (dose not known) (Hook et al. 1954).

No studies were located regarding cardiovascular effects in animals after inhalation exposure to organic mercury.

Gastrointestinal Effects

Metallic Mercury. Many instances of gastrointestinal effects have been reported in humans following acute inhalation exposure to metallic mercury vapor. A classical sign of mercury intoxication is stomatitis (inflammation of the oral mucosa). Accordingly, a number of case studies have reported stomatitis after acute-duration exposure to high concentrations of metallic mercury vapors (Bluhm et al. 1992a; Garnier et al. 1981; Haddad and Sternberg 1963; Snodgrass et al. 1981; Tennant et al. 1961). Occasionally, the stomatitis was accompanied by excessive salivation (Hallee 1969; Karpathios et al. 1991) or difficulty swallowing (Campbell 1948). Other gastrointestinal effects observed after acute-duration exposure to high levels of mercury include abdominal pains (Bluhm et al. 1992a; Campbell 1948; Haddad and Sternberg 1963; Milne et al. 1970; Teng and Brennan 1959), nausea and/or vomiting (Haddad and Sternberg 1963; Hallee 1969; Kanluen and Gottlieb 1991; Lilis et al. 1985; Milne et al. 1970; Rowens et al. 1991; Snodgrass et al. 1981; Soni et al. 1992; Taueg et al. 1992), and diarrhea (Bluhm et al. 1992a; Kanluen and Gottlieb 1991; Rowens et al. 1991; Taueg et al. 1992; Teng and Brennan 1959). The autopsy of a young child who was intoxicated with mercury vapor and died of pulmonary edema revealed a grayish, necrotic mucosa of the stomach and duodenum (Campbell 1948).

Intermediate-duration exposures to mercury spills have also resulted in similar gastrointestinal effects. A case study reported that teenage girls exhibited anorexia, intermittent abdominal cramps, mild diarrhea, painful mouth, and bleeding gingiva 2 weeks after a spill of metallic mercury in their home (on carpet) resulted in the release of metallic mercury vapor (Sexton et al. 1976). Air levels in the home were measured 6 months after the initial spill and ranged from 0.02 to 1 mg Hg/m^3, depending upon the degree of ventilation and proximity to the spill. Fagala and Wigg (1992) reported a case of colicky abdominal pain and diarrhea in a 12-year-old girl exposed to mercury vapors for approximately 6 months after a spill in her home.

Limited information was located regarding gastrointestinal effects in persons who are chronically exposed to elemental mercury vapors. Stomatitis was observed in 22 of 72 workers exposed to mercury vapors in the manufacture of thermometers in the 1940s (Bucknell et al. 1993). Drooling, sore gums, ulcerations of the oral mucosa, and/or diarrhea were observed in 5 of 9 workers in a thermometer-manufacturing plant (Vroom and Greer 1972). A correlation was also observed between mercury exposure levels and unspecified oropharyngeal symptoms in workers from a chloralkali plant (Smith et al. 1970).

Two animal studies assessed the gastrointestinal effects from mercury vapor exposure. In rabbits, effects ranging from mild pathological changes to marked cellular degeneration and some necrosis of the colon were observed following exposure to 28.8 mg/m^3 mercury vapor for 4–30 hours (Ashe et al. 1953). A single exposure to 28.8 mg/m^3 for 1–2 hours or multiple exposures of 6 mg/m^3 for 7 hours a day, 5 days a week for up to 11 weeks resulted in either no changes or mild pathological changes. The usefulness of these results is limited because the study did not specify the pathological changes nor distinguish between primary and secondary effects (i.e., pathological changes secondary to induced shock).

Organic Mercury. Gastrointestinal effects were reported in several case studies of humans exposed to organomercurial compounds. A 39-year-old farmer who had dressed his seeds for several seasons with phenylmercuric acetate exhibited a swollen mouth, reddened and tender gums, carious teeth, a thin blue line at the gums, and an infected and swollen posterior pharyngeal wall (Brown 1954). Similarly, two women who died following 3–5 months of occupational exposure to diethylmercury vapors exhibited inflammation of the mouth and gums, excessive salivation, and unspecified gastrointestinal disorders (Hill 1943). Marked salivation was observed in one man and nausea was observed in another occupationally exposed to alkyl-mercury compounds used for dressing seeds (Hook et al. 1954). Gastrointestinal effects were not, however, observed in four men after inhalation of dust containing methylmercury for several months (Hunter et al. 1940).

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to organic mercury.

Hematological Effects

Metallic Mercury. Initial exposure to high concentrations of elemental mercury vapors produces a syndrome similar to "metal fume fever," which is characterized by fatigue, fever, chills, and elevated leukocyte count. Evidence of moderate-to-high leukocytosis with neutrophilia was reported following acute inhalation exposure to metallic mercury vapor (Campbell 1948; Haddad and Sternberg 1963; Hallee 1969; Jaffe et al. 1983; Lilis et al. 1985; Matthes et al. 1958; Rowens et al. 1991).

Similarly, an elevated white cell count was observed in a 12-year-old girl with a 6-month exposure to mercury vapors from a spill of metallic mercury in her home (Fagala and Wigg 1992). Thrombocytopenia and frequent nosebleeds were reported in two of four family members exposed to mercury vapors in their

home as a result of a spill of metallic mercury (Schwartz et al. 1992). The authors considered this to be a unique reaction to the mercury exposure.

In volunteers with dental amalgam, significantly decreased hemoglobin and hematocrit and increased mean corpuscular hemoglobin concentrations were found compared to controls without dental amalgams (Siblerud 1990). δ-Aminolevulinic acid dehydratase activity in erythrocytes was decreased in workers exposed to elemental mercury in the manufacture of tungsten rods (Wada et al. 1969). The decreases correlated with increases in urinary mercury. The estimated exposure level to mercury in the plant was slightly less than 0.1 mg/m^3. In workers exposed to 0.106–0.783 mg/m^3 mercury vapor, there was a significant increase in α2-macroglobulin and ceruloplasmin (an α-globulin protein active in the storage and transport of copper) compared to unexposed workers (Bencko et al. 1990).

No studies were located regarding hematological effects in animals after inhalation exposure to inorganic mercury.

Organic Mercury. No studies were located regarding hematological effects in humans or animals after inhalation exposure to organic mercury.

Musculoskeletal Effects

Metallic Mercury. A number of studies have reported increases in tremors, muscle fasciculations, myoclonus, or muscle pains after acute (Adams et al. 1983; Bluhm et al. 1992a; Karpathios et al. 1991; McFarland and Reigel 1978), intermediate (Aronow et al. 1990; Barber 1978; Sexton et al. 1976; Taueg et al. 1992), or chronic (Albers et al. 1982, 1988; Bidstrup et al. 1951; Chaffin et al. 1973; Chapman et al. 1990; Fawer et al. 1983; Smith et al. 1970; Verberk et al. 1986; Vroom and Greer 1972; Williamson et al. 1982) exposure to metallic mercury vapor. These effects are probably neurally mediated and are discussed more fully in Section 2.2.1.4.

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to metallic mercury.

Organic Mercury. Exposure to unspecified alkyl mercury compounds has caused muscular effects (e.g., muscle fasciculations, absence of deep reflexes in arms, Babinski reflex) (Brown 1954; Hook et al. 1954;

Hunter et al. 1940). These effects may have been secondary to neurological changes and are discussed more fully in Section 2.2.1.4.

No studies were located regarding musculoskeletal effects in animals after inhalation exposure to organic mercury.

Hepatic Effects

Metallic Mercury. A case study described the acute poisoning of a young child who was exposed to mercury vapors that were produced from heating an unknown quantity of mercury (Jaffe et al. 1983). Hepatocellular effects were characterized by biochemical changes (e.g., elevated serum alanine aminotransferase [ALT]), ornithine carbamyl transferase, and serum bilirubin levels) and evidence of a decrease in the synthesis of hepatic coagulation factors. Similarly, hepatomegaly and central lobular vacuolation were observed in a man who died following acute-duration exposure to high levels of elemental mercury vapors (Kanluen and Gottlieb 1991; Rowens et al. 1991).

Serious liver effects have been noted in animals at high exposure concentrations. Acute inhalation exposure of rabbits to metallic mercury vapor concentrations of 28.8 mg/m^3 for 6–30 hours resulted in effects ranging from moderate pathological changes (unspecified) to severe liver necrosis (Ashe et al. 1953). These effects were less severe (mild effects to degeneration) at shorter exposure durations and following exposure to 6 mg/m^3 mercury vapors for 7 hours a day, 5 days a week for 1–5 weeks (Ashe et al. 1953). Effects ranging from moderate pathological changes to marked cellular degeneration and some necrosis were seen at mercury concentrations of 6 mg/m^3 for 7 hours a day, 5 days a week for 6–11 weeks (Ashe et al. 1953). No hepatic changes were present in a pathological examination of the livers of rats intermittently exposed to 3 mg/m^3 mercury vapor for only 3 hours a day, 5 days a week for 12–42 weeks (Kishi et al. 1978). The studies by Ashe et al. (1953) and Kishi et al. (1978) were deficient in quantitative data, and used a small number of animals. However, available human and animal data suggest that metallic mercury vapors can cause liver effects following acute exposures.

Organic Mercury. Midzonal necrosis in the liver was observed during the autopsy of a farmer who died after treating grain with phenylmercuric acetate for several seasons (Brown 1954). No conclusions can be drawn from this study, however, because other factors may have contributed to the hepatic effects in this subject.

No studies were located regarding hepatic effects in animals after inhalation exposure to organic mercury.

Renal Effects

Metallic Mercury. The kidney is a sensitive target organ of toxicity following inhalation exposure to metallic mercury. This sensitivity may be, in part, because of the relatively high accumulation of mercury in the kidneys. Acute high-concentration inhalation exposure in humans has resulted in effects ranging from mild transient proteinuria or s syndrome has been reported light changes in urinary acid excretion (Bluhm et al. 1992b; Soni et al. 1992); to frank proteinuria, hematuria, and/oliguria (Campbell 1948; Hallee 1969; Snodgrass et al. 1981); to acute renal failure with degeneration or necrosis of the proximal convoluted tubules (Campbell 1948; Jaffe et al. 1983; Kanluen and Gottlieb 1991; Rowens et al. 1991). Actual exposure concentrations are unknown in these cases, but urinary mercury excretion as high as 59–193 µg/hour has been reported (Bluhm et al. 1992b).

A nephrotic in two case studies of intermediate-duration exposure (Agner and Jans 1978; Friberg et al. 1953). In one report, the exposure was to a spill in the home (Agner and Jans 1978); in the other, the exposure was occupational (Friberg et al. 1953). The nephrotic syndrome was characterized by edema and proteinuria with albumin and hyaline casts in the urine. These changes usually abated within a few months following termination of exposure. Among a group of 10 patients who reported adverse effects associated with dental amalgams (the route of exposure in dental amalgams is probably a mixture of inhalation exposure to mercury vapor released from the amalgams, absorption of the vapor through the oral mucosa, and ingestion), a decrease in the ability to concentrate the urine and elevated urinary albumin were observed (Anneroth et al. 1992). Removal of one amalgam resulted in a significant decrease in urinary albumin (it is unknown whether other amalgams remained). In a study of renal function in 10 healthy volunteers having an average of 18 amalgam-filled tooth surfaces both before and after amalgam removal (Sandborgh-Englund and Nygren 1996), no signs of renal toxicity were found in conjunction with mercury released from the amalgam fillings. Although plasma mercury levels increased significantly one day after removal of the fillings (all removals were accomplished in one dental session), glomerular filtration rates were similar both before and after mercury exposure (amalgam removal). Blood, plasma, and urine mercury concentrations were significantly lower 60 days after amalgam removal.

The results from a number of studies show renal toxicity in workers chronically exposed to mercury vapor (Barregard et al. 1988; Bernard et al. 1987; Buchet et al. 1980; Cardenas et al. 1993; Danziger and

Possick 1973; Ehrenberg et al. 1991; Kazantzis et al. 1962; Langworth et al. 1992b; Piikivi and Ruokonen 1989; Roels et al. 1982; Stewart et al. 1977; Stonard et al. 1983; Sunderman 1978; Tubbs et al. 1982). Several of these reports have focused on workers with proteinuria (Danziger and Possick 1973; Kazantzis et al. 1962; Tubbs et al. 1982), while others have examined a variety of urinary parameters in exposed populations. Biopsies in the studies of workers with proteinuria have shown both proximal tubular and glomerular changes. In the report by Kazantzis et al. (1962), heavy albuminuria was reported to be accompanied by both proximal tubular damage and glomerulosclerosis. Examination of tissue samples from two other workers with proteinuria showed changes in the foot processes of cells associated with the glomerular basement membrane and deposition of IgG and C3 (Tubbs et al. 1982).

Comparisons of exposed populations to controls have shown a variety of changes in exposed workers, ranging from no effects (Bernard et al. 1987; Piikivi and Ruokonen 1989) to increases in urinary protein (Stewart et al. 1977), the specific gravity of the urine (Ehrenberg et al. 1991), and urinary *N*-acetyl-β-glucosaminidase (NAG) (Barregard et al. 1988; Boogaard et al. 1996; Langworth et al. 1992b). A detailed examination of markers for urinary dysfunction showed increases in urinary excretion of Tamm-Horsfall glycoprotein and tubular antigens and decreases in urinary pH and excretion of glycoamino-glycans, prostaglandin E2 and F2α, and thromboxane B2 (Cardenas et al. 1993). Several studies have also shown correlations with some of these parameters and urinary mercury content (Buchet et al. 1980; Cardenas et al. 1993; Ehrenberg et al. 1991; Langworth et al. 1992b; Roels et al. 1982; Stonard et al. 1983). Attempts to define threshold levels for effects have produced mixed results. A no-effect level of 72 µg Hg/g creatinine was determined for urinary excretion of albumin, β_2-microglobulin, or retinol binding protein (Bernard et al. 1987). However, other studies have shown increases in urinary albumin at urinary mercury levels >50 µg Hg/g creatinine (Buchet et al. 1980) and increases in urinary *N*-acetyl-β-glucosaminidase at urinary mercury levels of >50 or >100 µg Hg/g creatinine. Boogaard et al. (1996) reported that after exposure to mercury with urinary levels below the biological exposure index of 35 µg/g creatinine, a transient increase in NAG was observed, but there was no correlation with duration of exposure and that this increase was not an early indicator of developing renal dysfunction. More information on correlation between urinary mercury levels and renal toxicity can be found in Section 2.5.

Serious degenerative effects have been observed in the kidneys of animals exposed to moderate-to-high levels of metallic mercury vapors following acute- and intermediate-duration exposures (Ashe et al. 1953). Effects ranging from marked cellular degeneration to tissue destruction and widespread necrosis were observed in rabbits exposed to mercury vapor at a concentration of 28.8 mg/m^3 for 2–30 hours. Moderate

pathological changes (unspecified) were also seen for 1-hour exposures. As the duration of exposure increased to 30 hours, extensive cell necrosis in the kidneys became evident. These results and the following results are limited as to their usefulness because the pathological changes are not described.

In an intermediate-duration study, rabbits exposed to mercury vapor concentrations of 0.86 mg/m^3 for 7 hours a day, 5 days a week for 12 weeks exhibited moderate pathological kidney changes that were reversible with cessation of exposure (Ashe et al. 1953). Larger doses (6 mg/m^3) administered for 7 hours a day, 5 days a week for up to 11 weeks, produced effects that ranged from mild, unspecified, pathological changes to marked cellular degeneration and widespread necrosis (Ashe et al. 1953).

In rats, slight degenerative changes (i.e., dense deposits in tubule cells and lysosomal inclusions) in the renal tubular epithelium were evident following exposure to 3 mg/m^3 mercury vapor for 3 hours a day, 5 days a week for 12–42 weeks (Kishi et al. 1978).

Low-level chronic-duration inhalation exposures to 0.1 mg/m^3 metallic mercury vapor for 7 hours a day, 5 days a week for 72–83 weeks in rats, rabbits, and dogs produced no microscopic evidence of kidney damage (Ashe et al. 1953). Only two dogs were tested in the study.

Organic Mercury. An autopsy of a man who died after acute high-level exposure to alkyl mercury vapor revealed necrosis of the tubule epithelium, swollen granular protoplasm, and nonstainable nuclei in the kidneys (Hook et al. 1954). No studies were available on renal effects following intermediate or chronic-duration exposure to organic mercury vapors in humans.

No studies were located regarding renal effects in animals after inhalation exposure to organic mercury.

Endocrine Effects

Metallic Mercury. A 13-year-old boy exposed to mercury vapors for 2 weeks developed a thyroid enlargement with elevated triiodothyronine, and thyroxine; and low thyroid-stimulating hormone levels (Karpathios et al. 1991). Serum-free thyroxine (T4) and the ratio of free thyroxine to free 3,5,3'-triiodo-thyronine (T3) were found to be slightly, but significantly, higher in workers with the highest exposure concentrations in a study of chloralkali workers exposed an average of 10 years to metallic mercury vapor (Barregard et al. 1994a, 1994b). Further, serum-free T3 was inversely associated with cumulative mercury exposure, suggesting a possible inhibitory effect of mercury on 5'-deiodinases, which is responsible for the

conversion of T4 to the active hormone T3. In this study, serum total testosterone (but not free testosterone) was positively correlated with cumulative mercury exposure, while prolactin, thyrotrophin, and urinary cortisol concentrations were not associated with exposure. However, two other occupational studies found no relationship between mercury exposure (unspecified concentration) and endocrine function (i.e., testicular, thyroid, and pituitary) (Erfurth et al. 1990; McGregor and Mason 1991). Biochemical indices that were measured in the occupational study by McGregor and Mason (1991) to assess endocrine effects included serum testosterone, sex-hormone binding globulin, thyroid-stimulating hormone, and prolactin. Erfurth et al. (1990) measured both basal serum concentrations of thyrotropin, thyroxine, triiodothyronine, and cortisol, as well as the response to a thyrotropin challenge.

No studies were located regarding endocrine effects in animals after inhalation exposure to metallic mercury.

Organic Mercury. No studies were located regarding endocrine effects in humans or animals after inhalation exposure to organic mercury.

Dermal Effects

Metallic Mercury. Inhalation exposure of individuals to elemental mercury vapors for acute and intermediate durations has resulted in erythematous and pruritic skin rashes (Aronow et al. 1990; Bluhm et al. 1992a; Foulds et al. 1987; Karpathios et al. 1991; Schwartz et al. 1992; Sexton et al. 1976). Other dermal reactions to mercury exposure include heavy perspiration (Aronow et al. 1990; Fagala and Wigg 1992; Karpathios et al. 1991; Sexton et al. 1976) and reddened and/or peeling skin on the palms of the hands and soles of the feet (Aronow et al. 1990; Fagala and Wigg 1992; Karpathios et al. 1991).

No studies were located regarding dermal effects in animals after inhalation exposure to metallic mercury.

Organic Mercury. No studies were located regarding dermal effects in humans or animals after inhalation exposure to organic mercury.

Ocular Effects

Metallic Mercury. Ocular effects observed following acute exposure included red, burning eyes and conjunctivitis (Bluhm et al. 1992a; Sexton et al. 1976). Workers chronically exposed to mercury have also exhibited a peculiar grayish-brown or yellow haze on the outer surface of their lenses (Atkinson 1943; Bidstrup et al. 1951; Locket and Nazroo 1952). These case studies contained insufficient quantitative data for dose-response assessment.

No studies were located regarding ocular effects in animals after inhalation exposure to metallic mercury.

Organic Mercury. No studies were located regarding ocular effects in humans or animals after inhalation exposure to organic mercury.

Other Systemic Effects

Metallic Mercury. Initial exposure to high concentrations of elemental mercury vapors produces a syndrome similar to "metal fume fever," which is characterized by fatigue, fever, chills, and an elevated leukocyte count. Accordingly, several studies have reported fever and/or chills in humans after exposure to high concentrations of elemental mercury vapors (Aronow et al. 1990; Bluhm et al. 1992a; Garnier et al. 1981; Lilis et al. 1985; McFarland and Reigel 1978; Milne et al. 1970; Schwartz et al. 1992; Snodgrass et al. 1981).

Organic Mercury. No studies were located regarding other systemic effects in humans or animals after inhalation exposure to organic mercury.

2.2.1.3 Immunological and Lymphoreticular Effects

Metallic Mercury. The immune reaction in humans to mercury exposure appears to be idiosyncratic, with either increases or decreases in immune activity depending on individual genetic predisposition (see Section 2.4). Therefore, it is not surprising that several studies of workers exposed to elemental mercury vapor have failed to show consistent or marked changes in immune function parameters in large populations. For example, no effect on serum immunoglobulins (IgA, IgG, or IgM) and no increase in autoantibody titres were observed in a group of chloralkali workers exposed for an average of 13.5 years

(Langworth et al. 1992b). Similarly, no increases in antilaminin antibodies were observed in workers exposed for an average of 7.9 years (Bernard et al. 1987), and no increase in antiglomerular basement membrane antibodies or IgE was seen in workers exposed for between 1.5 and 25 years (Cardenas et al. 1993). Slight decreases in IgA and IgG were observed in workers after more than 20 years of exposure to metallic mercury vapors when compared to unexposed controls (Moszczynski et al. 1990b). No significant differences in the concentrations of immunoglobulins or complement components were found in a study of 76 chloralkali workers previously exposed to mercury vapor for an average of 7.9 years (range, 1.1–36.2 years) (Ellingsen et al. 1994). No increase in the prevalence of autoantibodies was observed between the formerly exposed worker group and a control group of 53 age-matched referents. The average time elapsed since the cessation of occupational exposure was 12.3 years (range, 1–35 years).

Evidence of a human autoimmune response has been obtained in a few studies. Examination of the kidneys of two workers with proteinuria revealed granular deposition of IgG and the complement C3 in the glomeruli (Tubbs et al. 1982). Among a group of 10 patients who reported adverse effects associated with dental amalgams (the route of exposure is probably a mixture of inhalation exposure to mercury vapor released from the amalgams and dermal exposure to the amalgams), 3 had increased antiglomerular basement membrane antibodies and 2 had elevated antinuclear antibodies (Anneroth et al. 1992). After removal of one amalgam, there was a significant decrease in IgE (it is unknown whether other amalgams remained). Also, 1 of 89 workers examined by Langworth et al. (1992b) showed a weak reaction to antiglomerular basement membrane, and 8 of 44 workers examined by Cardenas et al. (1993) showed an abnormally high anti-DNA antibody titre. Only two studies have shown increases in immune parameters in exposed populations. Increases in IgA and IgM were observed in workers in a mercury producing plant (Bencko et al. 1990). The study is limited by a lack of information on daily dose levels, duration of employment and potential confounding factors (smoking, alcohol). An increase in anti-DNA antibodies was observed in workers from a chloralkali plant (Cardenas et al. 1993).

Other experimental evidence suggests that mercury can alter a number of parameters of the host's immune system and lead to increased susceptibility to infections, autoimmune diseases, and allergic manifestations. In workers exposed to mercury vapor concentrations of 0.024–0.09 mg/m^3 for less than 10 and up to 31 years (Moszczynski et al. 1995), the stimulation of T-lymphocytes (as manifested by an increased number of T-cells [CD3+], T-helpers [CD4+], and T-suppressors [CD8+]) was observed in peripheral blood; however, no significant effect was seen on NK-cell (CD16+) count. A positive correlation was found between the T-helper cell count and the duration of exposure ($p<0.05$). The combined stimulation of

the T-cell line and an observed decrease in the helper/suppressor ratio were suggestive of an autoimmune response.

In a mercury-producing plant, neutrophil function was found to be significantly reduced in workers with a mean exposure duration of 8 months (range, 0.5–46 months) (Perlingeiro and Queiroz 1995). In this study, both chemotactic and chemical-specific reducing activities of the neutrophils of exposed workers were found to be affected. While improved industrial hygiene practices over a 6-month period resulted in a decrease in urine mercury concentration in the workers, it did not result in the return of neutrophil migration activity to within the normal range. There was, however, no observed increase in the incidence of infections in the mercury-exposed group compared to controls. Based on their observations, Perlingeiro and Queiroz (1995) suggested that even exposures to levels of mercury considered "safe" in some industrial settings may lead to impairment of neutrophil function.

Exposure of genetically susceptible mice to mercury vapor for a period of 10 weeks resulted in an autoimmune response similar to that seen in similar mice after treatment with mercuric chloride by subcutaneous injections and in drinking water (Warfvinge et al. 1995). This response was manifested as a syndrome, which included a general stimulation of the immune system, with hyperimmunoglobulinemia, anti-nucleolar-fibrillarin autoantibodies, and glomerular disease accompanied by vascular immune complex deposits. Actual inhalation exposure times for the 0.3–1 mg Hg/m^3 exposure concentrations varied from 0.5 to 19 hours a day (5 days a week), but doses for individual exposure groups were also expressed in µg/kg/week units. The LOAEL for serum antinucleolar antibodies was determined to be an absorbed dose of 0.170 mg Hg/kg/week (from a 1.5-hour daily exposure to 0.5 mg/m^3) and the corresponding NOAEL was a calculated absorbed dose of 0.075 mg/kg/day (from a 0.5-hour daily exposure to 0.0005 mg/m^3). Higher doses were required for B-cell stimulation and for the development of immune complex deposits.

The highest NOAEL values and all reliable LOAEL values for immunological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

Organic Mercury. No studies were located regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to organic mercury.

2.2.1.4 Neurological Effects

Metallic Mercury. The central nervous system is probably the most sensitive target organ for metallic mercury vapor exposure. Nervous system disorders following exposure to metallic mercury vapors are both consistent and pronounced. Acute-, intermediate-, and chronic-duration exposures elicit similar neurological effects. Symptoms intensify and may become irreversible as exposure duration and/or concentration increases. Most occupational studies discuss chronic-duration exposure to a time-weighted average (TWA) concentration or to a concentration range, thereby preventing the assessment of dose-response relationships within the populations studied. However, the average exposure levels for affected groups are similar in many of these studies.

In humans, several case studies have reported adverse neurological effects following acute inhalation of high concentrations of mercury vapor. A wide variety of cognitive, personality, sensory, and motor disturbances have been reported. The most prominent symptoms include tremors (initially affecting the hands and sometimes spreading to other parts of the body), emotional lability (characterized by irritability, excessive shyness, confidence loss, and nervousness), insomnia, memory loss, neuromuscular changes (weakness, muscle atrophy, muscle twitching), headaches, polyneuropathy (paresthesia, stocking-glove sensory loss, hyperactive tendon reflexes, slowed sensory and motor nerve conduction velocities), and performance deficits in tests of cognitive function (Adams et al. 1983; Bluhm et al. 1992a; Hallee 1969; Jaffe et al. 1983; Karpathios et al. 1991; Lilis et al. 1985; McFarland and Reigel 1978; Snodgrass et al. 1981). A few individuals have also noted hearing loss, visual disturbances (visual field defects), and/or hallucinations (Bluhm et al. 1992a; McFarland and Reigel 1978). In a case study of exposure to a calculated metallic mercury vapor level of 44 mg/m^3 for <8 hours, workers experienced long-lasting feelings of irritability, lack of ambition, and lack of sexual desire (McFarland and Reigel 1978). Three and one-half months after exposure to high levels of mercury vapor during 2 days of an industrial liquid mercury salvaging operation, a 54-year-old man exhibited a syndrome resembling amyotrophic lateral sclerosis, characterized by slowed conduction velocities (suggestive of peripheral nerve damage). Urinary mercury levels were 100 µg/g creatinine at the time of the exam; after an additional 2 months (no treatment administered), levels dropped to less than 30 µg/g creatinine and symptoms disappeared (Adams et al. 1983). In contrast, chelation therapy (2.3 dimercaptosuccinic acid [DMSA] or – acetyl-D,L-penicillamine [NAP]) and lowering of urinary mercury levels did not result in improvement in depression, anxiety, phobias, psychotic-like behavior, interpersonal sensitivity, and hostility observed in another group of workers exposed to high concentrations of mercury vapor for up to 16 hours (Bluhm et al. 1992a).

In case reports of individuals exposed to inorganic mercury vapor for an intermediate duration, similar effects were reported (Barber 1978; Fagala and Wigg 1992; Foulds et al. 1987; Friberg et al. 1953; Sexton et al. 1976; Taueg et al. 1992). After 6 months of exposure to a spill of metallic mercury in the place where she slept, a 12-year-old girl experienced dizziness, joint pains, weakness, insomnia, numbness and tingling in her palms, decreased pinprick and vibration sensations in the lower extremities, intentional tremors, a slowing of the background rhythms on electroencephalograms, irritability, outbursts of temper, shyness, sensitivity, auditory hallucinations, and photophobia (Fagala and Wigg 1992). Similarly, a 4-year-old boy exposed for approximately 1 month to mercury vapors released from paint containing phenylmercuric acetate exhibited irritability, personality change, insomnia, headaches, weakness, and nerve dysfunction in the lower extremities (Aronow et al. 1990). This study is not discussed under organic mercury because the exposure was to metallic mercury vapors released from the paint.

Two adolescents (ages 13 and 15) who were unintentionally exposed to concentrated mercury vapors for 3 months developed a variety of more immediate- and long-term effects (Yeates and Mortensen 1994). In the 15-year-old male, the earliest symptoms included declining school performance, irritability, depression, neurobehavioral complaints, tremor, rash, hypertension, cold intolerance, diaphoresis, headaches, sleep disturbance, paresthesias, and anorexia. He was referred to a pediatric teaching hospital, where he was diagnosed with acrodynia and mercury poisoning. Before undergoing two courses of chelation therapy with 2,3-dimercaptosuccoinic acid (DMSA), his average 24-hour urine mercury and blood mercury levels were 1,314 µg/L and 23 µg/L, respectively. His 13-year-old half-sister, who was also exposed, had pretreatment average 24-hour urine mercury and blood mercury levels of 624 µg/L and 69 µg/L, respectively; her pre-treatment medical symptoms included tremor, rash, anorexia, paresthesias, and neuropsychiatric complaints (e.g., irritability, social withdrawal, and emotional lability). On hospital admission, she was diagnosed with acrodynia and underwent three courses of DMSA treatment, which were complicated by severe peripheral neuropathy, accompanied by a significant weight loss. Although the neuropathy was relatively mild at the time of initial neurological evaluation, it became progressively worse, and eventually the patient required a wheelchair and assistance eating. The neuropathy had resolved by the 1-year follow-up neuropsychological evaluation; however, despite removal from exposure, return of blood and urinary mercury to acceptable levels, and resolution of clinical signs of mercury poisoning and associated neuropsychiatric symptoms, both patients continued to show major deficits in visuoperceptual and constructional skills, nonverbal memory, and abstract reasoning.

A worker (age, mid-40s) exposed to mercury in a thermometer factory for approximately 3.5 years experienced acute, intermediate, chronic, and delayed neurological effects (White et al. 1993). During his employment, he performed a variety of functions, including sweeping mercury off floors with a vacuum cleaner or hose blower, repairing and cleaning machines, disassembling machines containing mercury, and operating a machine that crushed instruments so that he could then separate the mercury from other materials for reuse. From approximately the beginning of his employment at the factory, he experienced a number of symptoms, including blurred vision, ocular pain, rash, a strange taste in the mouth, weakness, memory loss, rage, and irrational behavior. The month following his release by the factory, his urine mercury concentration was measured at 690 µg/L, which confirmed a diagnosis of mercury poisoning. He was treated by chelation with penicillamine over a 2-month period; approximately 2 months after the completion of treatment, his urine mercury level was only 17 µg/L. Approximately 21months after termination of his employment, neurological examination revealed nystagmus on upward gaze, bilateral manual tremor, diminished sensation to pain, peripheral neuropathy, and abnormalities in nerve conduction. An magnetic resonance imaging (MRI) examination revealed mild central and cortical atrophy, with punctiform foci of T2 in both frontal regions, especially underlying the precentral gyri and in the white matter (both subcortical and gyri). The MRI data were interpreted as consistent with diffuse and focal white matter disease. Neuropsychological testing conducted during the same time period revealed problems with cognitive function, fine manual motor coordination, visuospatial analysis and organization, memory for visuospatial information, affect, and personality almost 2 years after cessation of employment at the factory.

In contrast with the long-term (perhaps permanent) effects noted in the previous study, Yang et al. (1994) reported that recovery from chronic elemental mercury intoxication may be complete when patients are removed early from the exposure environment. A 29-year-old worker in a Taiwanese lampsocket-manufacturing facility, with an initial urinary mercury concentration of 610 µg/L (in a 24-hour sample) and a blood mercury concentration of 237 µg/L (reference range, <10 µg/L), exhibited a variety of symptoms, including blurred vision, dysarthria, prominent gingivitis, tremors (usually postural and intentional), unsteady gait, and slow mental response. The TWA concentration of mercury in the air in the room where he spent most of his working time during his 5 years on the job was 0.945 mg/m^3. The worker also had a higher blood lead concentration of 450 µg/L (reference range, <20 µg/L), and lead toxicity or interactions with mercury could have occurred. The man underwent an 8-week course of chelation with D-penicillamine, which resulted in a rapid improvement in gait; a complete recovery from all symptoms occurred over a 4-month period.

A 27-year-old female, who worked primarily in a room with a TWA mercury air concentration of 0.709 g/m^3 and who had been on the job for 1.5 years, showed a variety of symptoms, including gum pain, dizziness, poor attention, bad temper, some numbness, hypersalivation, hyperhidrosis, dizziness, and fatigue. She had initial urine and blood mercury levels of 408 µg/L and 105 µg/L, respectively, but did not require chelation; the symptoms abated fully approximately 2 months following discontinuation of exposure (Yang et al. 1994).

Other chronic-duration exposures to metallic mercury vapor have resulted in tremors (which may be mild or severe depending on the degree of exposure), unsteady walking, irritability, poor concentration, short-term memory deficits, tremulous speech, blurred vision, performance decrements in psychomotor skills (e.g., finger tapping, reduced hand-eye coordination), paresthesias, decreased nerve conduction, and other signs of neurotoxicity (Albers et al. 1988; Bidstrup et al. 1951; Chaffin et al. 1973; Chang et al. 1995; Chapman et al. 1990; Fawer et al. 1983; Langolf et al. 1978; Piikivi et al. 1984; Smith et al. 1970; Sunderman 1978; Uzzell and Oler 1986; Vroom and Greer 1972; Williamson et al. 1982). The majority of studies suggest that motor system disturbances are reversible upon exposure cessation, while cognitive impairments, primarily memory deficits, may be permanent (Chaffin et al. 1973; Hanninen 1982; Miller et al. 1975).

Several studies have noted correlations between exposure level or duration and effects (e.g., memory deficits, psychomotor coordination, motor and sensory nerve conduction velocities, electromyographic abnormalities, evidence of polyneuropathy, tremor, emotional changes, reflex abnormalities, and electroencephalographic changes) (Albers et al. 1982; Iyer et al. 1976; Levine et al. 1982; Smith et al. 1983; Vroom and Greer 1972; Williamson et al. 1982). Early studies suggested that frank neurotoxicity (pronounced tremors, erethism, restriction of visual fields, difficulty seeing) was generally observed at >300 µg mercury in a 24-hour urine (Bidstrup et al. 1951) or at >0.1 mg/m^3 (Smith et al. 1970). More recent studies using sensitive tests for psychomotor skills, tremor, and peripheral nerve function suggest that adverse effects may be associated with very low exposures (see below). However, conflicting information exists regarding thresholds for neurotoxic effects.

Several reports have presented essentially negative findings at low exposure levels (0.025–0.076 mg/m^3). Chloralkali workers exposed to low air levels of mercury vapors for at least 5 years (group average, 14 years) reported an increase in memory disturbances, sleep disorders, anger, fatigue, confusion, and hand tremors compared to the controls (Piikivi and Hanninen 1989). However, tests of psychomotor

coordination and memory showed no significant deficits in the exposed group. The exposed and control groups were matched for age, sex, vocational status, education, and mean number of amalgam fillings. A group-average exposure concentration of 0.025 mg/m^3 mercury vapors was estimated from repeated analyses of blood mercury concentration (mean, 51.3 nmol/L . 10 µg/L) (see the discussion regarding these estimated exposure levels in Section 2.5). Also, no effects on tremors, bimanual coordination, color determination, or reaction time were observed in chloralkali workers with more than 7 years of exposure to low levels of mercury; ambient air levels measured for 2 years prior to testing averaged 0.076 mg/m^3 and the average blood level in the workers was 19.9 µg/L (Schuckmann 1979). Negative findings were also noted when the results of tremor frequency spectra and psychometric tests of a group of chloralkali workers exposed for an average of 13.5 years were compared to unexposed controls (Langworth et al. 1992a). The TWA exposure level was estimated to be 0.025 mg/m^3, based on measurements taken at the time of the study, and blood levels in the workers averaged 55 nmol/L (. 11 µg/L). Despite the negative objective findings, subjective reports of fatigue, memory disturbances, and confusion were significantly higher in the exposed workers.

Boogaard et al. (1996) evaluated the effects of exposure to elemental mercury on the nervous system and the kidneys of workers producing natural gas in the Netherlands. Early signs of alterations in renal and neurological functions were studied in three groups of workers who were exposed to different levels of mercury that were below the current ACGIH biological exposure index of 35 µg/g creatinine. Air concentrations ranged from 10 to 1,500 µg/m^3 (median, 67) at locations where mercury exposure was anticipated; the potential 8-hour TWA exposure ranged from 33 to 781 µg/m^3 (median, 88). Air concentrations ranged from 0 to 6 µg/m^3 at locations where little mercury exposure was expected. Current mercury concentrations in urine were 23.7, 4.1, and 2.4 µg/g in high, low, and control exposure groups, respectively; mercury concentrations in blood were 3.5, 1.5, and 2.2 µg/L, respectively. There were no differences among the three study groups with respect to either motor nerve conduction velocity or tremor frequency spectra of physiological tremors. Also, no significant correlations were found between the results of the neurological tests and any of the present or historical biological monitoring data.

In contrast to the negative findings above, several studies have shown significant effects on tremor or on cognitive skills at comparable or lower group-average exposure levels (0.014–0.076 mg/m^3). Using the same paradigm as Langworth et al. (1992a), a significant difference was seen in the tremor frequency spectra in mercury-exposed workers from three industries who were exposed to low levels of mercury for an average of 15.3 years (range, 1–41 years) when compared to unexposed controls (Fawer et al. 1983).

The TWA mercury concentration measured in the work area at the time of the study was 0.026 mg Hg/m^3 (range not reported). It was assumed that the workers were exposed to the same concentration of mercury for the duration of their employment. However, the group size was small, and the results may have been influenced by a small number of more severely affected individuals. It is also possible that the tremors may have resulted from intermittent exposure to concentrations higher than the TWA. Urinary mercury levels in these workers averaged 11.3 µmol/mol creatinine (. 20 µg/g creatinine). Tremors have also been associated with occupational exposures that produced urinary concentrations of 50–100 µg/g creatinine and blood levels of 10–20 µg/L (Roels et al. 1982). Difficulty with heel-to-toe gait was observed in thermometer-plant workers subjected to mean personal-breathing-zone air concentrations of 0.076 mg/m^3 (range, 0.026–0.27 mg/m^3) (Ehrenberg et al. 1991).

Decreases in performance on tests that measured intelligence (a similarities test) and memory (digit span and visual reproduction tests) were observed in chloralkali workers exposed for an average of 16.9 years to low levels of mercury when compared to an age-matched control group (Piikivi et al. 1984). Significant differences from controls were observed among workers with blood levels >75 nmol/L (. 15 µg/L) and urine levels >280 nmol/L (. 56 µg/L).

Dentists (n=98, mean age 32, range 24–49) with an average of 5.5 years of exposure to low levels of mercury showed impaired performance on several neurobehavioral tests (Ngim et al. 1992). Exposure levels measured at the time of the study ranged from 0.0007 to 0.042 mg/m^3 (average, 0.014 mg/m^3) and blood levels ranged from 0.6 to 57 µg/L (average, 9.8 µg/L). Controls were matched for age, fish consumption, and number of amalgam fillings. Differences in education, sex distribution, and reported use of Chinese traditional medicines that might contain mercury were adjusted for in the statistical analysis. The dentists showed significantly poorer performance on finger tapping (measures motor speed), trail making (measures visual scanning), digit symbol (measures visuomotor coordination and concentration), digit span, logical memory delayed recall (measures visual memory), and Bender-Gestalt time (measures visuomotor coordination). The dentists had a higher aggression score than the controls. Correlations were observed for exposure levels and duration. This study is limited, however, by lack of blinding and failure to report control mercury levels; the statistical procedures used for confounders (use of traditional Chinese medicines) were not reported.

In a study of the relation between cumulative exposure to mercury and chronic health impairment, 298 dentists had their mercury levels measured by an X-ray fluorescence technique. Electrodiagnostic and neuropsychological findings in the dentists with more than 20 µg/g tissue (head and wrist) mercury levels

were compared with those of a control group consisting of dentists with no detectable mercury levels. Twenty-three out of 298 dentists with the highest mercury levels were administered neurological tests and compared to controls. The high mercury group had slowed conduction velocities in motor (median nerve) and sensory (suralnerve) nerves, mild neuropsychological impairment (increased errors in the Bender-Gestalt test), mild visuographic dysfunction, and higher distress levels (self-reported) than the control group. Seven of the high exposure dentists showed manifestations of polyneuropathy. Exposure concentrations were not specified. No polyneuropathies were detected in the control group (Shapiro et al. 1982). Abnormal nerve conduction velocities have also been observed at a mean urine concentration of 450 µg/L in workers from a chloralkali plant (Levine et al. 1982). These workers also experienced weakness, paresthesias, and muscle cramps. Prolongation of brainstem auditory-evoked potentials was observed in workers with urinary mercury levels of 325 µg/g creatinine (Discalzi et al. 1993). Prolonged somatosensory-evoked potentials were found in 28 subjects exposed to 20–96 mg/m^3 of mercury (Langauer-Lewowicka and Kazibutowska 1989).

In animals, as in humans, adverse neurological and behavioral effects are prominent following inhalation exposure to high concentrations of metallic mercury vapor. However, animals appear to be less sensitive than humans. Marked cellular degeneration and widespread necrosis were observed in the brains of rabbits following exposures to metallic mercury vapor at 28.8 mg/m^3 for durations ranging from 2 to 30 hours (Ashe et al. 1953). Exposures of 1 hour produced moderate (unspecified) pathological changes.

Intermediate-duration exposure of rabbits to 6 mg/m^3 mercury vapor for periods of 1–11 weeks produced effects ranging from mild, unspecified, pathological changes to marked cellular degeneration and some necrosis in the brain (Ashe et al. 1953). The more serious degenerative changes were observed at longer exposure durations (i.e., 8 and 11 weeks). Mild-to-moderate pathological changes were revealed in the brains of rabbits exposed to a metallic mercury vapor concentration of 0.86 mg/m^3 for 12 weeks (Ashe et al. 1953). The usefulness of these results is limited because the pathological changes are not specified and no distinction is made between primary and secondary effects (i.e., pathological changes secondary to induced shock).

Two of 6 rabbits exposed to 4 mg/m^3 metallic mercury vapor for 13 weeks exhibited slight tremors and clonus and had mercury concentrations of 0.8–3.7 µg/g wet tissue in the brain (Fukuda 1971). Following intermittent exposure to 3 mg/m^3 for 12–39 weeks, rats exhibited a decline in conditioned avoidance response; however, no histopathological changes were evident (Kishi et al. 1978). The change was

reversible within 12 weeks after exposure cessation and was associated with a decrease in the mercury concentration in brain tissue to below 10 µg/g wet weight (w/w). Mice exposed to an unspecified concentration of metallic mercury vapor intermittently for more than 3 weeks exhibited progressive neurological dysfunction (i.e., wobbling and unresponsiveness to light), beginning 22 days after initial exposure, and subsequently died 4 days later (Ganser and Kirschner 1985).

No studies were located regarding neurological effects in animals following chronic inhalation exposure to inorganic mercury.

Organic Mercury. Exposure to organic mercury via inhalation is extremely rare. The only reports of even its potential occurrence come from a few case histories. Case reports have described neurological effects in humans after inhalation exposure to organic mercury; however, no quantitative data were provided. Following acute inhalation exposure of dust containing methylmercury, four men had initial symptoms including numbness and tingling of limbs, unsteadiness in gait, difficulty in performing fine movements (e.g., buttoning a shirt), irritability, and constricted vision (Hunter et al. 1940). At least 2 years after these occupational exposures, the subjects had not fully recovered from their symptoms. Acute high-level exposure to an unspecified alkyl mercury compound has reportedly caused neurological symptoms (e.g., ataxia, unsteady gait, slurred speech, memory difficulties, tremors) in exposed workers (Hook et al. 1954; Lundgren and Swensson 1949).

A case study reporting neurological effects in a boy after exposure to mercury vapor released from paint containing phenylmercuric acetate (Aronow et al. 1990) was discussed under metallic mercury because the exposure was to metallic mercury vapors released from the paint.

Dimethylmercury is extremely volatile, and extremely toxic (in the 5 mg/kg body weight range). The following case history describes an accidental death due to an occupational spill of only a few drops of dimethylmercury. The primary exposure route is thought to have been dermal, but dimethylmercury is so volatile that inhalation exposure might also have occurred. Blayney et al. (1997) provided the first account of this tragic event. The case history was subsequently detailed by Nierenberg et al. (1998). The exposure occurred to a 48-year-old female chemistry professor who was admitted to the hospital 5 months (154 days) after, as best as can be determined, she inadvertently spilled several drops (estimated at 0.4–0.5 mL, about 1,500 mg) of dimethylmercury from the tip of her pipette onto the back of her disposable latex gloves. The spill was cleaned and the gloves disposed of. Hair analysis on a long strand

of hair revealed that after a brief lag time, mercury content rose rapidly to almost 1,100 ppm (normal level, <0.26 ppm; toxic level, >50 ppm), and then slowly declined with a half-life of 74.6 days. These results support the occurrence of one or several episodes of exposure, and are consistent with laboratory notebook accounts of a single accidental exposure. Testing of family members, laboratory coworkers, and laboratory surfaces failed to reveal any unsuspected mercury spills or other cases of toxic blood or urinary mercury levels. Permeation tests subsequently performed on disposable latex gloves similar to those the patient had worn at the time of the lone exposure revealed that dimethylmercury penetrates such gloves rapidly and completely, with penetration occurring in 15 seconds or less and perhaps instantly. Polyvinyl chloride gloves were equally permeable to dimethylmercury. Five days prior to hospital admission, the patient developed a progressive deterioration in balance, gait, and speech. During the previous 2 months, she had experienced brief episodes (spaced weeks apart) of nausea, diarrhea, and abdominal discomfort, and had lost 6.8 kg (15 lb). Medical examination revealed moderate upper-extremity dysmetria, dystaxic handwriting, a widely based gait, and "mild scanning speech." Routine laboratory test results were normal. Computed tomography (CT) and magnetic resonance imaging (MRI) of the head were normal except for the incidental finding of a probable meningioma, 1 cm in diameter. The cerebrospinal fluid was clear, with a protein concentration of 42 mg/dL and no cells. A preliminary laboratory report indicated that the whole-blood mercury concentration was more than 1,000 µg/L (normal range, 1–8 µg/L; toxic level, >200 µg/L). Chelation therapy with oral succimer (10 mg/kg orally every 8 hours) was begun on day 168 after exposure. Whole blood concentrations rose to 4,000 µg/L after one day of chelation, and urinary mercury levels were 234 µg/L (normal range, 1–5 µg/L; toxic level, >50 µg/L). Despite the initial success of chelation therapy, administration of vitamin E, and a blood exchange transfusion, at 176 days postexposure, the patient became comatose. Further aggressive general support and chelation therapy failed, life support ws removed (following the patient's advance directive), and the patient died 298 days postexposure. Autopsy results revealed diffusely thin cortex of the cerebral hemispheres (to 3 mm), and extensive gliosis of the visual cortex around the calcarine fissure and the superior surface of the superior temporal gyri. The cerebellum showed diffuse atrophy of both vermal and hemispheric folia. Microscope evaluation revealed extensive neuronal loss and gliosis bilaterally within the primary visual and auditory cortices, with milder loss of neurons and gliosis in the motor and sensory cortices. There was widespread loss of cerebellar granular-cell neurons, Purkinje cells, and basket-cell neurons, with evidence of loss of parallel fibers in the molecular layer. Borgmann's gliosis was well developed and widespread.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.5 Reproductive Effects

Metallic Mercury. No acute-duration exposure data were located regarding reproductive effects in humans after inhalation exposure to metallic mercury. However, several studies found no effect on fertility following intermediate or chronic inhalation exposure to metallic mercury in humans (Alcser et al. 1989; Cordier et al. 1991; Lauwerys et al. 1985). A retrospective cohort study reported that male workers in a U.S. Department of Energy (DOE) plant exposed for at least 4 months had urinary mercury concentrations of 2,144–8,572 µg/L (Alcser et al. 1989). This sample population showed no significant difference in fertility compared to controls (unexposed workers); however, they were never monitored for elemental mercury exposure. In a questionnaire study assessing the fertility of male workers exposed to mercury vapor from various industries (i.e., zinc-mercury amalgam, chloralkali, or electrical equipment product plants), there was no statistically significant difference in the number of children of the exposed group compared to a matched control group (Lauwerys et al. 1985). The concentration of mercury in the urine of these exposed workers ranged from 5.1 to 272.1 µg/g creatinine. No correlation was observed between prolactin, testosterone, luteinizing hormone, and follicle stimulating hormone levels and blood or urine mercury levels in male workers exposed to mercury vapors (Erfurth et al. 1990; McGregor and Mason 1991). Also, no effect on the response of these hormones to challenge with gonadotropin releasing hormone was observed (Erfurth et al. 1990).

Although no effect on fertility was observed in exposed workers, an increase in the rate of spontaneous abortions was reported in association with increased mercury concentrations in the urine of the fathers exposed to metallic mercury in chloralkali plants before the pregnancy (Cordier et al. 1991). There was a significantly increased risk of spontaneous abortion, at a rate of 18.4%, when fathers had more than 50 µg/L mercury in the urine, compared to a rate of 8.6% when fathers were unexposed. Sikorski et al. 1987) reported that women occupationally exposed to metallic mercury vapors (dentists and dental assistants) had more reproductive failures (spontaneous abortions, stillbirths, congenital malformations) and irregular, painful, or hemorrhagic menstrual disorders than a control (unexposed) group of women. The reproductive difficulties and menstrual disorders were correlated with mercury levels identified in scalp and pubic hair collected from the women. It should be noted that this study has been recently severely criticized for what Larsson (1995) calls "erroneous interpretation of results and distortion of conclusions." The Sikorski et al. (1987) paper is nonetheless presented in this toxicological profile as part of the available published data on reported human mercury exposure. Its presence here is based upon its publication in a

credible peer-reviewed international journal and is intended neither as endorsement nor condemnation of the data or conclusions in the 1987 paper.

Rowland et al. (1994) report that 418 women with high exposure to mercury (i.e., female dental assistants) were less fertile than unexposed controls. In this study, the probability of conception with each menstrual cycle (called "fecundability" by the authors) in women who prepared 30 or more amalgams per week and who were evaluated as having 4 or more poor mercury-hygiene practices was 63% of the fecundity of the unexposed controls. Rowland et al. (1994) noted that occupational groups with roughly the same potential for exposure often contain subjects whose actual exposures are quite different, depending on their particular work environment and their work practices within that environment. For example, 20% of the women in the final sample in this study reported preparing more than 30 amalgams per week with 4 or more poor hygiene factors. Among the women preparing the same number of amalgams, this study found differences in "fecundability," based upon each dental assistant's reported number of poor mercury-hygiene factors. One peculiar observation, however, was that women determined to have had low exposure to mercury in their dental occupation were found to be more fertile than unexposed controls. The reason(s) for the observed U-shaped dose-response curve were not known.

In animals, exposure to metallic mercury vapors causes prolongation of the estrous cycle. In a study by Baranski and Szymczyk (1973), female rats exposed via inhalation to metallic mercury (at an average of 2.5 mg/m^3, 6 hours a day, 5 days a week for 21 days) experienced longer estrous cycles than unexposed animals. In addition, estrous cycles during mercury exposure were longer than normal estrous cycles in the same animals prior to exposure. Although the initial phase of the cycle was protracted, complete inhibition of the cycle did not occur. During the second and third weeks of exposure, these rats developed signs of mercury poisoning including restlessness, seizures, and trembling of the entire body. The authors speculated that the effects on the estrous cycle were caused by the action of mercury on the central nervous system (i.e., damage to the hypothalamic regions involved in the control of estrous cycling).

Organic Mercury. No studies were located regarding reproductive effects in humans or animals after inhalation exposure to organic mercury.

The highest NOAELs and all reliable LOAELs for reproductive effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.6 Developmental Effects

Metallic Mercury. No association was demonstrated between inhalation exposure of the father and increased rates of major fetal malformations or serious childhood illnesses in a retrospective cohort study of workers at a U.S. DOE plant (Alcser et al. 1989).

A case study of a woman chronically exposed to an undetermined concentration of mercury vapor reported that her first pregnancy resulted in spontaneous abortion, and her second resulted in the death of the newborn soon after birth (Derobert and Tara 1950). It is unclear whether the reproductive toxicity experienced by the woman was due to the mercury exposure. However, after recovery from overt mercury poisoning, she gave birth to a healthy child. A woman occupationally exposed to mercury vapors for 2 years prior to pregnancy and throughout pregnancy was reported to have delivered a viable infant at term (Melkonian and Baker 1988). Urinary mercury in the woman at 15 weeks of pregnancy was 0.875 mg/L (normal levels are approximately 0.004 mg/L). Also, a case report of a woman exposed to mercury vapors in her home during the first 17 weeks of pregnancy reported that the woman delivered a normal child who met all developmental milestones (although the child was not formally tested for psychological development) (Thorpe et al. 1992). Although mercury exposure was not measured, the child was born with hair levels of 3 mg/kg (3 ppm) of mercury. This hair level is comparable to that observed in populations consuming fish once a week (WHO 1990) and suggests that exposure in this case may have been relatively low.

Exposure of neonatal rats to metallic mercury vapor at 0.05 mg/m^3 for 1 or 4 hours a day for 1 week during a period of rapid brain growth (postpartum days 11–17) resulted in subtle behavioral changes when the rats were tested at 4 and 6 months of age (Fredriksson et al. 1992). Offspring of rats exposed for 1 hour/day showed increases in the time necessary to finish a task in the radial arm maze (spatial learning). Offspring of rats exposed for 4 hours a day showed increases in both the time to finish the task and in the number of errors committed. When tested for locomotor activity at 2 months, an increase in rearing was observed in the 4 hour/day group, but repeat testing at 4 months showed lower locomotor, rearing, and total activity than controls. The 1-hour/day exposure group showed no difference from controls at 2 months, and increased activity and decreased rearing at 4 months when compared to controls.

Three groups of 12 pregnant Sprague-Dawley rats were exposed by inhalation to 1.8 mg/m^3 metallic mercury vapor on gestation days (Gd) 11–14 and 17–20 for 1 hour ("low dose") or 3 hours ("high dose").

Hg/kg/day ("high dose"). At postpartum day 3, each litter was reduced to 4 male and 4 female offspring. No significant differences between the mercury-treated offspring and the controls were observed for surface righting, negative geotaxis, pinna unfolding, and tooth eruption. Tests of spontaneous motor activity (locomotion, rearing, rearing time, and total activity) showed that the mercury-treated offspring were hypoactive at 3 months of age; at 14 months, only total activity differed between exposed and control groups. In spatial learning tasks, exposed offspring showed retarded acquisition in the radial-arm maze but no differences in the circular-swim maze. A simple test of learning, habituation to a novel environment (activity chambers), indicated a reduced ability to adapt. The authors conclude that prenatal exposure to mercury vapor results in behavior changes in the offspring similar to those reported for methylmercury. On postpartum days 3–4, the mercury contents in the brain, liver, and kidneys were 0.001, 0.004, and 0.002 mg Hg/kg, respectively, for control offspring; 0.005, 0.053, and 0.033 mg Hg/kg, respectively, for animals exposed for 1 hour a day; and 0.012, 0.112, and 0.068 mg Hg/kg, respectively, for animals exposed for 3 hours a day (Danielsson et al. 1993).

Four groups of 12 pregnant Sprague-Dawley rats were exposed to methylmercury or elemental mercury alone or in combination as follows: (1) administered 2 mg/kg/day methylmercury via gavage during Gd 6–9; (2) exposed by inhalation to 1.8 mg/m^3 metallic mercury (elemental mercury) vapor for 1.5 hours per day during Gd 14–19; (3) exposed to both methylmercury by gavage (2 mg/kg/day, Gd 6–9) and elemental Hg vapor by inhalation (1.8 mg/m^3, Gd 14–19) (methylmercury + elemental mercury); or (4) given combined vehicle administration for each of the 2 treatments (control). The inhalation regimen corresponded to an approximate dose of 0.1 mg Hg/kg/day. At postpartum day 3, each litter was reduced to 4 male offspring. There were no differences between any of the groups in maternal body weight gain before parturition. No differences in body weight, pinna unfolding, tooth eruption, surface righting reflex, and negative geotaxis were observed in the offspring. Offspring of dams exposed to elemental Hg showed hyperactivity in the spontaneous motor activity test chambers over all three parameters: locomotion, rearing, and total activity; this effect was potentiated in the animals of the methylmercury + elemental Hg group. In the swim maze test, the methylmercury + elemental mercury and elemental mercury groups evidenced longer latencies to reach a submerged platform, which they had learned to mount the day before, compared to either the control group or the methylmercury group. In the modified enclosed radial-arm maze, both the methylmercury + elemental Hg and elemental Hg groups showed more ambulations and rearings in the activity test prior to the learning test. During the learning trial, the same groups (i.e., methylmercury + elemental Hg and elemental Hg) showed longer latencies and made more errors in

acquiring all eight pellets. Generally, the results indicate that prenatal exposure to elemental mercury causes alterations to both spontaneous and learned behaviors, suggesting some deficit in the adaptive functions of the rats. Co-exposure to methylmercury, which by itself did not alter these functions at the dose given in this study, served to aggravate the changes significantly. Brain mercury concentrations in offspring were 1 ng/g w/w in the controls, 4 ng/g in the methylmercury group, 5 ng/g in the elemental Hg group, and 12 ng/g in the methylmercury + elemental Hg group (Fredriksson et al. 1996).

Adult female rats were exposed to metallic mercury vapor at 2.5 mg/m^3 for 3 weeks prior to fertilization and during Gd 7–20 (Baranski and Szymczyk 1973). A decrease in the number of living fetuses was observed in these dams compared to unexposed controls, and all pups born to the exposed dams died by the sixth day after birth. However, no difference in the occurrence of developmental abnormalities was observed between exposed and control groups. The cause of death of the pups in the mercury-exposed group was unknown, although an unspecified percentage of the deaths was attributed by the authors to a failure of lactation in the dams. Death of pups was also observed in another experiment in which dams were only exposed to the same dose level prior to fertilization, supporting the conclusion that high mortality in the first experiment was due, at least in part, to the poor health of the mothers. Without further information, this study must be considered inconclusive regarding developmental effects.

Newland et al. (1996) studied the offspring of pregnant squirrel monkeys exposed to 0.5 or 1 mg/m^3 of mercury vapor for 4 or 7 hours per day, 5 days per week during the last two-thirds or more of the gestation period. One female and 2 male offspring came from mothers exposed to 0.5 mg/m^3 mercury vapor during gestation weeks 5–19, 5–21, or 6–22 for a total of 247–510 hours, resulting in total doses of 1,304–2,900 µg (20–38 µg/day); and 3 male offspring came from mothers exposed to 1 mg/m^3 mercury vapor during gestation weeks 7–21, 3–18, or 8–21 for a total of 283–402 hours, resulting in total doses of 2,901–4,305 µg (42–62 µg/day). Five male offspring born about the same time as the exposed monkeys served as controls. Lever pressing was maintained under a Concurrent Random-Interval 30 schedule of reinforcement. Time allocation on each lever was examined during behavioral transitions and in a steady state. Median maternal blood levels ranged from 0.025 to 0.09 µg/g in animals exposed to 0.5 mg/m^3 and from 0.12 to 0.18 µg/g in animals exposed to 1 mg/m^3. No differences in birth weight, weight gain, or body weight at time of behavioral testing were observed between exposed and control offspring. No difference in sensitivity to reinforcer ratios was identified in the steady state, but there was much more variability in the steady-state performance of exposed monkeys, as indicated by the standard deviation of the regression, than in controls. Logistic regression was used to examine the transition to new schedule

parameters. Exposed monkeys were found to produce smaller or slower transitions than controls. The magnitude and stability of lever-press durations for controls and exposed monkeys were indistinguishable early in the experiment, but at the end, the exposed monkeys had longer lever-press durations and the session-to-session variability was much greater. One monkey's exposure began during the third week of gestation (earlier than any of the others) and its behavior was so erratic that some of the analyses could not be accomplished. Long-term effects of prenatal mercury vapor exposure included instability in lever-press durations and steady-state performance under concurrent schedules of reinforcement as well as aberrant transitions (Newland et al. 1996).

Organic Mercury. No studies were located regarding developmental effects in humans or animals after inhalation exposure to organic mercury.

The highest NOAELs and all reliable LOAELs for developmental effects in each species and duration category are recorded in Table 2-1 and plotted in Figure 2-1.

2.2.1.7 Genotoxic Effects

There is inconclusive evidence that occupational exposure to metallic mercury and to organic and inorganic mercury compounds, primarily through inhalation, causes structural and numerical chromosome aberrations in human lymphocytes. In one study, significant increases in the frequency of acentric fragments (chromosome breaks) occurred in 4 workers exposed to high concentrations of metallic mercury and in 18 workers exposed to a mixture of mercuric chloride, methylmercuric chloride, and ethylmercuric chloride (Popescu et al. 1979). Mercury concentrations in the workplace ranged from 0.15 to 0.44 mg/m^3; the urinary excretion level of mercury for both exposed groups was . 890 µg/L. The findings of this study are suspect because the control group was not matched for sex, smoking habits, or sample size. Additionally, one of the four individuals in the metallic mercury group had a history of benzene poisoning, which was reflected in the unusually high frequency of abnormal chromosome morphology seen in this individual. No difference in the incidence of aneuploidy was found between the exposed workers and the controls. In an earlier study, an apparent association between increased chromosome aberrations and workplace exposure to mercury (as measured by urinary mercury levels) was reported (Verschaeve et al. 1976). However, the study was not well controlled (i.e., not matched for sex, smoking habits, or sample size), and the only significant increase in structural aberrations occurred in the three workers exposed to ethylmercury. Significant increases in aneuploid were also noted for the exposure groups compared to the

control subjects. However, these data should also be interpreted with caution since age has an influence on aneuploidy, and in this study, there was a general trend toward a higher incidence of aneuploidy in the older exposed workers (ages 36–63 years). It is noteworthy that in a subsequent study performed by these investigators (Verschaeve et al. 1979), no adverse effects on the structure or number of chromosomes were demonstrated in 28 subjects exposed to moderate levels of metallic mercury (urinary levels of 50 µg/L). The authors concluded that the results from their 1976 study, showing an association between increased chromosomal aberrations and occupational exposure to mercury, may have been affected by factors other than exposure to mercury compounds.

No increased frequency of structural aberrations was found in 22 workers exposed to mercury vapors; no information was provided on numerical aberrations (Mabille et al. 1984). The mean duration of exposure was 4 years, and the mean urinary and blood mercury levels in the exposed group were 117 µg/g creatinine and 0.031 µg/mL, respectively. More recently, peripheral lymphocytes from 26 male chloralkali workers exposed to mercury vapors (25–50 $\mu g/m^3$), for a mean exposure time of 10 years, were analyzed for micronucleus induction. The results were compared to results obtained from 26 unexposed subjects (Barregard et al. 1991). Groups were matched for age (±7 years) and smoking habits; plasma, erythrocyte, and urine mercury levels were determined. Parallel lymphocyte cultures from each donor group were incubated in the presence of pokeweed mitogen, which stimulates both B- and T-lymphocytes, and phytohemagglutinin, which primarily activates T-cells. The analysis showed no significant increase in the frequency or the size of micronuclei in the exposed versus the control group. Nor was there a correlation between micronuclei induction and plasma, erythrocyte, or urinary levels of mercury. Within the exposed group, however, there was a significant correlation between micronuclei induction in phytohemagglutinin-stimulated lymphocytes and cumulative exposure (whole-blood mercury level over employment time); the response was independent of age or smoking habits. These results, suggesting a genotoxic effect on T-lymphocytes, are unusual since there is evidence that B-lymphocytes may be more sensitive indicators of chemically induced clastogenesis than T-lymphocytes (Högstedt et al. 1988). The authors stated that the evidence of a genotoxic response confined to T-lymphocytes could have been a random finding but hypothesized that long-term exposure to mercury may cause an accumulation of cytogenetic effects.

Similarly, there was no correlation between urinary mercury levels (60–245 µg/L) or the duration of exposure (11–34 years) and increased frequency of structural aberrations and micronuclei in the lymphocytes of 29 male workers exposed to mercury fulminate (Anwar and Gabal 1991). From the overall

results, the authors concluded that mercury in the manufacturing process may not have been the clastogen. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

Metallic Mercury. There is no evidence from epidemiological studies that indicates inhalation of metallic mercury produces cancer in humans (Cragle et al. 1984; Kazantzis 1981). No evidence of an association between metallic mercury exposure and cancer mortality was found in a group of workers employed in a facility utilizing the metal in a lithium isotope separation process (Cragle et al. 1984). Overall mortality in the mercury-exposed group was less than that of the standard white male population and that of a control group of men who were not exposed to mercury. Similarly, no excess of cancer of the kidneys or nervous system was found among a cohort of 674 Norwegian men exposed to mercury vapors for more than 1 year at 2 chloralkali plants (Ellingsen et al. 1993). An excess in lung cancer (type not specified) was found in Swedish chloralkali workers 10 years after the end of long-term, high-level exposure to metallic mercury (Barregard et al. 1990). However, these workers had also been exposed to asbestos. Furthermore, no data on smoking status was provided, although the study implied that the workers did not smoke much.

No studies were located regarding cancer in animals after inhalation exposure to metallic mercury.

Organic Mercury. Associations were reported between the use of mercury-containing fungicides (i.e., mercury levels in hair) and leukemia in farmers and between the use of mercury-containing seed dressings and leukemia in cattle (Janicki et al. 1987). However, the study was limited in reporting methodology used to conduct this study. Furthermore, the study did not adequately address exposure to other chemicals, or adjust for other leukemia risk factors.

No studies were located regarding cancer in animals after inhalation exposure to organic mercury.

2.2.2 Oral Exposure

The bulk of the information regarding toxicity resulting from oral exposure to inorganic mercury comes from studies of mercuric chloride. However, a few studies are also available on the effects of oral exposure to mercuric acetate, mercurous chloride (calomel), and mercuric sulfide (cinnabar). Discussion of these

compounds has not been separated in this section, but the specific inorganic compound responsible for any effect is noted both in the text and in Table 2-2 and Figure 2-2.

Health effects following oral exposure to organic mercury were observed in humans and animals. The majority of the studies used to derive the NOAELs and LOAELs shown in Table 2-3 and Figure 2-3 concern exposure to methylmercuric chloride; however, in several studies, exposure was to methylmercuric acetate, methylmercuric hydroxide, methylmercuric dicyanidiamide, or phenylmercuric acetate. These chemicals are discussed together in Table 2-3 and Figure 2-3. In order to facilitate a comparison of studies using different compounds of mercury (either organic or inorganic), all doses are expressed in terms of the mercury exposure (mg Hg/kg/day) rather than to the mercury compound (HgX or RHgX/kg/day) to which one is exposed. For example, a dose of 1 mg/kg (when the compound is methylmercuric chloride) refers to 1 mg/kg mercury rather than 1 mg/kg methylmercuric chloride.

2.2.2.1 Death

Inorganic Mercury. A lethal dose of mercuric chloride was estimated to be 10–42 mg Hg/kg for a 70-kg adult (Gleason et al. 1957). Death from oral exposure to inorganic mercury is usually caused by shock, cardiovascular collapse, acute renal failure, and severe gastrointestinal damage (Gleason et al. 1957; Murphy et al. 1979; Troen et al. 1951). Eighteen cases of human poisoning (suicide attempts in some cases) were reported by Troen et al. (1951); 9 patients died following oral ingestion of single doses of mercuric chloride (range, 29–>50 mg Hg/kg). The most common findings in these cases were gastro-intestinal lesions (e.g., mild gastritis to severe necrotizing ulceration of the mucosa) and renal involvement (e.g., albuminuria, anuria, and uremia). Death of a 50-year-old woman due to ingestion of an unspecified amount of mercurous chloride in Chinese medicine has also been reported (Kang-Yum and Oransky 1992). The death was attributed to renal failure.

In rats, the oral LD_{50} values (lethal dose, 50% kill) ranged from 25.9 to 77.7 mg Hg/kg as mercuric chloride (Kostial et al. 1978). The signs of acute mercury toxicity in animals were similar to those described above for humans. Male rats appeared to be slightly more sensitive to the lethal effects of mercuric chloride; 2 of 5 male rats and no female rats died when given gavage doses of 14.8 mg Hg/kg, 5 days a week for 2 weeks (Dieter et al. 1992; NTP 1993). Mice showed slightly less toxicity, with no deaths at 14.8 mg Hg/kg, death in 1 male at 29 mg Hg/kg, and deaths in 5 of 5 males and 4 of 5 females at 59 mg Hg/kg when administered by gavage over the same period (NTP 1993).

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat (Fischer- 344)	14 d 5 d/wk 1 x/d (GW)				14.8 M (2/5 males died)	Dieter et al. 1992; NTP 1993 MC
2	Rat	once (G)				25.9 (LD_{50})	Kostial et al. 1978 MC
3	Mouse (B6C3F1)	14 d 5 d/wk 1 x/d (GW)				59 (5/5 males; 4/5 females died)	NTP 1993 MC
	Systemic						
4	Human	once (C)	Gastro		30 F (nausea, vomiting, abdominal cramps, diarrhea)		Afonso and deAlvarez 1960 MC
			Renal			30 F (acute renal failure, oliguria, proteinuria, hematuria)	
5	Rat (Long- Evans)	6 d 1 x/d (GW)	Endocr		7.4 F (increased release of iodine from thyroid)		Goldman and Blackburn 1979 MC

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL				Reference Chemical Form
					Less serious (mg/kg/day)		Serious (mg/kg/day)		
6	Rat (Sprague-Dawley)	once (G)	Hemato		7.4 F	(9-10% decrease in hemoglobin, erythrocytes, hematocrit)			Lecavalier et al. 1994 MC
			Hepatic		7.4 F	(decreased lactate dehydrogenase)			
			Renal		7.4 F	(mild histopthological changes - protein casts, cellular casts, and interstitial sclerosis)			
			Bd Wt	9.2 F					
7	Rat (Fischer- 344)	14 d 5 d/wk 1 x/d (GW)	Renal	0.93[b]	1.9 M 3.7 F	(increased absolute and relative kidney weight)	7.4	(minimal to mild acute renal necrosis)	NTP 1993; Dieter et al. 1992 MC
			Bd Wt	7.4 M	14.8 M	(10% decreased body weight in males)			
8	Mouse (Bom:NMRI)	once (GW)	Renal	5 F	10 F	(decreased renal selenium-dependent glutathione peroxidase activity; minor renal tubular damage)	20	(proximal tubule necrosis)	Nielson et al. 1991 MC
9	Mouse (B6C3F1)	14 d 5 d/wk 1 x/d (GW)	Renal		3.7	(increased absolute and relative kidney weight)	59	(acute renal necrosis)	NTP 1993 MC
			Gastro	29	59	(stomach inflammation and necrosis)			
			Bd Wt	59					
10	Mouse (Swiss)	10 d 1 x/d (GW)	Endocr		6 F	(decreased serum triiodothryonine)			Sin et al. 1990 MS

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
11	Mouse (Swiss)	10 d 1 x/d (GW)	Endocr		6 F (decreased serum thyroxine and triiodothyronine)		Sin et al. 1990 MC
	Immunological/Lymphoreticular						
12	Mouse (B6C3F1)	14 d 5 x/wk 1 x/d (GW)		7.4 F	14.8 F (decreased thymus weight)		NTP 1993 MC
	INTERMEDIATE EXPOSURE						
	Systemic						
13	Rat (Charles Foster)	60-180 d ad lib (W)	Endocr		2.6 M (increased corticosterone levels in adrenal and plasma)		Agrawal and Chansouria 1989 MC
14	Rat (Wistar)	350 d ad lib (W)	Cardio		7 M (increased blood pressure and cardiac inotropy)		Boscolo et al. 1989 MC
			Renal		7 M (tubular degeneration and membraneous glomerulonephritis)		
15	Rat (Sprague-Dawley)	350 d ad lib (W)	Cardio		7 M (increased blood pressure and cardiac inotrophy)		Boscolo et al. 1989; Carmignani et al. 1989 MC
			Renal		7 M (hydropic degeneration and desquamation of the tubular cells)		

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
16	Rat (Wistar)	180 d ad lib (W)	Cardio		28 M (increased blood pressure; decreased cardiac contractility)		Carmignani et al. 1992 MC
			Renal			28 M (mesangial proliferative glomerulonephritis; decreased acid phosphatase in lysosomes of tubular cells)	
17	Rat (Fischer- 344)	26 wk 5 d/wk 1 x/d (GW)	Renal	0.23 [c]	0.46 (increased absolute and relative kidney weight)	0.93 M (tubular necrosis)	Dieter et al. 1992; NTP 1993 MC
			Bd Wt	1.9 M 0.46 F	3.7 M 0.93 F (10% decrease in body weight gain)		
18	Rat (Long- Evans)	40 d 1 x/d (G)	Endocr		5.3 F (increased thyroid activity; decreased triiodothyronine synthesis)		Goldman and Blackburn 1979 MC
19	Rat (Sprague-Dawley)	3 mo ad lib (F)	Resp			2.2 F (respiratory difficulties; forceful and labored breathing)	Goldman and Blackburn 1979 MC
			Endocr		2.2 F (decreased thyroidal iodine uptake, iodine release, and iodine turnover)		

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
20	Rat (Wistar)	4 wk ad lib (F)	Hepatic	5 M 11.1 F	10 M (decreased absolute liver 22.2 F weight)		Jonker et al. 1993b MC
			Renal			5 M (nephrosis and 5.5 F proteinaceous casts, increased relative kidney weight)	
			Endocr	10 M	20M (increased relative adrenal weight)		
				11.1 F	22.2 F (decreased absolute adrenal weight)		
			Bd Wt	5 M		10 M (21% decreased body weight)	
				11.1 F		22.2 F (27% decreased body weight)	
			Other		5 M (decreased food and 5.5 F water intake)		
21	Rat (Wistar)	4 wk ad lib (F)	Renal	1 M	8M (ketones in urine, increased relative weight of kidneys, slight histopathological changes to outer cortex basophilic tubules)		Jonker et al. 1993b MC
					1.1 F (increased absolute and relative kidney weight)		
			Bd Wt	8 M 8.9 F			
22	Mouse (B6C3F1)	7 wk ad lib (W)	Renal	0.6 M	2.9M (nuclear swelling in epithelial cells)		Dieter et al. 1983 MC
			Hepatic		2.9M (increased liver weight)		
			Endocr	14.3 M			

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)	
23	Mouse (SJL/N)	10 wk ad lib (W)	Renal	0.28 F	0.56 F (increased granular IgG deposits; slight glomerular endocapillary cell hyperplasia; slight tubular atrophy, inflammation, and fibrosis)		Hultman and Enestrom 1992 MC
24	Mouse (B6C3F1)	26 wk 5 d/wk 1 x/d (GW)	Renal	1.9 M 14.8 F	3.7 M (cytoplasmic vacuolation of tubule epithelium, increased absolute weight)		NTP 1993 MC
			Bd Wt	7.4 M 14.8 F		14.8 M (26% decrease in body weight gain in males)	
25	Mouse (Swiss)	4 wk 1 x/d (GW)	Endocr		6 F (decreased serum thyroxine)		Sin and Teh 1992 MS
	Immunological/Lymphoreticular						
26	Mouse (B6C3F1)	7 wk ad lib (W)		0.6 M	2.9 M (suppression of lymphoproliferative response to T-cell, concanavalin A and phytohemagglutinin)		Deiter et al. 1983 MC
	Neurological						
27	Rat (Sprague-Dawley)	3 mo ad lib (F)				2.2 F (inactivity; abnormal gait)	Goldman and Blackburn 1979 MC

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	CHRONIC EXPOSURE						
	Death						
28	Rat (Fischer- 344)	2 yr 5 d/wk 1 x/d (GW)				1.9 M (40/50 males died versus 24/50 control male deaths)	Dieter et al. 1992; NTP 1993 MC
	Systemic						
29	Rat (Fischer- 344)	2 yr 5 d/wk 1 x/d (GW)	Resp	1.9	3.7 (increase in nasal inflammmation)		NTP 1993 MC
			Gastro		1.9 M (forestomach epithelial hyperplasia; inflammation of the cecum)		
			Renal			1.9 M (marked thickening of glomerular and tubular basement membranes; degeneration and atrophy of tubule epithelium)	
			Bd Wt			1.9 (24% decrease in male body weight gain and 16% decrease in female body weight gain)	
30	Mouse (B6C3F1)	2 yr 5 d/wk 1 x/d (GW)	Renal		3.7 F (foci of proximal tubule with thickened basement membrane; basophilic cells with scant cytoplasm)		NTP 1993 MC

Table 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL			Reference Chemical Form
					Less serious (mg/kg/day)	Serious (mg/kg/day)		
	Cancer							
31	Rat (Fischer- 344)	2 yr 5 d/wk 1x/d (GW)				3.7	(CEL: forestomach squamous cell papillomas in males and females; thyroid follicular cell carcinomas in males)	NTP 1993 MC

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an acute oral Minimal Risk Level (MRL) of $7x10^{-3}$ mg mercury/kg/day; dose corrected for 5 day/week exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).
[c]Used to derive an intermediate oral MRL of $2x10^{-3}$ mg mercury/kg/day; dose corrected for 5 day/week exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; (GO) gavage with oil; (GW) gavage with water; Hemato = hematological; Hg = mercury; hr = hour(s); IgG = immunoglobulin G; LD_{50} = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; MA = mercuric acetate; MC = mercuric chloride; MN = mercuric nitrate; MS = mercuric sulfide; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; ppd = postpartum day (s); Resp = respiratory; (W) = drinking water; wk = week(s); x = times; yr = year(s)

Figure 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral

Acute (≤14 days)

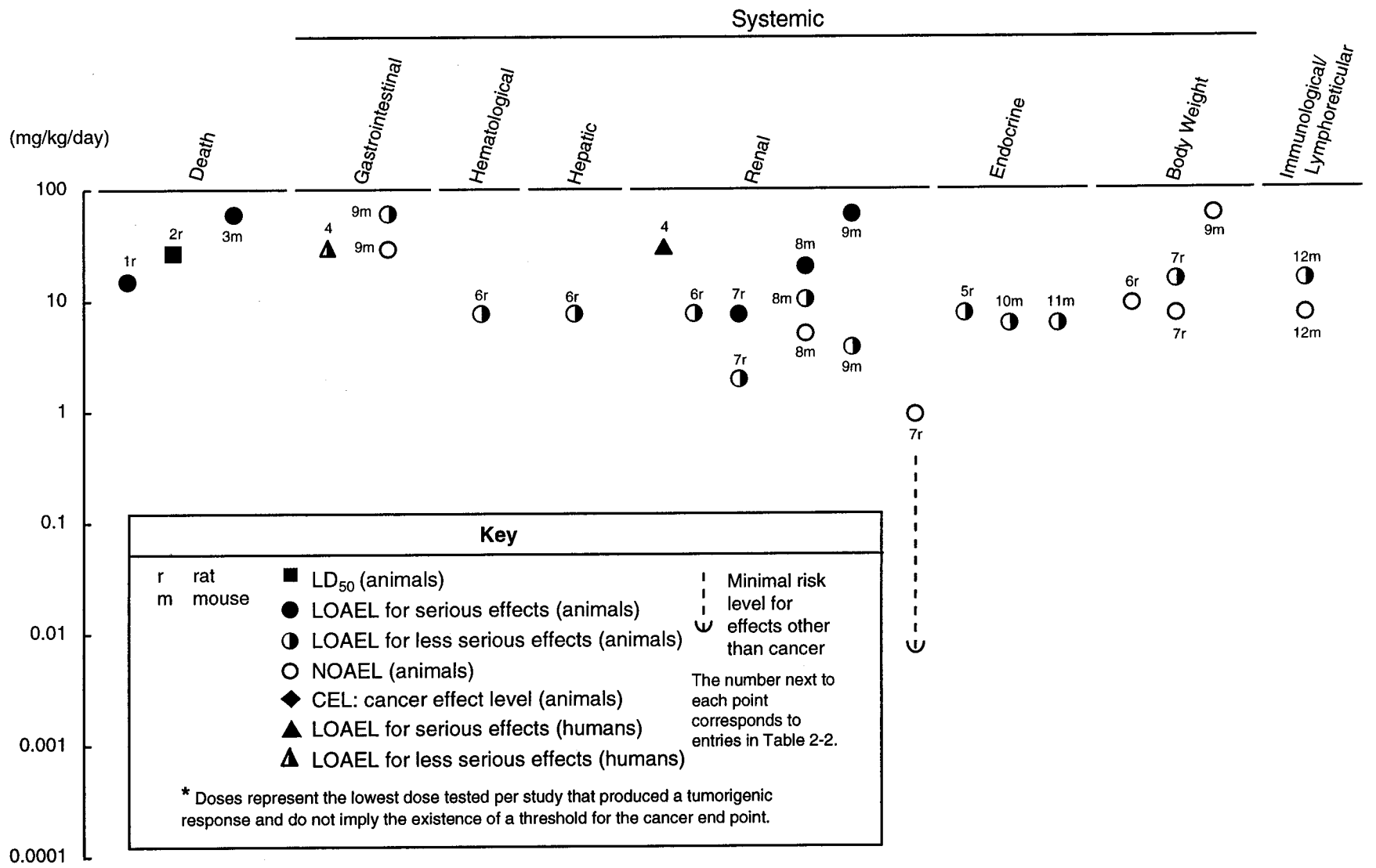


Figure 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (cont.)

Intermediate (15-364 days)

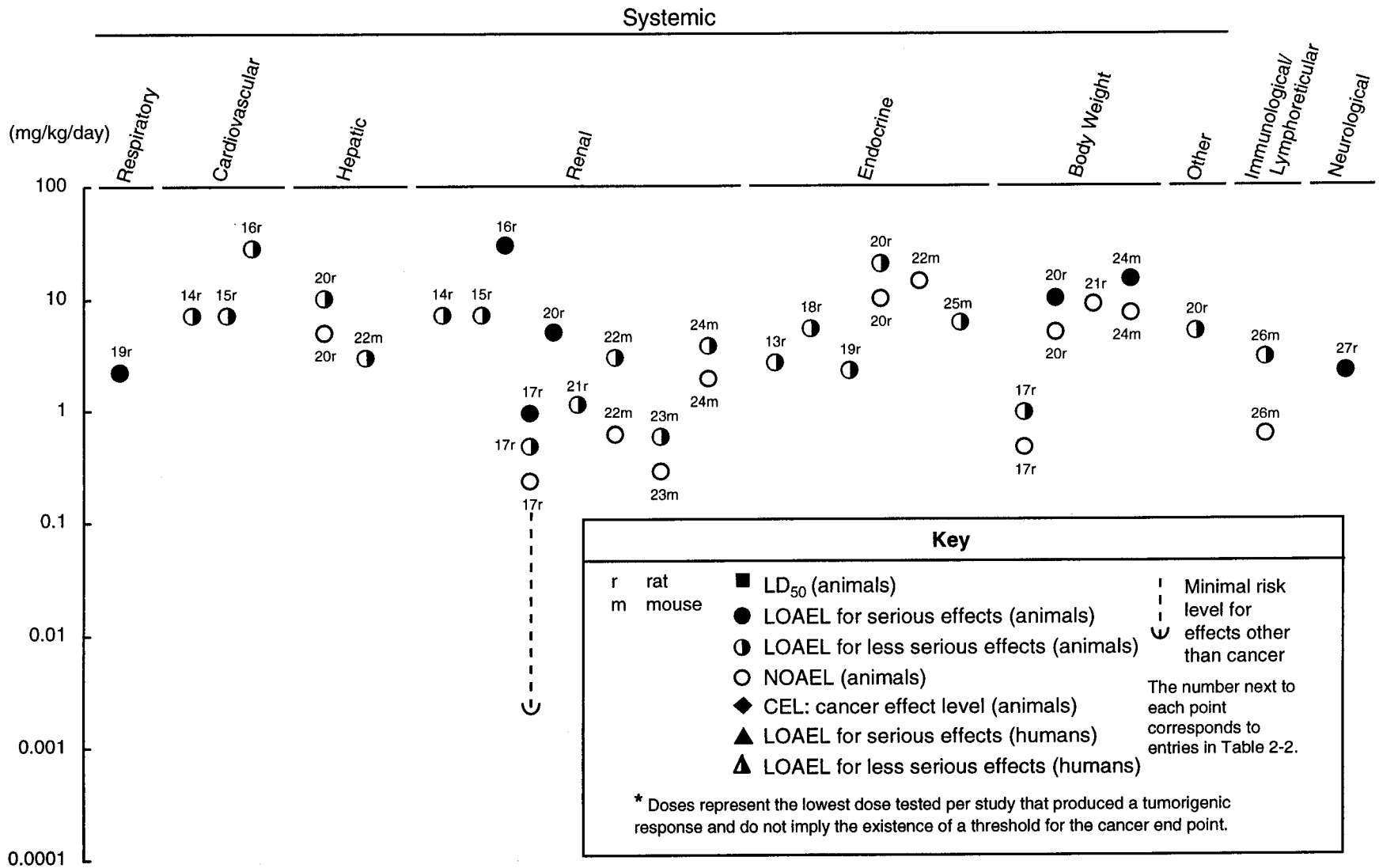


Figure 2-2. Levels of Significant Exposure to Inorganic Mercury - Oral (cont.)

Chronic (≥365 days)

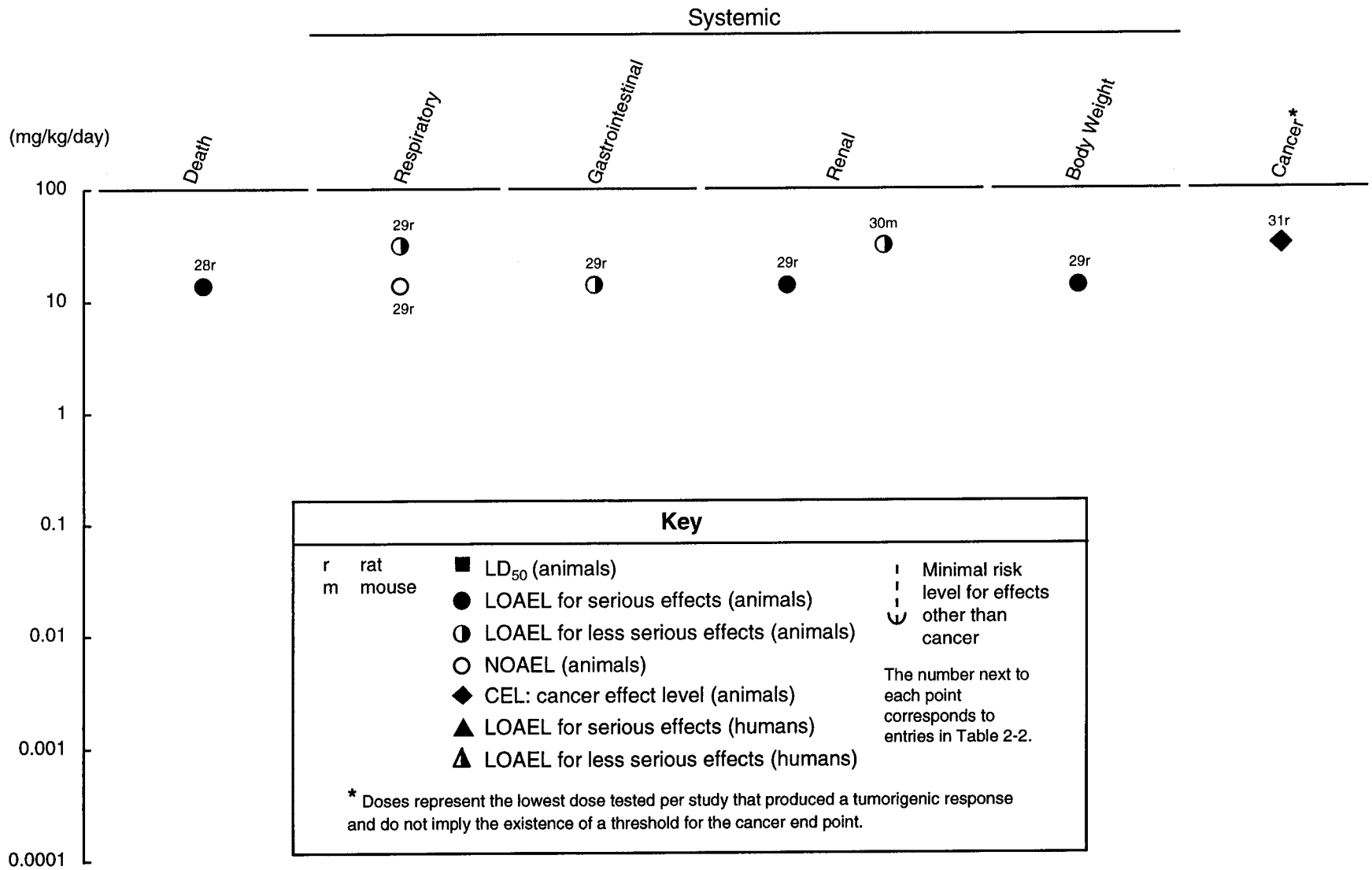


Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Mouse (C57BL/6N)	once (G)				16 M (4/6 died) 40 F (4/6 died)	Yasutake et al. 1991b MMC
	Systemic						
2	Rat (Sprague-Dawley)	2 d 1 x/d (GW)	Cardio		12M (18% decreased heart rate)		Arito and Takahashi 1991 MMC
			Other		12M (hypothermia)		
3	Mouse (C57BL/6N)	once (G)	Renal	8 M 24 F	16 M 32 F (decreased phenolsulfonphthalein excretion, increased serum creatinine, swollen tubular epithelial cells)		Yasutake et al. 1991b MMC
	Neurological						
4	Rat (Sprague-Dawley)	2 d 1 x/d (GW)		1.32 M	4M (decreased paradoxical sleep and increased slow-wave sleep)		Arito and Takahashi 1991 MMC
5	Rat (Sprague-Dawley)	once (G)			0.80 M (dye transport across blood-brain barrier)		Chang and Hartmann 1972b MMC
6	Rat (Wistar)	2 d 1 x/d (G)			10M (impaired performance in tilting plane test)	20 M (decreased nerve conduction velocity; edema and Wallerian degeneration of peripheral nerves)	Fehling et al. 1975 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
7	Rat (Wistar)	8 d 1 x/d Gd 7-14 (GW)		4 F		6 F (spasms; gait disturbance; hind limb crossing in dams)	Fuyuta et al. 1978 MMC
8	Rat (Wistar)	9, 13, or 21 d 1 x/d Gd 12-20, 0-12, or 0-20 (GW)		2 F		4 F (hindlimb crossing in dams)	Inouye and Murakami 1975 MMC
9	Rat (Wistar)	10 d 1 x/d (F)				6.9 M (ataxia; instability walking; peripheral nerve degeneration)	Miyakawa et al. 1974 MMS
10	Rat (Sprague-Dawley)	Once (G)		16 M		20 M (decreased activity in t-maze test)	Post et al. 1973 MMC
11	Rabbit (New Zealand)	1-4 d 1 x/d (G)				5.5 (degeneration of ganglion cells, cerebellum, and cerebral cortex)	Jacobs et al. 1977 MMA
	Reproductive						
12	Rat (Wistar)	7 d 1 x/d (G)				5 M (reduced mean litter size in untreated females)	Khera 1973b MMC
13	Rat (Fischer- 344)	once Gd 7 (G)				8 F (16.7% postimplantation loss, 32.3% decreased litter weight, 14.0% decrease in maternal weight gain)	Lee and Han 1995 MMC
14	Mouse (ICR)	once Gd 10 (GW)		16 F		20 F (increased resorptions; decreased fetuses per litter)	Fuyuta et al. 1979 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
15	Mouse (CFW)	once Gd 8 (G)		2 F		3 F (decreased number of pups per litter)	Hughes and Annau 1976 MMH
16	Mouse (Swiss-Webster)	5-7 d 1 x/d (G)		5 M			Khera 1973b MMC
17	Gn Pig (Hartley)	once Gd 21, 28, 35, 42 (GW)				11.5 F (increased abortions)	Inouye and Kajiwara 1988b MMC
18	Hamster	once Gd 8 (GW)		15.8 F		22 F (increased resorption)	Gale 1974 MA
	Developmental						
19	Human	NS (F)			0.0012 (delayed walking; abnormal motor scores)		Cox et al. 1989 MMC
20	Rat (Wistar)	4 d 1 x/d Gd 6-9 (G)		0.004	0.008 (reduction in behavioral performance of offspring)		Bornhausen et al. 1980 MMC
21	Rat (Sprague-Dawley)	Once Gd 15 (GW)			6.4 (decreased glutamate receptor binding affinity and decreased avoidance latency in offspring)		Cagiano et al. 1990 MMC
22	Rat (Sprague-Dawley)	4 d 1 x/d Gd 6-9 (G)		1.6			Fredriksson et al. 1996 (MM)

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
23	Rat (Wistar)	8 d 1 x/d Gd 7-14 (GW)		2			4	(decreased fetal weight; increased malformations [total]; hydrocephaly; wavy ribs)	Fuyuta et al. 1978 MMC
24	Rat (ddN)	once Gd 6, 7, 8, 9, 10 (GW)					24	(fetal deaths; edema; brain lesions; cleft palate)	Inouye and Murakami 1975 MMC
25	Rat (Wistar)	9, 13, or 21 d 1 x/d Gd 12-20, 0-12, or 0-20 (GW)					2	(fetal edema and brain lesions)	Inouye and Murakami 1975 MMC
26	Rat (Fischer- 344)	once Gd 7 (G)					8	(curved backbones, 9.6% reduced fetal body length)	Lee and Han 1995 MMC
27	Rat	9 d Gd 6-14 ad lib (W)		0.2	4	(increased number of fetuses with delayed ossification or calcification)			Nolen et al. 1972 MMC
28	Rat (Wistar)	4 d Gd 6-9 (G)		0.04	0.4	(increased startle response in offspring)	4	(dendritic spine abnormalities)	Stoltenburg-Didinger and Markwort 1990 MMC
29	Rat (Sprague-Dawley)	once Gd 15 (G)					6.4	(21.3-53% decr maximum number of muscarinic receptors in brain, signif. decr avoidance latency in offspring)	Zanoli et al. 1994 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
30	Mouse (C57BL/6N)	8 d 1 x/d Gd 6-13 (GW)					2	(increased malformations [total]; decreased ossification; absence of 1 or more sterebrae)	Fuyuta et al. 1978 MMC
31	Mouse (ICR)	once Gd 10 (GW)			8	(incomplete fusion of sternebrae)	12	(cleft palate; decreased fetal weight)	Fuyuta et al. 1979 MMC
32	Mouse (CFW)	once Gd 8 (G)		2	3	(decreased number of avoidances and increased escapes in offspring)			Hughes and Annau 1976 MMH
33	Mouse (C3H/HeN)	once Gd 13, 14, 15, 16 (GW)					16	(decreased survival of offspring; impaired righting response; gait and hindlimb crossing; decreased brain weight; dilated lateral ventricles; smaller caudate putamen)	Inouye et al. 1985 MMC
34	Mouse (Swiss-Webster)	12 d Gd 6-17 (GO)		1.0			5.0	(100% stillbirths; failure to litter)	Khera and Tabacova 1973 MMC
35	Mouse (ICR)	once Gd 10 or 12 (GW)		12			16	(cleft palate; dilation of renal pelvis; decreased fetal weight)	Yasuda et al. 1985 MMC
36	Gn Pig (Hartley)	once Gd 21, 28, 35, 42 (GW)					11.5	(retarded fetal brain development)	Inouye and Kajiwara 1988b MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
37	Hamster	once Gd 8 (GW)		2.5	5 (decreased crown-rump length)	22 (increased resorption)	Gale 1974 MA
38	Hamster (Golden Syrian)	once Gd 10 ; or 6d 1 x/d Gd 10-15 (GW)				1.6 (degeneration of cerebellar neurons in neonates)	Reuhl et al. 1981a MMC
39	Hamster (Golden Syrian)	Once Gd 10; or 56d 1 x/d Gd 10-15 (GW)				1.6 (degeneration of cerebellar neurons in offspring 10 months postexposure)	Reuhl et al. 1981b MMC
	INTERMEDIATE EXPOSURE						
	Death						
40	Mouse (ICR)	26 wk ad lib (F)				3.1 (51/60 males and 59/60 females died versus 1/60 male and 1/60 female controls)	Mitsumori et al. 1981 MMC
	Systemic						
41	Rat	12 wk ad lib (F)	Renal		0.08 (cytoplasmic mass in proximal tubule cells)		Fowler 1972 MMC
42	Rat (albino)	3-12 wk 5 d/wk (G)	Renal		0.84 F (fibrosis, inflammation, and large foci in renal cortex)		Magos and Butler 1972 MMD

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
43	Rat (Wistar)	23-28 d 7 d/wk or 1 x every 3 d for 13 d (G)	Cardio		0.4 M (increased systolic pressure)		Wakita 1987 MMC
44	Mouse (ICR)	26 wk ad lib (F)	Renal	0.15	0.6 (toxic epithelial degeneration of renal proximal tubules)		Hirano et al. 1986 MMC
45	Mouse (BALB/c)	12 wk ad lib (F)	Hepatic	0.5 F			Ilback 1991 MM
			Renal	0.5 F			
			Endocr		0.5 F (22% decrease in thymus weight)		
	Immunological/Lymphoreticular						
46	Mouse (BALB/c)	12 wk ad lib (F)			0.5 F (reduced natural killer T-cell activity; decreased thymus weight and cell number)		Ilback 1991 MM
	Neurological						
47	Monkey (Macaca fascicularis)	NS 1 x/d (G)		0.043 F		0.077 F (intention tremor)	Burbacher et al. 1984 MMH
48	Monkey (Macaca fascicularis)	4 mo 1 x/d (G)		0.06 F		0.08 F (slight tremor; gross motor incoordination; blindness)	Burbacher et al. 1988 MMH
49	Monkey (Macaca fascicularis)	6 mo (in apple juice)			0.05 F (72% increased number of reactive glia)		Charleston et al. 1994 MM

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
50	Monkey (macaca fascicularis)	150 d 1 x/d (W)		0.04 F			Petruccioli and Turillazzi 1991 MMC
51	Rat (Holtzman)	1-6 wk 7 d/wk (G)				0.8 M (focal cytoplasmic degeneration of dorsal root ganglia and cerebellum, severe ataxia)	Chang and Hartmann 1972a MMC
52	Rat	3-12 wk 5 d/wk (G)		0.84 F		1.68 F (ataxia; edema and necrosis of cerebellum)	Magos and Butler 1972 MMD
53	Rat (Sprague-Dawley)	15 d 1 x/3d (GO)			0.8 M (decreased synthesis of dopamine neurotransmitter)		Sharma et al. 1982 MMC
54	Rat (Wistar)	50 d 7 d/wk (G)			3.20 M (decreased neurotransmitter activities in cerebellum)		Tsuzuki 1981 MMC
55	Rat	8 wk 7 d/wk (G)				1.6 M (extensive degeneration of dorsal root fiber)	Yip and Chang 1981 MMC
56	Mouse (CD-1)	60 d 7 d/wk (G)		0.25 M		1.0 M (hindleg weakness; microgliocytosis and degeneration)	Berthoud et al. 1976 MMC
57	Mouse	28 wk ad lib (W)				1.9 M (degenerative changes of Purkinje cells and granule cell loss in cerebellum)	MacDonald and Harbison 1977 MMC
58	Cat	11 mo ad lib (F)				0.015 (degeneration of cerebellum and necrosis of dorsal root ganglia)	Chang et al. 1974 MM

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
59	Cat	44-243 d 1 x/d (GW)				0.25 (neuronal degeneration; distorted myelination)	Khera et al. 1974 MMC
	Reproductive						
60	Monkey (Macaca fascicularis)	4 mo 1 x/d (G)		0.04 F		0.06 F (abortion, stillbirth, decreased conception)	Burbacher et al. 1988 MMH
	Developmental						
61	Human	NS (F)			0.0012 (delayed walking; abnormal motor scores)		Cox et al. 1989 MMC
62	Monkey	28-29 d 1 x/d ppd 1-28 or 29 (W)				0.5 (loss of dexterity, locomotor activity; ataxia; blindness; comatose; neuronal degeneration)	Willes et al. 1978 MMC
63	Rat (Wistar)	2 wk prior to mating through weaning (W)			0.08 (impaired tactile-kinesthetic function in offspring)		Elsner 1991 MMC
64	Rat	47 d prior to and during gestation (W)		0.7	1.4 (depression of membrane synthesis, monoamine oxidase, and cytochrome oxidase in fetal hepatocyte mitochodrial membranes)		Fowler and Woods 1977 MMH

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)		LOAEL Serious (mg/kg/day)		Reference Chemical Form
65	Rat (Sprague-Dawley)	15-17 wk 11 wk, Gd 1-21, pp (F)			0.5	(decreased cell-mediated cytotoxicity, increased thymus lymphocyte activity in fetus)			Ilback et al. 1991 MM
66	Rat	approx 52 d ad lib (F)		0.05			0.25	(increased incidence of eye defects in fetuses)	Khera and Tabacova 1973 MMC
67	Rat (Sprague-Dawley)	approx 25 wks; 14 wks prior to mating through ppd 50 (F)			0.195	(increased norepinephrine levels in cerebellum of offspring, increased brain weight)			Lindstrom et al. 1991 MMC
68	Rat	68 d Gd 1 to ppd 42 (G)					0.10	(decreased swimming ability and righting reflex; retarded maze learning in offspring)	Olson and Boush 1975 MMH
69	Mouse (BALB/c)	15 wk ad lib (F)			5.0	(increased proliferatiuve response of pup splenocytes)			Thuvander et al 1996 MMC
	CHRONIC EXPOSURE								
	Death								
70	Mouse (B6C3F1)	104 wk ad lib (F)					0.69 M	(50/60 males died versus 31/60 controls)	Mitsumori et al. 1990 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Systemic						
71	Rat (Wistar)	2 yr ad lib (W)	Gastro	0.4 M		4.2 M (ulcerative cecitis)	Solecki et al. 1991 PMA
			Hemato	0.4 M		4.2 M (decreased hemoglobin, erythrocyte and hematocrit)	
			Renal			0.4 M (increased severity of renal nephrosis)	
			Endocr		4.2 M (significant increased adrenal absolute weight [5%])		
			Bd Wt		0.4 M (approximately 10% decrease in body weight gain)		
72	Rat (NS)	2 yr ad lib (F)	Resp	0.1			Verschuuren et al. 1976 MMC
			Cardio	0.1			
			Gastro	0.1			
			Hemato	0.1			
			Musc/skel	0.1			
			Hepatic	0.1			
			Renal	0.02	0.1 (increased kidney weight; decreased kidney enzymes)		
			Dermal	0.1			
			Ocular	0.1			
73	Mouse (ICR)	104 wk ad lib (F)	Renal	0.03 M 0.11 F		0.15 M (incr chronic nephropathy) 0.6 F	Hirano et al. 1986 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
74	Mouse (B6C3F1)	104 wk ad lib (F)	Gastro	0.14 M 0.6 F	0.69 M (stomach ulceration)		Mitsumori et al. 1990 MMC
			Renal	0.03 M 0.13 F		0.14 M 0.6 F (increased chronic nephropathy with epithelial cell degeneration; regeneration of the proximal tubules; interstitial fibrosis)	
	Neurological						
75	Monkey (Macaca fascicularis)	NS 1 x/d (G)		0.043 F		0.077 F (intention tremor)	Burbacher et al. 1984 MMH
76	Monkey (Macaca fascicularis)	12 or 18 mo			0.05 F (89-152% increased number of reactive glia)		Charleston et al. 1994 MM
77	Monkey (Cynomolgus)	6.5-7 yr 7 d/wk 1 x/d (G)				0.05 (decreased fine motor performance; diminished touch and pinprick sensitivity)	Rice 1989c MMC
78	Monkey (Cynomolgus)	3-4 yr 7 d/wk 1 x/d				0.05 (spatial visual impairment)	Rice and Gilbert 1982 MMC
79	Monkey (Cynomolgus)	7 yr 1 x/d (C)			0.05 (impaired high-frequency hearing)		Rice and Gilbert 1992 MMC
80	Rat (NS)	2 yr ad lib (F)		0.1			Verschuuren et al. 1976 MMC

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
81	Mouse (ICR)	104 wk ad lib (F)		0.11 F		0.6 F (degeneration or fibrosis of sciatic nerve)	Hirano et al. 1986 MMC
82	Mouse (B6C3F1)	104 wk ad lib (F)		0.14 M		0.69 M (sensory neuropathy; cerebral and cerebellar neuronal necrosis; posterior paralysis)	Mitsumori et al. 1990 MMC
83	Cat	2 yr 7 d/wk (F)		0.020	0.046 (impaired hopping reaction; hypalgesia)	0.074 (degeneration of dorsal root ganglia, cerebellar granular cell degeneration)	Charbonneau et al. 1976 MMC
	Reproductive						
84	Rat (NS)	2 yr ad lib (F)		0.1			Verschuuren et al. 1976 MMC
85	Mouse (ICR)	104 wk ad lib (F)		0.15 M		0.73 M (decreased spermatogenesis)	Hirano et al. 1986 MMC
86	Mouse (B6C3F1)	104 wk ad lib (F)		0.14 M		0.69 M (tubular atrophy of the testes)	Mitsumori et al. 1990 MMC
	Developmental						
87	Human	NS (F)		0.00062 BMDL			Crump et al. 1998 MM
88	Human	NS (F)		0.0013[b]			Davidson et al. 1998 MM
89	Human	NS (F)		0.0005			Myers et al. 1997 MM

Table 2-3. Levels of Significant Exposure to Organic Mercury - Oral (continued)

Key to[a] figure	Species (Strain)	Exposure/ duration/ frequency (Specific route)	System	NOAEL (mg/kg/day)	LOAEL Less serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
90	Monkey (Macaque)	328-907 d 1 x/d (W)				0.04-0.06 (impaired visual recognition memory in offspring)	Gunderson et al. 1988 MMH
	Cancer						
91	Rat (Wistar)	2 yr ad lib (W)				4.2 M (CEL: renal cell adenoma)	Solecki et al. 1991 PMA
92	Mouse (ICR)	104 wk ad lib (F)				0.73 M (CEL: renal epithelial adenocarcinoma in males)	Hirano et al. 1986 MMC
93	Mouse (ICR)	78 wk ad lib (F)				1.6 M (CEL: renal adenomas and adenocarcinomas)	Mitsumori et al. 1981 MMC
94	Mouse (B6C3F1)	104 wk ad lib (F)				0.69 M (CEL: renal epithelial cell adenomas and carcinomas)	Mitsumori et al. 1990 MMC

[a]The number corresponds to entries in Figure 2-3.
[b]Used to derive a chronic oral Minimal Risk Level (MRL) of $3x10^{-4}$ mg mercury/kg/day; the NOAEL dose was derived from hair levels, uncertainty factors of 1.5 for pharmacokinetic and 1.5 for pharmacodynamic variability in the relationship between mercury hair levels and mercury ingestion rates, and a modifying factor of 1.5 for domain-specific differences between the Faroe and Seychelles studies ((1.5 + 1.5) x 1.5 = 4.5). No other uncertainty factor was used since the children exposed in utero represent the most sensitive population.

ad lib = ad libitum; ALT = alanine amino transferase; AMC = ammoniated mercuric chloride; approx = approximately; AST = aspartate aminotransferase; Bd Wt = body weight; BMDL = benchmark dose, lower limit (95%); Cardio = cardiovascular; CEL = cancer effect level; d = day(s); Endocr = endocrine; F = female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestational day; Gn pig = guinea pig; (GO) gavage with oil; (GW) gavage with water; Hemato = hematological; Hg = mercury; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; M = male; MM = methylmercury; MMA = methylmercuric acetate; MMC = methylmercuric chloride; MMD = methylmercuric dicyandiamide; MMH = methylmercuric hydoxide; min = minute(s); mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; ppd = postpartum day(s); Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s); yr = year(s)

Figure 2-3. Levels of Significant Exposure to Organic Mercury - Oral

Acute (≤14 days)

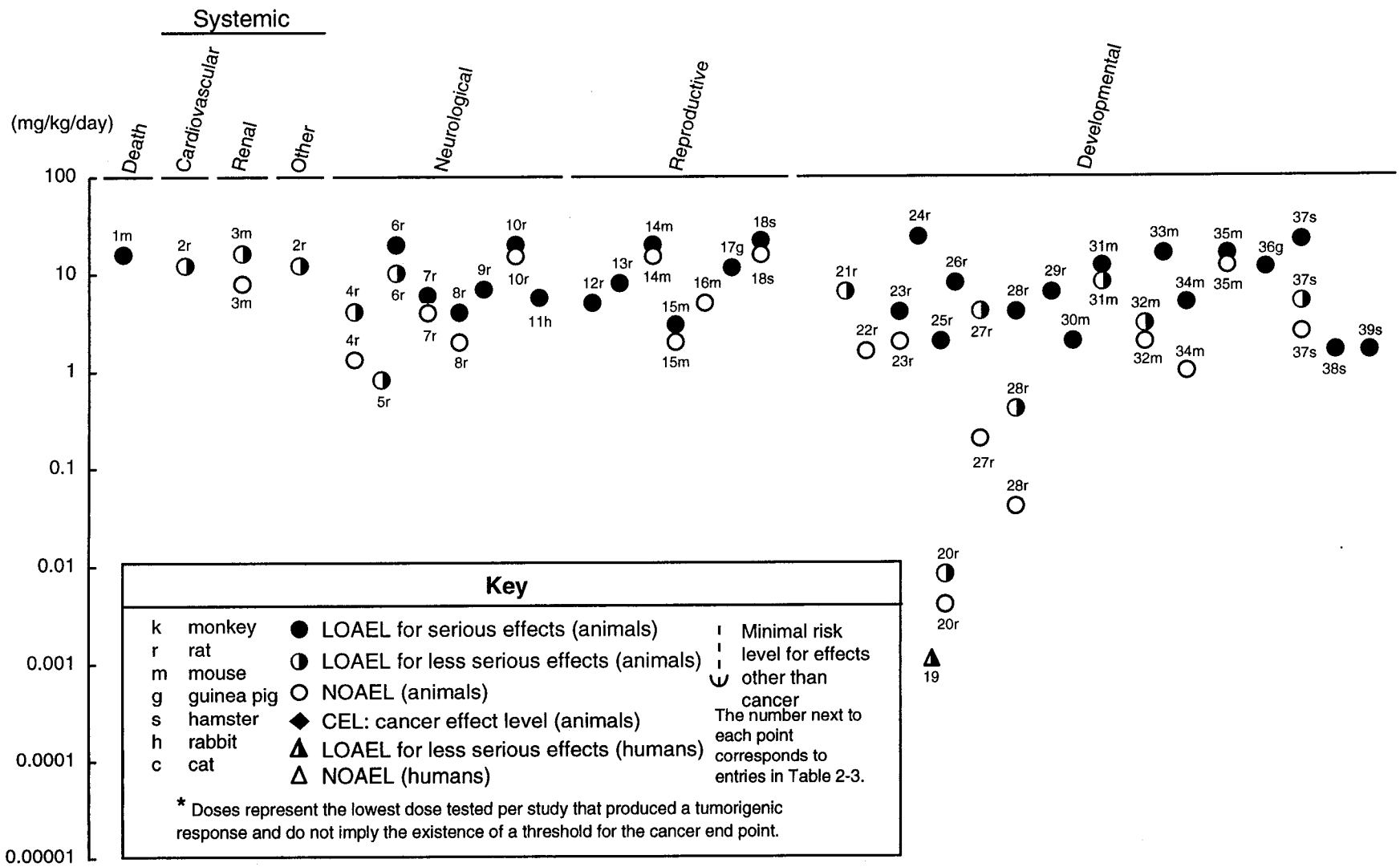


Figure 2-3. Levels of Significant Exposure to Organic Mercury - Oral (cont.)

Intermediate (15-364 days)

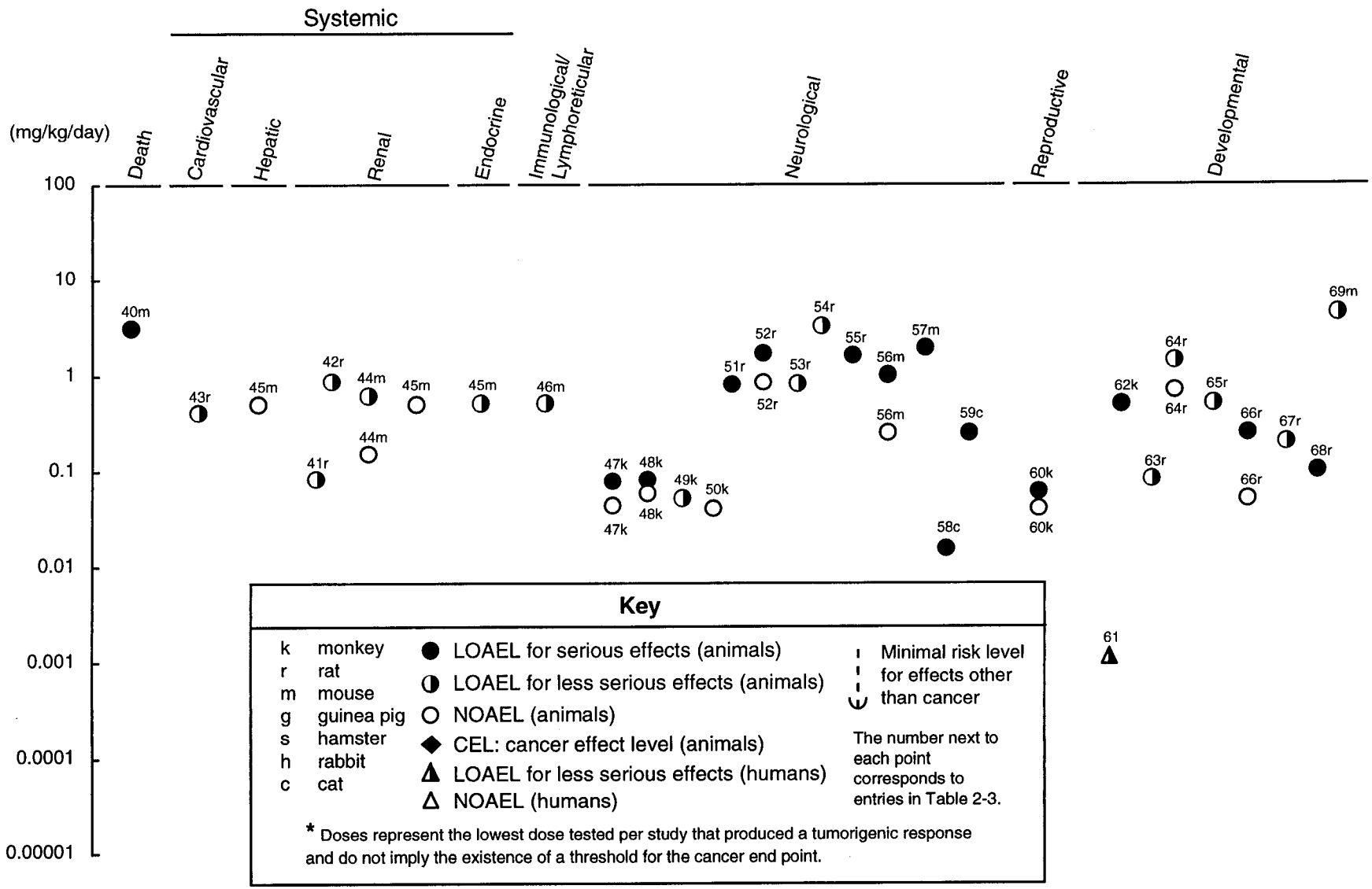
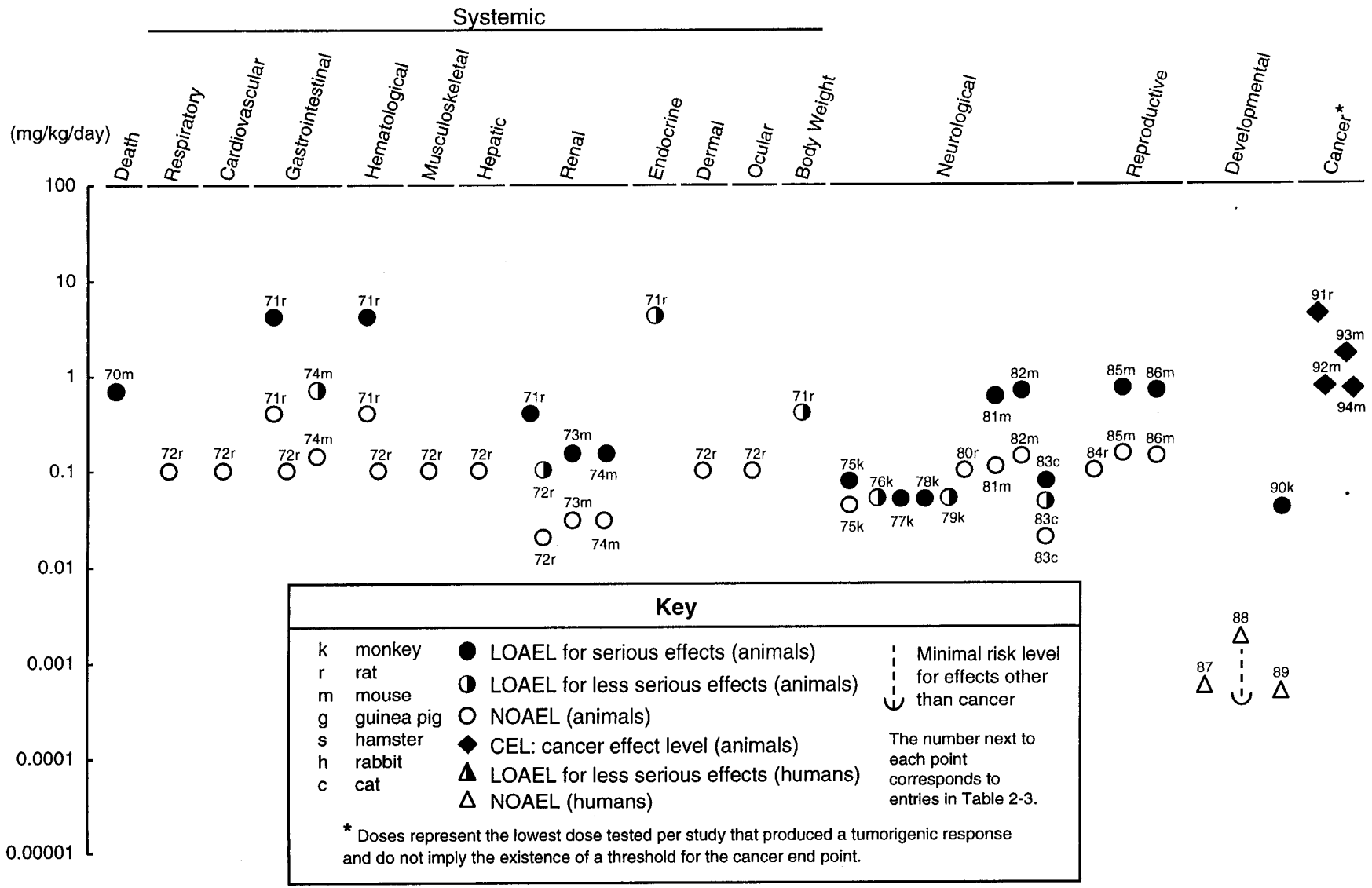


Figure 2-3. Levels of Significant Exposure to Organic Mercury - Oral (cont.)

Chronic (≥365 days)



Chronic exposure to mercuric chloride resulted in increased mortality in male rats at 1.9 mg Hg/kg/day but no increase in mortality in female rats at up to 3.7 mg Hg/kg/day or in either male or female mice at up to 7.4 mg Hg/kg/day (NTP 1993). Renal lesions in the male rats were thought to contribute to the early deaths in these animals.

The highest NOAEL values and all reliable LOAEL values for death for each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2 for inorganic mercury.

Organic Mercury. The acute lethal dose of organic mercury compounds for humans is difficult to assess from the available literature. Death resulting from organic mercury ingestion has been amply documented following outbreaks of poisoning (Minamata disease) after consumption of methylmercury-contaminated fish in Minamata, Japan (Tsubaki and Takahashi 1986) and after consumption of grains contaminated with methyl- and ethylmercury in Iraq (Al-Saleem and the Clinical Committee on Mercury Poisoning 1976; Bakir et al. 1973). Death occurred in two boys who ate meat from a butchered hog that had been fed seed treated with ethylmercuric chloride (Cinca et al. 1979). However, primarily because of the delay between mercury consumption and the onset of symptoms, the amount of organic mercury ingested in these cases is difficult to determine. Fatal doses estimated from tissue concentrations range from 10 to 60 mg/kg (EPA 1985b). A case-control study examining the cause of death for patients with Minamata disease compared to the cause of death in unexposed persons showed that those patients who died prior to 1970 had significantly increased noninflammatory diseases of the nervous system; Minamata disease was reported as the underlying cause of death (Tamashiro et al. 1984). For this group, pneumonia and nonischemic heart disease were reported as prominent secondary cause of death. For those patients who died between 1970 and 1980, significant increases in Minamata disease were reported as the primary cause of death. Nonischemic heart disease correlated with the incidence of Minamata disease, and noninflammatory central nervous system disease was a prominent secondary cause of death in this group.

Methylmercury toxicity is very strain- and sex-specific in mice. A single oral dose of methylmercuric chloride at 16 mg Hg/kg resulted in the death of 4 of 6 male mice (C57BL/6N Jcl strain) but no deaths in females (Yasutake et al. 1991b). No increase in mortality was observed in female mice until 40 mg Hg/kg was administered, at which dosage 4 of 6 females died. Twenty-six weeks of dietary exposure to methyl-mercuric chloride resulted in increased mortality in both male and female mice (ICR strain) at 3.1 mg Hg/kg/day (Mitsumori et al. 1981). Chronic (104 weeks) dietary exposure to methylmercuric