TOXICOLOGICAL PROFILE FOR LEAD

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 Lead, 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
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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:

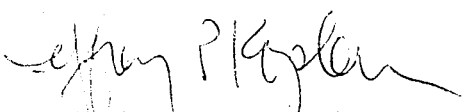
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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.



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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 the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are 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 Environmental Protection Agency (EPA). The availability of the revised priority list of the 275 hazardous substances was announced in the *Federal Register* on February 28, 1994 (59 FR 9486). For prior versions of the list of substances, see *Federal Register* notices dated 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); and October 28, 1992 (57 FR 48801).

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: 1-888-42-ATSDR (1-888-422-8737)
or 404-639-6357 ***Fax:*** 404-639-6359
E-mail: atsdric@cdc.gov ***Internet:*** http://www.atsdr.cdc.gov

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.

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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 lead. The panel consisted of the following members:

1. Dr. Deborah Cory-Slechta, Professor of Environmental Medicine, Neurobiology and Anatomy, Department of Environmental Medicine, University of Rochester, Rochester, New York;

2. Dr. Joseph P. Gould, Research Scientist, School of Civil Engineering, Georgia Institute of Technology, Atlanta, Georgia;

3. Dr. Shane Que Hee, Professor, Department of Environmental Health Sciences, UCLA School of Public Health, Los Angeles, California; and

4. Dr. Marty Kanarek, Professor, Department of Preventive Medicine, University of Wisconsin, Madison, Wisconsin.

These experts collectively have knowledge of lead'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 reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a 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 lead 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. Lead has been found in at least 1,026 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 lead 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 result in 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 lead, 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 you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS LEAD?

Lead is a naturally occurring bluish-gray metal found in small amounts in the earth's crust. It has no characteristic taste or smell. Metallic lead does not dissolve in water and does not burn. Lead can combine with other chemicals to form what are usually known as lead compounds or lead salts. Some lead salts dissolve in water better than others. Some natural and manufactured substances contain lead but do not look like lead in its metallic form. Some of these substances can burn—for example, organic lead compounds in some gasolines.

Lead has many different uses. Its most important use is in the production of some types of batteries. It is also used in the production of ammunition, in some kinds of metal products (such as sheet lead, solder, some brass and bronze products, and pipes), and in ceramic glazes. Some chemicals containing lead, such as tetraethyl lead and tetramethyl lead, were once used as gasoline additives to increase octane rating. However, their use was phased out in the 1980s, and lead was banned for use in gasoline for transportation beginning January 1, 1996. Other chemicals containing lead are used in paint. The amount of lead added to paints and ceramic products, caulking, gasoline, and solder has also been reduced in recent years to minimize lead's harmful effects on people and animals. Lead used in ammunition, which is the largest non-battery end-use, has remained fairly constant in recent years. Lead is used in a large variety of medical equipment (radiation shields for protection against X-rays, electronic ceramic parts of ultrasound machines, intravenous pumps, fetal monitors, and surgical equipment). Lead is also used in scientific equipment (circuit boards for computers and other electronic circuitry) and military equipment (jet turbine engine blades, military tracking systems).

Most lead used by industry comes from mined ores ("primary") or from recycled scrap metal or batteries ("secondary"). Human activities (such as the former use of "leaded" gasoline) have spread lead and substances that contain lead to all parts of the environment. For example, lead is in air, drinking water, rivers, lakes, oceans, dust, and soil. Lead is also in plants and animals that people may eat. See Chapter 3 for more information on the physical and chemical properties of lead. Chapter 4 contains more information on the production and use of lead.

1.2 WHAT HAPPENS TO LEAD WHEN IT ENTERS THE ENVIRONMENT?

Lead occurs naturally in the environment. However, most of the high levels found throughout the environment come from human activities. Before the use of leaded gasoline was banned, most of the lead released into the U.S. environment came from car exhaust. In 1979, cars released 94.6 million kilograms (kg; 1 kg equals 2.2 pounds) of lead into the air in the United States. In 1989, when the use of lead was limited but not banned, cars released only 2.2 million kg to the air. Since EPA banned the use of leaded gasoline for highway transportation in 1996, the amount of

lead released into the air has decreased further. Other sources of lead released to the air include burning fuel, such as coal or oil, industrial processes, and burning solid waste. Once lead goes into the atmosphere, it may travel thousands of miles if the lead particles are small or if the lead compounds easily evaporate. Lead is removed from the air by rain and by particles falling to the ground or into surface water.

The release of lead to air is now less than the release of lead to land. Most of the lead in inner city soils comes from old houses painted with paint containing lead and previous automotive exhaust emitted when gasoline contained lead. Landfills may contain waste from lead ore mining, ammunition manufacturing, or other industrial activities such as battery production.

Sources of lead in dust and soil include lead that falls to the ground from the air, and weathering and chipping of lead-based paint from buildings and other structures. Lead in dust may also come from windblown soil. Disposal of lead in municipal and hazardous waste dump sites may also add lead to soil. Mining wastes that have been used for sandlots, driveways, and roadbeds can also be sources of lead.

Higher levels of lead in soil can be measured near roadways. This accumulation came from car exhaust in the past. Once lead falls onto soil, it usually sticks to soil particles. Small amounts of lead may enter rivers, lakes, and streams when soil particles are moved by rainwater. Lead may remain stuck to soil particles in water for many years. Movement of lead from soil particles into underground water or drinking water is unlikely unless the water is acidic or "soft." Movement of lead from soil will also depend on the type of lead salt or compound and on the physical and chemical characteristics of the soil.

Sources of lead in surface water or sediment include deposits of lead-containing dust from the atmosphere, waste water from industries that handle lead (primarily iron and steel industries and lead producers), urban runoff, and mining piles.

Some of the chemicals that contain lead are broken down by sunlight, air, and water to other forms of lead. Lead compounds in water may combine with different chemicals depending on the acidity and temperature of the water. Lead itself cannot be broken down.

The levels of lead may build up in plants and animals from areas where air, water, or soil are contaminated with lead. If animals eat contaminated plants or animals, most of the lead that they eat will pass through their bodies. Chapters 4 and 5 contain more information about what happens to lead in the environment.

1.3 HOW MIGHT I BE EXPOSED TO LEAD?

People living near hazardous waste sites may be exposed to lead and chemicals that contain lead by breathing air, drinking water, eating foods, or swallowing or touching dust or dirt that contains lead. For people who do not live near hazardous waste sites, exposure to lead may occur in several ways: (1) by eating foods or drinking water that contain lead, (2) by spending time in areas where leaded paints have been used and are deteriorating, (3) by working in jobs where lead is used, (4) by using health-care products or folk remedies that contain lead, and (5) by having hobbies in which lead may be used such as sculpturing (lead solder) and staining glass.

Foods such as fruits, vegetables, meats, grains, seafood, soft drinks, and wine may have lead in them. Cigarette smoke also contains small amounts of lead. Lead gets into food from water during cooking and into foods and beverages from dust that contains lead falling onto crops, from plants absorbing lead that is in the soil, and from dust that contains lead falling onto food during processing. Lead may also enter foods if they are put into improperly glazed pottery or ceramic dishes and from leaded-crystal glassware. Illegal whiskey made using stills that contain lead-soldered parts (such as truck radiators) may also contain lead. The amount of lead found in canned foods decreased 87% from 1980 to 1988, which indicates that the chance of exposure to lead in canned food from lead-soldered containers has been greatly reduced. Lead may also be released from soldered joints in kettles used to boil water for beverages.

In general, very little lead is found in lakes, rivers, or groundwater used to supply the public with drinking water. More than 99% of all publicly supplied drinking water contains less than 0.005 parts of lead per million parts of water (ppm). However, the amount of lead taken into your body through drinking water can be higher in communities with acidic water supplies. Acidic water makes it easier for the lead found in pipes, leaded solder, and brass faucets to enter water. Public water treatment systems are now required to use control measures to make water less acidic. Sources of lead in drinking water include lead that can come out of lead pipes, faucets, and leaded solder used in plumbing. Plumbing that contains lead may be found in public drinking water systems, and in houses, apartment buildings, and public buildings that are more than twenty years old.

Breathing in or swallowing airborne dust and dirt that have lead in them is another way you can be exposed. In 1984, burning leaded gasoline was the single largest source of lead emissions. Very little lead in the air comes from gasoline now because EPA has banned its use in gasoline. Other sources of lead in the air include releases to the air from industries involved in iron and steel production, lead-acid-battery manufacturing, and non-ferrous (brass and bronze) foundries. Lead released into air may also come from burning of solid lead-containing waste, windblown dust, volcanoes, exhaust from workroom air, burning or weathering of lead-painted surfaces, fumes from leaded gasoline, and cigarette smoke.

Skin contact with dust and dirt containing lead occurs every day. Some cosmetics and hair dyes contain lead compounds. However, not much lead can get into your body through your skin. Leaded gasoline contains a lead compound that may be quickly absorbed.

In the home, you or your children may be exposed to lead if you take some types of home remedy medicines that contain lead compounds. Lead compounds are in some non-Western cosmetics, such as surma and kohl. Some types of hair colorants and dyes contain lead acetate. Read the labels on hair coloring products, use them with caution, and keep them away from children.

People who are exposed at work are usually exposed by breathing in air that contains lead particles. Exposure to lead occurs in many jobs. People who work in lead smelting and refining industries, brass/bronze foundries, rubber products and plastics industries, soldering, steel welding and cutting operations, battery manufacturing plants, and lead compound manufacturing industries may be exposed to lead. Construction workers and people who work at municipal waste incinerators, pottery and ceramics industries, radiator repair shops, and other industries that use lead solder may also be exposed. Between 0.5 and 1.5 million workers are exposed to lead in the workplace. In California alone, more than 200,000 workers are exposed to lead. Families of workers may be exposed to higher levels of lead when workers bring home lead dust on their work clothes.

You may also be exposed to lead in the home if you work with stained glass as a hobby, make lead fishing weights or ammunition, or if you are involved in home renovation that involves the removal of old lead-based paint. Chapter 5 contains further information on sources of exposure to lead.

1.4 HOW CAN LEAD ENTER AND LEAVE MY BODY?

Some of the lead that enters your body comes from breathing in dust or chemicals that contain lead. Once this lead gets into your lungs, it goes quickly to other parts of the body in your blood.

You may swallow lead by eating food and drinking liquids that contain it, and also by swallowing large particles (diameter greater than 5 micrometers; 1 micrometer is one millionth of a meter). Most of the lead that enters your body comes through swallowing, even though very little of the amount you swallow actually enters your blood and other parts of your body. In addition to the lead that may be present in food and drink, accidental ingestion of lead may occur due to skin contamination while eating, drinking, smoking, or applying cosmetics (including lip balm). The amount that gets into your body from your stomach partially depends on when you ate your last meal. It also depends on how old you are and how well the lead particles you ate dissolved in your stomach juices. Experiments using adult volunteers showed that, for adults who had just

eaten, the amount of lead that got into the blood from the stomach was only about 6% of the total amount taken in. In adults who had not eaten for a day, about 60–80% of the lead from the stomach got into their blood. In general, if adults and children swallow the same amount of lead, a bigger proportion of the amount swallowed will enter the blood in children than in adults.

Dust and soil that contain lead may get on your skin, but only a small portion of the lead will pass through your skin and enter your blood if it is not washed off. More lead can pass through skin that has been damaged (for example by scrapes, scratches, and wounds). The only kinds of lead compounds that easily penetrate the skin are the additives in leaded gasoline, which is no longer sold to the general public. Therefore, the general public is not likely to encounter lead that can enter through the skin.

Shortly after lead gets into your body, it travels in the blood to the "soft tissues" (such as the liver, kidneys, lungs, brain, spleen, muscles, and heart). After several weeks, most of the lead moves into your bones and teeth. In adults, about 94% of the total amount of lead in the body is contained in the bones and teeth. About 73% of the lead in children's bodies is stored in their bones. Some of the lead can stay in your bones for decades; however, some lead can leave your bones and reenter your blood and organs under certain circumstances, for example, during pregnancy and periods of breast feeding, after a bone is broken, and during advancing age.

Your body does not change lead into any other form. Once it is taken in and distributed to your organs, the lead that is not stored in your bones leaves your body in your urine or your feces. About 99% of the amount of lead taken into the body of an adult will leave in the waste within a couple of weeks, but only about 32% of the lead taken into the body of a child will leave in the waste. Under conditions of continued exposure, not all the lead that enters the body will be eliminated, and this may result in accumulation of lead in body tissues, notably bone. For more information on how lead can enter and leave your body, please refer to Chapter 2.

1.5 HOW CAN LEAD AFFECT MY HEALTH?

The effects of lead are the same whether it enters the body through breathing or swallowing. The main target for lead toxicity is the nervous system, both in adults and in children. Long-term exposure of adults to lead at work has resulted in decreased performance in some tests that measure functions of the nervous system. Lead exposure may also cause weakness in fingers, wrists, or ankles. Some studies in humans have suggested that lead exposure may increase blood pressure, but the evidence is inconclusive. Lead exposure may also cause anemia, a low number of blood cells. The connection between the occurrence of some of these effects (e.g., increased blood pressure, altered function of the nervous system) and low levels of exposure to lead is not certain. At high levels of exposure, lead can severely damage the brain and kidneys in adults or children. In pregnant women, high levels of exposure to lead may cause miscarriage. High-level exposure in men can damage the organs responsible for sperm production.

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.

We have no proof that lead causes cancer in humans. Kidney tumors have developed in rats and mice given large doses of lead. The animal studies have been criticized because of the very high doses used, among other things. The results of high-dose studies should not be used to predict whether lead may cause cancer in humans. The Department of Health and Human Services (DHHS) has determined that lead acetate and lead phosphate may reasonably be expected to be

capable of causing cancer, based on sufficient evidence from animal studies, but there is inadequate evidence from human studies. See Chapter 2 for more information on the health effects of lead.

1.6 HOW CAN LEAD 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.

Studies carried out by the Center for Disease Control and Prevention (CDC) show that the levels of lead in the blood of U.S. children have been getting lower and lower. This is because lead is banned from gasoline, residential paint, and solder that is used for food cans and water pipes. Still, about 900,000 U.S. children between the ages of 1 and 5 years are believed to have blood lead levels equal or greater than 10 μg/dL, the CDC level of concern.

Children are more vulnerable to lead poisoning than adults. Children are exposed to lead all through their lives. They can be exposed to lead in the womb if their mothers have lead in their bodies. Babies can swallow lead when they breast feed, or eat other foods and drink water that contains lead. Babies and children can swallow and breathe lead in dirt, dust, or sand while they play on the floor or ground. These activities make it easier for children to be exposed to lead than adults. The dirt or dust on their hands, toys, and other items may have lead particles in it. In some cases children swallow nonfood items such as paint chips; these may contain very large amounts of lead, particularly in and around older houses that were painted with lead-based paint. The paint in these houses often chips off and mixes with dust and dirt. Some old paint is 5–40% lead. Also, compared to adults, a bigger proportion of the amount of lead swallowed will enter the blood in children.

Children are more sensitive to the effects of lead than adults. Lead affects children in different ways depending how much lead a child swallows. A child who swallows large amounts of lead

may develop blood anemia, kidney damage, colic (severe “stomachache”), muscle weakness, and brain damage which can kill the child. A large amount of lead might get into a child’s body if the child ate small pieces of old paint that contained large amounts of lead. If a child swallows smaller amounts of lead, much less severe effects on blood and brain function may occur. In this case, recovery is likely once the child is removed from the source of lead exposure. In some cases, the amount of lead in the child’s body can be lowered by giving the child certain drugs that help eliminate lead from the body. At still lower levels of exposure, lead can affect a child’s mental and physical growth. Fetuses exposed to lead in the womb, because their mothers had a lot of lead in their bodies, may be born prematurely and have lower weights at birth. Exposure in the womb, in infancy, or in early childhood may also slow mental development and lower intelligence later in childhood. There is evidence that some effects may persist beyond childhood.

Health workers can find out whether a child may have been exposed to harmful levels of lead by taking a blood sample. They can also find out how much lead is in a child’s bones by taking a special type of X-ray of the finger, knee, or elbow. This, however, is not a routine type of test.

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

If your doctor finds that you have been exposed to significant amounts of lead, ask your doctor if children may also be exposed. When necessary your doctor may need to ask your state public health department to investigate.

The most important way families can lower exposures to lead is to know about the sources of lead in their homes and avoid exposure to these sources. Some homes or day-care facilities may have more lead in them than others. Families who live in or visit these places may be exposed to higher amounts of lead. These include homes built before 1978 that may have been painted with paint that contains lead (lead-based paint). If you are buying a home that was built before 1978, you may want to know if it contains lead based paint. Federal government regulations require a person selling a home to tell the real estate agent or person buying the home of any known lead-based hazards on the property. Adding lead to paint is no longer allowed. If your house was built

before 1978, it may have been painted with lead-based paint. This lead may still be on walls, floors, ceilings, and window sills, or on the outside walls of the house. The paint may have been scraped off by a previous owner, and the paint chips and dust may still be in the yard soil. In some states, homeowners can have the paint in their homes tested for lead by their local health departments. Families can lower the possibility of children swallowing paint chips by not allowing their children to chew or mouth these painted surfaces and be sure they wash their hands often, especially before eating. Families can also have a professional lead paint removal expert remove and dispose of peeling or flaking paint or painted surfaces, and repaint the surface. Using heat guns or dry scrapping of old lead containing paint during home reconstruction and remodeling can be a substantial source of lead exposure to children. Surfaces should be tested before such activities, and professional home repair personnel should be consulted to make sure that safe procedures are used and removed materials and dust are contained in order to keep exposures to children to a minimum. These repairs should not be made by homeowners themselves, unless they consult with a professional to get the information they need to prevent the possibility of lead poisoning during or after the repairs.

Older homes that have plumbing with lead or lead solder may have higher amounts of lead in drinking water. You cannot see, taste, or smell lead in water, and boiling your water will not get rid of lead. Running your water for 15 to 30 seconds before drinking or cooking with it will get rid of lead that may leach out from the pipes, especially if you have not used your water for a while, for example, overnight. You can contact your local health department or water supplier to find out about testing your water for lead.

You can bring lead home in the dust on your hands or clothes if lead is used in the place where you work. Lead dust is likely to be found in places where lead is mined or smelted, where car batteries are made or recycled, where electric cable sheathing is made, where fine crystal glass is made, or where certain types of ceramic pottery are made. Pets can also bring lead into the home in dust or dirt on their fur or feet if they spend time in places that have high levels of lead in the soil.

Lead may be taken up in edible plants from the soil by the roots; therefore, home gardening may also contribute to exposure if the produce is grown in soils that have high lead concentrations. Certain hobbies and home or car repair activities like radiator repair can add lead to the home as well. These include soldering glass or metal, making bullets or slugs, or glazing pottery. Some non-Western "folk remedies" contain lead. Examples of these include greta and azarcon used to treat diarrhea.

Some types of paints and pigments that are used as facial make-up or hair coloring contain lead. Cosmetics that contain lead include surma and kohl, which are popular in certain Asian countries. Read the labels on hair coloring products, and keep hair dyes that contain lead acetate away from children. Do not allow children to touch hair that has been colored with lead-containing dyes or any surfaces that have come into contact with these dyes because lead compounds can rub off onto their hands and be transferred to their mouths.

Swallowing of lead in house dust or soil is a very important exposure pathway for children. This problem can be reduced in many ways. Regular hand and face washing to remove lead dusts and soil, especially before meals, can lower the possibility that lead on the skin is accidentally swallowed while eating. Families can lower exposures to lead by regularly cleaning the home of dust and tracked in soil. Door mats can help lower the amount of soil that is tracked into the home; removing your shoes before will also help. Planting grass and shrubs over bare soil areas in the yard can lower contact that children and pets may have with soil and the tracking of soil into the home.

Families whose members are exposed to lead dusts at work can keep these dusts out of reach of children by showering and changing clothes before leaving work, and bagging their work clothes before they are brought into the home for cleaning. Proper ventilation and cleaning—during and after hobby activities, home or auto repair activities, and hair coloring with products that contain lead—will decrease the possibility of exposure.

It is important that children have proper nutrition and eat a balanced diet of foods that supply adequate amounts of vitamins and minerals, especially calcium and iron. Good nutrition lowers the amount of swallowed lead that passes to the bloodstream and also may lower some of the toxic effects of lead.

You can find out whether your child may have been exposed to lead by having your doctor take a blood sample.

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

The amount of total lead in the blood can be measured to determine if exposure to lead has occurred. This test can tell if you have been recently exposed to lead. Lead can be measured lead in teeth or bones by X-ray techniques, but these methods are not widely available. These tests tell about long-term exposures to lead. Exposure to lead can be evaluated by measuring erythrocyte protoporphyrin (EP) in blood samples. EP is a part of red blood cells known to increase when the amount of lead in the blood is high. However, the EP level is not sensitive enough to identify children with elevated blood lead levels below about 25 micrograms per deciliter (µg/dL). For this reason, the primary screening method is measurement of blood lead. For more information on tests to measure lead 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 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. Some regulations and recommendations for lead include the following:

CDC recommends that states develop a plan to find children who may be exposed to lead and have their blood tested for lead. They make basic recommendations for states to follow. These include testing children at ages 1 and 2. Children who are 3 to 6 years old should be tested if they have never been tested for lead before and they receive services from public assistance programs for the poor such as Medicaid or the Supplemental Food Program for Women, Infants and Children (WIC); if they live in a building or frequently visit a house built before 1950; if they visit a home (house or apartment) built before 1978 that has been recently remodeled; or if they have a brother, sister, or playmate who has had lead poisoning.

CDC considers children to have an elevated level of lead if the amount of lead in the blood is at least 10 µg/dL. Medical evaluation and environmental investigation and remediation should be done for all children with blood lead levels equal or greater than 20 µg/dL. Medical treatment may be necessary in children if the lead concentration in blood is higher than 45 µg/dL.

EPA requires that the concentration of lead in air that the public breathes be no higher than 1.5 micrograms per cubic meter ($\mu g/m^3$) averaged over 3 months. EPA regulations no longer

allow lead in gasoline. The Clean Air Act Amendments (CAAA) of 1990 banned the sale of leaded gasoline as of December 31, 1995.

EPA regulations also limit lead in drinking water to 0.015 milligrams per liter (mg/L). The 1988 Lead Contamination Control Act requires the Consumer Product Safety Commission (CPSC), EPA, and the states to recall or repair water coolers containing lead. This law also requires new coolers to be lead-free. In addition, drinking water in schools must be tested for lead, and the sources of lead in this water must be removed.

To help protect small children, CPSC requires that the concentration of lead in most paints available through normal consumer channels be not more than 0.06%. The Federal Hazardous Substance Act (FHSA) bans children's products containing hazardous amounts of lead.

The Department of Housing and Urban Development (HUD) develops recommendations and regulations to prevent exposure to lead. HUD requires that federally funded housing and renovations, public housing, and Indian housing be tested for lead-based paint hazards and that such hazards be fixed by covering the paint or removing it. When determining whether lead-based paint applied to interior or exterior painted surfaces of dwellings should be removed, the standard used by EPA and HUD is that paint with a lead concentration equal to or greater than 1.0 milligram per square centimeter (mg/cm^2) of surface area should be removed or otherwise treated. HUD is carrying out demonstration projects to determine the best ways of covering or removing lead-based paint in housing.

EPA has developed standards for lead paint hazards, lead in dust, and lead in soil. To educate parents, homeowners, and tenants about lead hazards, lead poisoning prevention in the home, and the lead abatement process, EPA has published several general information pamphlets. Copies of these pamphlets can be obtained from the National Lead Information Center or from various Internet sites, including http://www.epa.gov/opptintr/lead.

OSHA regulations limit the concentration of lead in workroom air to 50 μg/m^3 for an 8-hour workday. If a worker has a blood lead level of 50 μg/dL, then OSHA requires that worker be removed from the workroom where lead exposure is occurring.

FDA includes lead on its list of poisonous and deleterious substances. FDA considers foods packaged in cans containing lead solders to be adulterated. Tin-coated lead foil has been used as a covering applied over the cork and neck areas of wine bottles for decorative purposes and to prevent insect infestations. Because it can be reasonably expected that lead could become a component of the wine, the use of these capsules is also a violation of the Federal Food, Drug, and Cosmetic Act. FDA has reviewed several direct human food ingredients and has determined them to be "generally recognized as safe" when used in accordance with current good manufacturing practices. Some of these ingredients contain allowable lead concentrations that range from 0.1 to 10 parts per million (ppm).

Please see Chapter 7 for more information on federal and state regulations and guidelines for lead.

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 lead and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for lead based on toxicological an studies and epidemiological investigations.

2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals 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, developmental, reproductive, 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 for each route and duration are presented in tables and illustrated in figures. 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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine 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 tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers 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 (LOAEL) or exposure levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing

minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with the carcinogenic effects of lead are indicated in Table 2-4 and Figure 2-2.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability and extrapolation of data from laboratory animals to humans.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1989e), 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 will be revised.

This chapter will focus primarily on inorganic lead compounds (lead, its salts, and oxides/sulfides), the predominant forms of lead in the environment. The available data on organic (i.e., alkyl) lead compounds indicate that some of the toxicologic effects of alkyl lead are mediated through metabolism to inorganic lead and that during the combustion of gasolines containing alkyl lead, significant amounts of inorganic lead are released to contaminate the environment. In addition, the lead alkyl halides in automobile exhausts are quickly oxidized by sunlight and air, and do not appear to be present at hazardous waste sites in significant amounts. By far, most lead at hazardous waste sites is inorganic lead. The limited data available on alkyl lead compounds indicate that the toxicokinetic profiles and toxicological effects of these compounds are qualitatively and quantitatively different from those of inorganic lead (EPA 1985b).

The database for lead is unusual in that it contains a great deal of data concerning dose-effect relationships in humans. These data come primarily from studies of occupationally exposed groups and the general population. However, the dose data for humans are generally expressed in terms of absorbed dose, usually

measured as levels of lead in the blood (PbB). PbB reflects recent lead exposures and also historical lead exposure baselines caused by hematopoiesis (blood cell synthesis) in bone marrow.

Dose-effect data in terms of external exposure levels, or milligrams per kilogram per day (mg/kg/day) doses of lead by a single route of exposure, as in studies in animals, are not generally available for humans. In these studies, exposure to other chemical agents also occurred, and it is assumed that lead is the major toxicant. Exposure to lead in occupational studies is primarily through inhalation, although some contribution to body burden is derived from the oral route. Conversely, the general population, including children, is exposed to lead primarily through the oral route, but with some contribution to body burden through inhalation. The toxic effects of lead are the same regardless of the route of entry into the body, and they are correlated with internal exposure as PbB level. For these reasons, Section 2.2.1 of the profile will not attempt to separate human dose data by routes of exposure (unless these data are available) but will present it in terms of PbB levels. Most of the human data, therefore, cannot be displayed graphically by the methods previously described; these data require a different approach, based on PbB levels. Nonetheless, human data are the best basis for any assessment of potential health effects from lead exposure to persons living or working near hazardous waste sites or to other populations at risk. Experimental studies of lead toxicity in animals provide support for observations in human studies, with some consistency in types of effects and PbB-effect relationships. However, animal data on lead toxicity are generally considered less suitable as the basis for health effects assessments than are the human data. There is no absolutely equivalent animal model for the effects of lead on humans.

Data concerning dose-effect relationships in animals are available not only in terms of PbB levels but also in terms of external exposure levels or mg/kg/day doses. The animal data are presented in Sections 2.2.2, 2.2.3, and 2.2.4 and can be displayed graphically by methods previously described. However, the graphical presentation will be done primarily for consistency with other toxicological profiles in this series and is not recommended for use in assessing possible health hazards to persons living or working near waste sites. MRLs were not derived for lead because a clear threshold for some of the more sensitive effects in humans have not been identified. In addition, deriving an MRL would overlook the significant body of PbB literature. These data suggest that certain enzyme level changes and subtle neurobehavioral effects in children may occur at very low PbB levels. In lieu of MRLs, ATSDR has developed a framework to guide decisions at lead sites. This approach utilizes site-specific exposure data to estimate internal doses as measured by PbB levels (See chapter 2.5 and appendix D).

2.2.1 Effects in Humans Based on Blood Lead (PbB) Levels

As discussed in the introduction to Section 2.2, the bulk of the human data on the health effects of lead are expressed in terms of internal exposure, or PbB levels, rather than external exposure levels (i.e., mg/m^3 or mg/kg/day). For the general population, exposure to lead occurs primarily via the oral route with some contribution from the inhalation route, whereas occupational exposure is primarily by inhalation with some oral. Therefore, it is difficult to distinguish specific routes and levels of exposure. For this reason, the human health effects data for lead will be presented in terms of PbB levels in this section. Health effects associated with human exposures to lead and internal lead doses are shown in Table 2-1.

PbB concentrations reflect the absorbed dose of lead. However, the interpretation of PbB data depends on a knowledge of the past history of exposure to lead. This is because in the body, bone constitutes the major lead sink and this results in lead having a long body half-life. Thus, in the absence of intense exposure to lead for a considerable period up to its body half-life, the PbB concentrations reflect recent lead exposures. However, if intermittent exposure to lead is occurring in several distinct environments, the PbB concentration reflects both recent and past exposures to lead. Thus, biological effects for populations with the same PbB concentrations may not be the same since different exposure times scales may be involved. This is the reason why free erythrocyte protoporphyrin (FEP) and erythrocyte zinc protoporphyrin (ZPP) have been used as additional biological markers since their elevation is more related to chronic lead exposure than acute lead exposure (see Section 2.7).

A major limitation inherent in a good portion of the human health effects studies is that exposure durations, and sometimes PbB levels, are not specified. However, many of the studies deficient in experimental detail still provide useful information, and they will be discussed in this section even if they are not recorded in Table 2-1.

2.2.1.1 Death

Mortality studies for workers exposed occupationally to lead are available. These studies all report discrepant results, and all are limited with respect to study design. Therefore, no firm conclusions regarding cause and effect can be drawn from these studies relative to a minimum lethal dose. A cohort mortality study of employees at lead-producing facilities was conducted (Cooper 1988; Cooper et al.

Table 2-1. Health Effects Associated with Exposure to Lead and Internal Lead Doses in Humans

Duration of exposure	System	Effect	Blood lead levels at which effect was observed (µg/dL)	Reference
>1 year (occup)		Increase in death due to hypertension, nephritis, neoplasms	63–80	Cooper et al. 1985; Cooper 1988
NS (occup)		Increase in death due to cerebro-vascular disease, nephritis, and/or nephrosis	NS	Fanning 1988; Malcolm and Barnett 1982; Michaels et al. 1991
>3 years (occup)		Increased incidence of death from lung cancer	34–58 (means)	Lundstrom et al. 1996
NS		Acute encephalopathy resulting in death in children	125–750	NAS 1972
2 weeks to >1 year (occup)	Cardiovascular	Increased blood pressure	≥30–120	de Kort et al. 1987; Pollock and Ibels 1986; Marino et al. 1989; Weiss et al. 1986, 1988
>1 year (occup)	Cardiovascular	No effect on blood pressure	40 (mean)	Parkinson et al. 1987
>1 year (occup)	Cardiovascular	Ischemic electrocardiogram changes	51 (mean)	Kirkby and Gyntelberg 1985
NS (general population)	Cardiovascular	Increased blood pressure	44.9 (mean)	Khera et al. 1980b
NS (general population)	Cardiovascular	Increased systolic pressure by 1–2 mm Hg and increased diastolic pressure by 1.4 mm Hg with every doubling in blood lead level; effect most prominent in middle-aged white men	7–38	Coate and Fowles 1989; Harlan 1988; Harlan et al. 1988; Landis and Flegal 1988; Pirkle et al. 1985; Schwartz 1988; Proctor et al. 1996
NS (general population)	Cardiovascular	No significant correlation between blood pressure and blood lead levels	6–13 (median) or NS	Elwood et al. 1988; Grandjean et al. 1989; Neri et al. 1988; Staessen et al. 1990, 1991
NS (general population)	Cardiovascular	Degenerative changes in myocardium, electrocardiogram abnormalities in children	6–20	Silver and Rodriguez-Torres 1968
NS (children, environmental exposure)	Cardiovascular	1.8 mm Hg increase in systolic blood pressure increase and 0.9 mm increase in diastolic with blood lead increase from 10 to 30 µg/dL	37.3 (mean)	Factor-Litvak et al. 1996

Table 2-1. Health Effects Associated with Exposure to Lead and Internal Lead Doses in Humans (continued)

Duration of exposure	System	Effect	Blood lead levels at which effect was observed (µg/dL)	Reference
NS (acute) (general population)	Gastrointestinal	Colic in children	60–100	EPA 1986a; NAS 1972
NS (acute) (occup)	Gastrointestinal	Colic (abdominal pain, constipation, cramps, nausea, vomiting, anorexia, *weight loss)*	400–200	Awad et al. 1986; Baker et al. 1979; Haenninen et al. 1979; Holness and *Nethercott 1988; Kumar et al. 1987; Marino* et al. 1989; Matte et al. 1989; Muijser et al. 1987; Pagliuca et al. 1990; Pollock and Ibels 1986; Schneitzer et al. 1990
NS (occup)	Hematological	Increased ALAS and/or decreased ALAD	87 or NS (correlation with blood lead level)	Alessio et al. 1976; Meredith et al. 1978; Wada et al. 1973
NS (general population)	Hematological	Decreased ALAD	3–56 (adult) No threshold (children)	Chisholm et al. 1985; Hernberg and Nikkanen 1970; Lauwerys et al. 1978; Roels and Lauwerys 1987; Roels et al. 1976; Secchi et al. 1974
NS (occup)	Hematological	Increased urinary or blood ALA	>35 (adult) 25–75 *(children)*	Lauwerys et al. 1974; Meredith et al. 1978; *Pollock and Ibels 1986;* Selander and Cramer 1970; Solliway et al. 1996
NS (general population)	Hematological	Increased urinary ALA	>35 (adult) 25–75 (children)	NAS 1972; Roels and Lauwerys 1987
NS (general population)	Hematological	Increased FEP	≥25–35	Grandjean and Lintrup 1978; Roels et al. 1975
NS (general population)	Hematological	Increased EP	30–40 (males) 20–30 (females)	Roels and Lauwerys 1987; Roels et al. 1975, 1976, 1979; Stuick 1974
NS (general population)	Hematological	Increased ZPP	≥15 (children)	Hammond et al. 1985; Piomelli et al. 1982; Rabinowitz et al. 1986; Roels and Lauwerys 1987; Roels et al. 1976
1–28 years (occup)	Hematological	Increased ZPP and urinary ALA	51 (mean) 40–75 (range)	Gennart et al. 1992a
NS (general population)	Hematological	Increased urinary coproporphyrin	≥35 (children ≥40 (adults)	EPA 1986a

Table 2-1. Health Effects Associated with Exposure to Lead and Internal Lead Doses in Humans (continued)

Duration of exposure	System	Effect	Blood lead levels at which effect was observed (µg/dL)	Reference
NS (general population)	Hematological	Decreased hemoglobin	≥40 (children)	Adebonojo 1974; Betts et al. 1973; Pueschel et al. 1972; Rosen et al. 1974
NS (occup)	Hematological	Decreased hemoglobin with or without basophilic stippling of erythrocytes	≥40	Awad et al. 1986; Baker et al. 1979; Grandjean 1979; Lilis et al. 1978; Pagliuca et al. 1990; Tola et al. 1973; Wada et al. 1973
NS (general population)	Hematological	Anemia (hematocrit of <35%)	>20 (children)	Schwartz et al. 1990
NS (occup)	Hematological	Decreased Py-5'-N	NS	Buc and Kaplan 1978; Paglia et al. 1975, 1977
NS (general population)	Hematological	Decreased Py-5'-N	7–80 (children)	Angle and McIntire 1978; Angle et al. 1982
NS (acute) (general population)	Hepatic	Decreased mixed function oxidase activity	NS (children)	Alvares et al. 1975; Saenger et al. 1984
NS (chronic) (occup)	Renal	Chronic nephropathy	40–>100	Biagini et al. 1977; Chia et al. 1995a; Cramer et al. 1974; Lilis et al. 1968; Maranelli and Apostoli 1987; Ong et al. 1987; Pollock and Ibels 1986; Verschoor et al. 1987; Wedeen et al. 1979
1–30 years (occup)	Renal	No effect on renal function	40–75	Buchet et al. 1980; Huang et al. 1988a; Gennart et al. 1992a
NS (chronic) (general population)	Renal	Renal impairment with gout or hypertension	18–26	Batumen et al. 1981, 1983
NS (acute) (general population)	Renal	Aminoaciduria; Fanconi syndrome	>80 (children)	Chisolm 1962; Pueschel et al. 1972
NS (children, environmental exposure)	Renal	14% increase in NAG activity in urine per 10 µg/dL blood lead	34.2 (mean)	Verberk et al. 1996

Table 2-1. Health Effects Associated with Exposure to Lead and Internal Lead Doses in Humans (continued)

Duration of exposure	System	Effect	Blood lead levels at which effect was observed (µg/dL)	Reference
0.2–20 years (chronic) (occup)	Endocrine	Decreased thyroxin (T_4)	≥56	Tuppurainen et al. 1988
1–28 years (occup)	Endocrine	No effect on thyroid hormones, TSH, LH, and FSH	51 (mean) 40–75 (range)	Gennart et al. 1992a
NS (chronic) (general population)	Endocrine	No effect on thyroid function in children	2–77 (levels measured)	Siegel et al. 1989; Huseman et al. 1992
NS (general population)	Other	Negative correlation between blood lead and serum 1,25-dihydroxyvitamin D in children	12–120	Mahaffey et al. 1982; Rosen et al. 1980
NS (chronic) (general population)	Other	No effect on vitamin D metabolism in children	5–24 (levels measured)	Koo et al. 1991
NC (chronic) (general population)	Other	Growth retardation in children	≥30–60; tooth lead >18.7 µg/g	Angle and Kuntzelman 1989; Lauwers et al. 1986; Lyngbye et al. 1987; Huseman et al. 1992
NS (chronic) (general population)	Other	No association between blood lead levels and growth in children	10–47 (levels measured)	Greene and Ernhart 1991; Sachs and Moel 1989
NS (general population)	Other	Decreased growth rate	7.7	Shukla et al. 1989, 1991
NS (Mexican-American children)	Other	Decreased stature	≥9–10	Frisancho and Ryan 1991
<18 years (occup)	Immunological	Depression of cellular immune function, but no effect on humoral immune function	21–90	Alomran and Shleamoon 1988; Ewers et al. 1982
Mean, 6 years (occup)	Immunological	Decrease in some surface markers and IgG and IgM	38–100	Ündeger et al. 1996
Mean, 5.3 years (occup)	Immunological	No significant effects in wide range of tests	25–55	Pinkerton et al. 1998

Table 2-1. Health Effects Associated with Exposure to Lead and Internal Lead Doses in Humans (continued)

Duration of exposure	System	Effect	Blood lead levels at which effect was observed (µg/dL)	Reference
NS (acute)	Neurological	Encephalopathy (adults)	50–>300	Kehoe 1961a; Kumar et al. 1987; Smith et al. 1938
NS (older subjects, general population)	Neurological	Decreased performance in neurobehavioral tests	5.5 (mean)	Payton et al. 1998
NS (occup)	Neurological	No effect on neurobehavioral function in adults	40–60 (levels measured)	Milburn et al. 1976; Ryan et al. 1987
NS (occup)	Neurological	No effect on peripheral nerve function	60–80 (levels measured)	Ishida et al. 1996; Spivey et al. 1980
NS (acute and chronic) (occup)	Neurological	Neurological signs and symptoms in adults including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, paresthesia	40–80	Awad et al. 1986; Baker et al. 1979; Campara et al. 1984; Haenninen et al. 1979; Holness and Nethercott 1988; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Parkinson et al. 1986; Pasternak et al. 1989; Pollock and Ibels 1986; Schneitzer et al. 1990; Zimmerman-Tanselia et al. 1983
NS (occup)	Neurological	Neurobehavioral function in adults; disturbances in oculo-motor function, reaction time, visual motor performance, hand dexterity, IQ test and cognitive performance, nervousness, mood, coping ability, memory	40–80	Arnvig et al. 1980; Baker et al. 1983; Baloh et al. 1979; Campara et al. 1984; Glickman et al. 1984; Haenninen et al. 1978; Hogstedt et al. 1983; Mantere et al. 1982; Maizlish et al. 1995; Spivey et al. 1980; Stollery et al. 1989, 1991, 1996; Valciukas et al. 1978; Williamson and Teo 1986
NS (occup)	Neurological	Peripheral nerve function in adults; decreased nerve conduction velocity	30–≥70	Araki et al. 1980; Chia et al. 1996; Muijser et al. 1987; Rosen et al. 1983; Seppalainen et al. 1983; Triebig et al. 1984
NS (occup)	Neurological	Impaired postural balance	36 (mean)	Chia et al. 1996
NS (general population)	Neurological	Irritability, lethargy, behavioral problems and encephalopathy in children	60–450 (effects other than encephalopathy); >80–800 (encephalopathy)	Bradley and Baumgartner 1958; Bradley et al. 1956; Chisolm 1962, 1965; Chisolm and Harrison 1956; Gant 1938; Rummo et al. 1979; Smith et al. 1983

Table 2-1. Health Effects Associated with Exposure to Lead and Internal Lead Doses in Humans (continued)

Duration of exposure	System	Effect	Blood lead levels at which effect was observed (µg/dL)	Reference
NS (general population)	Neurological	Neurobehavioral function in children: slightly decreased performance on IQ tests and other measures of neuro-psychological deficits	40–200	de la Burde and Choate 1972, 1975; Ernhart et al. 1981; Kotok 1972; Kotok et al. 1977; Rummo et al. 1979
NS (general population)	Neurological	Neurobehavioral function in children: slightly decreased performance on IQ tests and other measures of neuro-psychological function	Tooth lead: 60–>30 µg/g Blood lead: 6–60	Bellinger and Needleman 1983; Bergomi et al. 1989; Fulton et al. 1987; Hansen et al. 1989; Hawk et al. 1986; Needleman et al. 1979, 1985, 1990; Schroeder and Hawk 1987; Schroeder et al. 1985; Silva et al. 1988; Wang et al. 1989
NS (general population)	Neurological	No correlation between blood lead levels and permanent effects on neurobehavioral development in children	10–15	Bellinger et al. 1989a; Cooney et al. 1989a; Dietrich et al. 1987a; Ernhart and Greene 1990; Harvey et al. 1984, 1988; Lansdown et al. 1986; McBride et al. 1982; McMichael et al. 1986; Pocock et al. 1989; Smith et al. 1983; Winneke et al. 1984
NS (children, environmental exposure)	Neurological	Blood lead correlated with alterations in visual evoked potentials	range, 1.4–17.4	Altmann et al. 1998; Winneke et al. 1994
NS (children, environmental exposure)	Neurological	Impaired motor and cognitive function	40–50, 20 years before testing; current mean, 2.9	Stokes et al. 1998
NS (general population)	Neurological	Altered auditory evoked potential latency and decreased hearing acuity in children	4–60	Holdstein et al. 1986; Robinson et al. 1985; Schwartz and Otto 1987
NS (children, environmental exposure)	Neurological	No evidence of auditory dysfunction	range, 6.2–128.2	Counter et al. 1997
NS (general population)	Neurological	Postural disequilibrium	11.9 geometric mean for first 5 years of age	Bhattacharya et al. 1993

Table 2-1. Health Effects Associated with Exposure to Lead and Internal Lead Doses in Humans (continued)

Duration of exposure	System	Effect	Blood lead levels at which effect was observed (µg/dL)	Reference
NS (general population)	Neurological	Peripheral neuropathy and reduced conduction velocity in children	20–30	Erenberg et al. 1974; Landringan et al. 1976; Schwartz et al. 1988; Seto and Freeman 1964
Prenatal (general population)	Developmental	Reduced birth weight and/or reduced gestational age, and/or increased incidence of stillbirth and neonatal death	12–17	Bornschein et al. 1989; McMichael et al. 1986; Moore et al. 1982; Ward et al. 1987; Wibberley et al. 1977
NS (general population)	Developmental	No association between blood lead levels and birth weight, gestational age, or other neonatal size measures	3–55	Factor-Litvak et al. 1991; Greene and Ernhart 1991
NS (general population)	Developmental	Impaired mental development in children	10–15	Baghurst et al. 1987; Bellinger et al. 1984, 1985a, 1985b, 1986a, 1986b, 1987a, 1987b; Bornschein et al. 1989; Deitrich et al. 1986, 1987a, 1987b; Ernhart et al. 1985, 1986, 1987; McMichael et al. 1988; Rothenberg et al. 1989a; Tong et al. 1996; Wigg et al. 1988; Winneke et al. 1985a, 1985b; Wolf et al. 1985; Vimpani et al. 1985, 1989
NS (general population)	Developmental	Impaired motor developmental status in 6-year-old children (Cincinnati cohort)	≥9.0 (mean lifetime)	Dietrich et al. 1993b
NS (general population)	Developmental	Moderate deficit in Wechsler Performance IQ in children 6.5 years old (Cincinnati cohort)	≥20 (average lifetime)	Dietrich et al. 1993a
NS (general population)	Developmental	Lower scores in test of Cognitive Function at 5 and 10 years of age	6.5 (mean at 24 months of age)	Bellinger et al. 1991, 1992
NS (general population)	Developmental	Inverse correlation between blood lead levels and ALA and ALAD activity	10–33 (mean)	Haas et al. 1972; Kuhnert et al. 1977; Lauwerys et al. 1978
NS (children, environmental exposure)	Developmental	Small association between abnormal behavior and blood lead at age 3	40.9 (geometric mean)	Wassermann et al. 1998
NS (occup)	Reproductive	Decreased fertility	37.2 (mean)	Lin et al. 1996

Table 2-1. Health Effects Associated with Exposure to Lead and Internal Lead Doses in Humans (continued)

Duration of exposure	System	Effect	Blood lead levels at which effect was observed (µg/dL)	Reference
NS (general population)	Reproductive	Increased incidence of miscarriages and stillbirths in exposed women	≥10 or NS	Baghurst et al. 1987; Hu et al. 1991; McMichael et al. 1986; Nordstrom et al. 1979; Wibberley et al. 1977
NS (general population	Reproductive	No association between blood lead levels and the incidence of spontaneous abortion in exposed women	2	Murphy et al. 1990
NC (occup)	Reproductive	Low sperm count, decreased sperm mobility, abnormal sperm	40–50	Alexander et al. 1996; Assennato et al. 1987; Braunstein et al. 1978; Chowdhury et al. 1986; Cullen et al. 1984; Lancranjan et al. 1975; Rodamilans et al. 1988; Wildt et al. 1983

ALA = δ-aminolevulinic acid; ALAD = δ-aminolevulinic acid dehydratase; ALAS = δ-aminolevulinic acid synthase; EP = erythrocyte protoporphyrins; FEP = free erythrocyte protoporphyrins; FSH = follicle stimulating hormone; IQ = intelligence quotient; LH = luteinizing hormone; NS = not specified; (occup) = occupational; Py-5'-N = pyrimidine-5-nucleotidase; TSH = thyroid stimulating hormone; ZPP = erythrocyte protoporphyrin

1985). Two cohorts of male lead workers, 4,519 battery plant workers and 2,300 lead production workers, all of whom had been employed for at least 1 year during the period 1946–1970, were studied for mortality from 1947 through 1980. Overall mortality and standardized mortality ratios (SMRs) were determined. From 1947 through 1972, mean PbB levels were 63 µg/dL for 1,326 battery plant workers and 80 µg/dL for 537 lead production workers (PbB data were not available for many of the workers and most of the monitoring was done after 1960). For both groups, the number of observed deaths from all causes combined was significantly greater ($p<0.01$) than expected, based on national mortality rates for white males. The increased mortality rates resulted in large part from malignant neoplasms; chronic renal disease, including hypertension and nephritis; and "ill-defined" causes.

Two studies of mortality in four lead acid battery plants in England were conducted (Fanning 1988; Malcolm and Barnett 1982). In the report by Malcolm and Barnett (1982), causes of death between 1925 and 1976 of workers with no, low, or high lead exposure were compared to national mortality rates. In the high lead exposure group, a slight, but not statistically significant, increase in deaths due to cerebrovascular disease was observed. However, among the workers aged 65–69 years, death due to cerebrovascular disease was significantly increased. In addition, a marginally significant increase in the incidence of deaths due to nephritis and nephrosis was observed in the combined low- and high-exposure groups during 1935–1958, but not at later periods. A significant increase in cancer of the digestive tract among the high-exposure group was observed among those workers who died during employment, but not among retirees. The relevance to lead effects was questioned by the authors. However, it may be that these retirees are the less susceptible members of the population.

The second study compared the causes of death among 867 workers exposed to lead from 1926 to 1985 with 1,206 workers having low or no lead exposure (Fanning 1988). Environmental lead levels and biological monitoring for body lead burdens were not available for the entire period. A significant increase in deaths due to cerebrovascular disease was found in lead workers that died between 1946 and 1965 as compared to controls. No other cause produced an excess of deaths in lead workers. The author suggested that the increased risk of death due to cerebrovascular disease was not present from 1965 to 1985 because of stricter occupational standards resulting in lower levels of exposure. Because environmental lead levels and/or lead body burdens were not quantified for the entire period of study, the possibility of misclassification of workers exists. Furthermore, various potentially confounding factors, such as age, smoking, etc., were not accounted for in this study.

Increased risk of death due to cerebrovascular disease was also observed in a cohort of 1,261 white male newspaper printers (typesetters) (Michaels et al. 1991). The cohort was followed from January 1961 through December 1984. While neither environmental levels of lead nor PbB levels were measured, the authors assumed that exposure was generally below the OSHA Permissible Exposure Limit (PEL) of 50 μg/m^3 based on historical industrial hygiene studies in the printing industry. Furthermore, these workers had little or no occupational exposure to any other potentially toxic agents. Information on death and length of employment (used as a surrogate for duration of exposure) was obtained from union records. It was assumed that lead exposure ceased in 1976 when the transition to computerized typesetting occurred. SMRs were calculated for 92 cause-of-death categories using the mortality rates of New York City as the comparison population. The authors found that there were no significantly elevated nonmalignant or malignant causes of death in this cohort. In fact, the SMRs were generally less than unity, indicating that there were less deaths than expected, which the authors attributed to the "healthy worker effect." However, the SMR for cerebrovascular disease was significantly elevated in those members of the cohort employed for more than 30 years. This was not accompanied by an excess of arteriosclerotic heart disease, which suggests that lead exposure may selectively increase the effect of cerebrovascular disease.

Another cohort mortality study compared the mortality rates due to various causes in 437 Swedish smelter workers with verified high lead exposure for at least 3 years from 1950 to 1974 (Gerhardsson et al. 1986b). The mortality data for these workers were compared with national and county mortality rates specified for cause, sex, and calendar periods. Environmental lead levels and PbB levels were available for all workers since 1950. Mean blood lead was 58 μg/dL in 1950 and 34 μg/dL in 1974. The group of 437 lead-exposed workers was further subdivided into high and low mean PbB levels and high and low peak blood levels based on the cumulative PbB dose 1950–1974 and peak PbB values. Of all the specific causes of death examined, only the SMR for lung cancer was increased, but the increase did not achieve statistical significance. In addition, no consistent dose-response patterns were seen in the subgroups. Limitations of this study include the fact that it did not account for various confounding factors, such as smoking, and the fact that all of the workers were exposed to other toxic chemicals, such as antimony, arsenic, cadmium, chromium, cobalt, lanthanum, selenium, zinc, benzo(a)pyrene, and short-lived free radicals. Results from a follow-up study of 1,992 workers at this smelter, 326 with high exposure, were reported by Lundstrom et al. (1997). Expected mortality in 1955–1987 and cancer incidence in 1958–1987 were calculated relative to the county rates, specified for cause, gender, 5-year age groups, and calendar years. Among the highest exposed group, the SMR for all malignancies was slightly increased to 1.5 (95% CI 0.8–2.4), but the SMR

for lung cancer was considerably higher (SMR 4.1, 95% CI 1.5–9.0). Since the workers may have been exposed to other carcinogens, including arsenic, the specific role of lead cannot be ascertained. An additional study of 664 Swedish male lead battery workers employed for at least 3 months during 1942–1987 found an increased overall mortality, and an increased mortality from ischaemic heart diseases and all malignant neoplasms among the cohort (Gerhardsson et al. 1995a). However, no dose-response pattern was found and the risk estimates did not increase when a latency period of 15 years was applied. The study also found an increased incidence of gastrointestinal malignancies among the workers exposed to lead; this tendency was related to employment before 1970 and not to lead dose or to latency time. Gerhardsson et al. (1995a) suggested that the results be interpreted with caution because of limited numbers and the lack of dietary and smoking data.

The possible effects of lead exposure on mortality were examined in a series of 454 pediatric patients at Boston's Children Hospital who were diagnosed with lead poisoning between 1923 and 1966 and who were traced through 1991 (McDonald and Potter 1996). Observed deaths were compared with expected deaths (O/E) using an updated version of the United States Death Rates computer program. Of the 454 patients eligible for the study, 88% had a history of paint pica or known lead exposure; 90% had radiologic evidence of skeletal changes consistent with lead poisoning; and 97% had characteristic gastrointestinal, hematologic, and/or neurologic symptoms. The average PbB level in 23 children tested was 113 μg/dL; PbB tests were performed routinely at the hospital only after 1963. Among the 454 eligible patients, 86 deaths were observed compared to 49.3 expected (O/E 1.7); 56 deaths were observed among males and 30 among females. Although the distribution of causes of mortality generally agreed with expectations, there was a statistically significant excess of death from cardiovascular disease (O/E 2.1, 95% CI 1.3–3.2). Three of four deaths from cerebrovascular accidents occurred in females, and 9 of 12 deaths from arteriosclerotic heart disease occurred in males. Two men died from pancreatic cancer (O/E 10.2) and 2 from non-Hodgkin's lymphoma (O/E 13.0). Chronic nephritis was not a significant cause of death.

Cocco et al. (1997) evaluated cause-specific mortality among workers of a lead-smelting plant in Italy. The cohort consisted of 1,388 men whose vital status was followed from January 1950, or 12 months after the date of hiring, whichever was later, through December 1992. For this period, reference mortality rates of the Italian male population were available from the mortality data base of the World Health Organization (WHO). The deaths from all causes, all malignant neoplasms, diseases of the nervous system, cardiovascular diseases, and digestive tract diseases were fewer than expected when compared with

the national mortality rates. A 4.5-fold excess mortality from pneumoconiosis and other diseases of the respiratory system was observed. Previous exposure to silica in other workplaces was suggested as a likely cause for this increase. Mortality from lung cancer was not increased. SMRs for genitourinary diseases and kidney cancer were not significantly elevated, but both risks increased significantly with duration of employment. Cocco et al. (1997) noted that as kidney cancer accounts for about 0.4% of the total deaths both at the national and regional level, the small size of the cohort may not have allowed detection of small increases over the very low background rate.

In summary, while no strong conclusions can be drawn based on these mortality studies, it is important to note that four of these studies (Fanning 1988; Malcolm and Barnett 1982; McDonald and Potter 1996; Michaels et al. 1991) reported some elevation in deaths due to cerebrovascular disease. No other studies reported increased mortality due to cerebrovascular disease caused by lead exposure.

High levels of lead have been suggested as a causative agent in Sudden Infant Death Syndrome (SIDS) (Drasch et al. 1988). PbB levels in 41 victims of SIDS (3.9±1.8 µg/dL) were compared to those of 77 living control babies (3.5±1.2 µg/dL) and 5 babies of the same ages who died from traumatic causes (3.5±2.1 µg/dL). The authors controlled for several factors that may influence PbB levels, including post-mortem shifts in blood water, age, sex, social class, nutrition, fever prior to death or sampling, birth weight, complications at birth, premature birth, and pregnancy history of the mothers. None of these factors differed significantly between the SIDS babies and the control babies. The post-mortem shift in blood water was accounted for by calculation of the lead concentration in blood dry weight. There was no significant difference between either the arithmetic or geometric means of the dry PbB concentration for the SIDS and control babies. However, a significantly greater number of the highest lead concentrations in dry blood were found in the SIDS group than in the control babies ($p<0.01$) as determined by Chi-square analysis. Based on these results, there may be an association between higher body burdens of lead and SIDS. Possibilities include an effect of lead on prenatal and/or postnatal neurological development. It should be noted, however, that the authors did not control for smoking, a known risk factor for SIDS (Haglund and Cnattingius 1990).

In children, entry of lead into the body occurs primarily by ingestion, although inhalation also contributes to body burden. Once lead intoxication proceeds to encephalopathy, the risk of death exists. Dose-response information on a pediatric population relating PbB levels with the occurrence of acute

encephalopathy and death was compiled by the National Academy of Sciences (NAS 1972) using unpublished data from groups of patients originally reported by Chisolm (1962) and Chisolm and Harrison (1956). The range of PbB levels associated with encephalopathy was approximately 90–800 µg/dL (mean, 330 µg/dL), and the range associated with death was approximately 125–750 µg/dL (mean, 327 µg/dL). All but 1 of the 98 cases of fatal encephalopathy had PbB levels $150 µg/dL.

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal, dermal, or ocular effects in humans after exposure to lead.

Respiratory Effects. The only information located regarding respiratory effects in humans associated with lead exposure was a case report of a 41-year-old man who was exposed to lead for 6 years while removing old lead-based paint from a bridge. At the time of the initial assessment, his PbB level was 87 µg/dL, and he complained of mild dyspnea for the last 2–3 years. No abnormalities in respiratory function were seen at clinical examination, so it is not possible to conclude that his respiratory symptoms were related to exposure to lead (Pollock and Ibels 1986).

Cardiovascular Effects. There is currently considerable scientific debate as to whether there is a causal relationship between lead exposure and hypertension. Another area of controversy is whether African Americans are more susceptible to the cardiovascular effects of lead than are whites or Hispanics. The evidence from both occupational studies and large-scale general population studies (i.e., National Health and Nutrition Examination Survey [NHANES II], British Regional Heart Study [BRHS]) is not sufficient to conclude that such a causal relationship exists between PbB levels and increases in blood pressure. The database on lead-induced effects on cardiovascular function in humans will be discussed by presenting a summary of several representative occupational studies followed by a discussion of the findings from the large-scale general population studies.

Cardiovascular effects have been noted in occupationally exposed workers after exposure to high levels of lead following exposure durations of as short as 4 weeks. Construction workers (race not specified) using oxyacetylene torches to cut a metal bridge that had been painted with lead-based paint were reported to exhibit increases in heart rate and blood pressure after 4 weeks of exposure (Marino et al. 1989). Steep

increases in PbB levels were observed only 2 weeks after work began. Peak PbB levels ranged from 48 to 120 µg/dL. Personal breathing zone exposure to airborne lead ranged from 600 to 4,000 µg/m^3. Hypertension was also observed in another group of men (race not specified) who removed lead-based paint from a metal bridge for varying lengths of time (Pollock and Ibels 1986). PbB levels measured in these workers ranged from 50 to 85 µg/dL; 2 of the 5 cases also exhibited nephropathy and one complained of angina.

Another occupational study compared 53 lead-exposed male workers (2 nonwhite, 51 white) (mean PbB, 47.4 µg/dL; range, 44–51 µg/dL) from a plant processing lead and cadmium compounds with a control group of 52 workers (8 nonwhite, 44 white) (mean PbB, 8.1 µg/dL, with none exceeding 20 µg/dL) from a nonlead industry (de Kort et al. 1987). Blood pressure levels were positively correlated with PbB and urine cadmium levels, but not with blood cadmium levels. The correlation for systolic blood pressure and PbB level remained significant after controlling for confounding variables.

The relationship of PbB level to systolic and diastolic blood pressure was determined in a study of 89 Boston policemen (race not specified) (Weiss et al. 1986, 1988). These policemen were under observation for health outcomes related to environmental work exposures (i.e., they had traffic exposure histories). After statistically adjusting for previous systolic blood pressure, body mass index, age, and cigarette smoking, high PbB level ($30 µg/dL) was a significant ($p=0.01$) predictor of subsequent elevation in systolic blood pressure of 1.5–11 mm Hg in the working policemen with normal blood pressure. Low PbB level (20–29 µg/dL) was not a predictor of subsequent systolic blood pressure elevations. Diastolic pressure was unrelated to PbB levels.

Each of the four studies discussed above (de Kort et al. 1987; Marino et al. 1989; Pollock and Ibels 1986; Weiss et al. 1986, 1988) involved cohorts of fewer than 100 subjects and failed to control for one or more possibly significant confounding factors, such as smoking and alcohol intake.

Another occupational study failed to reveal any significant correlation between occupational lead exposure and diastolic and systolic blood pressure (Parkinson et al. 1987). After controlling for known risk factors (e.g., age, education, income, cigarette usage, alcohol consumption, and exercise), the association between exposure and blood pressure was found to be small and nonsignificant when a group of randomly selected

white battery plant workers (n=270) was compared to 158 nonexposed workers. The average PbB of exposed workers was 40±13 µg/dL; in nonexposed workers it was 7±5 µg/dL.

One cohort mortality study (Fanning 1988) has reported an increased mortality rate due to circulatory disease, but three others found no such correlation (Cooper 1988; Gerhardsson et al. 1986b, 1995a) as discussed in Section 2.2.1.1 (Table 2-1). An increased risk of death due to cerebrovascular disease was observed in a cohort of 1,261 white male newspaper printers (typesetters) (Michaels et al. 1991) (see Section 2.2.1.1).

Cardiovascular effects other than blood pressure changes have also been observed in individuals occupationally exposed to lead. For example, 66% of a group of adults $46 years old, with chronic lead poisoning of occupational origin, had electrocardiographic (ECG) abnormalities, a rate four times the adjusted normal rate for that age group (Kosmider and Petelenz 1962). A study of 95 lead smelter workers (mean PbB, 51 µg/dL) and matched unexposed controls (mean PbB, 11 µg/dL) revealed a significantly higher incidence of ischemic ECG changes (20%) in the lead workers than in controls (6%) (Kirkby and Gyntelberg 1985). In addition, a slight (4–5 mm Hg) but significant increase in diastolic blood pressure was seen in the lead workers compared to controls. Systolic blood pressure was not affected. In contrast with the results from Kosmider and Petelenz (1962) and Kirkby and Gyntelberg (1985), Gennart et al. (1992a) found no effect of lead exposure on the R-R interval variations on the electrocardiogram in a group of 98 workers from a lead acid battery factory. The mean exposure duration was 10.6 years and the mean PbB level at the time of the examination was 51 µg/dL (range, 40–75 µg/dL). A group of 85 people not occupationally exposed to lead served as controls; the mean PbB in this group was 20.9 µg/dL (range, 4.4–39 µg/dL). No other cardiovascular end point was evaluated.

Hypertension has also been associated with lead exposure in the general population. In a case-control study of clinically defined groups, 38 male cardiovascular patients were compared with 48 matched normotensive patients (Khera et al. 1980b). The cardiovascular patients were found to have higher PbB levels (mean, 44.9 µg/dL) than the normotensive patients (mean, 29.0 µg/dL). However, this study is limited by small sample size and incomplete control of confounding factors.

Two large-scale general population studies, the BHRS (Pocock et al. 1984, 1985, 1988) and NHANES II (Coate and Fowles 1989; Gartside 1988; Harlan 1988; Harlan et al. 1985; Landis and Flegal 1988; Pirkle

et al. 1985; Schwartz 1988), examined the relationship between PbB levels and blood pressure in men. Relationships between PbB levels and hypertension were evaluated in a clinical survey of 7,735 men, aged 40–49 years, from 24 British towns in the BHRS (Pocock et al. 1984, 1985, 1988). A small but significant correlation between systolic blood pressure and PbB level was found. Of the 74 men with PbB levels higher than 37 µg/dL, a higher proportion had systolic or diastolic hypertension than did all other men combined. Reanalysis of the same data resulted in highly significant associations between both systolic and diastolic blood pressure and PbB levels when adjustments were made for variation due to site (town) in multiple regression analyses (Pocock et al. 1985). However, when these data were reanalyzed again, it was concluded that the relationship, although statistically significant, was extremely weak (Pocock et al. 1988). In the 1988 reanalysis (using multiple regression analysis), confounding factors, such as town of residence, alcohol consumption, body mass index, age, cigarette smoking, and social class were adjusted for, and it was found that a number of these factors (e.g., alcohol consumption) had a greater influence on pressure than did PbB level. This reanalysis found that mean systolic blood pressure increased by 1.45 mm Hg and diastolic blood pressure increased by 1.25 mm Hg for every doubling in PbB level, with the correlation coefficients attaining statistical significance only because of the very large number of subjects in the survey. Indeed, when separate univariate regression analyses were conducted on each town (i.e., smaller sample size), there was no consistency among the regression coefficients obtained, indicating the high random variability and the weakness of the association. In addition, when the PbB levels of 316 men who experienced cardiovascular events associated with major ischemic heart disease were compared to those of the rest of the cohort and adjustment was made for age, number of years smoking cigarettes, and town of residence, the excess in PbB level among the ischemic heart diseases cases was 0.014 µmole/L (0.03 µg/dL), not a statistically significant difference. Based on their reanalyses, these authors concluded that ". . . we see no convincing epidemiological evidence at present to support the claim that moderate elevations in body lead burden are of relevance to the risk of cardiovascular disease" (Pocock et al. 1988).

Simple correlational analysis of the NHANES II data by Harlan (1988) and Harlan et al. (1985) revealed statistically significant associations between PbB levels and systolic and diastolic blood pressure for both men and women, aged 12–74 years. Statistical analyses controlling for a number of other potentially confounding factors (e.g., age, race, and body mass index), however, indicated significant associations between PbB level and blood pressure only for the men. Based on these analyses, the effect of PbB concentration on blood pressure was estimated to be an increase in blood pressure of 7 mm Hg at PbB levels between 14 and 30 µg/dL.

Additional analyses of the same data set by Pirkle et al. (1985) focused on white males (40–59 years of age) revealed significant correlations between PbB level and blood pressure. No threshold was found below which PbB level was not significantly related to systolic or diastolic blood pressure across a range of 7–38 µg/dL. Moreover, the analysis by Pirkle et al. (1985) showed that large initial increments in blood pressure occurred at relatively low PbB levels, with a diminution of blood pressure increments at higher PbB levels. Lead was a significant predictor of diastolic blood pressure of $90 mm Hg, the criterion now employed in the United States to define diastolic hypertension.

Other analyses of the NHANES II data for men have addressed the issue of possible time-trend effects confounded by variations in sampling sites (Landis and Flegal 1988; Schwartz 1988). These analyses confirm that correlations between systolic or diastolic blood pressure and PbB levels in men remain significant when site is included as a variable in multiple regression analyses. In a separate analysis of the NHANES II data, Gartside (1988) examined the relationship between PbB and systolic and diastolic blood pressure for 26 different age groups, and concluded that there was no convincing evidence of an association between PbB and blood pressure as reported by Schwartz (1988). Forward stepwise regression analyses revealed statistically significantly correlation coefficients in only 24 of the 156 analyses (15%). Systolic blood pressure increased about 1.1–4.4 mm Hg for every doubling of PbB in white males, and the largest values were obtained in the older age groups. However, none of these achieved statistical significance. Changes in systolic blood pressure ranged from a loss of 0.9 mm Hg to a gain of 0.7 mm Hg for every doubling of PbB in white females; none of these changes were statistically significant. Systolic blood pressure changes ranged from a loss of 4.7 mm Hg in the older blacks to a gain of 5.7 mm Hg in the younger blacks. Only the changes in the younger age groups achieved statistical significance. All age groups, sexes, and races grouped together resulted in an overall average increase of 1.1 mm Hg in systolic blood pressure and 1.4 mm Hg in diastolic blood pressure for every doubling of PbB level. Based on this reanalysis, it can be concluded that the NHANES II data provide only a negligible or weak association between PbB level and blood pressure.

Problems with the NHANES II data cast some doubt on its usefulness for analyzing the relationship between PbB levels and blood pressure. When the NHANES II data were reanalyzed, correcting for the questionable blood pressure data, the significance and magnitude of the PbB-blood pressure relationship reported by previous studies (Harlan 1988; Harlan et al. 1985; Landis and Flegal 1988; Pirkle et al. 1985; Schwartz 1988) were far less than reported (Coate and Fowles 1989).

A study of 1,627 pregnant women in south central Los Angeles (73% immigrants) found a positive relationship between blood lead levels and blood pressure only in the immigrant group (Rothenberg et al. 1999a). From the 5th to 95th blood lead percentiles (0.9–6.2 µg/dL) in immigrants, systolic blood pressure increased 2.8 mm Hg and diastolic blood pressure increased 2.4 mm Hg. The geometric mean PbB was 2.3 µg/dL in the immigrant group compared with 1.9 µg/dL in the non-immigrant group. Since most potential confounders were accounted for, these results suggest that past lead exposure in the immigrant group may have contributed to their slightly higher PbB and to the observed association between PbB and blood pressure.

Several other general population studies failed to detect a convincing association between PbB levels and blood pressure. Two studies were conducted in Wales (the Caerphilly Collaborative Heart Disease Studies and the Welsh Heart Programme) in which PbB levels and blood pressure were measured in a cohort of 1,164 men and another cohort of 868 men and 856 women (Elwood et al. 1988). The geometric mean PbB level was 12.7 µg/dL in the first cohort and 11.6 (males) and 9.0 µg/dL (females) in the second cohort. Linear regression analysis, adjusting for age only, revealed no statistically significant relationship between PbB level and blood pressure. The authors suggest that even if the correlation coefficients were significant, the effect of PbB on blood pressure would be small. At most a mean rise in both systolic and diastolic pressures of approximately 0.7 mm Hg for every 10-µg/dL difference in PbB was predicted for this population.

A similar study was undertaken in Denmark in a cohort consisting of 451 men and 410 women (Grandjean et al. 1989). A weak but statistically significant association was seen, particularly in the men, between PbB and systolic and diastolic blood pressures. However, when multiple regression analysis was conducted, adjusting for exercise, smoking, alcohol intake, occupation, height-adjusted weight index, blood hemoglobin, serum cholesterol, and serum triglycerides, no statistically significant association between PbB level and blood pressure was seen in this cohort. Hemoglobin concentration and alcohol intake correlated best with both PbB levels and blood pressure; when one or both of these confounders were included in the regression analysis, any statistically significant relationship between blood pressure and PbB levels was lost for this population.

A negative correlation was found between PbB and systolic pressure in Belgian men in the Cadmibel study (a cross-sectional population study of the health effects of environmental exposure to cadmium) (Staessen

et al. 1991). In this study, blood pressure and urinary cation (positive ions found in the urine, such as sodium, potassium, and calcium) concentration data were obtained from 963 men and 1,019 women; multiple stepwise regression analyses were conducted adjusting for age, body mass index, pulse rate, γ-glutamyltranspeptidase, smoking habits, and use of a contraceptive pill. The only statistically significant association found between PbB and blood pressure was negative, leading the authors to conclude that there is no biologically significant correlation between PbB levels and blood pressure for this population. Similar findings were subsequently published by the same groups of investigators based on observations collected in a random population studied in Belgium for 1985 through 1989 (baseline) and reexamined for 1991 through 1995 (follow-up) (Staessen et al. 1996). The study group totaled 728 subjects (49% men) age 20 to 82 years old. Multivariate analysis controlled for most known potential confounders. At baseline, the mean systolic/diastolic blood pressure was 130/77 mm Hg, the mean PbB was 8.7 µg/dL, and the mean ZPP was 1.0 µg/g hemoglobin. At follow-up, mean blood lead dropped to 2.9 µg/dL, systolic blood pressure decreased 1.5 mm Hg, diastolic increased 1.7 mm Hg, and ZPP increased 0.5 µg/g hemoglobin. Multivariate analysis showed that blood pressure was not correlated with PbB or ZPP concentrations in all men; the same was true for all women, except that diastolic blood pressure tended to be positively correlated with PbB. However, the association lost statistical significance after further adjustment for hematocrit or hemoglobin. Analysis of the results also showed that of 501 initially normotensive subjects, 51 became borderline hypertensive and 47 became definitively hypertensive, but the risk of becoming hypertensive was not associated with blood lead or ZPP concentrations at baseline.

A study of 398 male and 133 female civil servants in London, England, measured blood pressure, PbB, and serum creatinine concentration; the study found no correlation between blood pressure and PbB after adjustment for significant covariates, including sex, age, cigarette smoking, alcohol intake, and body mass index in a stepwise multiple regression analysis (Staessen et al. 1990).

Both cross-sectional and longitudinal data collected in Canada indicated that there might be a slight association between PbB and blood pressure (Neri et al. 1988). Analysis of the data from the cross-sectional sampling of the general population (2,193 people, aged 25–64 years) resulted in a zero-order correlation between diastolic blood pressure and a PbB level of 0.115 that was statistically significant at the $p<0.001$ level. These results can be translated into a PbB level in excess of the median value of 10 µg/dL being associated with a 37% higher risk of having a diastolic pressure above 90 mm Hg. The authors showed that the variability in the blood pressure data that was estimated to be at most 3.0 mm Hg

(0.064 mm Hg per unit of PbB) exceeded any difference in blood pressure that could be attributed to PbB. Using these same data, multiple regression analyses were conducted including age, body weight/height index, serum zinc, and hemoglobin as possible confounders, and there was no longer a statistically significant relationship between PbB and blood pressure. These same authors also conducted a longitudinal study of an occupationally exposed group of foundry workers in an attempt to eliminate the high variability in blood pressure seen in the general Canadian population data and to compare blood pressure and PbB level rises and falls within individuals. Multiple regression analyses, accounting for age and body weight, detected a weak association between PbB and blood pressure; diastolic and systolic blood pressure increased by 0.298 mm Hg and 0.210 mm Hg, respectively, for every µg/dL increase in PbB. However, since the foundry workers were also exposed to cadmium, analysis of the association of cadmium and blood pressure was conducted, and it was found that urinary cadmium levels also correlated with PbB levels. Therefore, the association observed may be due to lead or cadmium, or both in combination.

The role of dietary calcium in the relationship between PbB and blood pressure was examined in a group of 798 male subjects who were participants in the Normative Aging Study (NAS), a longitudinal study of aging established by the Veterans Administration in 1961 (Proctor et al. 1996). The age range of the subjects was 43–93 years (mean, 66.1 years) and the PbB concentration ranged from 0.5 µg/dL to 35 µg/dL (median, 5.6 µg/dL). Approximately 85% of the cohort had PbB level <10 µg/dL and only 1% had PbB levels >20 µg/dL. The mean systolic/diastolic blood pressure was 133.7/80.1 mm Hg. The mean PbB concentration in 334 men who had a daily intake of calcium of #800 mg (the RDA is 800 mg/day) was 6.7 µg/dL compared to 6.2 µg/dL in men who ingested >800 mg calcium/day. For the cohort overall, neither PbB nor dietary calcium were significantly correlated with blood pressure. In multivariate regression analyses that adjusted for age, body mass index, dietary calcium intake, (adjusted for total calorie intake), alcohol consumption, sitting heart rate, kilocalories/week expended in exercise, hematocrit, and smoking status, a unit increase in PbB predicted an increase of 1.2 mm Hg in diastolic blood pressure (95% CI, 0.11, 2.2, p=0.03). Adjusted calcium intake of 800 mg/day predicted a decrease of 3.2 mm Hg in systolic blood pressure (95% CI, -0.56, -0.24, p=0.03). There was no evidence of an interaction between dietary calcium and PbB on blood pressure. When the analyses were limited to men #74 years old, a unit increase in PbB predicted an increase of 1.6 mm Hg in diastolic blood pressure. However, when men on antihypertensive medication were excluded, PbB was not significantly associated with increased diastolic blood pressure and neither was adjusted calcium intake associated with systolic blood pressure.

Taken together, the results of both the occupational and general population studies do not provide conclusive evidence that lead exposure, as assessed by PbB levels, is positively associated with hypertension. The evidence is suggestive for adult men aged 40–59 years old and for systolic rather than diastolic pressure. This association is most apparent for PbB levels as low as 7 µg/dL for middle-aged men, and a mean increase in systolic blood pressure of 1.0–2.0 mm Hg appears to occur for every doubling in PbB levels in middle-aged men with the increase being somewhat less in adult women. However, when the existing data are adjusted for important confounding factors (e.g., age, body weight index, alcohol consumption, cigarette smoking), the results do not allow for the establishment of a relationship between PbB levels and hypertension. Future studies should control for anti-hypertensive medication status and type of medication.

A study in children reported a small association between PbB concentration and blood pressure (Factor-Litvak et al. 1996). The authors examined a group of 281 children age 5.5 years from the Kosovo, Yugoslavia prospective study (see Section 2.2.1.6 for more details on this cohort). Approximately half the children (n=137) lived in a town with heavy lead contamination and the other half (n=144) were relatively unexposed. The mean PbB in the exposed town was 37.3 µg/dL compared with 8.7 µg/dL among the referents. Mean systolic blood pressures in the exposed and unexposed towns were 100.5 mm Hg and 98.4 mm Hg, respectively; the corresponding mean diastolic blood pressures were 59.1 mm Hg and 58.4 mm Hg. In unadjusted data it was found that an increase in PbB from 10 to 30 µg/dL was associated with a 1.8 mm Hg increase in systolic blood pressure and a 0.9 mm Hg increase in diastolic blood pressure. Adjusting for relevant covariates reduced the magnitude of the unadjusted regression coefficient for systolic blood pressure by 40%, but did not modify the association with diastolic blood pressure. The magnitude of the association between PbB concentration and blood pressure also decreased after adjusting for maternal blood pressure and hemoglobin concentration at age 5.5 years.

The hypothesis that long-term lead accumulation, as reflected by levels of lead in bone, is associated with an increased odds of developing hypertension was tested in a study by Hu et al. (1996a). A total of 590 male subjects participants in the NAS were evaluated. At the time of the evaluation, ages of the subjects ranged from 48 to 92 years (mean 66.6 years). Blood lead levels, measured beginning in 1988, ranged from <1 to 28 µg/dL. Levels of lead in the tibia (representing cortical bone) and the patella (representing trabecular bone) were measured starting in 1991 with a K X-ray fluorescence instrument. The outcome chosen, hypertension rather than blood pressure *per se*, was defined as taking daily medication for the

treatment of hypertension or systolic blood pressure higher than 160 mm Hg or diastolic blood pressure of 90 mm Hg or higher during the time of the examination. Analysis of the results showed that an increase in tibia bone lead from the middle of the lowest quintile (8 µg/g bone mineral) to the middle of the highest quintile (37 µg/g) of 29 µg/g was associated with an increased odds ratio of hypertension of 1.5 (95% confidence interval, 1.1–1.8) after adjusting fro body mass index, family history of hypertension, and tibia lead. Among the study limitations recognized by the authors were crude estimations of long-term ethanol ingestion and smoking habits and uncertain estimates of past dietary habits.

Qualitative evidence linking lead exposure to cardiac effects includes the finding of degenerative changes in cardiac muscle, reported as the proximate cause of death in five fatal cases of lead poisoning in young children with histories of pica (Kline 1960). Additional evidence indicates that ECG abnormalities are fairly common in cases of childhood lead encephalopathy but disappear following chelation therapy (EPA 1986a). For example, abnormal electrocardiograms occurred in 21 of 30 overtly lead-intoxicated children prior to chelation therapy, but in only 4 of these children after therapy (Silver and Rodriguez-Torres 1968).

In adults, a study of 75 autopsies of persons who had resided in a soft-water, leached soil region of North Carolina found a positive correlation between lead level in the aorta and death from heart-related disease (Voors et al. 1982). The association persisted after adjustment for the effect of age. A similar correlation was found between cadmium levels in the liver and death from heart-related disease. (Aortic lead and liver cadmium levels were considered to be suitable indices of exposure.) The effects of the two metals appeared to be additive. Potential confounding variables other than age were not included in the analysis. The investigators stated that fatty liver (indicative of alcohol consumption) and cigarette smoking did not account for the correlations between lead, cadmium and heart-disease death.

Gastrointestinal Effects. Colic is a consistent early symptom of lead poisoning in occupationally exposed cases or in individuals acutely exposed to high levels of lead, such as occurs during the removal of lead-based paint. Colic is characterized by a combination of the following symptoms: abdominal pain, constipation, cramps, nausea, vomiting, anorexia, and weight loss. Although gastrointestinal symptoms typically occur at PbB levels of 100–200 µg/dL, they have sometimes been noted in workers whose PbB levels were as low as 40–60 µg/dL (Awad et al. 1986; Baker et al. 1979; Haenninen et al. 1979; Holness and Nethercott 1988; Kumar et al. 1987; Marino et al. 1989; Matte et al. 1989; Muijser et al. 1987; Pagliuca et al. 1990; Pollock and Ibels 1986; Schneitzer et al. 1990).

Colic is also a symptom of lead poisoning in children. EPA (1986a) has identified a LOAEL of approximately 60–100 µg/dL for children. This value apparently is based on a National Academy of Sciences (NAS 1972) compilation of unpublished data from the patient groups originally discussed in Chisolm (1962, 1965) and Chisolm and Harrison (1956) in which other signs of acute lead poisoning, such as severe constipation, anorexia, and intermittent vomiting, occurred at $60 µg/dL.

Hematological Effects. Lead has long been known to have profound effects on heme biosynthesis. In summary, lead inhibits the activity of certain enzymes involved in heme biosynthesis, namely, δ-aminolevulinic acid dehydratase (ALAD), and ferrochelatase. As a consequence of these changes, heme biosynthesis is decreased and the activity of the rate limiting enzyme of the pathway, δ-aminolevulinic acid synthetase (ALAS), which is feedback inhibited by heme, is subsequently increased. The end results of these changes in enzyme activities are increased urinary porphyrins, coproporphyrin, and δ-aminolevulinic acid (ALA); increased blood and plasma ALA; and increased erythrocyte protoporphyrin (EP); FEP; and ZPP (EPA 1986a). However, the adverse effects of decreased ALAD and pyrimidine-5'-nucleotidase activities seen at low PbB levels in the absence of detectable effects on hemoglobin levels and erythrocyte function or survival are of questionable biological significance.

Increases in ALAS activity have been observed in lead workers (Meredith et al. 1978). Leukocyte ALAS was stimulated at a PbB level of 87 µg/dL (Meredith et al. 1978), a level at which ALAD activity is already significantly inhibited. ALAD activity correlated inversely with PbB levels in occupationally exposed individuals (Alessio et al. 1976; Wada et al. 1973), as has been seen in subjects with no occupational exposure (Secchi et al. 1974). Erythrocyte ALAD and hepatic ALAD activities were correlated directly with each other and correlated inversely with PbB levels in the range of 12–56 µg/dL (Secchi et al. 1974).

General population studies indicate that the activity of ALAD is inhibited at very low PbB levels, with no threshold yet apparent. ALAD activity was inversely correlated with PbB levels over the entire range of 3–34 µg/dL in urban subjects never exposed occupationally (Hernberg and Nikkanen 1970). Other reports have confirmed the correlation and apparent lack of threshold in different age groups and exposure categories (children—Chisolm et al. 1985; children—Roels and Lauwerys 1987; adults—Roels et al. 1976). Inverse correlations between PbB levels and ALAD activity were found in mothers (at delivery) and their newborns (cord blood). PbB levels ranged from approximately 3 to 30 µg/dL (Lauwerys et al. 1978).

Inhibition of ALAD and stimulation of ALAS result in increased levels of ALA in blood or plasma and in urine. For example, in a case report of a 53-year-old man with an 11-year exposure to lead from removing old lead-based paint from a bridge, a PbB level of 55 µg/dL was associated with elevated urinary ALA (Pollock and Ibels 1986). The results of the Meredith et al. (1978) study on lead workers and controls indicated an exponential relationship between PbB and blood ALA. Numerous studies reported direct correlations between PbB level and log urinary ALA in workers. Some of these studies indicated that correlations can be seen at PbB levels of <40 µg/dL (Lauwerys et al. 1974; Selander and Cramer 1970; Solliway et al. 1996), although the slope may be different (less steep) than at PbB levels of >40 µg/dL. In a study of 98 occupationally exposed subjects (51 µg/dL, mean PbB) and 85 matched controls (20.9 µg/dL, mean PbB) it was found that log ZPP and log ALA in urine correlated well with PbB levels (Gennart et al. 1992a). In the exposed group, the mean ZPP was 4 times higher than in the controls, whereas urinary ALA was increased 2-fold.

Correlations between PbB levels and urinary ALA similar to those observed in occupationally exposed adults have also been reported in non-occupationally exposed adults (Roels and Lauwerys 1987) and children (unpublished data of J.J. Chisolm, Jr., reported by NAS 1972). Linear regression analyses conducted on data obtained from 39 men and 36 women revealed that increases in urinary ALA may occur at PbB levels of >35 µg/dL in women and >45 µg/dL in men (Roels and Lauwerys 1987). A significant linear correlation between PbB level and log ALA was obtained for data in children 1–5 years old with PbB levels of 25–75 µg/dL. The correlation was seen primarily at PbB levels >40 µg/dL, but some correlation may persist at <40 µg/dL (NAS 1972).

A dose-related elevation of EP or ZPP in lead workers has been documented extensively (Herber 1980; Matte et al. 1989). Correlations between PbB levels and log EP or ZPP indicate an apparent threshold for EP elevation in male workers at 25–35 µg/dL (Grandjean and Lintrup 1978; Roels et al. 1975) for FEP and a threshold of 30–40 µg/dL for EP (Roels and Lauwerys 1987; Roels et al. 1979). The threshold for EP elevation appears to be somewhat lower (20–30 µg/dL) in women than in men (Roels and Lauwerys 1987; Roels et al. 1975, 1976, 1979; Stuik 1974), regardless of whether exposure is primarily by inhalation (occupational) or oral (nonoccupational). These studies were controlled for possible confounding factors such as iron deficiency or age, both of which increase erythrocyte ZPP.

Many studies have reported the elevation of EP or ZPP as being exponentially correlated with PbB levels in children. However, peak ZPP levels lag behind peak levels of PbB. The threshold for this effect in children is approximately 15 µg/dL (Hammond et al. 1985; Piomelli et al. 1982; Rabinowitz et al. 1986; Roels and Lauwerys 1987; Roels et al. 1976), and may be lower in the presence of iron deficiency (Mahaffey and Annest 1986; Marcus and Schwartz 1987). A study by Koren et al. (1990) suggested that the current Centers for Disease Control and Prevention (CDC) standard for acceptable blood FEP levels among children up to 10 years of age is not applicable to newborns. The measurement of the maternal and umbilical cord lead levels and FEP among 95 mother-infant pairs from Toronto showed a significant inverse correlation. Most (99%) infants had cord PbB levels below 7 µg/dL; in 11 cases the levels were below the detection limit. The cord blood FEP levels were higher than the maternal levels. This may reflect immature heme synthesis and increased erythrocyte volume rather than lead poisoning, or perhaps an early effect of lead poisoning.

An increase in urinary coproporphyrin has long been recognized in workers and children with lead poisoning and used as an indicator of excessive exposure to lead (EPA 1986a). EPA (1986a) identified a LOAEL for elevated coproporphyrin at a PbB level of 40 µg/dL for adults and 35 µg/dL for children, but did not present the basis for this conclusion.

The threshold PbB level for a decrease in hemoglobin in occupationally exposed adults is estimated by EPA (1986a) to be 50 µg/dL, based on evaluations of the data of Baker et al. (1979), Grandjean (1979), Lilis et al. (1978), Tola et al. (1973), and Wada et al. (1973). For example, 5% of smelter workers with PbB levels of 40–59 µg/dL, 14% with levels of 60–79 µg/dL, and 36% with levels of >80 µg/dL had anemia. In a study of 98 workers from a lead acid battery factory with a mean PbB level of 51 µg/dL, the mean hemoglobin concentration was not significantly different than in a control unexposed group of 85 subjects. However, 4 exposed workers, but no controls, had hemoglobin levels below the level considered as the limit value for defining anemia (13 g/dL) (Gennart et al. 1992a). The mean erythrocyte counts did not differ significantly between the two populations. Solliway et al. (1996) also reported no significant differences in hemoglobin concentration between a group of 34 workers from a battery factory (mean PbB 40.7 µg/dL, range 23–66 µg/dL) and a group of 56 nonexposed persons (mean PbB 6.7 µg/dL, range 1–13 µg/dL). However, red blood cell count was significantly lower in exposed workers than in the controls. Lead-induced anemia is often accompanied by basophilic stippling of erythrocytes (Awad et al. 1986; Pagliuca et al. 1990). The PbB threshold for decreased hemoglobin levels in children is judged to be approximately

40 µg/dL (EPA 1986a; WHO 1977), based on the data of Adebonojo (1974), Betts et al. (1973), Pueschel et al. (1972), and Rosen et al. (1974). However, a cross-sectional epidemiologic study was conducted to assess the association between blood lead level and hematocrit in 579 children 1–5-years old who lived in close proximity to a primary lead smelter; the study revealed that adverse effects on hematocrit may occur at even lower PbB levels in children (Schwartz et al. 1990). Anemia was defined as a hematocrit of <35% and was not observed at PbB below 20 µg/dL. Analyses revealed that there is a strong negative nonlinear dose-response relationship between PbB levels and hematocrit (i.e., there was a strong association between elevation of PbB level and the probability of anemia). Between 20 µg/dL and 100 µg/dL, the decrease in hematocrit was greater than proportional to the increase in PbB concentration. The effect was strongest in the youngest children. The analysis also revealed that at PbB levels of 25 µg/dL there is a dose-related depression of hematocrit in young children. Similarly, a study of 200 Saudi Arabian boys found a negative correlation between PbB levels and all hematological values when the study group was subdivided into "high" PbB (>15 µg/dL; mean 19±3 µg/dL) versus "normal" PbB (<15 µg/dL; mean 6.5 µg/dL) (Kutbi et al. 1989). Hematocrit and mean corpuscular volume values were marginally below the normal range; red blood cells and hemoglobin were at the low normal range; and mean corpuscular hemoglobin concentration and white blood cells were within normal range. The authors state that this pattern is predictive of the early stages of microcytic anemia, and suggest that low PbB levels once considered to be safe (e.g., 25 µg/dL) may induce the early stages of microcytic anemia. However, it should be noted that both the higher and lower exposure groups had low hematological readings for all of the parameters examined in the study, and the lowest values recorded were in the lowest lead exposure group. This suggests that other factors, such as poor iron or mineral status, could be contributing to the effects reported.

Erythrocyte pyrimidine-5'-nucleotidase activity was inhibited in lead workers, with the greatest inhibition and marked accumulations of pyrimidine nucleotides apparent in workers with overt intoxication, including anemia (Paglia et al. 1975, 1977). PbB levels in these workers ranged between 45 and 110 µg/dL, and 7 of 9 were anemic. Pyrimidine-5'-nucleotidase activity was correlated inversely with PbB when corrected for an enhanced population of young cells due to hemolytic anemia in some of the workers (Buc and Kaplan 1978). Erythrocyte pyrimidine-5'-nucleotidase is inhibited in children at very low PbB levels. A significant negative linear correlation between pyrimidine-5'-nucleotidase and PbB level was seen in 21 children with PbB levels ranging from 7 to 80 µg/dL (Angle and McIntire 1978). Similar results were seen in another study with 42 children whose PbB levels ranged from <10 to 72 µg/dL (Angle et al. 1982). Additional

findings included a direct correlation between cytidine phosphate levels and PbB levels (log-log). There was no indication of a threshold for these effects of lead in these two studies.

Hepatic Effects. In children, exposure to lead has been shown to inhibit formation of the heme-containing protein cytochrome P-450, as reflected in decreased activity of hepatic mixed-function oxygenases (Alvares et al. 1975; Saenger et al. 1984). Two children with clinical manifestations of acute lead poisoning did not metabolize the test drug antipyrine as rapidly as did controls (Alvares et al. 1975). Significantly reduced 6 β-hydroxylation of cortisol was observed in children who had positive (urinary excretion of lead $500 µg/24 hours) calcium sodium ethylenediamine tetraacetate (EDTA) tests as compared with an age-matched control group, controlling for free cortisol (Saenger et al. 1984). These reactions are mediated by hepatic mixed-function oxygenases.

Abnormal liver function tests (alkaline phosphatase, aspartate transaminase, and gamma glutamyl transferase) and mild hepatitis revealed at necropsy were observed in a 52-year-old man who was occupationally exposed to lead following the oxyacetylene cutting of red lead painted ironwork (Pagliuca et al. 1990). The man's PbB level upon hospital admission was 203 µg/dL. It is not clear whether this relatively high level of lead exposure was responsible for the liver toxicity observed in this man, since nothing was reported about his medical history, drinking habits, or other factors that may have contributed to hepatotoxicity.

Renal Effects. The characteristics of early or acute lead-induced nephropathy in humans include nuclear inclusion bodies, mitochondrial changes, and cytomegaly of the proximal tubular epithelial cells; dysfunction of the proximal tubules (Fanconi's syndrome) manifested as aminoaciduria, glucosuria, and phosphaturia with hypophosphatemia; and increased sodium and decreased uric acid excretion. These effects appear to be reversible. Characteristics of chronic lead nephropathy include progressive interstitial fibrosis, dilation of tubules and atrophy or hyperplasia of the tubular epithelial cells, and few or no nuclear inclusion bodies, reduction in glomerular filtration rate, and azotemia. These effects are irreversible. The acute form is reported in lead-intoxicated children, whose primary exposure is via the oral route, and sometimes in lead workers. The chronic form is reported mainly in lead workers, whose primary exposure is via inhalation. Animal studies provide evidence of nephropathy similar to that which occurs in humans, particularly the acute form (see Section 2.2.3.2).

In a study of 102 cases of occupational lead poisoning, 17 cases of clinically verified chronic nephropathy were found (Lilis et al. 1968). Endogenous creatinine clearance was <80 µg/dL. The mean PbB level for the entire study population was 80 µg/dL (range, 42–141 µg/dL). Nephropathy was more common among those exposed to lead for more than 10 years than among those exposed for less than 10 years.

Histopathological evidence of renal damage has been observed in lead-exposed workers. Renal ultrastructure and function were examined in five men with heavy occupational exposure to lead (Cramer et al. 1974). In addition, renal function was evaluated in two men from whom renal biopsies were not obtained. PbB levels ranged from 71 to 138 µg/dL. Renal function tests were normal in all except for a reduced glomerular filtration rate in one worker. Two subjects with relatively short exposure to lead (6 weeks and 8 months) and PbB levels of 89–129 µg/dL had intranuclear inclusions in the proximal tubules. Renal biopsies from workers with longer periods of lead exposure (4–20 years, PbB levels of 71–138 µg/dL) had diffuse interstitial or peritubular fibrosis. Glomeruli were normal in all subjects. Two men exposed to lead for 15–25 years while removing old lead-based paint from a bridge also exhibited clinical and histopathological signs of nephropathy (Pollock and Ibels 1986). In one man (PbB level = 80 µg/dL) who had 2 episodes of pyelonephritis over the past 11 years and hematuria, renal biopsy revealed sclerotic and obliterated glomeruli. In the other, who complained of gouty arthritis and nocturia for the past 10 years, renal biopsy revealed sclerotic glomeruli and nephronal hypertrophy with interstitial scars.

Renal function was evaluated by means of clinical, functional, and morphological studies in 11 patients diagnosed as having "plumbism" based on job background and laboratory findings (criteria not specified) (Biagini et al. 1977). PbB levels in these patients ranged from 50 to 200 µg/dL. Negative associations between urinary lead excretion following chelation with EDTA and clearance of *p*-aminohippuric acid (PAH), glomerular filtration rate and duration of lead exposure were the only statistically significant effects observed. Renal biopsies of these patients revealed signs of degeneration (swollen mitochondria, dilated endoplasmic reticulum, scanty microvilli), signs of probable regeneration (poorly differentiated cells with few microvilli, shallow infoldings of basal cell membrane), and signs of metabolic hyperactivity (intranuclear granular inclusions) in the proximal tubules.

In a study of lead workers, Wedeen et al. (1979) identified 15 who had no other risk factors for renal disease and who had previously unsuspected lead nephropathy (detected as reduced glomerular filtration

rates). Only 3 of the 15 men had ever experienced symptoms of lead poisoning. Blood lead levels were as follows: >80 µg/dL in 1 subject, 40–80 µg/dL in 11 subjects, and <40 µg/dL in 3 subjects. Examination of renal biopsies from 12 of these men revealed focal interstitial nephritis in 6, in addition to nonspecific changes, including deformed mitochondria, in the proximal tubules.

Other studies where no renal biopsies were conducted have yielded varying results with regard to occupational lead exposure and nephropathy. The inconsistencies can be partially explained by differences in the renal functional parameters measured. Various indicators of renal function were assessed in 155 male lead workers and 126 male control workers (Verschoor et al. 1987). Workers were matched for factors such as age, smoking habits, socioeconomic status, and duration of employment. Parameters measured included PbB levels, ZPP, urinary lead levels, serum creatinine, serum urea, serum uric acid, serum $\beta_{2\mu}$-globulin, serum retinal binding protein (RBP-S), creatinine in urine, uric acid in urine, total urinary protein, urinary albumin, urinary $\beta_{2\mu}$-globulin, urinary retinal binding protein (RBP-U), immunoglobulin G, and *N*-acetyl-β-D-glucosaminidase (NAG). The length of exposure to lead was not explicitly stated. Exposure levels were not available, but indicators of lead body burden or effect were: PbB level = 33.8–63.2 µg/dL in the exposed workers and 5.6–12 µg/dL in the controls; ZPP = 34–292 µmol/mol hemoglobin in the exposed workers and 10–35 µmol/mol hemoglobin in the controls. The highest PbB level measured was 97.6 µg/dL. No significant difference between exposed and control workers was found with respect to the tubular or glomerular parameters studied, all urinary and serum parameters were within normal ranges, there was no difference in protein excretion patterns, and there were no signs of clinical renal impairment. Furthermore, no relationship was found between any of the renal parameters and duration of exposure. The NAG levels in the lead-exposed workers were significantly increased over control values, and significantly increased with increasing PbB level and ZPP. NAG is a lysosomal enzyme that is present in renal tubular cells. It has been shown to be a sensitive indicator of early, subclinical renal disease. These results indicate that lead exposure resulting in PbB levels #62 µg/dL can affect renal tubular function more so than glomerular function.

Blood lead levels, urinary lead levels, serum creatinine, blood urea nitrogen (BUN), creatinine clearance (CCT), and NAG were measured in 158 male and 51 female workers in a lead battery factory or a lead smelting plant in Japan (Ong et al. 1987). Controls consisted of 30 professional and laboratory staff members with no history of renal disease or lead exposure. The length of exposure to lead averaged 10.8±8.0 years with a range of 1–36 years. Exposure levels were not available, but indicators of lead body

burden in the exposed workers were: PbB level = 3.0–80.0 µg/dL and urinary lead level = 0.5–49.7 µg/dL. The highest PbB level measured was 80 µg/dL, and only five workers (3%) had PbB level levels over 60 µg/dL. Control values for these indicators of lead body burden were not provided. A weak but statistically significant positive association was found between PbB level and BUN, PbB level and serum creatinine; CCT was reduced with increased PbB level. The same associations were found with urinary lead level. The NAG levels in the lead-exposed workers were significantly increased over control values, and significantly increased with increasing PbB level and urinary lead level (when the data were adjusted for age). These results indicate that lead exposure resulting in relatively low PbB levels can affect renal function.

Various indicators of renal function were assessed in 60 workers diagnosed as having "lead poisoning" (Maranelli and Apostoli 1987). No criteria for "lead poisoning" were specified. Controls consisted of patients hospitalized for respiratory ailments with no history of lead exposure. Parameters measured included PbB levels, urinary lead excretion following chelation with EDTA (PbU-EDTA), ZPP, urinary δ-aminolevulinic acid (ALA-U), and serum creatinine and serum uric acid clearance. The length of exposure to lead averaged 10.8±8.0 years with a range of 1–34 years, and the occupations of the workers varied considerably. Exposure levels were not available, but indicators of lead body burden or effect in the "poisoned workers" were: PbB level = 71.9±16.6 µg/dL; PbU-EDTA = 3,375±2,737 µg/24 hours; ZPP = 12.8±6.9 µg/g hemoglobin; and ALA-U = 1.4±1.2 mg/24 hours. Control values for these indicators of lead body burden were not provided. The only parameters of renal function that differed significantly from the control group were increases in BUN and serum uric acid. There was no definitive correlation between indicators of lead body burden or effect and parameters of renal function.

A study of 137 lead-exposed workers found that of various indices of exposure, time integrated index of PbB was the best predictor of variation in serum $\beta_{2\mu}$-globulin, serum $\alpha_{1\mu}$-globulin, and urinary albumin (Chia et al. 1995a). Another index of exposure examined was the number of times the PbB level was above critical values (e.g., 40, 50, 60 µg/dL). Serum $\beta_{2\mu}$-globulin was the only marker showing a significantly higher prevalence rate ratio of abnormalities (increase) among lead-exposed workers. Based on associations between abnormal serum $\beta_{2\mu}$-globulin and urinary albumin values and the number of times the PbB was above critical values, Chia et al. (1995a) suggested that the threshold of 70 µg/dL for PbB may not prevent the occurrence of nephropathy.

Renal function in workers exposed to lead has also been examined in relation to bone lead, since this measurement of exposure provides a better assessment of cumulative dose of lead to the kidneys than PbB. The study was conducted in a group of 76 male lead workers and 68 controls matched for age, sex, socioeconomic status, general environment, and workshift characteristics (Roels et al. 1994). The average exposure duration was 18 years. Ten blood and urinary markers of nephrotoxicity were monitored. An additional parameter measured was the increase in glomerular filtration rate (GFR) that occurs after acute consumption of protein. GFR was evaluated in terms of creatinine clearance. The mean geometric lead concentration in the tibia from workers and controls was 66 and 21 µg lead/g bone mineral, respectively. Workers had higher mean PbB levels (43 µg/dL) than controls (14 µg/dL) and also higher mean urinary lead than controls (40 versus 7.5 µg lead/g creatinine). Stepwise multiple regression analysis revealed that none of the 10 renal markers measured was related to lead exposure. Furthermore, neither PbB, urinary lead, or blood ZPP predicted baseline or peak GFR after the protein challenge. However, bone lead showed a modest but positive and statistically significant association with both baseline and peak creatinine clearance. No associations with lead in blood or urine, and blood ZPP were found in controls or lead-exposed workers. The authors concluded that PbB levels <70 µg/dL do not cause adverse renal effects in most adult male workers.

Other occupational studies have yielded negative results with regard to lead exposure and renal function. Various serum and urinary indicators of renal function were assessed in 25 male lead smelter workers and 88 male control workers (Buchet et al. 1980). Factors such as age, smoking habits, socioeconomic status, and duration of employment were examined for both groups. Parameters measured included PbB levels, urinary lead levels, FEP, and various enzymes and proteins. The length of exposure to lead was 3.1–29.8 years. Exposure levels were not available, but indicators of lead body burden or effect were: PbB level = 33.8–61.3 µg/dL in the exposed workers and 5.5–34.2 µg/dL in the controls; and urinary lead levels = 15.2–297.9 µg/g creatinine in the workers, 2.53–42.9 µg/g creatinine in the controls. No significant difference between exposed and control workers was found with respect to any of the parameters of renal function, and there were no signs of clinical renal impairment. FEP and ALA in urine were increased in the lead group, and the concentration of urinary ALA was found to correlate positively with blood lead levels. The results of this study of 25 lead smelter workers indicate that lead exposure leading to PbB levels of #62 µg/dL does not result in nephrotoxicity. Another study examined kidney function in a group of 98 workers from a lead acid battery factory (Gennart et al. 1992a). Kidney function was assessed by measurements of urinary retinol-binding protein, $\beta_{2\mu}$-globulin, albumin, NAG, and serum measurements of creatinine and $\beta_{2\mu}$-globulin. The mean duration of employment was 10.6 years, and the

mean PbB level at the time of the evaluation was 51 µg/dL (range, 40–75 µg/dL). A group of 85 subjects non-occupationally exposed to lead served as controls; the mean PbB level in this group was 20.9 µg/dL. The results showed no effect of lead on the renal parameters whether the comparison was made on the basis of mean values or on the basis of prevalence of abnormal values. It should be noted that since in these two studies some control subjects had PbB levels of 20 µg/dL and above, the extent to which they serve as true controls for normal function may be questionable, thus lead effects may been missed or underestimated.

Renal function was evaluated in a group of 36 male and 4 female lead smelter workers (Huang et al. 1988a). The workers were exposed to lead for 1–10.4 years (mean, 5.4 years). Renal function was assessed by means of a medical history, physical exam, routine urinalysis, total urinary protein, urinary IgG, urinary and serum $\beta_{2\mu}$-globulin, and urinary creatinine. The presence of proteinuria is usually indicative of nephrotoxicity; increased urinary $\beta_{2\mu}$-globulin without an increase in serum $\beta_{2\mu}$-globulin can indicate tubular dysfunction; and increased excretion of IgG combined with excess total protein can indicate glomerular damage. Serum $\beta_{2\mu}$-globulin levels, however, are closely related to glomerular filtration rate. All parameters were compared to average values in the healthy Chinese from Beijing obtained in previous studies. The mean PbB level in the exposed workers was 41.8 µg/dL and the mean urinary lead level was 71 µg/L. The only statistically significant finding was an increase in urinary $\beta_{2\mu}$-globulin in the lead group which may indicate subclinical tubular dysfunction.

A cohort mortality study was conducted to compare the mortality rates due to chronic renal disease in 4,519 battery plant workers and 2,300 lead production or smelter workers from 1947 to 1980 (Cooper 1988; Cooper et al. 1985). The mortality data for these workers were compared with national mortality rates for white males. Environmental lead levels and PbB levels were available for only about 30% of all workers for varying time periods from 1947 to 1972. Statistically significant increases in mortality from "other hypertensive disease" and "chronic nephritis" were seen in both lead cohorts. Limitations of this study include the fact that various confounding factors, such as smoking, were not accounted for, and the workers were probably exposed to other toxic chemicals.

Taken together, these studies provide some evidence for the association of chronic nephropathy in occupationally exposed workers with PbB levels ranging from 60 to >100 µg/dL. It should be noted, however, that PbB levels measured at the time of renal function testing may not fully reflect the exposure history that contributed to the development of chronic nephropathy in lead workers.

Excessive lead exposure has been implicated as a causative agent in kidney disease associated with gout (Batuman et al. 1981). A correlation was found between the amount of mobilizable lead and the degree of renal impairment in 44 veterans with gout. The 44 gout patients were similar with respect to age, duration of gout, hypertension, history of lead exposure, serum uric acid concentration, PbB concentration, and ZPP. A 3-day EDTA lead mobilization test was administered to all 44 gout patients, and kidney function was assessed by measuring serum creatinine concentration, creatinine clearance, and 24-hour urinary protein excretion. The results of the 3-day EDTA lead mobilization test were significantly different for the gout patients with renal impairment than for the gout patients without renal impairment. The gout patients with renal impairment excreted 806±90 μg lead over the 3 days, compared to 470±52 μg lead over 3 days in patients with gout but no renal impairment. The upper limit of normal in this test is 600 μg lead excreted over 3 days. To rule out the possibility that the renal impairment itself was the cause of excessive mobilizable lead in patients with gout, 10 patients with renal disease but no gout were used as controls for the EDTA lead mobilization test. These controls excreted approximately the same amount of lead over the 3 days as the gout patients without renal impairment (424±72 μg lead). In addition, the severity of renal impairment (as determined by the serum creatinine concentration) was directly correlated with the amount of mobilizable lead measured in the EDTA test. It is important to note that the gout patients with high mobilizable lead and renal impairment had blood lead levels and ZPP concentrations that were no different from the rest of the group, indicating that there was no indication of lead overexposure in these individuals until the EDTA lead mobilization test was administered. Based on these results, it may be concluded that more extracellular lead accumulates in the renal impairment associated with some forms of gout.

Excessive lead exposure has also been implicated as a causative agent in kidney disease associated with essential hypertension (Batuman et al. 1983). The 3-day EDTA lead mobilization test was administered to 70 veterans; 48 had essential hypertension (27 of which also were diagnosed with renal impairment) and the 22 that served as controls had renal failure but no hypertension. The 48 patients with essential hypertension were similar with respect to age, blood lead concentration, and history of exposure to lead. Kidney function was assessed by measuring serum creatinine concentration, creatinine clearance, and 24-hour urinary protein excretion. A significant difference was found between the hypertensive patients with renal impairment and those without with respect to the amount of mobilizable lead excreted over 3 days in the EDTA test; the patients with both hypertension and renal impairment excreted 860±101 μg lead as compared to 340±39 μg lead in the hypertensive patients without renal impairment. To rule out the possibility that the renal impairment itself was the cause of excessive mobilizable lead in patients with gout,

22 patients with renal disease but no hypertension were used as controls for the EDTA lead mobilization test. The amount of lead excreted over the 3 days by this group was not significantly different from that excreted by the hypertensive patients without renal impairment (440±50 µg lead). In addition, the severity of renal impairment (as determined by the serum creatinine concentration or creatinine clearance rate) was directly correlated with the amount of mobilizable lead measured in the EDTA test. Based on these results, it may be concluded that more extracellular lead accumulates in both the development of renal impairment and essential hypertension.

The results from a longitudinal study provide information regarding low-level lead exposure and renal function (Kim et al. 1996a). The cohort consisted of 459 men randomly selected from the participants of the Normative Aging Study (NAS). The NAS is a longitudinal study of aging established by the Veterans Administration in 1961. The main outcome measured, serum creatinine concentration, was determined at each examination between 1979 and 1994. PbB was assayed in thawed samples of packed red blood cells collected between 1979 and 1991 and in fresh whole blood for the period 1992 to 1994. The following potential covariates known to be associated with blood lead and/or serum creatinine were considered: age, body mass index, current smoking status, daily alcohol intake, hypertensive status, and educational level at the inception of the cohort. Subjects were classified as hypertensive if they had a diastolic blood pressure of 95 mm Hg, or a systolic blood pressure of 160 mm Hg, or if they were on antihypertensive medications. The mean age of the study subjects was 56.9 years (range, 37.7–87.5) at the first visit (baseline). At this time the mean serum creatinine concentration was 1.22 mg/dL and the mean PbB concentration was 9.9 µg/dL. After adjustment for the selected covariates, PbB was positively and significantly associated with concurrent concentration of serum creatinine. The association between lead levels and change in serum creatinine concentration was positive but statistically not significant, with additional controls for baseline serum creatinine (reflecting baseline level over time) and time elapsed since the initial examination (reflecting age related change). A 10-fold increase in PbB level predicted an increase of 0.08 mg/dL in serum creatinine concentration. The association was also significant among subjects whose PbB levels had never been $10 µg/dL throughout the study period. The results also showed that the age-related increase in serum creatinine was earlier and faster and more linear among subjects in the highest quartile than among those in the lowest quartile. Based on the results, Kim et al. (1996a) concluded that low-level exposure to lead may impair renal function in middle-aged and older men; however, the biological significance of a 0.08 mg/dL increase in serum creatinine is unknown.

The relationship between lead exposure and renal function was also investigated in the Cadmibel Study (Staessen et al. 1992). The cohort consisted of a random population sample of 965 men and 1,016 women between 20 and 88 years old. Lead exposure was estimated by PbB levels and ZPP; creatinine clearance rate was also calculated in all subjects. The geometric mean PbB in men and women was 11.4 µg/dL (range, 2.3–72.5) and 7.5 µg/dL (range, 1.7–60.3), respectively. The mean ZPP was 1.0 and 1.1 µg/g hemoglobin in men and women, respectively. Analyses of the data showed that creatinine clearance rate was inversely correlated with blood lead and ZPP in men and women, both before and after adjustment for age, body mass index, and diuretic treatment (blood and urinary cadmium were among covariates considered in the analysis). A 10-fold increase in PbB was associated with a reduction of 10–13 mL/minute in creatinine clearance. There was a positive correlation between serum $\beta_{2\mu}$-globulin and PbB in men, between serum $\beta_{2\mu}$-globulin and ZPP in both sexes, and between serum creatinine and ZPP in men. These results suggest that environmental lead exposure may impair renal function in the general population. However, the alternative hypothesis that renal impairment may lead to an increase in PbB was not excluded.

Full Fanconi syndrome has been reported to be present in some children with lead encephalopathy (Chisolm 1968; Chisolm et al. 1955). According to the National Academy of Sciences (NAS 1972), the Fanconi syndrome is estimated to occur in approximately one out of three children with encephalopathy and PbB levels of approximately 150 µg/dL. Aminoaciduria occurs at PbB levels >80 µg/dL in children with acute symptomatic lead poisoning (Chisolm 1962). The aminoaciduria and symptoms of lead toxicity disappeared after treatment with chelating agents (Chisolm 1962).

In a study of children with slight neurological signs indicative of lead toxicity, aminoaciduria was found in 4 of 43 children with average PbB levels of 35 µg/dL (Pueschel et al. 1972). The highest PbB level for the 43 children was 68 µg/dL. Although PbB levels were not reported specifically for the children with aminoaciduria, it may be assumed that they were probably at the high end of the range.

A study of 55 adolescents who had been treated for lead intoxication in early childhood (11–17 years earlier) revealed no evidence of chronic nephropathy, as evidenced by endogenous creatinine clearance, BUN, serum uric acid, and routine urinalysis (Chisolm et al. 1976). PbB levels during the acute poisoning episode ranged from 100 to 650 µg/dL; all patients received immediate chelation therapy. At the time of the study, their PbB levels had decreased to less than 40 µg/dL.

A study of 151 children ages 3-6 years old living near a lead smelter in town in Romania found a significant relationship between PbB concentration and NAG activity in the urine (Verberk et al. 1996). The mean PbB concentration among the children was 34.2 µg/dL. NAG activity was found to increase 14% per 10 µg/dL PbB. No significant relationship was found between PbB and other urinary markers of renal function such as albumin, $\alpha_{1\mu}$-globulin, retinol binding protein, or alanine aminopeptidase. It was unlikely that the increase in NAG activity was due to exposure to cadmium since cadmium in blood was less than 2 µg/L.

On the basis of the more recent study by Verberk et al. (1996), it seems that tubular damage may occur in children at PbB levels of <40 µg/dL.

Endocrine Effects. The effects of lead exposure on thyroid function have been examined in occupationally exposed workers and in children. Blood lead levels, EP, total thyroxin (T_4), free thyroxin (FT_4) total triiodothyronine (T_3), and thyroid stimulating hormone (TSH) were measured in 172 black male workers in 2 Kenyan car battery factories and one secondary lead smelter (Tuppurainen et al. 1988). The mean duration of exposure to lead was 7.6±5.1 years (range, 0.1–20 years). The mean PbB level was 56±24 µg/dL (range, 15–134 µg/dL) and the mean EP was 16.3±5.1 µmol/L (range, 2–104 µmol/L). No correlation was found between PbB level and T_4, T_3, or TSH, as determined by regression analyses. However, there was a weak, but statistically significant, negative correlation between duration of exposure and levels of T_4 and FT_4. This association was even more apparent when only workers considered to have "high" lead exposure (i.e., PbB level of $56 µg/dL) were analyzed. Although these results suggest that lead may adversely affect the thyroid over time, the authors did not control for confounding factors (such as preexisting conditions that may affect thyroid function or exposure to other chemicals) and lead exposures may have varied considerably in the workers. An additional study examined some endocrine parameters (T_3, FT_4, T_4, TSH, follicle-stimulating hormone, and luteinizing hormone) in a group of 98 workers from a lead acid battery factory (Gennart et al. 1992a). The mean duration of exposure was 10.6 years and the mean PbB concentration at the time of the evaluation was 51 µg/dL (range, 40–75 µg/dL). A group of 85 non-occupationally exposed subjects served as controls (mean PbB, 20.9 µg/dL; range, 4.4–39.0 µg/dL). The results showed no lead-related alterations in the parameters examined. It should be noted that the mean PbB level of 20.9 µg/dL in the control group may not be low enough to be considered a true control and could have lessened the possibility of finding a lead effect in the more highly exposed group.

No effects of lead on thyroid function have been found in children. Thirty-six male and 32 female children ranging in age from 11 months to 7 years (median age of 25 months) took part in a study of the effects of lead exposure on thyroid function in inner city children (Siegel et al. 1989). Blood lead levels, T_4, and T_4 uptake were determined, and sex, race, socioeconomic status, and hemoglobin were also assessed for each child. The PbB levels ranged from 2.0 to 77 µg/dL, with a mean of 25 µg/dL. Forty-four percent of the children had elevated lead levels (>24 µg/dL). Linear regression analysis revealed that there was no association between PbB levels and either T_4 or FT_4. This is contrary to what has been observed in adults (i.e., others have shown that there is a relationship between PbB levels and T_4 levels in lead-exposed workers) (Tuppurainen et al. 1988). The authors offered four possible explanations for the apparent lack of effect of lead on thyroid function in children. Children may be less susceptible to the toxic effects of lead on the thyroid gland. However, this is not consistent with the greater susceptibility of children to the other toxic effects of lead (e.g., neurotoxicity). The lead-exposed workers had higher PbB levels than the children in this study (51.9 µg/dL versus 25 µg/dL). However, no effect on thyroxine was seen even in the children with PbB of $60 µg/dL. The workers had a longer duration of exposure (average exposure of 7.6 years versus 2.8 years in the children). T_4 levels may not be a sensitive enough indicator of thyroid function. On the other hand, the positive findings in the adults described above are of limited value because the authors did not control for confounding factors (such as preexisting conditions that may affect thyroid function or exposure to other chemicals).

The results of a study by Siegel et al. (1989) are consistent with the findings of Huseman et al. (1992) who examined a group of 12 children (2–5 years old) from the Omaha Lead and Poison Prevention Program with PbB levels in the range of 41 to 72 µg/dL. The authors found that basal TSH, prolactin, T_4 and T_3 were not affected by PbB. Also, TSH and prolacting responses to thyrotropin-releasing hormone, and cortisol responses to insulin were not altered by PbB. However, Huseman et al. (1992) did find that the peak human growth hormone (hGH) response to an L-dopa and insulin test, although within normal limits, was significantly lower in children with toxic levels of lead compared with the peak response in children with lower PbB levels (<30 µg/dL). Furthermore, the mean 24-hour hGH in children with high PbB was not only significantly lower than those of normal children, but was comparable with that of children with hGH neurosecretory dysfunction. High PbB levels were also associated with a lower mean insulin-like growth factor I.

Other Systemic Effects.

Effects on Vitamin D Metabolism. Lead interferes with the conversion of vitamin D to its hormonal form, 1,25-dihydroxyvitamin D. This conversion takes place via hydroxylation to 25-hydroxyvitamin D in the liver followed by 1-hydroxylation in the mitochondria of the renal tubule by a complex cytochrome P-450 system (Mahaffey et al. 1982; Rosen and Chesney 1983). Evidence for this effect comes primarily from studies of children with high lead exposure.

Lead-exposed children with PbB levels of 33–120 µg/dL had marked reductions in serum levels of 1,25-dihydroxyvitamin D (Rosen et al. 1980). Even in the range of 33–55 µg/dL, highly significant depressions in circulating 1,25-dihydroxyvitamin D were found, but the most striking decreases occurred in children whose PbB lead levels were >62 µg/dL. In addition, children with PbB levels of >62 µg/dL also had significant decreases in serum total calcium and ionized calcium and significant increases in serum parathyroid hormone. These conditions would tend to enhance production of 1,25-dihydroxyvitamin D; thus, the inhibition caused by lead may have been greater than was indicated by 1,25-dihydroxyvitamin D levels. Serum levels of 1,25-dihydroxyvitamin D returned to normal within 2 days after chelation therapy. These results are consistent with an effect of lead on renal biosynthesis of 1,25-dihydroxyvitamin D. A strong inverse correlation between 1,25-dihydroxyvitamin D levels and PbB was also found among children with PbB levels ranging from 12 to 120 µg/dL, with no change in the slope of the line at levels less than 30 µg/dL (Mahaffey et al. 1982).

However, results obtained by Koo et al. (1991) indicate that low to moderate lead exposure (average lifetime PbB level range of 4.9–23.6 µg/dL, geometric mean of 9.8 µg/dL, n=105) in young children with adequate nutritional status, particularly with respect to calcium, phosphorus, and vitamin D, has no effect on vitamin D metabolism, calcium and phosphorus homeostasis, or bone mineral content. The authors attribute the difference in results from those other studies to the fact that the children in their study had lower PbB levels (only 5 children had PbB levels >60 µg/dL and all 105 children had average lifetime PbB levels <45 µg/dL at the time of assessment) and had adequate dietary intakes of calcium, phosphorus, and vitamin D. They concluded that the effects of lead on vitamin D metabolism observed in previous studies may, therefore, only be apparent in children with chronic nutritional deficiency and chronically elevated PbB levels. Similar conclusions were reached by IPCS (1995) after review of the epidemiological data.

Effects on Growth. Since the report by Nye (1929) of runting in overtly lead-poisoned children, a number of epidemiological studies have reported an association between PbB levels and decreased growth in children, who take in lead primarily through the oral route (Johnson and Tenuta 1979). Although these findings in the early epidemiological studies were suggestive of an effect, many of the studies failed to control for possible confounding factors such as age, race, sex, or nutritional status. However, results from some more recent and better conducted epidemiological studies have suggested an association between PbB levels and decreased growth.

In a study that ruled out possible confounding effects of socioeconomic status on lead absorption, a set of biometric measurements (including stature and weight) for children with PbB levels of less than 30 µg/dL and for children with PbB levels of 40–60 µg/dL was compared (Lauwerys et al. 1986). When only the children #8 years old were considered, the results indicated that slight decreases in biometric values occurred in the high-lead group as compared with the lower-lead group. Huseman et al. (1992) found that in a small group of 6 children (2–5 years old) with PbB levels between 41 and 72 µg/dL the growth rate averaged 4.2 cm/year before chelation therapy, and 9.0 cm/year following chelation therapy.

Stronger evidence for an association between lead exposure and growth retardation is available in the analyses by Schwartz et al. (1986) of data for 2,695 children #7 years old from the NHANES II study. Stepwise multiple regression analyses indicated that PbB levels (range, 4–35 µg/dL) were a statistically significant predictor of children's height, weight, and chest circumference, after controlling for age, race, sex, and nutritional covariates. The strongest relationship was observed between PbB and height, with segmented regression models indicating no evident threshold for the relationship down to the lowest observed PbB level of 4 µg/dL. Parental stature was not considered as a variable, but analysis showed that age, sex, nutrition, and PbB level accounted for 91% of the variance in height. The authors concluded that the mean PbB level of the children at the average age of 59 months appeared to be associated with a reduction of approximately 1.5% in the height that would be expected if the PbB level had been zero. The impact on weight and chest circumference was of the same magnitude. This study is limited in that environmental factors (in particular parental smoking) were not controlled for.

PbB concentrations in the range of 2.8 to 40 µg/dL were related with decreased stature in a cohort of 1,454 Mexican-American children aged 5 to 12 who were participants in the Hispanic Health and Nutrition Examination Survey (HHANES) conducted in 1982–1984 (Frisancho and Ryan 1991). Height was

considered the dependent variable in the multiple regression analyses, and age, poverty index, hematocrit, hemoglobin, transferrin saturation, and blood lead were the independent variables. The mean PbB concentration in males and females was 10.6 and 9.3 µg/dL, respectively. Eighty-two percent of the variance in height in males was accounted for by hematocrit and PbB; in females the same 82% was accounted for by age, poverty index, and PbB. After adjusting for these covariates, children whose PbB levels were above the median for their age and sex (9–10 µg/dL range) were 1.2 cm shorter than children with PbB levels below the median.

In a preliminary report of a cohort study of Danish children of homogeneous social/ethnic background joining the first grade in 1982–1983, tooth lead was significantly associated with decreased height after controlling for other variables (e.g., child's medical history, dietary history, behavior, tobacco smoking of parent, and sociodemographic factors) (Lyngbye et al. 1987). Exposed children had tooth lead levels of greater than 18.7 µg/g, while controls had tooth lead levels less than 5 µg/g. The average PbB level in the exposed cohort was <60 µg/dL.

A retrospective study of the growth of 54 children from birth to 48 months of age was undertaken (Angle and Kuntzelman 1989). Children were initially chosen for the study based on finding high EP (>35 µg/dL) between 12 and 23 months of age. Blood lead levels were used to subdivide the children into 2 groups: the low-lead <30 µg/dL (n=24), and the high-lead $30 µg/dL (n=30). The two groups were comparable with respect to gender and skin color. None of the children were considered to have clinical signs of lead toxicity. The mean annual PbB level increased from 17.0±1.7 µg/dL at 12–23 months to 18.5±3.5 µg/dL at 35–48 months in the low-lead group. The mean annual PbB level decreased from 46.7±3.5 µg/dL at 12–23 months to 40.5±2.4 µg/dL at 35–48 months in the high-lead group. The mean EP level decreased with age in the low-lead children but remained consistently elevated in the high-lead children. The rate of weight gain was significantly increased at 15 months, and mean weight was significantly increased at 24 months in the high-lead group. Even though the high-lead children showed initial increased growth, analysis of the rates of height and weight gain from birth to 36 months showed a significant decrease in growth of high-lead children when compared to the low-lead group. The authors state that the increased growth rate at 15 months in the high-lead children is associated with increased food intake (particularly of finger foods), therefore increasing the probability of lead ingestion from dust on the fingers. The contribution of prenatal lead burden and iron deficiency to the growth patterns observed could not be determined. This study suggested that after an initial acceleration in growth, high PbB may be associated

with growth retardation, and that food and hand dust are among the primary sources of lead in the first year of life.

A study was conducted on 21 children, aged 18 to 36 months, to examine the potential relationship between the amounts of lead ingested in food and anthropometric measurements (height, weight, head circumference, and mid-upper arm circumference) (Stanek et al. 1998). The children resided in homes located in an urban area with potentially high lead levels. The main outcomes measured were lead contamination in food and on hands, and blood lead levels. The mean PbB concentration was 6.4 µg/dL, and the total intake of lead from food was 4.95 µg/day. Home-handled foods, canned foods, and hand-wipe lead were significant predictors of lead content in food. When the anthropometric measurements were compared with mean PbB levels, a negative relationship with head circumference was found. Regression analyses showed that, in addition to blood lead, total energy intake was significantly related to head circumference, suggesting possible nutritional influence. The influence of other factors such as prenatal care, nutrition, and genetics was also mentioned as being possibly responsible for the findings.

Two studies failed to establish an association between PbB levels and growth. In a study designed to look at the effect of lead exposure on stature (height and weight) among 104 high-lead subjects and 27 sibling controls, PbB did not affect growth or the genetic predisposition for eventual adult height (Sachs and Moel 1989). The high-lead subjects had PbB that ranged from 10 to 47 µg/dL, and their nonexposed sibling controls had PbB levels that ranged from 1 to 4 µg/dL. PbB levels, height, and weight were measured in 1974 (the year of their first post-treatment recall for evaluation, when the mean age was 8 years) and 1985 (the year of their sixth recall, when their mean age was 18 years). Between 70% and 77% of the high-lead subjects ranked in or above the 50th percentile for height in 1974; in 1985, 84% of the high-lead subjects ranked in or above the 50th percentile for height. These percentages were not different from those seen in the sibling controls.

A follow-up of the 260 infants from the Cincinnati cohort (see Section 2.2.1.6 for a description of this cohort) revealed that postnatal growth rates, measured as covariate-adjusted increases in stature from 3 to 15 months of age, were inversely correlated with postnatal increases in blood lead levels from 3 to 15 months of age (Shukla et al. 1987, 1989). This relationship was significant only for infants with relatively higher prenatal lead exposures (i.e., those whose mothers had prenatal PbB levels of $7.7 µg/dL). During the second and third years of life, 235 infants from this cohort were reevaluated

(Shukla et al. 1991). Mean PbB during the period of 18 to 33 months was chosen as an integrated index for lead exposure for this period. Mean PbB concentration for the cohort during this period was 17 µg/dL (range, 5.7–53.9 µg/dL); mean PbB levels during the period of 3 to 15 months was 11.8 µg/dL. Length measurements were conducted at 18, 21, 24, 27, 30, and 33 months. The results of the statistical analyses showed that mean PbB levels during the second and third years were negatively associated (p=0.002) with attained height at 33 months of age. However, this association was significant only among those children who had mean PbB levels greater than the cohort median ($10.8 µg/dL) during the 3–15 months interval. It also appeared that the effect of lead exposure (both prenatal and during the 3–15 month interval) was transient as long as subsequent exposure was not excessive.

Two sets of analyses were conducted on the data from the Cleveland Prospective Study to assess the association between PbB levels and size from a cohort of 359 mother-infant pairs (Greene and Ernhart 1991). The first analyses investigated the association between prenatal lead exposure and neonatal size measures as well as growth through the preschool years. The second analyses were concerned with the relationships between preschool PbB indices (at 6 months, 2 years, 3 years, and 4 years 10 months) and concurrent and subsequent measurements of weight, length, and head circumference. The possible interaction between prenatal and preschool lead exposure and its effect on reduced size were also studied. Weight, length, and head circumference were measured at birth and during five subsequent in-home visits; cord and maternal PbB levels were used as a measure of prenatal lead exposure, and preschool PbB samples were taken at 6 months, 3 years, and 4 years 10 months. The analyses controlled for a variety of possible confounding factors. Multivariate longitudinal analyses revealed no statistically significant effect of PbB levels on growth from birth through age 4 years 10 months.

The results from a study that examined the effect of chronic lead exposure on body mass index (BMI, weight in kg divided by the square of the height in meters), as well as on weight and height, have recently become available (Kim et al. 1995). The cohort consisted of children who attended first and second grades in the period between 1975 and 1978 in Chelsea and Somerville, Massachusetts, who were evaluated at a 13-year interval (see also Needleman et al. 1979 in Sections 2.2.1.4 and 2.2.1.6). A total of 236 subjects provided complete information for the study of cross-sectional relationship between dentin lead levels and physical growth in 1975–1978 (Study 1). Independent variables other than $\log_{10}$ dentin levels were age, sex, birth weight, and mother's socioeconomic status as of 1975–1978. Fifty-eight subjects provided data on the relationship between the dependent variable (change in physical growth between 1978–1978 and

1989–1990) and $\log_{10}$ dentin lead levels in 1975–1978 (Study 2). Also, 54 children provided information on the relationship between changes in growth between 1975–1978 and 1989–1990, and lead in bone (tibia, patella, or mean bone lead) in 1975–1978 (Study 3). Other independent variables adjusted in Studies 2 and 3 were age as of 1975–1978, age increase between 1975–87 and 1989–1990, sex, mother's socioeconomic status as of 1975–1978, and physical parameters (weight, height, or BMI). Analysis of the results showed that $\log_{10}$ dentin lead was significantly associated with BMI, but not with weight or with height, after controlling for age as of 1975–1978, sex, birth weight, and mother's socioeconomic status. Also, after adjusting for BMI as of 1975–1978, age increase, age as of 1975–1978, sex, and mother's socioeconomic status, $\log_{10}$ dentin lead was significantly associated with BMI change between 1975–1978 and 1989–1990. No significant associations were found between $\log_{10}$ dentin lead and weight, or between $\log_{10}$ dentin lead and height. Furthermore, no significant associations were observed between bone lead as of 1989–1990 and any of the changes in physical growth between 1975–1978 and 1989–1990. Further analysis of the results showed that a 10-fold increase in dentin lead level was associated with an increase of 1.02 kg/m^2 in BMI at the age of 7 years, and a 10-fold increase in dentin level was also associated with an increase in BMI change of 2.65 kg/m^2 from age 7 to age 20. Kim et al. (1995) indicate that because dentin lead level reflects chronic exposure to lead during the several years prior to shedding of teeth, the results suggest that children exposed to lead during childhood had greater BMI gain between age 7 and 20 than those less exposed.

2.2.1.3 Immunological Effects

The data on immunological effects in occupationally exposed humans following exposure to lead are inconsistent and limited, with some indication that lead may have an effect on the cellular component of the immune system, while the humoral component is relatively unaffected. Lead workers with PbB levels of 21–90 µg/dL (median, 55 µg/dL) had more colds and influenza infections per year and had a significant suppression of secretory IgA levels (Ewers et al. 1982). Secretory IgA is a major factor in the defense against respiratory and gastrointestinal infections (Koller 1985). Serum immunoglobulin levels were not significantly altered. Immune function in lead workers exposed occupationally for 4–30 years, whose PbB levels at the time of testing ranged from 25 to 53 µg/dL (mean, 38.4 µg/dL), was no different from controls whose PbB levels at the time of testing ranged from 8 to 17 µg/dL (mean, 11.8 µg/dL) (Kimber et al. 1986b). There were no differences between the workers and controls with regard to serum concentrations of IgG, IgA, or IgM and no correlation between PbB levels and serum immunoglobulin levels. In addition,

responses to the mitogen phytohemagglutinin (PHA) (a stimulator of T lymphocytes) and natural killer (NK) cell activity were not altered in workers compared with controls. Lymphocyte transformation (*in vitro*) and serum IgG and IgA levels were studied in 39 male lead storage battery workers who had exposure to lead oxides, in 10 age-matched nonexposed health volunteers, and in 9 nonexposed management personnel (Alomran and Shleamoon 1988). The length of exposure was not precisely specified, but the range was 0 to about 18 years. The mean PbB level in these workers had been previously shown to be 64 µg/dL, and the air concentration of lead oxide within the plant was reported to be 266 µg/m^3. No specifics were given regarding how this measurement was obtained. The lymphocytes from the exposed workers were significantly less responsive to stimulation by PHA and concanavalin A (con A) than those from the controls, and the severity of the depression was related to the duration of exposure. There was no effect on IgG and IgA levels.

Fischbein et al. (1993) examined the phenotypic parameters and functional integrity of peripheral blood lymphocytes in a group of 51 firearm instructors employed in the New York Metropolitan area. A group of 36 industrial workers with no known exposure to lead served as control subjects. Fifteen of the 51 firearm instructors had PbB levels $25 µg/dL (mean 31.4 µg/dL), whereas the rest had a mean PbB concentration of 14.6 µg/dL. The control group tested negative for lead. The results showed a significant decrease in percentage and number of $CD3^+$ and $CD4^+$ cells in the high-exposure group relative to the low-exposure group. In addition, cell-mediated immunity, assessed by the response of lymphocytes to T-cell mitogens and by the mixed-lymphocyte culture, was impaired in lead-exposed subjects. Other cell types including $CD8^+$, the B-lymphocyte, or the NK cells were not significantly altered relative to controls. The authors proposed that a likely mechanism for the observed lead effects may be its high affinity for the sulfhydryl groups on the surface receptors of the affected cell types.

A significant decrease in the number of $CD4^+$ cells as well as C3 and C4 complement levels among lead-exposed workers (n=25) relative to unexposed controls (n=25) was also reported by Ündeger et al. (1996). The mean PbB level in the exposed workers was 74.8 µg/dL (range, 38–100 µg/dL) compared to 16.7 µg/dL (range, 11–30 µg/dL) among the controls. The mean duration of exposure was 6 years (range, 0.5–15 years) These authors also found a significantly reduced number of T-helper lymphocytes and reduced serum IgG and IgM levels among the exposed workers. However, they found no significant alterations in the number or percentage of other subsets of peripheral lymphocytes such as T-suppressor, B

cells, and NK cells. No information was provided regarding the current or past health status of the exposed cohort.

Sata et al. (1998) did not find significant differences in the number or percentages of CD4+ or CD3+ cells between a group of 71 male workers engaged in the manufacturing of lead stearate who had a mean PbB level of 19 µg/dL (range, 7–50 µg/dL) and a control group of 28 workers with no known occupational exposure to lead (PbB levels in the controls were not measured). However, the exposed workers had a significant reduction in the number of $CD3^+CD45RO^+$ (memory T) cells and a significant increase in the percentage of $CD8^+$ cells compared with controls. Also, there was a significant correlation between the percentage of $CD3^+CD45RA^+$ cells and PbB levels in the exposed workers. At the time of the study, no subject had any signs or symptoms indicative of infection.

Pinkerton et al. (1998) evaluated a comprehensive panel of immunologic parameters among 145 lead-exposed male workers from a large secondary lead smelter in the United States with a median PbB level of 39 µg/dL (range, 25–55 µg/dL). A group of 84 unexposed workers with a mean PbB level of <2 µg/dL (range, 2–12 µg/dL) served as controls. The primary exposure at the smelter was lead. According to company monitoring data, air concentration of other metals was negligible. The mean age of the exposed workers was 32.9 years, and the mean duration of employment was 5.3 years. The following were considered candidate covariates: age, race, smoking habits, alcohol consumption, marijuana use, whether the subject worked first or second shifts, exposure to five or more hours of direct sunlight during the last week, cold or flu symptoms in the last week, and hours of sleep the evening prior to the test. The covariates for all final models were age, race, whether the subject worked first or second shifts, and current smoking status. The study found no significant differences in the percentages of $CD3^+$ cells, $CD4^+$ T cells, $CD8^+$ T cells, B cells, or NK cells between exposed and unexposed workers. In addition, there were no differences between exposed and unexposed workers in serum immunoglobulin levels, salivary IgA, C3 complement levels, or lymphoproliferative responses with tetanus toxoid. The study did find that on average, exposed workers had a significantly lower percentage of monocytes than unexposed workers, although the magnitude was small. Among exposed workers the percentage and number of B cells were positively associated with current blood lead level, serum IgG was negatively associated with cumulative lead exposure, and the percentage and number of $CD4^+/CD45RA^+$ cells was positively associated with cumulative lead exposure. Pinkerton et al. (1998) concluded that their results provided no evidence for a marked immunotoxic effect of lead at the exposure levels studied. They also suggested that differences

between their results and those of others, such as Fischbein et al. (1993) and Ündeger et al. (1996), may reflect methodological differences.

The data available on the immunologic effects of lead exposure on children are very limited. In a comparison of 12 preschool children having PbB levels $40 µg/dL and elevated FEP with 7 preschool children with lower PbB levels (14–30 µg/dL), it was found that there were no differences between groups with respect to complement levels, immunoglobulin levels, or antitoxoid titers following booster immunization with tetanus toxoid (Reigart and Graher 1976). The small number of children, the lack of unexposed controls, and the fact that PbB levels of up to 30 µg/dL were seen in the comparison group limit the conclusions that can be drawn from this report.

2.2.1.4 Neurological Effects

Neurological Signs and Symptoms in Adults. The most severe neurological effect of lead in adults is lead encephalopathy, which is a general term to describe various diseases that affect brain function. Early symptoms that may develop within weeks of initial exposure include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. The condition may then worsen, sometimes abruptly, to delirium, convulsions, paralysis, coma, and death (Kumar et al. 1987). Histopathological findings in fatal cases of lead encephalopathy in adults are similar to those in children (see discussion below).

Severe lead encephalopathy is generally not observed in adults except at extremely high PbB levels (e.g., 460 µg/dL [Kehoe 1961a]). Other data (Smith et al. 1938) suggest that acute lead poisoning, including severe gastrointestinal symptoms and/or signs of encephalopathy, can occur in some adults at PbB levels that range from approximately 50 to >300 µg/dL, but the data are somewhat ambiguous.

Occupational exposure to lead has often been associated with signs of neurotoxicity. The literature contains numerous case reports and small cohort studies that describe a higher incidence of these symptoms, including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, and paresthesia at PbB levels that range from approximately 40 to 120 µg/dL following acute-, intermediate-, and chronic-duration occupational exposure (Awad et al. 1986; Holness and Nethercott 1988; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Pasternak et al. 1989;

Pollock and Ibels 1986; Schneitzer et al. 1990). For example, significantly increased central and peripheral nervous system and gastrointestinal symptoms were reported among 25 lead workers with maximum PbB levels of 50–69 µg/dL and significantly increased central nervous system symptoms among 20 lead workers with maximum PbB levels <50 µg/dL (Haenninen et al. 1979). Controls (n=23) had average PbB levels of 11.9 µg/dL. In another study, no smelter workers with PbB levels of <40 µg/dL had signs or symptoms of lead intoxication, while 13% of the workers with PbB levels of 40–79 µg/dL had extensor muscle weakness or gastrointestinal symptoms (Baker et al. 1979).

A study comparing 288 lead-exposed workers (current or historical PbB level of >35 µg/dL) at 3 battery plants with 181 workers with current PbB level of #35 µg/dL at a truck frame plant reported a few differences in neurobehavioral or psychosocial indices (Parkinson et al. 1986). Because the lead-exposed workers were younger, less educated, employed for fewer years, and earned less income than the unexposed workers, the analysis adjusted for age, education, and income. Exposed workers had mean current, time-weighted average and peak PbB levels of 40.0, 48.8, and 78.8 µg/dL, respectively. PbB data for unexposed workers were not characterized in this manner. Exposed workers had an increase in the number of work-related accidents and poorer performance in a motor speed/manual dexterity test with the nondominant hand, and greater levels of conflict in interpersonal relationships as compared with unexposed workers. When multiple regression analyses were performed on the data for exposed workers, only the levels-of-conflict measure showed a significant dose-response relationship with current or cumulative PbB levels.

Twenty low-exposure men (mean blood lead level, 20.4 µg/dL; range, 11.1–27.1 µg/dL), 20 intermediate-exposure men (mean PbB level, 31.7 µg/dL; range, 26–35 µg/dL), and 20 men high-exposure men (mean PbB level, 52.5 µg/dL; range, 45–60 µg/dL) at an storage battery plant were studied (Campara et al. 1984; Zimmerman-Tanselia et al. 1983). Consistent and significant dose-response trends were observed in symptoms such as loss of appetite, paresthesia in lower limbs, weakness of upper limbs, and dropping of objects, with the most marked increases in neurological symptoms in the high-lead group (Zimmerman-Tanselia et al. 1983). In addition, the high-lead workers performed significantly less well on neuro-behavioral tests, with general performance on cognitive and visual-motor coordination tasks and verbal reasoning ability most markedly impaired (Campara et al. 1984).

The results of these studies showing neurological effects at lower exposure levels of lead indicate that the lowest levels for overt signs and symptoms of neurotoxicity in adults is in the range of 40–60 µg/dL. These neurological signs and symptoms occur at roughly the same PbB levels as do other overt signs and symptoms of lead intoxication, such as gastrointestinal complaints.

Behavioral Function in Adults. Neurobehavioral testing has revealed effects in adults at PbB levels (i.e., 40–80 µg/dL) below those causing encephalopathy (>400 µg/dL). Evaluations of occupationally exposed adults include several affected parameters at PbB levels between 40 and 80 µg/dL. Disturbances in oculomotor function (saccadic eye movements) in lead workers with mean PbB levels of 57–61 µg/dL were reported in a study by Baloh et al. (1979) with follow-up by Spivey et al. (1980) and in a study by Glickman et al. (1984). Deficits in hand-eye coordination and reaction time were reported in 190 lead-exposed workers (mean PbB level, 60.5 µg/dL) (NIOSH 1974). Most of the workers had been exposed for between 5 and 20 years. A similar study, however, reported no differences in arousal, reaction time, or grip strength between controls (mean PbB, 28±10 µg/dL) and workers who had been exposed to lead for 12±9.5 years (mean PbB level, 61±12 µg/dL) (Milburn et al. 1976). Disturbances in reaction time, visual motor performance, hand dexterity, IQ test and cognitive performance, nervousness, mood, or coping ability were observed in lead workers with PbB levels of 50–80 µg/dL (Arnvig et al. 1980; Haenninen et al. 1978; Hogstedt et al. 1983; Mantere et al. 1982; Valciukas et al. 1978).

As previously noted, Campara et al. (1984) found that workers with PbB levels of 45–60 µg/dL performed less well on neurobehavioral tests. Impaired memory and learning ability were observed in workers with time-weighted average PbB of 27–52 µg/dL (Hogstedt et al. 1983). In another study, impaired verbal concept formation, memory, and visual/motor performance and increased rates of depression, confusion, anger, fatigue, and tension were found among workers with PbB levels of >40 µg/dL (Baker et al. 1983). Similar findings were reported in a cohort of 43 Venezuelan workers from a lead smelter who had a mean employment duration of 4 years and a mean PbB concentration of 42 µg/dL (Maizlish et al. 1995). The workers were evaluated with the WHO neurobehavioral core test battery and the results showed a significant association between altered mood states and current, peak, and time-weighted average (TWA) blood lead levels. Other parameters such as memory, perceptual speed, reaction time, and manual dexterity tended to be poorer with increasing exposure, but the magnitude of the effect was small. A limitation of this study may be that fact that neither the subjects nor the interviewers were blinded to the exposure results.

No neurobehavioral effects were seen in 288 randomly selected males who were occupationally exposed to lead as compared to 181 demographically similar controls (Ryan et al. 1987). The mean PbB level in the exposed workers was 40.1 µg/dL and that of the controls was 7.2 µg/dL. Nineteen tests of neuropsychological performance were conducted. The lead-exposed workers performed no differently from controls on all measures except psychomotor speed and manual dexterity. The authors discounted this difference due to the observation that conflicting results were obtained in two different tests of motor speed and manual dexterity and possible confounding effects of age. There was no evidence that history of previous very high exposure had any effect on performance.

Ninety-one workers divided into three groups based on PbB levels (<20 µg/dL, 21–40 µg/dL, 41–80 µg/dL) underwent a battery of neuropsychological testing including syntactic reasoning, serial reaction time, category search, visual spatial memory, and category search recall (Stollery et al. 1989). They also completed a mood checklist. There was no significant difference in mood in the three exposure groups. Workers with high PbB concentrations showed evidence of impairment on tests of serial reaction time and category search, with only weak impairment on tasks measuring syntactic reasoning and delayed verbal free recall. In general, the magnitude of the impairment correlated with PbB levels. The impairment of serial reaction time was the best predictor of PbB levels. A follow-up evaluation of 70 these workers confirmed the results of the previous study (Stollery et al. 1991). The main deficit was a slowing of sensory motor reaction time, which was seen most clearly when the cognitive demands of the task were low. The response tended to be restricted to workers in the high PbB level group. A subsequent study examined the performance of the 70 workers on a five-choice unprepared reaction time test to elucidate the basis for the slowing (Stollery 1996). Performance was assessed by analyzing the distributional properties of correct reaction times. The results showed that lead impaired both the speed of making simple movements, as well as decisions, and suggested that decision slowing is due to central rather than peripheral factors. Limitations of these studies include the fact that there were no lead-free controls, subjects had variable durations of exposure, and only cross-sectional exposure data were available (i.e., no history of PbB levels in the past were available).

One study has reported effects on neurobehavioral function in lead-exposed workers at mean PbB levels of 50 µg/dL (Williamson and Teo 1986). Neurobehavioral function was measured using tests that are based on information processing theory in 59 lead workers and 59 controls matched for age, type of job, time on the job, education level, smoking history, and alcohol consumption. Statistically significant decreases in

the lead-exposed workers were seen for critical flicker fusion reaction, simple reaction time, tracking speeds, hand steadiness tests, and sensory store memory. Sensory store memory speed showed a low but statistically significant correlation with PbB concentrations. Measurements of neurobehavioral function seemed well chosen, and repeated measures with associated appropriate statistics were used. The performance of the lead-exposed workers was significantly impaired. The critical flicker fusion threshold may reflect retinal or intermediate visual pathway function as well as cortical arousal.

A recent study examined the correlation between short- and long-term measures of exposure to lead and performance on neuropsychological tests among a group of 467 Canadian male lead smelter workers (Lindgren et al. 1996). The current PbB concentration was 27.5 µg/dL, and mean duration of employment was 17.7 years. Three measures of exposure were evaluated: current PbB concentration, time-weighted average (TWA), and time integrated blood lead (IBL), a cumulative dose estimate. Based on these three measures estimates, the workers were divided into exposure terciles. Multivariate analyses of the covariance showed that none of the three measures of exposure were significant. When years of employment, a suppressor variable (a variable which improves the overall predictive validity of another variable by removing irrelevant variance) was included as a covariate, IBL exposure groups differed significantly in 5 of the 14 neuropsychological variables. The affected neuropsychological variables tested primarily visuomotor skills. Lindgren et al. (1996) indicated that the lack of an association between current blood lead or TWA PbB and neuropsychological performance was not necessarily inconsistent with other studies that found such an association since in their study the current mean PbB levels were lower than in other studies. Current PbB as well as TWA blood lead may have lacked the sensitivity to detect the decrement in performance.

In summary, in studies where adults were exposed occupationally to lead, a number of neurobehavioral parameters were affected. Current PbB levels in these workers were between 40 and 80 µg/dL. However, some measures of cumulative exposure may be better predictors of impaired performance in workers with current PbB levels <40 µg/dL.

The effects of lead exposure on cognitive dysfunction in nonoccupational cohorts of older persons has been evaluated in two recent studies. Muldoon et al. (1996) conducted a wide range of cognitive tests designed to assess memory, language, visuospatial ability, and general intellectual status, as well as sensorimotor function in a group of 530 female participants in the Study of Osteoporotic Fractures. The cohort

consisted of 325 rural dwellers and 205 urban dwellers with geometric mean PbB concentrations of 4.5 µg/dL and 5.4 µg/dL, respectively; the overall range was 1–21 µg/dL. The corresponding mean ages were 71.1 and 69.4 years. For the group, the scores on the various tests were average, consistent with normal values reported for older women. Analyses of the relationship between PbB concentrations and neuropsychological function showed significant inverse associations with performance only among the rural dwellers. After adjusting for age, education, and tobacco and alcohol consumption, women with blood levels $8 µg/dL performed significantly worst in tests of psychomotor speed, manual dexterity, sustained attention, and mental flexibility than women with PbB concentrations #3 µg/dL. Similar results were found for reaction time tests after further adjusting for history of diabetes and/or arthritis. Muldoon et al. (1996) stated that the reason for the inconsistency between the urban and rural cohorts is unclear; however, the results suggest that factors other than lead have a bigger influence in the outcomes measured. A similar study was conducted in a cohort of 141 men participants in the NAS (Payton et al. 1998). In this study, in addition to PbB levels, lead in bone (tibia and patella) was also measured. The mean PbB concentration among the participants was 5.5 µg/dL (range not provided), and the mean age was 66.8 years. Tibial and patellar bone lead showed a stronger correlation with each other than either of them with blood lead. After adjusting for age and education, the results showed that men with higher levels of blood lead recalled and defined fewer words, identified fewer line-drawn objects, and required more time to attain the same level of accuracy on a perceptual comparison test as men with the lowest level of PbB. In addition, men with higher blood and tibial lead copied spatial figures less accurately, and men with higher tibial lead had slower response for pattern memory. Payton et al. (1998) stated that the results are consistent with the hypothesis that even within the relatively low range of exposure, higher levels of blood lead are associated with poorer performance on some cognitive tests. The results showed that PbB was the strongest predictor of performance on most tests. Also of interest was the finding that lead in the tibia, which changes at a slower rate, showed more significant relationships with cognitive test scores than patellar bone lead, which changes more rapidly. Limitations of the study recognized by the authors included the possibility of unknown confounders, the greater error associated with bone lead measurements compared with PbB measurements, and the need for a greater number of participants with higher PbB to minimize Type II errors.

Peripheral Nerve Function in Adults. There are numerous studies available on peripheral nerve function that measured the conduction velocity of electrically stimulated nerves in the arm or leg of lead workers. The most important studies are summarized below. In prospective occupational studies,

decreased nerve conduction velocities (NCVs) were found in workers with PbB levels of 30–48 µg/dL (Seppalainen et al. 1983), but another study found no significant differences in NCVs in workers with PbB levels of 60–80 µg/dL, relative to controls (Spivey et al. 1980). Decreased NCVs were seen in the median (motor and sensory) and ulnar (motor and sensory) nerves of newly employed high-exposure workers after 1 year of exposure and in the motor nerve conduction velocity of the median nerve of this group after 2 or 4 years of exposure (Seppalainen et al. 1983). Although the severity of the effects on NCV appeared to lessen with continued exposure, several of the high-exposure workers in this study quit 1 or 2 years after starting. Thus, the apparent improvement in NCVs may have been due to a healthy worker effect. A similar healthy worker effect may have accounted for the negative results of Spivey et al. (1980) who tested ulnar (motor and slow fiber) and peroneal (motor) nerves in 55 workers exposed for 1 year or more. The studies differed in design; one prospectively obtained exposure history, while the other did it retrospectively. The end points that were measured also differed; Spivey et al. (1980) did not test the median nerve, which was the most sensitive end point in the study by Seppalainen et al. (1983).

In cross-sectional occupational studies, significant decreases in NCVs were observed in fibular (motor) and sural (sensory) nerves as a function of PbB levels with duration of exposure showing no effect (Rosen and Chesney 1983). In another study, decreases in NCVs of ulnar (sensory, distal) and median (motor) nerves were seen primarily at PbB levels of >70 µg/dL (Triebig et al. 1984). Duration of exposure and number of lead-exposed workers in these 2 studies were 0.5–28 years and 15 workers (Rosen and Chesney 1983), and 1–28 years and 133 workers (Triebig et al. 1984). Results of an earlier study by Araki et al. (1980) suggest that the decrease in NCV is probably due to lead since median (motor) NCVs in workers with a mean PbB level of 48.3 µg/dL were improved significantly when PbB levels were lowered through $CaNa_2EDTA$ chelation therapy.

There is suggestive evidence indicating that the changes in NCV associated with lead exposure may be transient. Muijser et al. (1987) investigated the effects of a 5-month exposure to lead during the demolition of a steel structure coated with lead-based paints. The motor and sensory nerve conduction velocities were measured in the median and ulnar nerves of eight exposed workers and compared with unexposed referents as well as themselves at 3 and 15 months after the termination of exposure. The mean PbB levels in the exposed workers were 82.5±18.9 µg/dL at the termination of exposure, 50.3±9.9 µg/dL 3 months after the termination of exposure, and 29±11.8 µg/dL 15 months after the termination of exposure. Following termination of the exposure, the motor nerve conduction velocity and distal motor latency were slowed as

compared to the referents. However, the distal sensory conduction velocity was not affected by lead exposure. Three months after exposure, these affected parameters showed improvement, and 15 months after exposure were not different from the referents. These results suggest that a limited (5-month) exposure to lead results in NCV deficits that are specific to motor nerves and are reversible in nature.

The results of these studies indicate that NCV effects occur in adults at PbB levels <70 µg/dL, and possibly as low as 30 µg/dL. Ehle (1986), in reviewing many of the studies of NCV effects, concluded that a mild slowing of certain motor and sensory NCVs may occur at PbB levels below 60 µg/dL, but that the majority of studies did not find correlations between PbB and NCV below 70 µg/dL and that slowing of NCV is neither a clinical nor a subclinical manifestation of lead neuropathy in humans. Ehle (1986), however, did not cite or analyze the studies by Rosen and Chesney (1983) or Seppalainen et al. (1983). Other reviewers have pointed out that decreases in NCV are slight in peripheral neuropathies (such as that induced by lead) that involve axonal degeneration (Le Quesne 1987), and that although changes in conduction velocity usually indicate neurotoxicity, considerable nerve damage can occur without an effect on conduction velocity (Anderson 1987). EPA (1986a) noted that although many of the observed changes in NCV may fall within the range of normal variation, the effects represent departures from normal neurological functioning. NCV effects are seen consistently across studies and although the effects may not be clinically significant for an individual, they are significant when viewed on a population basis. This is further supported by the meta analysis of effects of lead exposure on NCV conducted by Davis and Svendsgaard (1990).

More recent studies have also produced mixed results. Chia et al. (1996a) measured NCV in a group of 72 male workers from a lead battery manufacturing factory and 82 unexposed referents. Measurements of NCV in the median and ulnar nerves, as well as of blood lead were performed every 6 months over a 3-year period. Of the 72 original workers and 82 referents, only 28 and 4, respectively, completed the 3-year period. The geometric mean PbB concentration for the exposed workers at the beginning of the study was 36.9 µg/dL compared to 10.5 µg/dL for the referents; the mean for the 28 workers who completed the study was 39.7 µg/dL. Baseline measurements revealed significant slower NCV in workers, mostly in the median nerve. Serial measurements in the exposed workers over the 3-year period showed a peak in PbB in the third test which was followed by a decrease in median sensory conduction velocity and ulnar sensory nerve conduction velocity in the fourth test. Evaluation at the end of the study of the 28 workers who completed the 3-year period showed significant associations between PbB and 5 out 8 parameters

measured. The same was observed when only workers with blood lead concentrations of $40 µg/dL were included in the analysis, but no significant association was found among workers with PbB concentrations of <40 µg/dL. Ishida et al. (1996) found no significant association between PbB concentrations in the range of 2.1 µg/dL to 69.5 µg/dL and median nerve conduction velocity among a group of 58 male and 70 female ceramic painters. They also found no significant association between blood lead and a test designed to measure parasympathetic function. However, they did find a significant association between lead and an indirect measure of sympathetic function, but could not conclude that the alteration in test result with increasing blood lead truly reflected sympathetic nerve dysfunction. Yeh et al. (1995) evaluated nerve conduction velocity and electromyographic (EMG) activity in a group of 31 workers from a battery recycling factory and 31 sex and age matched controls. The mean duration of exposure to lead was 30.4 months and the mean PbB concentration was 63 µg/dL (range, 17–186 µg/dL). Eighty percent of the workers (n=25) had extensor weakness of the distal upper limbs and six of these workers had weakness in dorsiflexion of the foot; data for the control group were not provided. These 25 workers were classified as the lead neuropathy subgroup and the remaining 6 as the lead exposure subgroup. Studies of motor nerve conduction experiments showed a significantly increased distal latency in the median nerve from exposed workers relative to controls, but no such effect was seen in the ulnar, peroneal, and tibial nerves. Studies of sensory nerve conduction did not reveal any significant differences between exposed and control workers. Ninety-four percent of the exposed workers had abnormal EMG, but no mention was made regarding the control group. After controlling for age and sex, the authors found a significant positive association between an index of cumulative exposure to lead (ICL) and the distal motor latencies of tibial nerves and significant negative association between ICL and the NCVs of sural nerves. No correlation was found between current PbB or duration of exposure and neurophysiological data.

Effects on Other Neurological End Points in Adults. Recent studies have provided evidence that exposure to lead affects postural balance. For example, Chia et al. (1996b) evaluated the possible association between postural sway parameters and current PbB concentration, cumulative PbB at different years of exposure, and an index of total cumulative exposure to lead in a group of 60 workers; 60 unexposed subjects served as a control group. The current PbB concentrations were 36 µg/dL (range, 6.4–64.5 µg/dL) among the workers and 6.3 µg/dL (range, 3.1–10.9 µg/dL) among the referents. Exposed and referents differed significantly in postural sway parameters when the tests were conducted with the eyes closed, but not with the eyes open. Analyses of Pearson's correlation coefficients showed that postural sway parameters were not significantly correlated with current PbB concentration or with total cumulative

lead exposure, but a significant correlation existed with cumulative exposure the 2 years prior to testing. Also, some parameters had a significant correlation with cumulative lead exposure during the 9 years before the tests were conducted. Further analysis showed that the association observed with the previous 2-year exposure was not affected by the group of workers with longer exposure. The authors speculated that the lack of correlation between postural sway and cumulative lead exposure could be due to underestimation of cumulative exposure and/or to the effects of lead being reversible. A similar study of 49 male lead workers employed at a chemical factory producing lead stearate found that an increase in postural sway with the eyes open in the anterior-posterior direction observed in exposed workers was related to current PbB levels (18 µg/dL) (Yokoyama et al. 1997). Also, an increase in sway with the eyes closed in the right-left direction was significantly related to the mean blood concentration in the past. According to Yokoyama et al. (1997), the change in the vestibulo-cerebellum seemed to reflect current lead absorption, whereas the change in the anterior cerebellar lobe reflected past lead absorption.

No significant association was found between exposure to lead and the latencies of visual and brainstem auditory evoked potentials in a group of 36 female glass workers (Murata et al. 1995). The mean PbB concentration among the workers was 55.6 µg/dL (range, 25.8–79.3 µg/dL) and the mean exposure duration was 7.8 years. On the other hand, parameters of peripheral autonomic function, assessed as electrocardiographic R-R interval variability, were significantly depressed compared to a group of 17 referents with no known occupational exposure to lead. However, another study found no significant alterations on the R-R interval variability among lead workers with a mean PbB concentration of 20.9 µg/dL (range, 4.4–39.0 µg/dL) (Gennart et al. 1992a).

Neurological Signs and Symptoms in Children. High-level exposure to lead produces encephalopathy in children. The most extensive compilation of dose-response information on a pediatric population is the summarization by NAS (1972) of unpublished data from the patient populations reported in Chisolm (1962, 1965) and Chisolm and Harrison (1956). This compilation relates the occurrence of acute encephalopathy and death in children in Baltimore, Maryland, to PbB levels determined by the Baltimore City Health Department between 1930 and 1970. Other signs of acute lead poisoning and blood lead levels formerly regarded as asymptomatic were also summarized. An absence of signs or symptoms was observed in some children at PbB levels of 60–300 µg/dL (mean, 105 µg/dL). Acute lead poisoning symptoms other than signs of encephalopathy were observed at PbB levels of approximately 60–450 µg/dL (mean, 178 µg/dL). Signs of encephalopathy such as hyperirritability, ataxia, convulsions, stupor, and

coma were associated with blood lead levels of approximately 90–800 µg/dL (mean, 330 µg/dL). The distribution of PbB levels associated with death (mean, 327 µg/dL) was virtually the same as for levels associated with encephalopathy.

Additional evidence from medical reports (Bradley and Baumgartner 1958; Bradley et al. 1956; Gant 1938; Rummo et al. 1979; Smith et al. 1983) suggests that acute encephalopathy in the most susceptible children may be associated with PbB levels in the range of 80–100 µg/dL. However, a recent study reported 19 cases of acute encephalopathy in infants of mean age 3.8 months and with mean PbB levels of 74.5 µg/dL (range, 49.7–331 µg/dL) following use of traditional medicines containing lead (surma, Bint al Thahab) (Al Khayat et al. 1997a). Seven cases had PbB levels #70 µg/dL. In this report, lead level at 2 months post chelation was a significant predictor of abnormal neurological outcome.

Histopathological findings in fatal cases of lead encephalopathy in children include cerebral edema, altered capillaries, and perivascular glial proliferation. Neuronal damage is variable and may be caused by anoxia (EPA 1986a).

Numerous studies clearly show that childhood lead poisoning with encephalopathy results in a greatly increased incidence of permanent neurological and cognitive impairments. Additional studies indicate that children with symptomatic lead poisoning without encephalopathy (PbB level, >80–100 µg/dL) also have an increased incidence of lasting neurological and behavioral damage.

Behavioral Function in Children. A number of studies of asymptomatic children with relatively high lead body burdens have been published. These children were identified through lead screening programs or other large-scale programs focusing on mother-infant health relationships and early childhood development. Studies that were conducted rigorously enough to warrant consideration of their findings were those of de la Burde and Choate (1972, 1975), Ernhart et al. (1981), Kotok (1972), Kotok et al. (1977), and Rummo et al. (1979). These studies found that, in general, groups with high lead exposure performed less well on IQ or other psychometric tests than did referent control groups with lower lead exposures. Some of these studies did not control for important confounding variables, such as parental IQ or educational background; when reanalyzed taking these variables into account, the authors found that differences between lead-exposed and control children were reduced or lost statistical significance. In addition, many of the referent control groups tended to have what are now recognized to be elevated PbB

levels (averaging 20–40 µg/dL, or 55 µg/dL in the case of Kotok [1972]). Nevertheless, the consistent pattern of lower IQ values and other neuropsychologic deficits among the children exposed to higher lead levels in these studies indicates that cognitive deficits occur in apparently asymptomatic children with markedly elevated PbB levels (starting at 40–60 µg/dL and ranging up to $70–200 µg/dL).

The average decrement of approximately 5 IQ points observed in studies by de la Burde and Choate (1972), and Rummo et al. (1979), described in more detail below, represents a reasonable estimate of the magnitude of full-scale IQ decrements associated with markedly elevated PbB levels (mean: approximately 50–70 µg/dL) in asymptomatic children.

A mean Stanford-Binet IQ decrement of 5 points, fine motor dysfunction, and altered behavioral profiles were found in 70 preschool children exhibiting pica for paint and plaster and elevated PbB levels (>40 µg/dL, mean of 58 µg/dL), when compared with results for matched control subjects not engaged in pica for paint and plaster (de la Burde and Choate 1972). A follow-up study on these children (ages 1–3 years) at 7–8 years of age (de la Burde and Choate 1975) reported a mean Wechsler Intelligence Scale for Children (WISC) full-scale IQ decrement of 3 points and impairment in learning and behavior, despite decreases in PbB levels since the original study. These studies, however, did not report the PbB levels in controls.

Additional evidence of lead-induced decrement in children's IQ was provided by Rummo et al. (1979) who observed hyperactivity and a decrement of approximately 16 IQ points on the McCarthy General Cognitive Index (GCI) among children who had previously had encephalopathy and whose average maximum PbB levels at the time of encephalopathy were 88 µg/dL (average PbB level, 59–64 µg/dL). Asymptomatic children with long-term lead exposures and average maximum PbB levels of 68 µg/dL (average PbB level, 51–56 µg/dL versus 21 µg/dL in a control group) had an average decrement of 5 IQ points on the McCarthy GCI. Their scores on several McCarthy Subscales were generally lower than those for controls, but the difference was not statistically significant (at $p<0.05$). Children with short-term exposure and average maximum PbB levels of 61 µg/dL (average PbB level, 46–50 µg/dL) did not differ from controls. PbB levels in the referent group averaged 21 µg/dL, which is high for so-called “controls.” In these studies, the environmental exposure levels and the durations of lead exposure were not reported.

A number of general population studies available evaluated asymptomatic children with lower lead body burdens than those evaluated in the above studies. Some of these studies provide evidence of an association between neurobehavioral effects and the relatively low body burdens of lead representative of general pediatric populations. The effects of PbB on IQ may have major implications for public health when considered on a population basis as discussed by Davis and Svendsgaard (1987) and Grant and Davis (1989). A study of 158 first- and second-grade children by Needleman et al. (1979) provides evidence for the association of full-scale IQ deficits of approximately 4 points and other neurobehavioral defects with tooth dentin lead values that exceed 20–30 ppm. Corresponding average PbB values would probably range from 30 to 50 µg/dL (EPA 1986a). In comparison with children having low dentin lead levels (<10 ppm), children having high dentin lead levels (>20 ppm) had significantly lower full-scale WISC-Revised scores; IQ deficits of approximately 4 points; and significantly poorer scores on tests of auditory and verbal processing, on a test of attentional performance as measured by reaction time under conditions of varying delay, and on a teachers' behavioral rating. The frequency of non-adaptive classroom behavior as rated by teachers increased in a dose-related fashion to dentin lead levels (Needleman et al. 1979). The distribution of verbal IQ scores was shifted downward in the high-lead group, such that none of the children in the high-lead group had verbal IQ scores of >125, whereas 5% of the children in the low-lead group had verbal IQ scores of >125. Furthermore, children in the high-lead group were three times more likely to have verbal IQ scores of <80 than were children in the low-lead group. Using regression analysis, Bellinger and Needleman (1983) found that IQ scores of children in the high-lead group (with >20 ppm dentin lead) fell below those expected based on their mothers' IQ scores and that the amount by which a child's IQ fell below the expected IQ increased with increasing dentin lead levels in a nonlinear manner. These data indicate that dentin lead level was not significantly correlated with IQ residuals in the low-lead children (with >10 ppm dentin lead) or in the high-lead children (with 20–29.9 ppm dentin lead) but was significantly correlated with IQ residuals in high-lead children with 30–39.9 ppm dentin lead.

The study by Needleman et al. (1979) has been reanalyzed in additional reports (Bellinger and Needleman 1983; Needleman et al. 1985) and critically evaluated by EPA, as well as by other investigators.

In a later study, a subset (n=132) of a cohort of children studied as primary school students was reexamined as young adults (mean age, 18.4 years) (Needleman et al. 1990). Neurobehavioral functioning had been

found to be inversely related to dentin lead levels at the earlier examination (see discussion above). When the 132 were reexamined 11 years later, impairment of neurobehavioral function was still found to be related to the lead content of teeth shed at the ages of 6 and 7 years. In this study, higher lead levels in childhood were significantly associated with lower class standing in high school, increased absenteeism, lower grammatical-reasoning scores, lower vocabulary, poorer hand-eye coordination, longer reaction times, and slower finger tapping. However, no significant associations were found with the results of 10 other tests of neurobehavioral functioning. These later effects could stem from a poor academic start as opposed to effects of lead exposure; however, it could also be that the early lead exposure resulted in long-term consequences.

Other investigators have also found that parameters of neurobehavioral function are associated with tooth lead levels. A cross-sectional cohort of school children in first grade was ascertained in the city of Aarhus, Denmark (Hansen et al. 1989), where the population is very homogeneous with regard to ethnicity and language. A total of 2,412 children were contacted and asked to contribute a shed deciduous tooth. A total of 1,291 children responded (response rate = 54%). Lead was determined in the circumpulpal dentin and averaged 10.7 µg/g. A nested case-control study was set up within this cohort. Children with lead levels above 18.7 µg/g (n=110) were matched by sex and socioeconomic status with children with levels <5.0 µg/g in order to identify risk factors for exposure to lead. The cases and controls were reviewed and excluded if risk factors (other than lead) for neurobehavioral effects were present. Psychometric tests were administered to 162 children. The high-lead children scored lower on the WISC than the low-lead controls. No significant difference was seen between the high- and low-exposure groups on the Performance IQ and on several experimental tests. Impaired function associated with lead exposure was also found on the Bender Visual Motor Gestalt Test ($p<0.001$) and on a behavioral rating scale ($p<0.01$). These results suggested that some children may be affected in neuropsychological functioning at low lead levels seen in minimally polluted areas. A group of 141 children from this cohort were reassessed at age 15 (Damm et al. 1993). At this time, mean dentin lead levels in the low- and high-lead groups were unchanged from the values obtained when the children were 8 years old. At age 9, the geometric mean of the PbB concentration was 5.7 µg/dL in 78 children from the high-lead group and 3.7 µg/dL in 83 children from the low-lead group. Analysis of the results showed that most differences observed between the low-lead group an high-lead group observed at age 8 years had decreased to nonsignificant levels. However, in children with a history of neonatal jaundice, increased lead exposure was associated with mild neurobehavioral deficits, as indicated by lower verbal IQ and decreased visuomotor coordination. The authors indicate that although neonatal jaundice in this study did not exceed levels indicating clinical intervention, hyperbilirubinemia or some other factor associated with it may have reduced the threshold to lead neurotoxicity.

The possible relationship between children's behavior and levels of lead in hair has also been investigated. The study cohort consisted of 277 first grade students (51% male, 96% white) enrolled in the public schools in a western Massachusetts city (Tuthill 1996). The study location had no known problem with heavy metals. The children's behavior in the classroom was evaluated by the teachers as they completed the abbreviated Boston's Teachers Rating Scale (ABTR) and by the parents, who completed a short questionnaire. According to Tuthill (1996), the ABTR scale identifies children's inability to focus attention in a relatively structured classroom learning situation. Each child provided approximately 0.5 g of hair from the nape of the neck. Cut pieces of hair were thoroughly washed to rule out external contamination. The concentration of lead in hair ranged form <1 µg/g to 12 µg/g. The high lead group was defined as those whose hair had $3 µg lead/g; this group contained approximately the upper quartile of hair lead levels and teacher deficit ratings. The results of unadjusted data showed a strong association between high lead concentration in hair and high deficit teacher ratings. Gender and ethnicity were also found to be related to both lead level and teacher's scores. Controlling for gender, ethnicity, child's age, education and occupation of main wage earner, and socioeconomic status did not reduce the original association below the level of statistical significance. In a final logistic regression model into which gender, ethnicity, age, and socioeconomic status were forced before lead level, gender and hair lead levels were the only two significant variables that accounted for the variance in teacher's attention-deficit ratings. While only 13.5% of children with hair lead below 1 µg/g had high deficit scores, 62.5% in the highest group with $6 µg/g had high deficit scores. The results showed also a strong association between hair lead levels and the diagnosis of attention deficit hyperactivity disorder (prevalence odds ratio of 4.41). Although the results of this study point to an association between hair lead and altered behavior, it should be noted that hair is not considered a valid marker of lead exposure due to the extensive contamination possibilities and the extent to which it relates to other usual markers of lead is not clear (Tracqui et al. 1994).

The association between lead burden, assessed by K X-ray fluorescence spectroscopy of the tibia, and social adjustment was evaluated by Needleman et al. (1996). From a population of 850 boys in the first grade at public schools, 503 were selected on the basis of a risk scale for antisocial behavior, and 212 of these children (31% white) were analyzed in the study. Reports of antisocial behavior came from the parents, teachers, and the subjects themselves at 7 and 11 years of age. Also evaluated in relation to bone lead were attentional function, neurobehavioral, and academic performance. To minimize confounding, the authors controlled for nine relevant social and economic variables covering the areas of maternal intelligence, socioeconomic status, and quality of children rearing. Bone lead measures and psychological measures

were determined at the mean age of 10.2 years and again at the mean age of 12 years. After adjustment for covariates, the results showed borderline associations between teachers' aggression, delinquency, and externalization scores and bone lead at 7 years of age. At age 11, the parents reported a significant association between lead and somatic complaints and delinquent, aggressive, internalizing, and externalizing behavior. Also at age 11, teachers reported significant increases in scores associated with bone lead on somatic complaints, anxious/depressed, social problems, attention problems, delinquent behavior, aggressive behavior, internalizing, and externalizing. In addition, high-lead subjects reported higher scores in self-reports on delinquency and were more likely to obtain worse scores on all items of the Child Behavior Checklist during the 4-year period of observation. Lead concentration in bone was found to be positively related to verbal and full-scale IQ, but social rearing factors were much more influential than lead. This study has been criticized on the basis of uncertainties related to the X-ray fluorescence technique, lack of control for factors such as parental supervision and discipline and parent criminality.

The relationships between current and long-term indicators of lead exposure were studied to establish which indicator correlated best with psychometric test scores, and to determine the most suitable neurological test to evaluate the early effects of low-level lead exposure (Bergomi et al. 1989). Children (131 males and 106 females), whose average age was 7 years 8 months, living in an area of northern Italy with a high density of ceramics factories were chosen. The daily air levels of lead decreased from 2.4–3.8 μg/m^3 in 1975 to 0.20–1.81 μg/m^3 in 1985, the year of the study. The biological indicators of lead exposure measured in this study were PbB, tooth lead, hair lead, and ALAD activity. The following psychometric tests were conducted: WISC-Revised IQ, including two verbal and two performance tests; Bender Gestalt test to assess visual-motor performance; Trail Making test to evaluate visual-motor and sequential ability; Toulouse Pieron cancellation test to evaluate ability in figure identification, discrimination, and attention; and a test for delayed reaction time. The influence of potentially confounding variables (e.g., age, sex, and parental socioeconomic status) was evaluated and accounted for in the regression analyses that were performed. Higher levels of hair and tooth lead and the IQ test were found to be affected by socioeconomic status. The geometric means of PbB, hair lead, and tooth lead were 11.0 μg/dL, 6.8 μg/g, and 6.1 μg/g, respectively. Mean ALAD activity was 51 milliunits (mU)/mL red blood cells. Statistical analyses revealed that total and verbal WISC-R IQ and Toulouse Pieron test results were negatively correlated with levels of lead in teeth. ALAD values were also related to WISC-R IQ scores. The most predictive measure of lead exposure was tooth lead (which is indicative of chronic lead exposure). Blood lead (which is indicative of recent exposure) and hair lead (which is indicative of short-term exposure) were of little or no

predictive value. These results indicate that neuropsychological impairment is associated with long-term lead exposure. Limitations of this study include the fact that there was no control for parental IQ and HOME scores.

Schroeder et al. (1985) and Schroeder and Hawk (1987) evaluated 104 black children of lower socio-economic status at ages 10 months to 6.5 years, using the Bayley Mental Development Index (MDI) or Stanford-Binet IQ Scale. Hierarchical backward stepwise regression analyses indicated that PbB levels (range: 6–59 µg/dL) were a significant source of the variance in IQ and MDI scores after controlling for socioeconomic status and other factors. Fifty of the children were examined again 5 years later, at which time PbB levels were #30 µg/dL. The 5-year follow-up IQ scores were inversely correlated with contemporary and initial blood lead levels, but the effect of lead was not significant after covariates, especially socioeconomic status, were included in the analysis.

The above study was replicated later with 75 asymptomatic black children, 3–7 years old, of uniformly low socioeconomic status (Hawk et al. 1986; Schroeder and Hawk 1987). Backward stepwise multivariate regression analysis revealed a highly significant negative linear relationship between Stanford-Binet IQ scores and contemporary PbB levels over the entire range of 6–47 µg/dL (mean, 20.8 µg/dL). The association was nearly as striking when past maximum or mean blood lead levels were used. Because socioeconomic status was uniformly low, it was not a significant covariate. These results indicate that it may be much easier to detect the effects of lead from a susceptible high risk group of homogeneous low socioeconomic background.

Fulton et al. (1987) examined a total of 501 children, 6–9 years old, and of higher and less uniform socioeconomic status, from Edinburgh, Scotland, exposed to lead primarily via drinking water. The children were selected from a larger sample of 855 (mean PbB level, 10.4 µg/dL) by taking all subjects in the top quartile of the PbB distribution from each of the 18 participating schools plus a random approximately 1 in 3 subsample of the remaining children. The mean PbB level of the study population was 11.5 µg/dL, with a range of 3.3–34 µg/dL. A PbB level >25 µg/dL was found in 10 children. Multiple regression analyses revealed a significant inverse correlation between log PbB and the British Ability Scales Combined (BASC) score and attainment test scores for number skills and word reading after adjustment for confounding variables. Further analysis divided the children into 10 groups of approx-imately 50 each based on PbB level and plotted the group mean lead values against the group mean

difference from the school mean score, adjusted for covariates. The authors reported that this analysis revealed a dose-effect relationship extending from the mean PbB level of the highest lead groups (22.1 µg/dL) down through the mean PbB level of the lowest-lead group (5.6 µg/dL), without an obvious threshold. Although this study provides evidence that PbB levels of less than 25 µg/dL may result in IQ deficits, the size of the effects of lead were small relative to that of other factors.

Two studies reported findings at even lower blood lead levels. Wang et al. (1989) reported on school children residing near a battery plant in Shanghai, China. A significant dose-effect relationship was found between blood lead levels and neuropsychological performance in children without any obvious signs of lead poisoning. The PbB levels in these children (6–14 years old) ranged from 10 to >30 µg/dL; IQ decreased as PbB level increased. This dose-response existed after confounding variables were controlled. The study estimated that an increase of 10 µg/dL of PbB would result in a lowering of verbal IQ of 8 points, performance IQ of 7 points, and full-scale IQ of 9 points.

In the second study Silva et al. (1988) evaluated intelligence, reading and behavior problems in 579 11-year-old children (both of European and Maori/Pacific Island descent) in New Zealand. Mean PbB lead levels were 11.1 µg/dL (range, 4–50 µg/dL). The authors found a significant increase in behavioral problems (inattention and hyperactivity) with increased PbB levels.

On the other hand, several studies have been published that suggest that there is no association between PbB levels and neurobehavioral development (Cooney et al. 1989a; Ernhart and Greene 1990; Harvey et al. 1984, 1988; Lansdown et al. 1986; McMichael et al. 1986; Pocock et al. 1989; Smith et al. 1983), or that some effects are not permanent (Bellinger et al. 1989a; Dietrich et al. 1987a). A cohort of Australian children was investigated in a study that was designed to test the hypothesis that low-level ambient lead exposure in the prenatal or early postnatal periods affects mental or motor development at age 4 (Cooney et al. 1989a). Stringent selection criteria were used to ensure a homogeneous sample (n=207) so that potential confounders could be minimized and the statistical power of the study enhanced. PbB levels were obtained at birth (cord blood), at 6-month intervals to 4 years, and again at 5 years. This sample was drawn from a well-educated, middle-class population. Mean PbB levels increased from birth to 18 months, then steadily declined to 48 months. At 42 months, the percentage of the sample reaching the Australian level of concern (25 µg/dL) was 1.5%; at 48 months, this percentage was 0.5%. The geometric mean PbB level at 48 months was 10.1 µg/dL. This study found no association between current or any previous PbB

level with any developmental outcomes at age 4. Several prospective studies that focused on neurobehavioral effects of prenatal exposure to lead are summarized in Section 2.2.1.6.

Eighteen separate measures were made on a total of 201 boys and girls aged 5.5 years to assess a variety of cognitive, performance, neuropsychological, and behavioral end points (Harvey et al. 1988). The children were randomly selected from birth records from the inner city area of Birmingham, United Kingdom. The selection criteria were quite stringent to control for confounding factors in neuropsychological development. There were no significant correlations between PbB and any of the three IQ measures. Birth order and mother's IQ were good predictors of IQ. The Factual Performance Test time decreased with increasing PbB levels (an improvement in performance), but results of the star copying test were poorer as lead levels increased. The authors concluded that the effects of lead found in this inner urban area (mean PbB, 13.05 µg/dL) in the United Kingdom are small and generally not significant.

Results by Smith et al. (1983), indicated an association between lead burden (mean PbB, 12.8 µg/dL; range, 7–27 µg/dL) and intelligence in 6-year-old children in London. However, no association between blood lead levels and intelligence and other psychological tests remained once social factors were controlled. Lansdown et al. (1986) conducted an investigation in children of the same age, living near a main road in London. In these children, the mean PbB level was 13 µg/dL (range, 7–24 µg/dL). The authors found no evidence of the previously observed original association, which may have been due to different social compositions of the two groups. The second study group consisted of more middle-class families than the first group.

Pocock et al. (1989) further investigated the influence of confounding factors (sex, social group, family size, length of gestation, birth weight, hospital stay after birth, mother's IQ and mental health, parent's marital relationship and interest in child, and family characteristics score) in addition to lead that may impact upon children's IQ. The investigators used the cohort from the study by Smith et al. (1983). Body burden of lead was determined by lead concentration in teeth (low = 2.5 µg/g; medium = 5.5 µg/g; and high = >8 µg/g). Rather than dividing the children into groups of low, medium, and high lead concentration, the actual tooth concentration was used as a continuous variable. When all factors were considered, parental IQ was the best predictor for child IQ along with family size, social class, and quality of marital relationship. Tooth lead concentration was not associated with child IQ.

The studies by Ernhart et al. (1988) and Ernhart and Greene (1990) found no associations between prenatal lead exposure and intelligence or language development, whereas those by Dietrich et al. (1987a) and Bellinger et al. (1989a) demonstrated that some effects that may have been present early in life were no longer present after 2 years. These and many additional pediatric prospective epidemiological studies which evaluated sensory and motor development rather than solely IQ are described in detail in Section 2.2.1.6, Developmental Effects.

In conclusion, PbB levels of 40–60 µg/dL are considered to be markedly elevated in children, and neurobehavioral effects are distinct. There are no clear definitions of what constitutes low versus moderate PbB levels, and effects observed at the lower levels (particularly <15 µg/dL), have proven more difficult to separate from socioeconomic and other variables. Many of the cross-sectional studies that showed neurobehavioral and other deficits, did so at mean PbB levels of >15 µg/dL. The studies that used dentin lead as an indicator of exposure, mostly fall into this category of exposure level. Two well-designed studies (Fulton et al. 1987; Silva et al. 1988) demonstrated effects on behavior, number skills, and word reading at mean PbB levels in children as low as 11 µg/dL. Earlier studies by McBride et al. (1982) and Winneke et al. (1984) showed no effects on intelligence at PbB levels of 14 and 8 µg/dL, respectively. A meta-analysis of 13 studies (providing data on an inverse relationship between blood lead and children's IQ) concluded that the joint probability of obtaining the reported results was less than 3 in a billion (Needleman 1987b; Needleman and Bellinger 1987). This analysis indicates that the effects observed at the lower levels of PbB are real and do not constitute findings by chance.

The results of a neurological evaluation of young adults who were exposed to lead during childhood (20 years earlier) while living near a lead smelter in the Silver Valley, Idaho, were recently published (Stokes et al. 1998). The cohort consisted of 917 young adults 19–29 years of age who were from 9 months to 9 years of age during the period January 1974 to December 1975. This period was chosen because the smelter was known to have operated without appropriate emissions reduction devices during this period. Data from past PbB surveillance of this population showed that mean PbB concentrations among 9-month-old to 9-year-old children were 50 µg/dL in 1974 and 39.6 µg/dL in 1975. The referent group consisted of 754 subjects. From the exposed and referent groups, a randomly selected subsample of 281 exposed and 287 referents were included in the study. Further exclusions due, for example, to conditions such as traumatic injury to the hand, arm, or shoulder, or consumption of medications that would affect the PNS or CNS reduced the groups to 257 exposed and 276 referents. The tests were

designed to evaluate peripheral and central motor and sensory function, as well as cognitive function and mood. K X-ray fluorescence (K-XRF) of tibia lead content (µg Pb/g bone mineral) was used to assess lead burden. Differences in mean test scores between exposed and unexposed groups were compared with simple *t* tests. Subsequently, backward elimination stepwise multiple linear regression models were fitted separately to each of the 20 neurobehavioral test score variables to control for potentially confounding effects of important covariates of the neurological and neurobehavioral outcomes of the population evaluated. Current PbB levels for the exposed and control groups were 2.9 µg/dL and 1.6 µg/dL, respectively. Mean tibia lead concentrations were 4.6 and 0.6 µg Pb/g bone mineral in exposed and referents, respectively. When the subjects were stratified into 4 groups according to bone lead, 44% of exposed had tibia lead >5 µg Pb/g bone mineral compared to 25% of referents. The results showed significant differences in crude mean values for 11 out of 12 motor and cognitive function tests (results of other tests are summarized under Peripheral Function). After controlling for relevant covariates, the exposure group was significantly associated with poorer performance on the hand-eye coordination, simple reaction time, trails B, symbol digit, serial digit learning, Raven progressive matrices, and vocabulary tests. Also, the score from the Swedish Q16 questionnaire for neuropsychiatric evaluation was significantly associated with exposure groups after controlling for relevant covariates. When tibial bone lead concentration was forced into the model rather than exposure, of all the tests (neurological and neurobehavioral), only vocabulary score approached significance. Similar results were obtained when stratified tibial bone lead was used in the models rather than tibial bone lead as a continuous measure. Based on the results, Stokes et al. (1998) concluded that tibial bone lead measurements may not have the precision necessary to measure community-based exposure to lead in young adults.

The issue of whether neurobehavioral deficits associated with lead burden can be reversed by reducing lead body burden has been investigated. For example, Ruff et al. (1996) conducted such a study in 42 children ages 18 to 30 month with PbB levels between 25 and 55 µg/dL. Cognitive function was assessed upon enrollment into an intervention program and 6 months later. The intervention program consisted of chelation therapy, if appropriate, iron supplementation, if needed, and steps aimed at eliminating the source of lead in the home environment. Prescription for chelation and/or iron supplementation was based on the results of the lead mobilization test (assessment of changes in urinary lead excretion in response to $CaNa_2EDTA$ administration) and/or serum ferritin levels, respectively. Depending on the diagnostic outcomes, the children received both forms of treatment, neither form, or either one of them alone. The dependent measure of cognitive function was the MDI of the Bayley Scales of Infant Development.

Analyses showed that the improvement in MDI scores over 6 months (particularly in perceptual motor performance) was related to an interaction between change in PbB and initial iron status, such that in iron-sufficient children, there was an increase of 1.2 points for every 1 μg/dL decrease in PbB. No such relationship was observed in iron-deficient children. In the latter, however, a change in MDI results was related to change in hemoglobin levels. It was also noticed that iron-deficient-children experience a lower decline in PbB lead than iron-sufficient children. Ruff et al. (1996) suggested that low iron may have interfered with the relationship between MDI scores and declines in blood lead by influencing absorption and/or excretion of lead (see Section 2.3). Another possibility suggested was that iron levels are associated with cognitive performance either directly or indirectly. This was supported by the finding that the performance of the iron-deficient children seemed to change along with changes in hemoglobin and MCV, and the observation that in this group there was an association between MDI and initial hemoglobin concentration.

Electrophysiological Evidence of Neurotoxicity in Children. Electrophysiological studies have provided evidence suggestive of effects on central nervous system function at PbB levels lower than 30 μg/dL, but findings were inconsistent. Linear dose-effect relationships were observed in slow-wave voltage during conditioning in a series of studies (Otto et al. 1981, 1982, 1985) on the same subjects studied by Schroeder et al. (1985). The association was linear throughout the range of PbB values (6–59 μg/dL). No such relationships were observed in a replicate test, performed on the same subjects studied by Schroeder and Hawk (1987). A study of 384 6-year-old German children with a geometric mean PbB concentration of 4.3 μg/dL (range, 1.4–17.4 μg/dL) from three environmentally contaminated areas in East and West Germany found significant lead-related deficits for two out of three visual evoked potentials (VEP) interpeak latencies after adjusting for confounding effects (Altmann et al. 1998). No association was found between PbB concentrations and VEP amplitudes. These results confirmed previous findings from the same group of investigators (Winneke et al. 1994). Altmann et al. (1998) also measured visual contrast sensitivity and found no significant association between this parameter and lead.

Brainstem auditory evoked potential (BAEP) latency (Holdstein et al. 1986; Otto et al. 1985; Robinson et al. 1987), pattern-reversal visual evoked potential (PREP) latency and their amplitude were also correlated with blood lead levels (Holdstein et al. 1986; Otto et al. 1985). The specific components affected and the direction of effect varied across studies. Some of these studies did not specify the route and the duration of lead exposure and only accurately measured recent lead exposure; they revealed little about the exposure

history of the individual. A study of 30 infants, the Mexico City Prospective Lead Study (see Section 2.2.1.6) found alterations in BAEP (decreased wave III latency and increased III–V interpeak interval) measured in the first weeks of life (Rothenberg et al. 1994). These effects were associated ($p<0.1$) with mid-pregnancy maternal PbB levels in the range 2.5–35 µg/dL. Retesting at age 3 months showed that maternal PbB levels at 20 and 36 weeks of pregnancy and cord PbB were associated with increased III–V interpeak intervals. The authors indicate, however, that since they did not attempt to correct test-wise error (possibility of false positives due to multiple regressions) in the multiple independent statistical tests, some of the reported correlations could have been due to chance alone. In a subsequent publication, the authors reported an association between altered acoustic cry parameters in some of these infants and maternal log PbB concentrations at various times during pregnancy (Rothenberg et al. 1995). Since they found a negative correlation between the latencies of peak III and peak V of the BAEP with percent nasal cry, they speculated that some changes in 15- and 30-day cry characteristics, which were associated with lead exposure, might be secondary to lead-induced alteration in auditory function.

Suggestive evidence of a lead-related decrease in hearing acuity in children has been reported by Robinson et al. (1985) and Schwartz and Otto (1987, 1991). Hearing thresholds at 2,000 Hertz increased linearly with maximum blood lead levels, indicating that lead adversely affects auditory function. The PbB levels in 75 asymptomatic black children, 3–7 years old, ranged from 6 to 59 µg/dL (mean, 26.7 µg/dL). The children were healthy and did not have middle ear infections at the time of testing. These results were confirmed in an examination of a group of 3,545 subjects aged 6–19 years who participated in the Hispanic Health and Nutrition Survey (Schwartz and Otto 1991). For the left ear, lead was associated with an increased risk of elevated hearing thresholds at the four frequencies tested, 500, 1,000, 2,000, and 4,000 Hz, whereas for the right ear the relationship was insignificant at 4,000 Hz. An increase in PbB from 6 µg/dL to 18 µg/dL was associated with a 2-dB loss in hearing at all frequencies, and an additional 15% of the children had hearing thresholds that were below the standard at 2,000 Hz.

NHANES II data, including audiometric results, developmental milestones (age at which a child first sat up, walked, and spoke, according to parent's recollection) and presence of hyperactivity and speech difficulties in 4,519 children (4–19 years old) were analyzed by Schwartz and Otto (1987). The analyses included possible covariates or confounding variables that were then available from NHANES II data (e.g., race, sex, head of household, education level, income, dietary factors, indices of iron deficiency and anemia [for developmental milestones], history of signs of ear infection [for audiometric results]). Because

children's PbB levels decrease with age but tend to remain in the same percentile within age group, data were analyzed in two different ways: with current PbB as an independent variable and with PbB percentile rank within age group as an independent variable. Logistic regression analysis revealed that the probability of elevated hearing thresholds for both ears at 500, 1,000, 2,000, and 4,000 Hertz increased significantly with increasing blood lead levels; this relationship was apparent across the entire range of PbB levels from <4 to >50 µg/dL. When the regression analysis used PbB percentile rank within age group as the independent variable, the association with hearing was not significant. According to the investigators, the lack of association with lead rank indicated that the effect of lead was due to current rather than past lead exposure. The probability that a child was hyperactive increased significantly with increasing PbB levels (as PbB percentile rank within age group). The probability of speech impairment, however, was not related to blood lead levels. Linear regression analysis demonstrated that PbB levels (as PbB percentile rank within age group) were significantly associated with delays in all three developmental milestones.

These three studies indicate that exposure to low levels of lead may impact negatively upon children's hearing. However, the authors of the Robinson study did not state whether age and other possible confounding variables were controlled for. Similarly, in the NHANES study, age may have been a confounding variable.

In contrast with the suggestive evidence of impaired hearing in lead exposed children from the studies summarized above, Counter et al. (1997) found normal wave latencies and neural transmission times, and no correlation between PbB and interpeak latencies among a group of 54 children (7–8 years old) with a median PbB concentration of 40 µg/dL (range, 6.2–128.2 µg/dL). Furthermore, audiological tests showed normal cochlear function and no statistical relation between auditory thresholds and PbB concentration. The cohort evaluated in this study were children living in Andean villages of Ecuador exposed to lead as a result of extensive production of lead glazed tiles and artisan crafts.

Bhattacharya et al. (1993) have presented evidence relating lead exposure and postural disequilibrium in children. The authors evaluated 109 children from the Cincinnati Lead Program Project (see Section 2.2.1.6, Developmental Effects, for a more detailed description of this cohort). The mean age of the children was 5.8 years and the geometric mean PbB for the first 5 years of life was 11.9 µg/dL (range, 5.1–28.2 µg/dL). Balance was assessed in a system that provided a quantitative description of postural sway by measuring the movement pattern of the body’s center of gravity during testing. Sway area was

significantly correlated with PbB level in tests performed with the eyes closed, but not in a test performed with the eyes open. This led the authors to suggest that lead-induced sway impairment might be related to modifications of the functions of vestibular and proprioception systems, on which close-eye tests rely more. Sway length was significantly correlated with blood lead under all test conditions. Three out of 4 postural sway responses showed significant improvement in an 8-year-old child after an initial chelation trial with CaEDTA followed by 7 chelation regimens with succimer over a 19-month period (Bhattacharya et al. 1998). The child's PbB concentration fluctuated considerably during therapy from a pre-therapy concentration of 81 µg/dL to a minimum of 27 µg/dL after the third dose of succimer; at the end of therapy, the PbB concentration was 54 µg/dL. According to the authors, the three responses that showed improvement rely relatively less on higher centers for balance compared to the response that did not improve, which rely primarily on the vestibular system for balance maintenance.

Peripheral Nerve Function in Children. Effects of lead on peripheral nerve function have been documented in children. Frank peripheral neuropathy has been observed in children at PbB levels of 60–136 µg/dL (Erenberg et al. 1974). Of a total of 14 cases of childhood lead neuropathy reviewed by Erenberg et al. (1974), 5 also had sickle cell disease (4 were black), a finding which the authors suggested might indicate an increased susceptibility to lead neuropathy among children with sickle cell disease. However, effects of race cannot be eliminated. A case study (Seto and Freeman 1964) reported signs of peripheral neuropathy in a child with a PbB level of 30 µg/dL, but lead lines in the long bones suggested past exposures leading to peak PbB levels of $40–60 µg/dL and probably in excess of 60 µg/dL (EPA 1986a). NCV studies have indicated an inverse correlation between peroneal NCV and PbB levels over a range of 13–97 µg/dL in children living near a smelter in Kellogg, ID (Landrigan et al. 1976). These data were reanalyzed to determine whether a threshold exists for this effect. Three different methods of analysis (segmental, logistic, and quadratic regressions) revealed evidence of a threshold for NCV at PbB levels of 20–30 µg/dL (Schwartz et al. 1988).

A recent study used tibial bone lead to assess lead burden among a group of 281 young adults who were exposed to lead during childhood (20 years earlier) while living near a lead smelter in the Silver Valley, Idaho (Stokes et al. 1998). A group of 287 referents served as controls (a summary of the study design can be found under Behavioral Function in Children). The study found that crude mean sural sensory amplitude and peroneal motor amplitudes were slightly smaller among the exposed group than among the referent group. The corresponding nerve conduction velocities were similar between the two groups. The

results of behavioral tests of peripheral nerve function showed significant differences between exposed and referents regarding crude means for vibrotactile thresholds of the finger and standing steadiness both with eyes open and eye closed. However, crude means for visual contrast sensitivity, and vibrotactile thresholds of the toes did not differ significantly between the two groups. After controlling for relevant covariates, the differences between means remained significant and the difference in vibrotactile thresholds of toes achieved significance. When tibial bone lead concentration was forced into the model rather than exposure, of all the tests, only finger and toes vibrotactile thresholds approached significance. Similar results were obtained when stratified tibial bone lead was used in the models rather than tibial bone lead as a continuous measure. As previously mentioned, Stokes et al. (1998) concluded that tibial bone lead measurements may not have the precision necessary to measure community based exposure to lead in young adults.

2.2.1.5 Reproductive Effects

A large body of literature clearly indicates that high levels of lead cause adverse effects on both male and female human reproductive functions. Women in particular, who are exposed during pregnancy, have experienced miscarriages and stillbirths. Although the mechanisms underlying these effects are unknown at this time, many factors could contribute to such results. These factors range from indirect effects of lead on maternal nutrition or hormonal status before and during pregnancy to more direct gametogenic effects that could affect parental fertility in both sexes. Human data have largely been derived from studies involving relatively small numbers of subjects and therefore do not allow for discriminating statistical analysis. Reproductive effects of exposure to chronic low levels of lead are less known. The results of 2 studies in females with blood lead levels of 10 µg/dL indicate no effect on the rate of spontaneous abortions. Studies in males indicated that effects on sperm may start to appear at PbB levels around 40 µg/dL.

Selected studies are discussed below and include reports on occupational exposure to lead for females and males followed by environmental (low level) exposure to lead in females and males.

An increased frequency of spontaneous abortion was reported in women living close to a lead smelter (Nordstrom et al. 1979). Moreover, the female workers at the smelter had an increased frequency of spontaneous miscarriage when employed at the smelter during pregnancy, or when employed at the smelter prior to pregnancy and still living near the smelter. Women who worked in more highly contaminated areas

of the smelter were more likely to have aborted than were other women. These studies were confounded by the presence of other toxic agents and by the lack of controlling for socioeconomic status.

Pregnancies were evaluated in the center of Port Pirie, a lead smelter town in South Australia (high environmental lead exposure; mean maternal mid-pregnancy PbB level was 10.6 µg/dL; n=645) and in the surrounding areas (low environmental lead exposure; mean maternal mid-pregnancy PbB level was 7.6 µg/dL; n=185). While no association was found between PbB levels and spontaneous abortions, 22 of 23 miscarriages and 10 of 11 stillbirths occurred in the Port Pirie residents, with only 1 miscarriage and 1 stillbirth occurring in residents outside Port Pirie (Baghurst et al. 1987; McMichael et al. 1986). Maternal PbB levels were lower in the cases of stillbirth than in the cases of live birth, but fetal and placental levels in this and another study (Wibberley et al. 1977) were higher than in cases of normal birth. Davis and Svendsgaard (1987) suggested that these findings may be due to a transfer of lead from mother to fetus, which is toxic to the fetus. This study is discussed more fully in the section on developmental toxicity (see Section 2.2.1.6) because the study focuses primarily on the effects of prenatal exposure to low levels of lead on fetal and early childhood development.

The rates of spontaneous abortions were compared in a prospective study (Murphy et al. 1990) in females living close to a lead smelter (n=304; mid-pregnancy mean PbB concentration of 15.9 µg/dL) and females living 25 miles away (n=335; mid-pregnancy mean PbB concentration of 5.2 µg/dL). Women were recruited at mid-pregnancy and their past reproductive history (first pregnancy; spontaneous abortion=fetal loss prior to 7th month; stillbirth=fetal loss from 7th month) was examined. The results indicated no difference between the towns regarding the rate of spontaneous abortions. The rates were 16.4% and 14.0% for the lead smelter town and the unexposed town, respectively. Similar results had been reported by Alexander and Delves (1981) in a study of two groups of pregnant women, one from an urban area and the other from a rural area based on a mining town. Mean PbB levels in the pregnant women were not significantly different than in same-location nonpregnant controls (12–13 µg/dL in rural area as opposed to 16–17 µg/dL in urban area).

The time to pregnancy was studied in a group of 121 women biologically monitored for exposure to lead at the Finnish Institute of Occupational Health from 1973 to 1983 (Sallmen et al. 1995). The exposure assessment was based on the self-report of lead exposure, detailed work description, and biological measurements. Very low exposure was defined as having a PbB level <10 µg/dL, low exposure

corresponded to PbB levels between 10 and 19 µg/dL, and the moderate-to-high category corresponded to PbB $20 µg/dL. All other women were classified as nonexposed. Multivariate analysis revealed no systematic differences in the distribution of time to pregnancy between exposed and nonexposed women. Following adjustment for exposure to carcinogens, age, parity, use of alcohol, use of coffee, vaginitis, and frequency of intercourse, the data showed that exposure to lead was not significantly associated with decreased fecundability. However, among the eight most heavily exposed women (PbB between 29 and 50 µg/dL measured during time to pregnancy or during pregnancy), there was a suggestive association between blood lead and decreased fecundability.

Hu (1991) examined the long-term consequences among survivors of childhood plumbism. Survivors consisted of children admitted to the Boston Children's Hospital from 1930 to 1944 for childhood plumbism. Matched controls (age, sex, and neighborhood) were enlisted through the use of town books. All participants were asked to respond to a self-administered questionnaire. Information on all pregnancies engendered (men) or carried (women); outcome; and intellectual development of resulting children were given. Among the matched females, the rate of spontaneous abortion or stillbirths among pregnancies was higher than for the controls (relative risk = 1.60; 95% confidence interval = 0.6–4.0). In addition, the offspring from a matched female plumbism subject was more likely to experience learning disabilities (relative risk = 3.0; 95% confidence interval = 0.9–10.2). Although this study included only a small number of plumbism survivors, the results indicate that women significantly exposed during childhood may be at risk even later in life for adverse reproductive outcomes.

Lead-induced effects on male reproductive functions have been reported in humans (Assennato et al. 1987; Chowdhury et al. 1986; Lancranjan et al. 1975; Lerda 1992; Wildt et al. 1983). A group of 150 workmen with long-term lead exposure were categorized by clinical and toxicological data into four groups: lead-poisoned (mean PbB level, 74.5 µg/dL), and moderately (mean, 52.8 µg/dL), slightly (mean, 41 µg/dL), or physiologically (mean, 23 µg/dL) exposed to lead (Lancranjan et al. 1975). The lead-poisoned group and the moderately exposed group had decreases in fertility, as measured by asthenospermia, hypospermia, and teratospermia. The effect of lead was thought to be directly on the testes because tests for changes in gonadotropin secretion were negative. Secretion of androgens by the testes was not affected.

Another study compared two groups of men in a Swedish battery factory (Wildt et al. 1983). The men exposed to high levels of lead had PbB levels of $50 µg/dL at least once prior to the study and had mean

PbB levels of 46.1 and 44.6 µg/dL (range, 25–75 µg/dL) during fall and spring test periods. The controls (exposed only to low environmental levels of lead) had PbB levels that seldom exceeded 30 µg/dL, and had mean PbB levels of 21.1 and 21.5 µg/dL (range, 8–39 µg/dL) during fall and spring test periods. The high-lead group tended to exhibit decreased prostate/seminal vesicle function as measured by seminal plasma constituents, low semen volumes, and lower functional maturity of sperm (as measured by swelling of the sperm heads in detergent [sodium dodecyl sulfonate] solution).

Chowdhury et al. (1986) reported that occupational exposure of 10 men to lead caused a significant decrease in sperm count and motility and an increased percentage of abnormal spermatozoa. The average PbB concentration in the lead-exposed group was higher (42.5 µg/dL) compared to controls (14.8 µg/dL). Assennato et al. (1987) reported decreased sperm production in 39 battery factory workers with high PbB levels ranging from 50 to 61 µg/dL, compared to 39 nonexposed workers. Lerda (1992) reported significant decreases in sperm count and motility, as well as increases in the percent of dead sperm and in sperm with anomalies in a group of 30 workers in a battery factory compared to 30 controls. PbB levels in the exposed workers ranged from 40 to 98 µg/dL, whereas the range in controls was 18–26 µg/dL. Although some parameters were within the normal range for the general population, they were significantly different than those from the referent group. These studies, however, were limited by the small sample size. Alexander et al. (1996) published the results of the evaluation of a much bigger cohort (n=2,469) of males employed at a lead smelter; 152 workers provided blood samples and 119 also provided semen samples. The workers were divided into four groups according to their current PbB concentration: <15, 15–24, 25–39, and >40 µg/dL; the geometric mean sperm concentrations were, respectively, 79.1, 56.5, 62.7, and 44.4 million cells/mL and the geometric mean total sperm counts were 186, 153, 137, and 89 million cells. The p value for the trend was 0.04. Workers with current PbB concentration of $40 µg/dL had an increased risk of below normal sperm and total sperm count relative to those with PbB concentrations of <15 µg/dL. Independent of current lead exposure, sperm concentration, total sperm count, and total motile sperm count were inversely related to measures of long-term lead exposure. The authors also found no association between lead exposure and measures of lead motility, sperm morphology, or serum concentrations of reproductive hormones.

The effect of lead exposure on male fertility was examined in a group of 74 workers in a lead factory (Gennart et al. 1992b). Fertility was assessed by examining the birth experiences of their wives through a logistic regression model. Workers had a mean age of 39 years, had been exposed for a mean of

10.7 years, and had a current mean PbB level of 46.3 µg/dL. They were compared with a group of 138 unexposed individuals whose mean PbB concentration was 10.4 µg/dL. In the exposed workers there was a tendency before exposure to an increased birthrate. However, a significant decrease in fertility was observed during the period of exposure relative to the unexposed group; duration of exposure was also associated with decreased fertility. As indicated by the authors, the main limitation of the study was the fact that the worker's wives could not be interviewed, and therefore, the medical and occupational factors that might also have affected their reproductive system could not be assessed. The results of an assessment of male fertility in a much bigger cohort evaluated 4,256 lead-exposed workers and 5,148 matched comparison subjects (Lin et al. 1996). Exposed workers were defined as having a PbB level $40 µg/dL before 1986 or $25 µg/dL for the study period (1981–1992). The results showed that the lead-exposed workers had fewer births than expected relative to the comparison group, and this was observed among all age categories with the exception of the 51- to 55-year-old group. Those with the highest cumulative exposure (mean PbB level x duration) had the most obvious reduction in fertility. However, Lin et al. (1996) stated that the study conclusion may be limited by the inability to control for some confounders such as marital status or contraceptive use.

In contrast with the results summarized above, two studies found no significant effects of lead exposure on fertility. Coste et al. (1991) conducted a person-year analysis and reported no effects on fertility (defined as the number of live births to a couple) among men exposed to lead in a French battery factory. Exposed workers (229) were categorized into groups with PbB levels of <40 µg/dL, 40–60 µg/dL, and >60 µg/dL. Nonexposed workers (125) did not have their PbB levels recorded. In agreement with these results are the findings of a study that examined fertility among 1,349 male battery plant employees and 9,596 reference workers at 3 Danish plants (Bonde and Kolstad 1997). The mean PbB concentration in a subset of 400 workers who provided 4,639 blood samples was 39.2 µg/dL. This study found no association between employment at the plants and changes in fertility in terms of birth rate, either during years of employment or during subsequent years. The authors point out, however, that their findings do rule out that the time taken to achieve a pregnancy is increased among battery workers because most pregnancies in Denmark are planned.

The relation between concentration of circulating pituitary and testicular hormones was evaluated in a group of 122 workers in three lead battery factories (Ng et al. 1991). A group of 49 nonexposed subjects was used for comparison. The mean PbB level in workers was 35.2 µg/dL (mean in controls was

8.3 µg/dL) and the mean duration of exposure was 6 years. The results showed that increasing age was significantly associated with increases in luteinizing hormone (LH) and follicle stimulating hormone (FSH) concentrations, but not with testosterone or prolactin concentrations. Smoking was significantly associated with decreased prolactin concentrations. Compared with control subjects, workers exposed for less than 10 years had normal testosterone but significantly higher levels of FSH and LH; those exposed for 10 or more years had lower testosterone, but normal FSH and LH. As a group, the exposed workers had testosterone levels comparable to controls; however, older ($40 years) workers had significantly lower testosterone levels than older control subjects. LH and FSH concentrations showed a moderate increase with PbB in the 10–40 µg/dL range; no clear association was observed for prolactin and testosterone. These results are in general agreement with those of earlier studies of lead workers with higher PbB levels ($66 µg/dL), which indicates that lead acts directly on the testes to cause severe depression of sperm count and peritubular testicular fibrosis, and also produces reduced testosterone synthesis or disrupts regulation of LH secretion at the hypothalamic-pituitary level (Braunstein et al. 1978; Cullen et al. 1984; Rodamilans et al. 1988). Although some of these studies had limitations such as concomitant exposure of workers to other chemicals, lack of matched control group, small sample size, and in some cases a possibility of observed effects being precipitated by the EDTA chelation (as in Braunstein et al. 1978), taken together they provide evidence for lead-induced endocrine disturbances and reproductive dysfunction in male workers.

2.2.1.6 Developmental Effects

The best data regarding potential developmental consequences of low-level prenatal exposure to lead are provided by several recent human studies. Because of improved analytical techniques for measuring low lead levels in blood, the availability of large numbers of subjects, and careful consideration of potential confounding factors, these human studies provide useful information on the developmental effects of lead. Less emphasis has been placed on studies conducted in animals because of the availability of good human data, although a large body of animal data is available and the results are in agreement with those of the human studies. (See review by Davis et al. [1990]) for a comparison of human and animal data in developmental neurotoxicity.)

In most of these studies, prenatal exposure was generally estimated through maternal and/or cord blood lead concentrations. Exposure of the mothers can be assumed to have been primarily through the oral

route, but with contribution from the inhalation route as well. The most relevant studies are discussed below, along with results from a few investigations of different markers for lead exposure.

No reports were found indicating low levels of lead as a cause of major congenital anomalies. Needleman et al. (1984), however, demonstrated an association between blood lead levels and minor congenital anomalies. Using logistic regression modeling techniques and controlling for a number of possible confounders, the authors reported a significant association between cord blood lead levels and the collective occurrence of minor anomalies in 4,354 infants born in Boston. Data were obtained from hospital records. The most common of these anomalies were hemangiomas, lymphangiomas, minor skin anomalies (tags and papillae), and undescended testicles. No individual anomaly was significantly associated with blood lead levels. Major malformations, birth weight, and gestational age were not associated with PbB lead levels.

A cross-sectional study of 236 mothers and their infants in Glasgow, Scotland, demonstrated reductions in gestational age with increasing cord or maternal PbB lead levels (Moore et al. 1982). In the 11 cases of premature birth (gestational age <38 weeks), maternal PbB levels averaged approximately 21 µg/dL, and cord PbB lead levels averaged approximately 17 µg/dL at delivery. The overall geometric mean PbB levels at delivery were 14 µg/dL (maternal) and 12 µg/dL (cord). Statistical analyses showed significant negative coefficients for length of gestation against log-transformed maternal or cord PbB levels. Birth weight was not associated with PbB lead levels.

The association between low birth weight and parental occupational lead exposure variables was studied by Min et al. (1996). The study comprised 220 cases (birth weight <2,500 g) and 522 controls (birth weight $2,500 g) selected among 3,572 participants in the Baltimore-Washington Infant Study. Parental occupational exposure was inferred from jobs held during the period 6 months before pregnancy to the end of pregnancy. Only a few mothers were potentially exposed to lead either directly or indirectly during the exposure period of interest; therefore, the analysis included fathers only. Twenty-one percent of the fathers were potentially exposed to lead either directly or indirectly. Univariate analyses of low birth weight in relation to various measures of lead exposure showed that the risk of low birth weight was significantly increased only among infants of fathers with direct and high levels of lead exposure. This association persisted after adjusting for relevant confounders. Although reports of sperm abnormalities and reduced fertility among lead-exposed men (Section 2.2.1.5) would support a direct male-mediated effect, Min et al. (1996) suggested that a direct paternal preconceptional effect on birth weight, which is gained after 24

weeks of gestation, is unlikely. A more likely explanation discussed is that prenatal exposure occurs by indirect maternal contact with contaminated work clothing or tools brought home. Limitations of the study include lack of actual measures of exposure in the workplace, possible additional non-occupational exposure to lead, and simultaneous occupational exposure to other chemicals.

An ongoing prospective study of the effects on child development following prenatal and postnatal lead exposure in the lead smelter town of Port Pirie, South Australia, and its surrounding areas, has provided information on congenital anomalies, length of gestation, birth weight, and stillbirth or miscarriage (McMichael et al. 1986), and on neurobehavioral development (Baghurst et al. 1987, 1992; Vimpani et al. 1985, 1989). Of 831 pregnant women, 774 pregnancies were followed to completion (McMichael et al. 1986). Although still relatively low, PbB levels during pregnancy and at delivery in women who lived in Port Pirie were significantly higher than in those who lived in adjacent towns and rural areas (e.g., at delivery: 11.2 µg/dL in Port Pirie and 7.5 µg/dL in the surrounding areas). No association was found between the PbB lead levels and the occurrence of congenital anomalies when pertinent risk factors, such as smoking and alcohol consumption, were controlled for. As was the case with Needleman's study (Needleman et al. 1984), hospital records were used to detect congenital anomalies. This may have caused a lack of precision and uniformity. Also, the relatively small number of subjects may not have been sufficient for detection of differences in low frequencies of anomalies. Multivariate analysis revealed a significant association between preterm delivery (before the 37th week of pregnancy) and maternal blood lead levels at delivery. The relative risk of preterm delivery increased more than 4-fold at PbB levels of >14 µg/dL compared with a relative risk of 1 at PbB levels of #8 µg/L. The incidence of low birth weight (<2,500 g at gestational age $37 weeks) was greater in Port Pirie than in the surrounding areas, but maternal and cord PbB levels at delivery were somewhat lower in the low-birth-weight pregnancies. Similarly, 22 of the 23 miscarriages and 10 of the 11 stillbirths in this study occurred in the Port Pirie mothers, but the average maternal PbB level at delivery was significantly lower for stillbirths than for live births.

The results of McMichael et al. (1986) are puzzling because the proportion of Port Pirie pregnancies (delivery maternal PbB, 10.4 µg/dL) resulting in low-birth-weight infants was more than twice that for outside pregnancies (delivery maternal PbB lead, 5.5 µg/dL). Yet the maternal and cord PbB levels were somewhat lower in low-birth-weight pregnancies than in pregnancies with birth weights >2,500 g. A similar phenomenon was seen with regard to stillbirths, which occurred primarily in the Port Pirie

pregnancies, but which were associated with lower maternal PbB levels than were live births. Davis and Svendsgaard (1987) suggested that the findings for blood lead versus birth weight or stillbirth in the Port Pirie study suggest an increased transfer of lead from mother to fetus, which is toxic to the fetus. This suggestion is supported by the inverse correlation between placental lead levels and birth weight, head circumference, and placental weight reported by Ward et al. (1987) and the increased levels of lead in the placenta reported by Wibberley et al. (1977) in cases of stillbirth and neonatal death. Alternatively, it has been suggested that such findings may indicate that lead accumulates in the placenta in times of fetal stress (Wibberley et al. 1977).

In a prospective study by Factor-Litvak et al. (1991), prenatal lead exposure versus reproductive outcome (intrauterine growth and preterm delivery) were assessed in pregnant women from two towns in Kosovo, Yugoslavia. Titova Mitrovica is a lead smelter town, while Pristina is an unexposed town 25 miles further south. At mid-pregnancy, 401 and 506 women were recruited from T. Mitrovica and Pristina, respectively, with mean PbB concentrations of 0.92 and 0.27 µmol/L (19 and 5.6 µg/dL) in the respective group; at time of delivery, these concentrations were 1.13 and 0.33 µmol/L (23.4 and 6.8 µg/dL), respectively. No differences were found between the two areas for either birth weight or length of gestation. In addition, no associations were observed between PbB concentrations (maternal and cord, at mid-term and time of delivery) and birth weight, length of gestation, or preterm delivery (<37 weeks). Children from this cohort were reevaluated at age 4 (Wasserman et al. 1994). The study was conducted in a group of 332 children. The geometric mean PbB level in children from the smelter town rose from 22.4 µg/dL at birth to 39.9 µg/dL at age 4; in children from Pristina, it rose from 5.4 µg/dL to 9.6 µg/dL. Of all the potential confounders examined, the Home Observation for Measurement of the Environment (HOME) scores, maternal age, intelligence, education, language, birthweight, and gender accounted for 42.7% of the variance of the McCarthy Scales General Cognitive Index (GCI). After adjusting for these confounders and concurrent hemoglobin concentration, it was found that PbB, measured every 6 months from birth to age 4, was significantly associated with a decrease in GCI at each age point. It was also found that 4-year GCI scores declined by an estimated 4 points as PbB, measured between 24 and 48 months, increased from 10 to 25 µg/dL, and similar patterns were seen for five other subscales of the McCarthy. Interestingly, blood lead measured at 24 months or later accounted for a greater portion of the variance in the subscales than did prenatal PbB or that measured during infancy. Also, of the five subscales examined, the Perceptual-Performance subscale appeared to be the most sensitive to lead exposure. These findings are consistent with those of other prospective studies (see below). A group of 309 children from this cohort

was evaluated again at age 7 years (6.5–7.5 years) (Wasserman et al. 1997). At this time the investigators examined the association between lifetime lead exposure, estimated by the area under the blood lead versus time curve, and intelligence, assessed by the WISC-III. Geometric mean PbB concentration at age 7 was 34 µg/dL in children from Mitrovica versus 8 µg/dL in children from Pristina. There were no differences in serum ferritin levels or hemoglobin concentration between the two towns. Consistent with results from other studies, covariates such as HOME, birth weight, gender, number of siblings, maternal age, ethnicity, and education explained 41–47% of the variance in Full Scale, Performance, and Verbal IQ. Furthermore, before covariate adjustment, lifetime lead exposure was not related to IQ. However, after adjustment, lifetime lead exposure explained a significant 2.8–4.2% of the variance in IQ, and a change in lifetime PbB lead from 10 to 30 µg/dL was associated with an estimated decrease in 4.3 Full Scale IQ points. The decreases in Verbal and Performance IQ were 3.4 and 4.5 points respectively. It was also found that lifetime lead exposure was significantly inversely related to three WISC-III factor scores: Freedom from Distractibility, Perceptual Organization, and Verbal Comprehension; of these, Perceptual Organization showed the strongest association, suggesting that perceptual motor skills are significantly more sensitive than are the language related aspects of intelligence.

Information regarding behavior problems in children from the Yugoslavian cohort were recently published (Wasserman et al. 1998). The evaluation was conducted when the children were 3 years old. A total of 379 children comprised the sample. At that time, the geometric mean PbB concentration was 40.9 µg/dL in the exposed children (Mitrovica) versus 9.8 µg/dL in the referents (Pristina). The mothers in the study had completed Infant Characteristics Questionnaire at child-age 2, from which the authors included scores on the Difficult Temperament scale. When the children were 3 years old, the mothers completed the Child Behavior Checklist/2–3 (CBCL), which generates 6 subscales: Destructive, Aggressive, Somatic Problems, Withdrawn, Anxious-Depressed, and Sleep Problems. Seven to 18% of the variance on the CBCL subscales was explained by a set of sociodemographic confounders. After controlling for confounders, and prior to examination of Difficult Temperament scores, log PbB at age 3 accounted for an incremental 4% of the variance in Destructive and Withdrawn scores, 2% of the variance in Somatic Problems and Sleep Problems, and 1% of the variance on the Anxious-Depressed subscale. However, only tests on the Destructive and Withdrawn subscale achieved a $p<0.01$ level of significance. Log PbB at age 3 was most strongly associated with behavior across all subscales; log PbB other ages showed no clear pattern of association with behavior. Difficult temperament was also significantly associated with 5 of the 6 subscales, accounting for 2–5% of their variances, but had little impact on the association between log

blood lead and behavior. Log PbB at age 3 remained significantly associated with scores on the Destructive and Withdrawn subscales, even after control for prior difficult temperament. Wasserman et al. (1998) concluded that lead/behavior associations are significant but small compared with the effects of social factors.

Numerous others studies have found that exposure to low levels of lead interferes with the mental development of children. Preliminary results of blood lead and neurobehavioral testing of 592 children from the Port Pirie study were reported by Baghurst et al. (1987), Vimpani et al. (1985, 1989), and Wigg et al. (1988). In these children, geometric mean PbB levels increased from approximately 14 µg/dL at 6 months of age to approximately 21 µg/dL at 15 and 24 months. At 24 months, approximately 20% of the children had PbB levels >30 µg/dL. Neurobehavioral tests—the Bayley MDI and Bayley Psychomotor Development Index (PDI)—were conducted at 24 months. Multiple regression analyses indicated that reduced MDI scores were significantly ($p=0.07$) associated with higher integrated postnatal blood lead levels and with 6-month PbB levels, but not with prenatal delivery or cord PbB levels. Controlling for both maternal IQ and HOME scores, the association between 6-month PbB and 24-month MDI scores remained significant, with a 2-point deficit in MDI for every 10-µg/dL increase in PbB. A follow-up of this cohort involved PbB testing at 3 and 4 years of age and neurobehavioral assessment using the McCarthy Scales of Children's Abilities (McMichael et al. 1988). Multiple regression analyses showed that children's scores on these tests were significantly and inversely correlated with log PbB levels at 6, 24, and 36 months and with the integrated average for birth to 4 years. The estimated decrease in the GCI score was approximately 7.2 points, for an increase in integrated average PbB from 10 to 30 µg/dL. The neurobehavioral development of this cohort, as assessed by the WISC was again studied at 7 years of age (n=494) (Baghurst et al. 1992). Multiple regression analysis adjusting for sex, parents' level of education, maternal age at delivery, parents' smoking status, socioeconomic status, quality of the home environment, maternal IQ, birth weight, birth order, feeding method, duration of breast-feeding, and whether the child's natural parents were living together revealed a statistically significant inverse relationship between IQ and blood lead levels from birth through 7 years of age. This relationship was more evident for PbB levels at 15 months to 4 years. The IQ was reduced by 4.4–5.3 points for an increase in PbB levels of 10–30 µg/dL. In a later publication, the authors examined the relationship between lead concentration in deciduous central upper incisor teeth from 262 Port Pirie children and intellectual functioning (McMichael et al. 1994). Intellectual functioning was assessed with the revised WISC (WISC-R) when the children were in their eighth year; the average age at which the teeth were shed was 6.8 years. The results showed

that there was an inverse relation between tooth lead concentration and intellectual development. Twelve of 13 scales/subscales assessed were inversely associated with tooth lead concentration (p#0.10). A particularly strong inverse association was found for the Block Design subscale, which tests a subject's perceptual organization and synthesis, spatial visualization, nonverbal concept formation, and visual-motor coordination. After adjusting for all the measured covariates, it was found that the full-scale IQ declined 2.6 points for each natural-log unit increase in tooth lead concentration, expressed in ppm. The results also showed no statistically significant interaction between a child's sex and tooth lead concentration for any of the WISC-R scales. A subsequent study of this cohort, also at age 7 years (mean PbB, 11.6 µg/dL), showed a dose-related inverse association between both prenatal and postnatal PbB concentrations and children's visual motor performance, assessed with the Beery Developmental Test of Visual-Motor Integration (VMI) (Baghurst et al. 1995). The children's mean VMI score was 13.4 points. The analyses showed that for an increase in lifetime average PbB concentration from 10 to 30 µg/dL, the expected deficit was estimated to be 1.6 points. The association between PbB and VMI scores were stronger in girls and in children from lower socioeconomic background. Baghurst et al. (1995) pointed out that visual-motor integration may be a more sensitive index than global measures of development, such as IQ. They also stated that although a decrease of 1.6 points in VMI in an individual may not be considered clinically or biologically important, a change of this magnitude across an entire community may be worrisome.

The Port Pirie cohort was evaluated again at the age of 11–13 years (Tong et al. 1996). The cohort consisted of 375 children whose current geometric mean blood level was 7.9 µg/dL (range, 0.6–30.9 µg/dL). The revised version of the WISC was used to assess the cognitive abilities of each child. Unadjusted analyses of the results revealed a consistent inverse relation between PbB and scores for all 12 subscales of the WISC-R. This association held for PbB concentrations at all ages, except at birth. The magnitude of the deficit in IQ with increased PbB was similar for the verbal and performance scales. The larger IQ deficits were associated with PbB concentrations measured at earlier ages and with lifetime average PbB concentration. Simple regression analyses showed that all measures of PbB except those of the cord sample, were significantly inversely associated with IQ. In multiple regression analyses after the effects of potential confounders were adjusted for, the inverse associations between PbB concentration and IQ were attenuated. In particular, the associations of children's IQ with maternal and cord PbB concentrations lost significance. However, the inverse association between various measures of PbB concentrations over the range 15 months to 7 years and IQ remained significant or marginally significant after adjusting for potential confounders. The mean score for full scale IQ declined 3 points for a doubling

of lifetime PbB from 10 to 20 µg/dL. Individual subscales scores showed varying degrees of inverse association with lifetime PbB lead levels. However, those showing the strongest associations were the information, arithmetic, block design, and maze subscales. Analyses of the association between PbB concentrations stratified by thirds, between the ages of 2 and 11–13 years, and developmental status showed that the adjusted differences in developmental scores between the top and bottom thirds of exposure were 4 points on the Bayley mental developmental index at age 2; 4.8 points on the McCarthy general cognitive index at age 4; and 4.9 and 4.5 IQ points at 7 years and 11–13 years, respectively, after accounting for confounders.

In other prospective studies (Bellinger et al. 1984, 1985a, 1985b, 1986a, 1986b, 1987a, 1987b), cord PbB levels were determined at delivery, for 249 middle-class and upper-middle class Boston children. PbB levels and MDI and PDI scores were measured every 6 months thereafter. Infants born at <34 weeks of gestation were excluded from the study. Cord PbB lead values were <16 µg/dL for 90% of the subjects, with the highest value being 25 µg/dL. On the basis of cord PbB lead levels, the children were divided into low-dose (<3 µg/dL; mean = 1.8 µg/dL), medium-dose (6–7 µg/dL; mean = 6.5 µg/dL), and high-dose ($10 µg/dL; mean = 14.6 µg/dL) exposure groups. A slight but not significant direct correlation between cord PbB lead category and length of gestation was seen. However, analysis within gestational age categories indicated no correlation between cord PbB lead category and length of gestation (Bellinger et al. 1984, 1985a). The percentage of infants that were small for their gestational age increased with increasing cord PbB, although the trend was not statistically significant (Bellinger et al. 1984). Multivariate regression analysis revealed an inverse correlation between cord PbB levels and MDI scores at 6, 12, 18, and 24 months of age (Bellinger et al. 1985a, 1985b, 1986a, 1986b, 1987a). The high-lead group had an average deficit of 4.8 points on the covariate-adjusted MDI score as compared with the low-lead group. MDI did not correlate with postnatal PbB lead levels. No correlations between PDI and cord or postnatal blood lead levels were seen. The findings of earlier studies (Bellinger et al. 1985a, 1985b, 1986a, 1986a, 1987b) were confirmed in subsequent studies (Bellinger et al. 1989a, 1989b) and suggest that the younger the infants are, the more vulnerable they are to lead-induced developmental toxicity. Moreover, the decline in MDI scores varied with the child's age at exposure, the level of exposure, and socioeconomic status (Bellinger et al. 1989b). Infants in lower socioeconomic groups showed deficits at lower levels of prenatal exposure (mean PbB levels, 6–7 µg/dL) than children in higher socioeconomic groups. The early postnatal PbB levels (range, 10–25 µg/dL) were also associated with lower MDI scores, but only among children in lower socioeconomic groups. Follow-up evaluation of these children at approximately 5 years of age

showed that deficits in GCI scores correlated significantly with PbB levels at 24 months of age (mean 7 µg/dL), but not with prenatal PbB levels (Bellinger et al. 1991). These results suggest that prenatal PbB levels are a better predictor of cognitive development in infants than in 4–5-year-old children and that early developmental deficits associated with elevated PbB may not persist to 4–5 years of age, especially in socioeconomically advantaged families.

Bellinger and coworkers have presented preliminary findings regarding the association between pre- and postnatal lead exposure and problem behavior in the Boston children at the age of 8 years (Bellinger et al. 1994). Problem behavior was rated on the Teacher Report Form of the Child Behavior Profile. Prenatal and postnatal lead exposure was assessed by umbilical cord PbB (mean 6.8 µg/dL) and dentin lead of a shed deciduous tooth (mean 3.4 µg/g). The results showed that cord PbB level was not associated with overall prevalence or nature of problem behaviors. However, tooth lead was significantly associated with total problem behavior scores in both crude and adjusted analyses, and with both internalizing and externalizing scores. The association was not limited to children manifesting the most problems or the highest levels of tooth lead but was nevertheless considered modest; tooth lead accounted for less than 1% of the variance in total problem behavior scores. Furthermore, the authors recognized that the study provided little basis for distinguishing alternative hypothesis about temporal features of the association between tooth lead and problem behavior. According to Bellinger et al. (1994) two factors not measured in the study that could have influenced the outcome were the family history of psychiatric illness and the family microenvironment.

A neuropsychological evaluation of 148 of the Boston cohort children at age 10 years confirmed the continued presence of the association noted at 5 years of age (Bellinger et al. 1992). The primary end points evaluated were the WISC-R and the Kaufman Test of Educational Achievement (K-TEA). Analysis of the unadjusted data showed that all postnatal blood lead levels were inversely associated with Full Scale IQ measured at age 10; however, only the associations involving PbB level at ages 10 years, 57 months, and 24 months were statistically significant. This was also seen for both Verbal and Performance IQ scores. After adjusting for confounding, only the coefficient associated with 24-month blood lead level remained significant. It was also shown that the association between 24-month PbB and Full Scale IQ at age 10 years was not due simply to the high correlation between GCI scores at age 5 years and IQ. The decline in Full Scale IQ corresponded to 5.8 points per 10 µg/dL increase in 24-month PbB. PbB at 24 months was also significantly associated with Verbal IQ and five WISC-R subtest scores. Only PbB

levels at 24 months were significantly associated with adjusted K-TEA scores. For each 10 µg/dL increase in 24-month PbB the battery composite score declined 8.9 points. The results suggested that timing of exposure may be more important than magnitude alone and supported the hypothesis of an age-specific vulnerability.

Interim results of an investigation of 185 subjects and later results from the complete follow-up sample of 305 subjects in a prospective study of inner-city children (>80% black) born in Cincinnati, Ohio, were reported by Dietrich et al. (1986, 1987a, 1987b). Maternal PbB levels were measured at the first prenatal visit; cord PbB was measured at delivery; infant PbB levels were measured at 10 days and at 3 months of age; and neurobehavioral tests were performed at 3 and 6 months of age. Mean PbB levels were as follows: prenatal (maternal)—8.0 µg/dL (range, 1–27 µg/dL); umbilical cord—6.3 µg/dL (range, 1–28 µg/dL); 10-day-old and 3-month-old infants—4.6 and 5.9 µg/dL (range, 1–22 µg/dL for each). Multiple regression analyses, with perinatal health factors such as birth weight and gestational age treated as confounders, showed inverse correlations between prenatal or cord PbB levels and performance on the MDI at 3 months, and between prenatal or 10-day neonatal PbB levels and performance on the MDI at 6 months. No significant correlation of PbB level with PDI was seen. Male infants and low socioeconomic status infants appeared to be more sensitive to the effect on the MDI. Multiple regression analyses for male or low socioeconomic status infants showed covariate-adjusted decrements of 0.84 or 0.73 MDI points per µg/dL of prenatal or 10-day neonatal PbB, respectively (i.e., an approximate 8-point deficit for a 10-µg/dL increase in PbB) (Dietrich et al. 1987a).

Further analyses by structural equation modeling in the study by Dietrich et al. (1987a) showed that the effect of prenatal lead exposure on MDI was in part mediated through its effects on birth weight and gestational age. Higher prenatal PbB levels were associated with reduced birth weight and reduced gestational age, which were each significantly associated with reduced MDI scores (Dietrich et al. 1987a). Separate preliminary analyses of the data from the Cincinnati study by Bornschein et al. (1989) indicated that for each natural log unit increase in PbB, the decrease in birth weight averaged 114 g, but ranged from 58 to 601 g depending on the age of the mother. The authors reported that the threshold for this effect could be approximately 12–13 µg/dL PbB. In addition, a decrease in birth length of 2.5 centimeters per natural log unit of maternal PbB was seen, but only in white infants. In a later report, the PbB levels during prenatal (maternal PbB, 8.2 µg/dL; range, 1–27 µg/dL) and neonatal (4.8 µg/dL, range, 1–23 µg/dL) periods were found to be inversely related to a complex of sensorimotor developmental indices at 6 and

12 months of age. The prenatal maternal blood level was also related to lower birth weight, which in turn was related to poorer sensorimotor performance in infants during the first year of age (Dietrich et al. 1989).

The cognitive development of 258 children from the Cincinnati Lead Study was examined when the children were 4 years old (Dietrich et al. 1991). Cognitive development was assessed by the Kaufman Assessment Battery for Children (K-ABC), which measures general intelligence, information processing, and achievement for children between the ages of 2.5 and 12.5 years. The results showed that higher neonatal PbB levels were associated with poorer performance in all K-ABC subscales; however, there was a significant interaction between neonatal PbB and socioeconomic status. Results from separate regression analysis conducted to determine the nature of the interaction revealed that the association was limited to children from the poorest families. This, according to the authors, suggested that children from less advantaged environments express cognitive deficits at lower PbB levels than do children from families of relatively higher socioeconomic status. Prenatal (maternal) PbB levels were not related to 4-year cognitive status. Significant negative associations between postnatal PbB levels and K-ABC subscales were found in unadjusted regression analyses. These associations were most consistently significant for PbB levels at ages 3–4 years and mean lifetime PbB levels; PbB levels at ages 1–2 years were usually unrelated to K-ABC performance. No statistically significant effects of postnatal PbB on any of the K-ABC subscales was found after covariate adjustment. A subsequent evaluation of the same cohort at age 5 found that fetal (maternal), neonatal, and postnatal PbB levels were significantly and inversely associated with performance on the Filtered Word Subtest (FWS) of the SCAN (a screening test for auditory processing disorders) (Dietrich et al. 1992). In addition, higher postnatal PbB levels were associated with poorer performance on all cognitive developmental subscales of the K-ABC; however, after controlling for HOME scores and maternal intelligence most of the observed relationships lost statistical significance.

Two hundred and fifty-three children from the Cincinnati lead study cohort were administered the WISC-R again at approximately 6.5 years of age (Dietrich et al. 1993a). In this cohort, mean prenatal and neonatal PbB concentrations were 8.3 µg/dL and 5 µg/dL, respectively. Examination of the PbB concentration for the group from 3 to 60 months of age showed that PbB peaked at approximately 2 years of age and declined thereafter. Analysis of unadjusted data showed that prenatal and neonatal PbB were unrelated to intellectual capacity at 6.5 years, but almost every index of postnatal exposure was associated with Wechsler Performance IQ, including PbB at 66 and 72 months of age. Verbal IQ was associated only with

PbB close to the time of testing. When PbB regression coefficients were adjusted for HOME score, maternal IQ, birth weight, birth length, child sex, and cigarette consumption during pregnancy, postnatal PbB continued to be associated with lower Performance IQ. Also, the mean PbB concentrations during the 5th and 6th year of life were inversely associated with Wechsler Full Scale IQ. It was also found that, of the various cofactors, maternal IQ was usually the strongest predictor of a child's Full Scale IQ. Further analysis of the results suggested that averaged lifetime PbB concentrations in excess of 20 µg/dL were associated with deficits in Performance IQ on the order of about 7 points when compared with children with mean PbB concentrations #10 µg/dL. The authors noted that many of the children with lifetime average PbB 20 µg/dL had fairly high PbB levels at earlier ages. Dietrich et al. (1993a) stressed that the statistical significance was retained after adjustment for covariates such as maternal IQ and HOME scores and suggested that this may be a function of the increased reliability and precision of measurement which is gained when testing older children.

Two hundred and forty-five children from the same cohort examined by Dietrich et al. (1993a) were also evaluated at approximately 72 months of age with a comprehensive and standardized assessment of gross- and fine-motor functioning using the Bruininks-Oseretsky Test of Motor Proficiency (BOTMP) (Dietrich et al. 1993b). The authors hypothesized that measures of motor development may be less confounded with sociohereditary cofactors in lower socioeconomic status populations than cognitive or other language-based indices. In the BOTMP, gross motor skills are assessed with the subtests of Running Speed and Agility, Balance, Bilateral Coordination, and Strength, while fine-motor skills are indexed by the subtests of Response Speed, Visual-Motor Control, and Upper Limb Speed and Dexterity. As a group, the children showed average performance on the Bilateral Coordination, Strength, Upper-Limb Coordination, and Upper-Limb Speed and Dexterity subsets, but did poorly on the Balance, Response Speed, and Visual-Motor Control subtests relative to national norms. Prior to covariate adjustment, the results showed that prenatal, neonatal, and postnatal PbB levels were unrelated to Balance, Strength, Upper-Limb Coordination, or Response Speed. However, neonatal and/or postnatal PbB were significantly associated with lower scores on the Bilateral Coordination, Visual-Motor Control, and Upper-Limb Speed and Dexterity subtests as well as the Fine Motor Composite. After adjusting for HOME scores, maternal IQ, social class, and child sex and race, Bilateral Coordination, Visual-Motor Control, Upper-Limb Speed and Dexterity, and the Fine Motor Composite retained some significant relationships to neonatal and/or postnatal PbB. Again, prenatal (maternal) PbB was not related to BOTMP performance. However, neonatal PbB levels were significantly associated with lower scores on the Upper-Limb Speed and Dexterity subtests and the Fine Motor

Composite and marginally related to lower scores on the Bilateral Coordinations subtests. Further analysis of the results revealed that children having a mean lifetime PbB of $9 µg/dL appeared to experience a deficit on both the Bilateral Coordination subtests and Fine Motor Composite relative to children in the lowest PbB quartile.

Some neurobehavioral effects (decreased ability to self-quiet and to be consoled) seemed to be associated with a rise in maternal blood lead levels from 36 weeks gestation to birth (Rothenberg et al. 1989a). Absolute PbB levels did not appear to be associated with effects. These results were obtained on 42 mother-infant pairs selected in the Mexico City pilot study. Blood samples were obtained at 36 weeks gestation from the mother. At birth, cord blood samples and maternal samples were obtained. The Brazelton Neonatal Behavioral Assessment Scale (NBAS) was administered by psychologists certified in the use of this instrument. The principal shortcoming of this study is the small sample size (42–50 mother-baby pairs, depending on the end point measured). Large numbers of statistical analyses were performed, increasing the likelihood that some significant associations would occur by chance.

Emory et al. (1999) evaluated 103 African-American newborns with the NBAS. Maternal PbB levels were obtained at 6–7 months of pregnancy. No significant differences were found between quartiles across Brazelton Cluster scores. The researchers then compared the low quartile group (maternal PbB #1 µg/dL; mean=0.855 µg/dL; n=26) with the high quartile group (maternal PbB $2.5 µg/dL; mean=4.01 µg/dL; n=14) and found modest detrimental effects as determined by four Brazelton item scores related to motor control and attention. A slight trend was observed when PbB levels were plotted against motor maturity and hand-to-mouth activity.

In a prospective study of mothers and infants in Cleveland, Ohio (Ernhart et al. 1985, 1986, 1987; Wolf et al. 1985), mean PbB levels at the time of delivery were 6.5 µg/dL (range, 2.7–11.8 µg/dL) for 185 maternal samples and 5.8 µg/dL (range, 2.6–14.7 µg/dL) for 162 cord samples. There were 132 mother-infant pairs of data. The infants were evaluated for anomalies using a systematic, detailed protocol and for neurobehavioral effects using the NBAS and part of the Graham-Rosenblith Behavioral Examination for Newborns (G-R), including a Neurological Soft Signs scale. Hierarchical regression analysis was performed. No evidence of an association between PbB levels and morphological anomalies was found. This relatively small number of subjects, however, may not have been sufficient for the detection of differences in low frequencies of anomalies. Using the complete set of data, abnormal reflexes and

neurological soft signs scales were significantly related to cord PbB lead levels and the muscle tonicity scale was significantly related to maternal PbB level. Using data from the mother-infant pairs, the only significant association found was between the Neurological Soft Signs score and cord PbB levels, which averaged 5.8 µg/dL and ranged up to only 14.7 µg/dL; no association with maternal PbB levels was seen (Ernhart et al. 1985, 1986). A brief, preliminary report on later outcomes from this study reported a significant association between the Neurological Soft Signs measure and the MDI scores at 12 months (Wolf et al. 1985). Hence, it is possible to infer an indirect effect of cord PbB on MDI (Davis and Svendsgaard 1987; EPA 1986a), although Ernhart et al. (1985, 1986) did not reach such a conclusion. The effects noted by these investigators were significantly related to cord PbB levels that averaged 5.8 µg/dL and ranged upward to only 14.7 µg/dL.

A later analysis (Ernhart et al. 1987) related PbB levels obtained at delivery (maternal and cord blood) and at 6 months, 2 years, and 3 years of age to developmental tests (MDI, PDI, Kent Infant Development Scale [KID], and Stanford-Binet IQ) administered at 6 months, 1 year, 2 years, and 3 years of age, as appropriate. After controlling for covariates and confounding risk factors, the only significant associations of blood lead with concurrent or later development were an inverse association between maternal (but not cord) blood lead and MDI, PDI, and KID at 6 months, and a positive association between 6-month PbB and 6-month KID. The investigators concluded that, taken as a whole, the results of the 21 analyses of correlation between blood lead and developmental test scores were "reasonably consistent with what might be expected on the basis of sampling variability," that any association of blood lead level with measures of development was likely to be due to the dependence of both PbB and development on the caretaking environment, and that if low-level lead exposure has an effect on development the effect is quite small. Ernhart et al. (1987) also analyzed for reverse causality (i.e., whether developmental deficit or psychomotor superiority in infants at 6 months of age contributes to increases in subsequent blood lead levels). No significant correlations were observed when covariates were controlled. Greene and Ernhart (1991) conducted further analyses of the 132 mother-infant pairs in the Cleveland Prospective Study searching for a potential relationship between prenatal lead exposure and neonatal size measures (weight, height and head circumference) and gestational age. No such relationship was observed.

The predictive value of different markers of lead exposure for neurobehavioral performance (WISC verbal, performance, and full-scale IQs; Wiener [Vienna] reaction performance tests; Cued Reaction Time) was investigated by Winneke et al. (1985a, 1985b). This investigation involved the follow-up, at 6–7 years of

age, of 114 children from an original study population of 383 children born in Nordenham, Germany. At delivery, the mean maternal PbB level was 9.3 µg/dL (range, 4–31 µg/dL), and the mean cord PbB level was 8.2 µg/dL (range, 4–30 µg/dL); most of the PbB levels were #15 µg/dL. Cord and maternal PbB levels were highly correlated. Stepwise multiple regression analyses indicated that maternal PbB levels at delivery accounted for nearly as much of the variance in neurobehavioral test scores at 6–7 years as did contemporary PbB levels in the children. With either exposure marker, significance was seen only in increased errors on the Wiener Reaction Performance tests.

Bonithon-Kopp et al. (1986b) investigated another potential marker for lead exposure. Maternal and infant hair lead levels, determined from hair samples taken at birth, were found to be correlated inversely with results on neurobehavioral tests (McCarthy Scales of Children's Abilities) when the children were tested at 6 years of age. Other studies have also reported associations between hair lead levels and behavioral or cognitive test scores, but measures of lead in hair may not accurately reflect internal body burden of lead, and such data should not be used to evaluate internal dose-response relationships (EPA 1986a).

A few studies have reported associations between prenatal lead exposure and changes in heme metabolism. In a study of 294 mother-infant pairs, Haas et al. (1972) reported mean PbB levels of 16.98 µg/dL for mothers and 14.98 µg/dL for newborns. Infant PbB levels and ALA-U were positively correlated. The authors, however, did not report the levels of ALA-secretion in infants and mothers with no lead exposure. In pregnant urban women (Kuhnert et al. 1977), cord erythrocyte lead levels ranged from 16 to 67 µg/dL of cells (mean: 32.9 µg/dL) and were inversely correlated with ALAD activity, as were maternal erythrocyte lead levels. In a study of 500 mothers at delivery, Lauwerys et al. (1978) reported negative correlations between PbB levels and ALAD activity in both mothers and their infants (cord blood). No correlation between PbB level and erythrocyte protoporphyrin was seen. PbB levels averaged 10.2 µg/dL with a range of 3.1–31 µg/dL in the mothers and 8.4 µg/dL with a range of 2.7–27.3 µg/dL in the infants. Taken together, the results of these studies indicate that ALAD activity may be a more sensitive indicator of lead effects on fetal heme synthesis than erythrocyte protoporphyrin or ALA-U levels (EPA 1986a). In contrast to the findings of Lauwerys et al. (1978), the measurement of maternal and umbilical cord PbB levels and FEP levels for 95 mother-infant pairs from Toronto showed a significant inverse correlation. Most infants had cord PbB levels below 7 µg/dL; the cord blood FEP levels were higher than the maternal levels (Koren et al. 1990). The higher FEP levels may reflect immature hematopoiesis.

Developmental effects that have been observed in humans following exposure to low levels of lead include reduced birth weight, reduced gestational age and neurobehavioral deficits or delays. No evidence of an association with major congenital malformations has been found, although one study reported an association between cord PbB levels and the collective occurrence of minor anomalies. The evidence for an association between PbB levels and reduced birth weight and gestational age is inconsistent. The weight of evidence indicates that there may not be a direct association. There is a predominance of negative results, with the most recent (and presumably best designed) studies showing no such association. The evidence in support of neurobehavioral deficits or delays is more consistent, with most of the studies indicating that there is an association between lead exposure at low levels and developmental neurobehavioral effects.

2.2.1.7 Genotoxic Effects

Results of assays made following *in vivo* exposure from occupational sources are contradictory, but do suggest that lead may have an effect on chromosomes. Increased frequency of sister chromatid exchange was not observed in one study of occupationally exposed adults with blood lead levels of 48.7 µg/dL (Maki-Paakkanen et al. 1981) or in environmentally exposed children with PbB levels of 30–63 µg/dL (Dalpra et al. 1983). A slight positive correlation between sister chromatid exchanges and increasing duration of exposure has been reported in lead-exposed workers (Grandjean et al. 1983). This observation was independent of PbB level. Similar slight increases of sister chromatid exchanges in lead-exposed workers that may have been confounded by age effects were reported in a study that used too few controls to show conclusive results (Leal-Garza et al. 1986). Increased frequencies of chromosomal aberrations (primarily chromatid-type) were seen in 21 battery factory workers; these elevations were positively correlated with PbB levels, and showed a marked increase when PbB levels reached 50 µg/dL. Sister chromatid exchanges were also significantly elevated in these workers when PbB levels reached 80 µg/dL (Huang et al. 1988b). This study examined a fairly small number of workers, but appropriate selection criteria were used in order to minimize the effects of other potential genotoxic factors, such as smoking, drinking, viral diseases, exposure to medical X-rays, chelation agents, or use of medications with known clastogenic effects. A common problem in these occupational studies is possible concurrent exposures to many other agents in the occupational environment.

Occupational exposure to lead is associated with increased mitotic activity in peripheral lymphocytes, increased rate of abnormal mitosis (Forni et al. 1976; Sarto et al. 1978; Schwanitz et al. 1970), and

increased incidence of chromosomal aberrations (Al-Hakkak et al. 1986; Forni et al. 1976, 1980; Nordensön et al. 1978; Schwanitz et al. 1970) at PbB levels ranging from 22 to 89 µg/dL. While a positive correlation between PbB levels and the frequency of chromosomal aberrations has been reported (Nordensön et al. 1978), most of the available data on occupationally exposed workers show no increase in the frequency of chromosomal aberrations when PbB levels ranged from 38 to 120 µg/dL (Bauchinger et al. 1977; Maki-Paakkanen et al. 1981; O'Riordan and Evans 1974; Schmid et al. 1972; Schwanitz et al. 1975) or in environmentally exposed children with PbB levels of 12–33 µg/dL (Bauchinger et al. 1977). Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

The information available regarding the association of occupational exposure to lead with increased cancer risk is generally limited in its usefulness because the actual compound(s) of lead, the route(s) of exposure, and level(s) of lead to which the workers were exposed were often not reported. Furthermore, potential for exposure to other chemicals including arsenic, cadmium, and antimony occurred, particularly in lead smelters, and smoking was a possible confounder (Cooper 1976; IARC 1987). These studies, therefore, are not sufficient to determine the carcinogenicity of lead in humans, and the following discussion is restricted to the most comprehensive of these studies.

The most extensive was a series of reports of a large number of workers at 6 domestic lead production plants (smelters and recycling plants) and 10 battery plants (Cooper 1976; Cooper and Gaffey 1975). A total of 7,032 individuals were studied. PbB lead levels were available for 1,850 individuals, and the distribution was as follows: 1,433 had a PbB concentration $40 µg/dL, 488 had $70 µg/dL, 188 had $80 µg/dL, and 77 had $100 µg/dL. Increased incidences of total malignant neoplasms were observed for both categories of lead workers, but the increase was statistically significant only for lead production workers. The increase in total malignancies appeared to be due to small, statistically nonsignificant increases in digestive and respiratory tract tumors (evident in both the lead production and battery workers) and urinary tract tumors (in production workers). In a statistical reanalysis of the Cooper and Gaffey (1975) data, Kang et al. (1980) determined that the incidence of total malignant neoplasms, cancers of the digestive tract, and cancers of the respiratory tract were statistically elevated in both lead production workers and battery workers.

In a follow-up to the original study, Cooper (1981) reported that lead had no cancer-inducing properties, although standard mortality ratios (SMRs) of 125–149% for total malignant neoplasms, 172% for respiratory cancer, and 229% for cancers of other sites were reported in battery workers. In a subsequent evaluation of a more select subset from the original study, Cooper et al. (1985) reported increased SMRs for total malignancies in both groups of workers (statistically significant only in the battery workers) attributed to digestive and respiratory cancers. These small excesses of cancer deaths could not be correlated with onset, duration, or level of exposure. In addition, no adjustments could be made for other concomitant industrial exposures or for smoking. The attributable risk of smoking could easily explain the small increase in respiratory cancer in an industrial cohort that contained an excess of heavy smokers. Also, a marginally significant increase in digestive tract cancer in acid-lead battery workers was observed during the early years of lead exposure (when lead levels were presumably higher than in later years) (Fanning 1988; Malcolm and Barnett 1982).

In a historical cohort mortality study of 1,990 primary lead smelter workers, an SMR of 2.04 for mortality from renal cancer was calculated (Selevan et al. 1985). The cohort consisted of workers who had worked at least 1 year, with at least 1 day of employment at the smelter between 1940 and 1965. The cohort had been heavily exposed to lead and in 1976 the PbB levels averaged 56.3 µg/dL. Exposures to cadmium and arsenic were generally minor. A follow-up study of this cohort was conducted from 1977 through 1988 (Steenland et al. 1992). Analysis of the follow-up study revealed an excess of kidney cancer, particularly in the high-lead group (SMR 2.39). Although, as the authors indicate, the study is limited by lack of detailed data on lead exposures, potential confounding exposures to cadmium and arsenic, lack of smoking data, and small cohort size, the results are of interest because animal studies associate lead exposure with kidney cancer (see Section 2.2.2.8). In addition, two cases of renal cancer have been reported in occupationally exposed men who had symptoms of lead poisoning and high blood lead levels (Baker et al. 1980; Lilis 1981). In one case, the tumor was reported to contain a high level of lead and to have histopathological characteristics similar to those of kidney tumors induced by lead in animals (Baker et al. 1980).

In a study of cancer incidence in workers exposed to tetraethyl lead, a statistically significant association was found between exposure to this compound and rectal cancer (odds ratio = 3.7; 90% confidence limits of 1.3–10.2) (Fayerweather et al. 1997). The odds ratio increased four times at the high-to-very high cumulative exposure level, demonstrating a dose-response relationship. When a 10-year latency was

assumed, the association became even more pronounced. No increases in the incidence of cancer at other sites (i.e., brain, kidney, lung, spleen, and bone) were observed in the exposed workers. A study that comprised 20,700 Finnish workers exposed to lead during 1973–1983 found a 1.4-fold increase in the overall cancer incidence and a 1.8-fold increase in the incidence of lung cancer among workers who had ever had a blood lead level $21 µg/dL (Anttila et al. 1995). The overall mortality for the whole cohort, however, was less than expected, and there was no clear excess mortality for specific causes of death. In order to examine the association of lung cancer with indices of lifetime exposure to lead and to obtain information on potential confounders, the authors conducted a case-referent study on lung cancer within the study base. Analysis of the results showed an increased odds ratio for lung cancer for concomitant exposure to lead and engine exhaust. In a subsequent study of this same cohort, an excess risk of nervous system cancer, specifically gliomas, was found in workers with a PbB concentration $29 µg/dL compared with those whose PbB concentration had not exceeded 14.4 µg/dL (Anttila et al. 1996). However, the authors stated that no firm conclusions could be drawn because of the small number of cases, the rather short follow-up time, and the low response rate.

2.2.2 Inhalation Exposure

2.2.2.1 Death

Deaths associated with occupational exposure to inorganic lead (which is predominantly by the inhalation route of exposure) are discussed in Section 2.2.1.1. No studies were located regarding death in animals after inhalation exposure to inorganic lead.

2.2.2.2 Systemic Effects

No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, dermal, or ocular effects in humans or animals after inhalation exposure to inorganic lead.

Respiratory Effects. No studies were located regarding respiratory effects in humans after inhalation exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the respiratory effects of lead in humans after multi-route exposure.

Lung weights in mice continuously exposed to lead nitrate at a concentration of 1.6 mg lead/m^3 for 28 days were slightly but significantly elevated. The lungs from these mice appeared hemorrhagic at necropsy. These effects were most likely due to pulmonary edema resulting from an irritative response to the inhalation of lead aerosol for 28 days (Hillam and Ozkan 1986). Increased lung weight and hemorrhage were not observed in the lungs of mice similarly exposed for 14 days, indicating that the effects observed in mice exposed for 28 days were exposure duration dependent (Hillam and Ozkan 1986). This LOAEL is presented in Table 2-2 and plotted in Figure 2-1.

Hematological Effects. As discussed in Section 2.2.1.2, lead has long been known to affect heme biosynthesis by affecting the activities of several enzymes of the heme biosynthetic pathway. Lead inhibits the activity of certain enzymes involved in heme biosynthesis, namely, ALAD, and ferrochelatase. The mechanisms for these effects are discussed in detail in Section 2.4. As a consequence of these changes, the activity of the rate limiting enzyme of the pathway, ALAS, is subsequently increased. The end results of these changes in enzyme activities are increased urinary porphyrins, coproporphyrin, and ALA; increased blood levels of ALA; and increased EP, FEP, and ZPP (EPA 1986a).

In one study, adult male volunteers were exposed to particulate lead in air at 0.003 or 0.01 mg lead/m^3 for 23 hours a day for 3–4 months. Mean PbB levels increased from 20 µg/dL (preexposure) to 27 µg/dL at the 0.003 mg/m^3 exposure level and from 20 µg/dL (preexposure) to 37 µg/dL at the 0.01 mg/m^3 exposure level. ALAD decreased to approximately 80% of preexposure values in the 0.003 mg/m^3 group after 5 weeks of exposure and to approximately 53% of preexposure values in the 0.01 mg/m^3 group after 4 weeks of exposure (Griffin et al. 1975b). These results are presented in Table 2-2 and plotted in Figure 2-1.

Hepatic Effects. A significant increase in liver weight was observed in mice continuously exposed to 1.6 mg/m^3 lead nitrate for 14 or 28 days as compared to air-exposed control animals (Hillam and Ozkan 1986). Although the authors suggest that these results indicate that inhalation exposure to lead may be toxic to the liver, no functional (i.e., serum enzyme) or histopathological studies were conducted. Therefore, the toxicological significance of this increase in liver weight is not known. These results are presented in Table 2-2 and plotted in Figure 2-1.

Renal Effects. No studies were located regarding renal effects in humans after inhalation exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the other systemic effects of lead in humans after multi-route exposure.

Table 2-2. Levels of Significant Exposure to Lead - Inhalation

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
ACUTE EXPOSURE							
Immunological/Lymphoreticular							
1	Mouse (Swiss-Webster)	14 d 7 d/wk 24 hr/d			1.6 (decreased spleen and thymus weight; decreased splenic and thoracic lymph node antibody forming cells; decreased total leukocyte count)		Hillam and Ozkan 1986 Pb(NO3)2
2	Rabbit (New Zealand)	4 d 3 hr/d			0.028 M (altered lung macrophage function including decreased phagocytosis, increased production of oxygen radicals, and increased LDH and lysozyme activities)		Zelikoff et al. 1993 PbO
INTERMEDIATE EXPOSURE							
Systemic							
3	Human	18 wk 23 hr/d	Hemato		0.011 M (47% decrease in ALAD activity)		Griffin et al. *1975b*
4	Rat (NS)	3 wk 7 d/wk 24 hr/d	Hemato		1 F (decreased ALAD activity)		Prigge and Greve 1977

Table 2-2. Levels of Significant Exposure to Lead - Inhalation (continued)

Key to[a] figure	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (mg/m3)	LOAEL Less serious (mg/m3)	LOAEL Serious (mg/m3)	Reference Chemical Form
5	Mouse (Swiss-Webster)	28 d 7 d/wk 24 hr/d	Resp		1.6 (increased lung weight; lung hemorrhage)		Hillam and Ozkan 1986 Pb(NO3)2
			Hepatic		1.6 (increased liver weight)		
			Renal	1.6			
			Bd Wt	1.6			
Immunological/Lymphoreticular							
6	Mouse (Swiss-Webster)	28 d 7 d/wk 24 hr/d			1.6 (decreased spleen and thymus weight, decreased leukocyte count, decrease in antibody titer following intraperitoneal immunization; decreased splenic antibody forming cells)		Hillam and Ozkan 1986 Pb(NO3)2
Developmental							
7	Rat (NS)	Gd 1-21 21 d 24 hr/d			1 (decreased ALAD in fetus)		Prigge and Greve 1977

[a]The number corresponds to entries in Figure 2-1.

ALAD = aminolevulinic acid dehydratase; d = day(s); F = female; Gd = gestational day; Hemato = hematological; hr = hour(s); LDH = lactatate dehydrogenase; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s).

Figure 2-1. Levels of Significant Exposure to Lead - Inhalation

Acute (≤14 days)

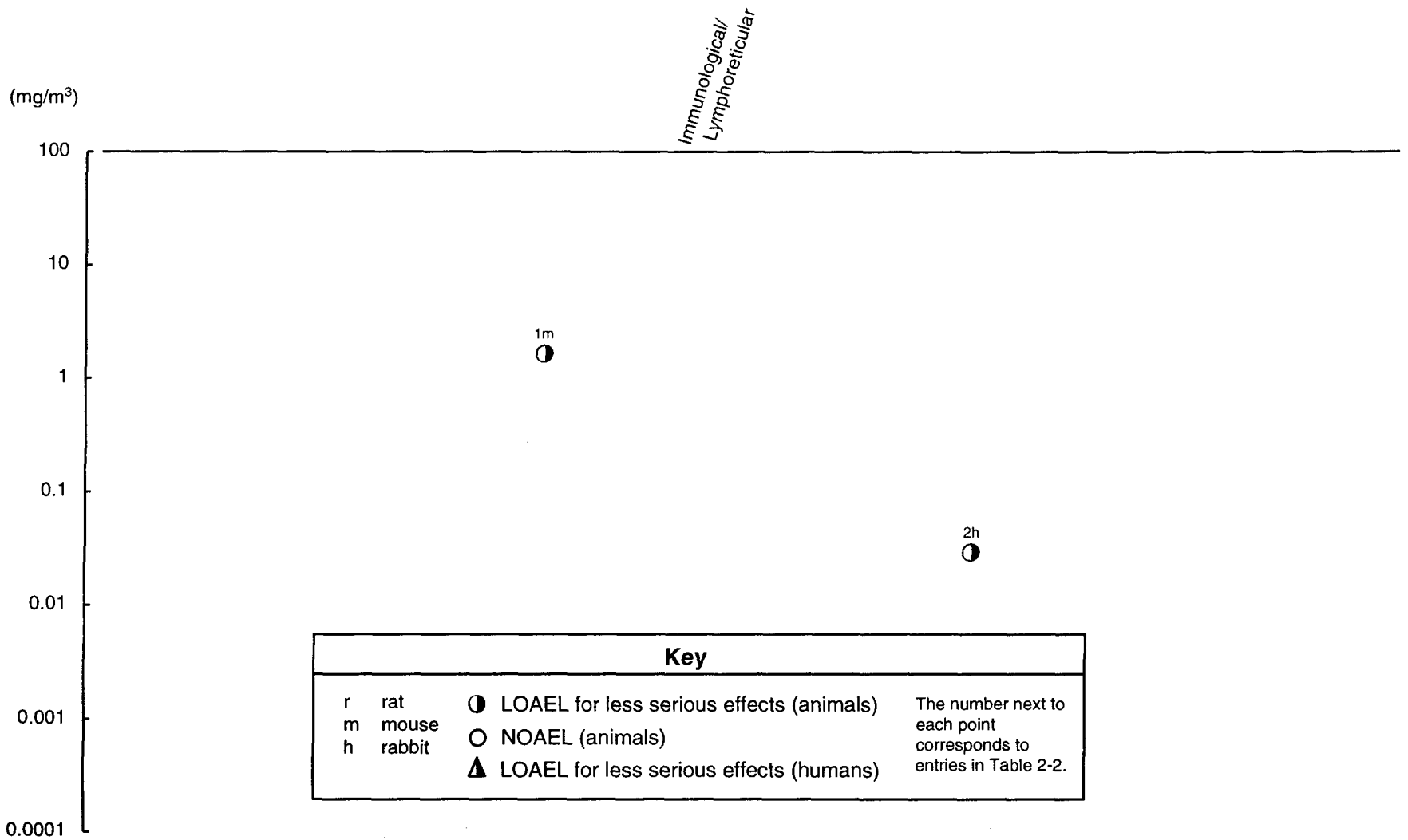
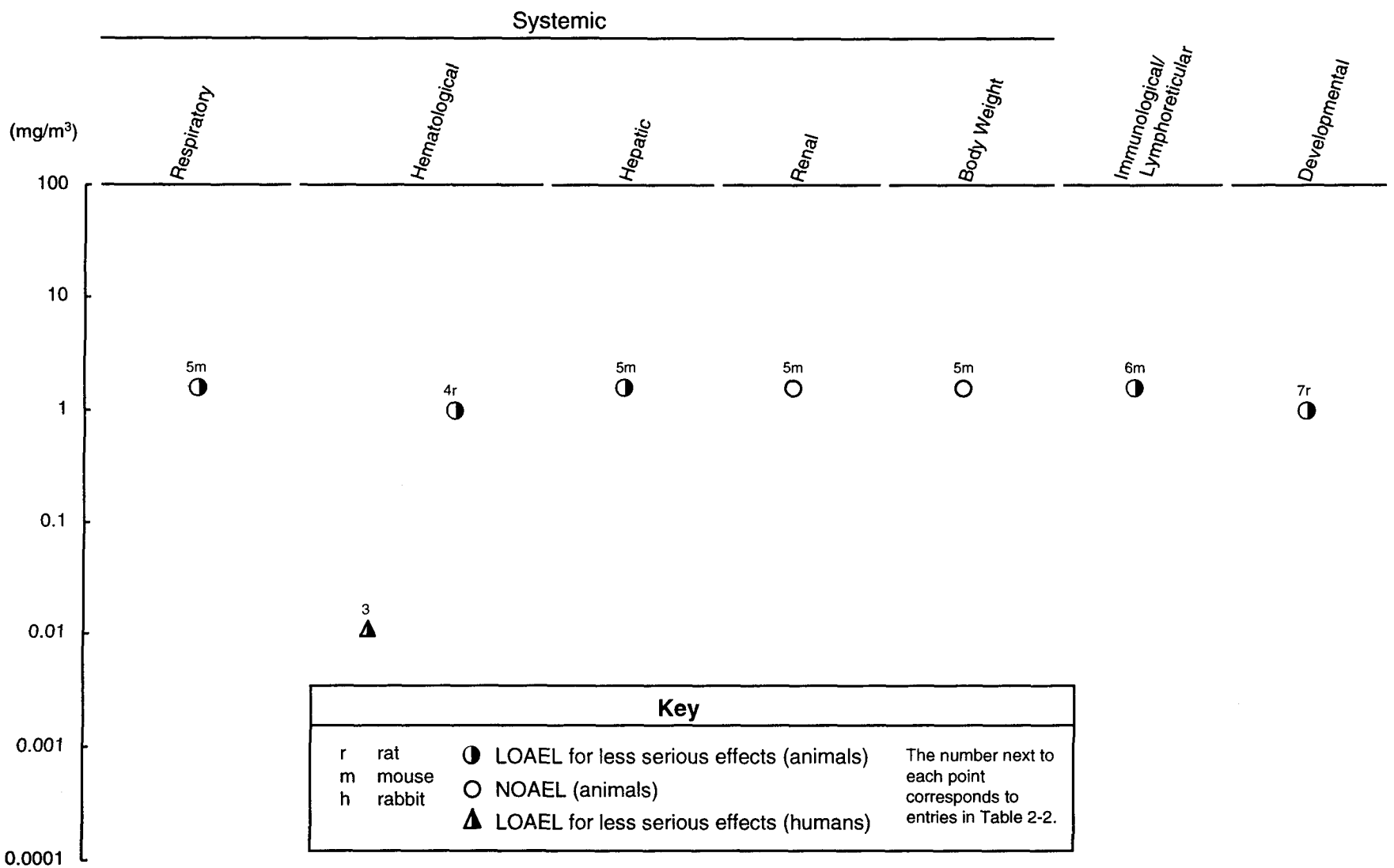


Figure 2-1. Levels of Significant Exposure to Lead - Inhalation (cont.)

Intermediate (15-364 days)



No increase in kidney weight was noted in mice continuously exposed to 1.6 mg lead/m^3 as lead nitrate for 28 days (Hillam and Ozkan 1986). No other studies were located regarding renal effects in animals after inhalation exposure to inorganic lead. These results are presented in Table 2-2 and plotted in Figure 2-1.

Body Weight Effects. No studies were located regarding body weight effects in humans after inhalation exposure to inorganic lead. See Section 2.2.1.2 for a discussion of effects of lead on growth in humans after multi-route exposure.

No effects on body weight were noted in mice continuously exposed to 1.6 mg lead/m^3 as lead nitrate for 28 days (Hillam and Ozkan 1986). No other studies were located regarding body weight effects in animals after inhalation exposure to inorganic lead. These results are presented in Table 2-2 and plotted in Figure 2-1.

2.2.2.3 Immunological Effects

One study was identified that examined the effects of acute-duration exposure to lead via inhalation on macrophage function in rabbits (Zelikoff et al. 1993). Lung macrophage function (phagocytosis, production of reactive oxygen intermediates, and biological activity of tumor necrosis factor-α [TNF]) were examined *in vitro* up to 72 hours after nose-only exposure to particulate PbO at a concentration of 0.028 mg Pb/m^3 for 3 hours per day for 4 days. Exposure to lead decreased phagocytic activity, increased spontaneous production of hydrogen peroxide by macrophages, and increased stimulated production of superoxide anion radicals. While spontaneous release of TNF was not altered by exposure to lead oxide, lipopolysaccharide-stimulated TNF activity was significantly decreased immediately and 24 hours after the last exposure; this was followed by a significant increase in activity relative to controls at 72 hours. Exposure to PbO also resulted in a significant increase in lactate dehydrogenase activity (marker of lung cell damage) and lysozyme levels (marker of lysosomal membrane permeability) in the fluid 24 and 72 hours after the final exposure. The concentration of lead in blood from the lead-exposed rabbits remained near control levels (1–2 μg/dL).

The effects of acute- and intermediate-duration inhalation lead exposure on local and systemic immune function following intratracheal, intraperitoneal, or intravenous immunization were studied in mice continuously exposed to lead nitrate for 14 or 28 days (Hillam and Ozkan 1986). Several parameters of local and systemic immune function were measured in the immunized, lead-exposed mice. Lead content

was significantly higher in the liver, spleen, thymus, lung, and kidney as compared to the control group in both the 14-day and 28-day exposure groups, but the effect was more pronounced in the 28-day exposure group. Both splenic and thymic weights were significantly decreased in all of the lead-exposed animals as compared to the controls. Decreases in leukocyte counts, circulating antibodies, and antibody forming cells were noted in different lead exposed groups. These results suggest that lead induces immunosuppression. Furthermore, since only the thoracic lymph node response was suppressed after intravenous immunization, it seems that inhaled lead does not cause systemic immunosuppression. These results also demonstrate that inhaled lead accumulates in the body, since higher tissue levels were observed following 28 days of exposure as compared to 14 days of exposure, and the immunosuppressive effects were more pronounced in the mice exposed for 28 days as compared to those exposed for 14 days.

The LOAEL from these studies are presented in Table 2-2 and plotted in Figure 2-1.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans or animals after inhalation exposure to inorganic lead. See Section 2.2.1.4 for a discussion of the neurological effects of lead in humans after multi-route exposure.

2.2.2.5 Developmental Effects

No studies were located regarding developmental effects in humans after inhalation exposure to inorganic lead. See Section 2.2.1.6 for a discussion of the developmental effects of lead in humans after multi-route exposure.

The data from the only available animal study (Prigge and Greve 1977) indicate that inhaled lead is not teratogenic. However, it impaired heme synthesis in both rat dams and fetuses. In this study, dams were exposed to 1, 3, or 10 mg lead/m^3 (chemical species not provided) throughout gestation (days 1–21). Maternal and fetal ALAD were inhibited at all exposure levels in a dose-related manner, and fetal (but not maternal) hematocrit and body weight were decreased at the 10-mg/m^3 lead level. These results suggest that the fetuses were more sensitive to lead-induced toxicity than were the dams.

The LOAEL from this study is presented in Table 2-2 and plotted in Figure 2-1.

2.2.2.6 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to inorganic lead. See Section 2.2.1.5 for a discussion of these effects in humans after multi-route exposure to inorganic lead.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans or animals after inhalation exposure to inorganic lead. See Section 2.2.1.7 for a discussion of these effects in humans after multi-route exposure to inorganic lead.

Genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after inhalation exposure to inorganic lead. See Section 2.2.1.8 for a discussion of cancer in humans following multi-route exposure to inorganic lead.

2.2.3 Oral Exposure

2.2.3.1 Death

Oral LD_{50} values for lead or its inorganic or organic salts were not found in the available literature. LD_{LO} values for a number of lead compounds have been estimated (Sax 1984, see Table 2-3). An LD_{LO} is defined as the lowest dose of a substance given over any given period of time in one or more divided portions reported to have caused death (Sax 1984). Furthermore, unlike LD_{50} values, these values are not derived statistically, and comparisons between compounds and species are difficult.

Table 2-3. Oral LD_{LO} Values for Lead Compounds

Compound	Species	LD_{LO} (mg/kg)[a]	LD_{LO} (mg lead/kg)
Lead acetate	Dog	300	191
Lead chloride	Guinea pig	2,000	1,490
Lead nitrate	Guinea pig	500	313
Lead oxide	Dog	1,400	1,300
Lead sulfate	Dog	2,000	1,366
	Guinea pig	30,000	20,500

[a] Based on the weight of individual compounds

Source: Sax 1984

LD_{LO} = lowest dose expected to cause death

Increased mortality was observed in a 2-year feeding study in rats (Azar et al. 1973). However, the increased mortality did not occur in a dose-related manner. The apparent lack of a dose-response relationship in either sex precludes meaningful conclusions regarding effect levels for mortality in this study. Increased mortality was reported in mice exposed to 0.5% lead acetate in the drinking water in a 3-generation study (Rasile et al. 1995). This level of lead in the water provided approximately 605 mg lead/kg/day.

The LOAEL values for mortality are presented in Table 2-4 and Figure 2-2.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory effects in humans or animals following oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the respiratory effects of lead in humans after multi-route exposure.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the cardiovascular effects of lead in humans after multi-route exposure.

Most of the animal database concerns effects of lead acetate, a “bioaccessible” form of lead that does not mimic the bioaccessibility of lead oxide, lead sulfide, or other forms of geologic lead. Lead acetate has been used as a paint pigment and hair dye. There is a large database that describes cardiovascular (primarily hypertensive) effects in laboratory animals resulting from exposure to lead. In the earlier studies, relatively high doses of lead were administered (i.e., 70 mg/day), and it is difficult to determine whether the hypertension observed in the treated animals was due to a direct effect of lead or was secondary to lead-induced renal damage (Victery 1988). Furthermore, increases in blood pressure were not always observed in these studies; sometimes decreases in blood pressure were observed, and PbB levels were not always quantified, making comparisons across studies difficult because of considerable experimental design differences (Victery 1988). The more recent chronic-duration exposure studies at doses that are otherwise nontoxic clearly indicate that lead ingestion is associated with an elevation in blood pressure that is sustained over a considerable portion of the animal's life span. For example, male rats given lead acetate at 50 ppm lead in the drinking water for 160 days had markedly increased blood pressure

Table 2-4. Levels of Significant Exposure to Lead - 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						
	Systemic						
1	*Human*	*5 d* 1x/d (C)	*Hemato*		0.03 M (24-61% decrease in ALAD activity)		Cools et al. 1976 PbAc
2	Human	3-14 d 7 d/wk 1x/d (C)	Hemato		0.02 (decreased ALAD activity)		Stuik 1974 PbAc
3	Rat (Wistar)	once (GW)	Hemato		17.5 F (increased activity of ALA-S in liver and kidney)		Chmielnicka et al. 1994 PbAc
4	Rat (Sprague-Dawley)	10 d ad lib (W)	Bd Wt		17.5 F (approximately 19% decreased body weight gain)		Minnema and Hammond 1994 PbAc
			Other		17.5 F (approximately 18% and 27% reductions in food and water intake, respectively)		
5	Rat (Fischer- 344)	6 d ad lib (W)	Hemato		146 M (decreased erythrocyte ALAD activity; increase urinary coproporphyrins)		Simmonds et al. 1995 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
6	Rat (Holtzman)	1-2 wk ad lib (F)	Other		734.7 M (blockage of calcium intestinal transport response to vitamin D)		Smith et al. 1981 PbAc
	Immunological/Lymphoreticular						
7	Mouse (Swiss-Webster)	14 d 7 d/wk 1x/d (G)			2.6 (decreased spleen and thymus weight, leukopenia)		Hillam and Ozkan 1986 Pb(NO3)2
	Neurological						
8	Rat (Wistar)	ppd 9-18 1x/d (GW)				50 M (impaired latent learning)	Massaro and Massaro 1987 PbAc
	Reproductive						
9	Rat (COBS)	Gd 6-16 11 d 1x/d (GW)		39 F		390 F (decreased number of pregnancies)	Kennedy et al. 1975 PbAc
10	Mouse (CD-1)	Gd 5-15 11 d 1x/d (GW)		39 F		390 F (decreased number of pregnancies)	Kennedy et al. 1975 PbAc
	Developmental						
11	Rat (COBS)	Gd 6-16 11 d 1x/d (GW)		39		390 (increased fetal resorptions, retarded skeletal development)	Kennedy et al. 1975 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
	INTERMEDIATE EXPOSURE						
	Death						
12	Mouse (HET)	multi gen (W)				605 F (increased fatality rates)	Rasile et al. 1995 PbAc
	Systemic						
13	Human	7 wk 7 d/wk 1x/d (C)	Hemato		0.01 M (decrease ALAD activity; increased RBC porphyrin)		Cools et al. 1976 PbAc
14	Human	21 d 7 d/wk 1x/d (C)	Hemato		0.02 (increased protoporphyrin IX in RBC of females)		Stuik 1974 PbAc
15	Monkey (Rhesus)	174 d (2 d at 10 mg/kg, 12 d at 3 mg/kg, 160 d at 0.7 mg/kg) 1x/d (GW)	Hemato		0.7 (increased ZPP)		Levin et al. 1988 PbAc
			Other	0.7			
16	Rat (Sprague-Dawley)	6 wk ad lib (W)	Cardio		873 M (myofibrillar fragmentation, mitochondrial swelling)		Asokan 1974 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
17	Rat (Fischer- 344)	30 d (F)	Hemato	1.5 M	5 M (increased urinary excretion of aminolevulinic acid)		Dieter et al. 1993 PbAc
			Renal	0.5 M	1.5 M (mild to moderate enlargement of nuclei in renal tubules)		
			Bd Wt	1.5 M	5 M (14-20% reduction in weight gain)		
			Other	5 M			
18	Rat (Fischer- 344)	30 d (F)	Hemato	1.5 M	5 M (increased urinary excretion of aminolevulinic acid)		Dieter et al. 1993 PbO
			Renal	1.5 M	5 M (mild to moderate enlargement of nuclei in renal tubules)		
			Bd Wt	1.5 M	5 M (14-20% reduction in weight gain)		
			Other	5 M			

Table 2-4. Levels of Significant Exposure to Lead - 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
19	Rat (Fischer- 344)	30 d (F)	Hemato	5 M			Dieter et al. 1993 PbS
			Renal	5 M			
			Bd Wt	5 M			
			Other	5 M			
20	Rat (Fischer- 344)	30 d (F)	Hemato	5 M			Dieter et al. 1993 Pb Ore
			Renal	5 M			
			Bd Wt	5 M			
			Other	5 M			
21	Rat (Wistar)	50 d (F)	Musc/skel		1 F (Decreased trabecular bone mass and thickness)		Escribano et al. 1997 PbAc
			Bd Wt	1 F			

Table 2-4. Levels of Significant Exposure to Lead - 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)	
22	Rat (albino)	4 wk ad lib (W)	Hemato		109 M	(decreased ALAD activity and hemoglobin; increased urinary excretion of ALA and increased blood zinc protoporphyrin)		Flora et al. 1993 PbAc
			Hepatic		109 M	(increased hepatic lipid peroxidation)		
			Bd Wt		109 M	(decreased body weight gain, but not quantitated)		
23	Rat (hooded)	3 wk ad lib (W)	Ocular				0.5 F (rod degeneration)	Fox and Chu PbAc
24	Rat (hooded)	3 wk ad lib (W)	Ocular				0.5 F (alterations in rod photo-receptors)	Fox and Farber 1988 PbAc
25	Rat (Long- Evans)	21 d Ld 1-21 (W)	Ocular		0.08 F	(decreased rod sensitivity and range of dark adaptation)		Fox and Katz PbAc
26	Rat (hooded)	3 wk ad lib (W)	Ocular		0.5 F	(decreased retinal sensitivity, rhodopsin, and rod outer segment length)		Fox and Rubinstein 1989 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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)	
27	Rat (Fischer- 344)	44 d ad lib (F)	Hemato		0.9 M (reduction in blood ALAD activity)		Freeman et al. 1996 PbAc
			Bd Wt	6.4 M			
			Other	6.4 M			
28	Rat (Fischer- 344)	44 d ad lib (F)	Hemato		6.4 M (reduction in blood ALAD activity)		Freeman et al. 1996 PbS
			Bd Wt	6.4 M			
			Other	6.4 M			
29	Rat (Fischer- 344)	44 d ad lib (F)	Hemato		0.9 M (reduction in blood ALAD activity)		Freeman et al. 1996 Pb Soil
			Bd Wt	6.4 M			
			Other	6.4 M			
30	Rat (Sprague-Dawley)	1-12 months (W)	Musc/skel		7.5 M (Decreased femur density)		Gruber et al. PbAc
31	Rat (Long- Evans)	26 d (W)	Musc/skel		145 M (altered bone development)		Hamilton and O'Flaherty 1995 PbAc
			Bd Wt		145 M (13% reduced weight relative to controls)		
			Other		145 M (decreased food intake)		

Table 2-4. Levels of Significant Exposure to Lead - 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)	
32	Rat (Wistar)	20 d ad lib (W)	Hemato		11.1 M	(36% decrease in ALAD activity in erythrocytes on day 20)	Hayashi et al. 1993 PbAc
			Hepatic	11.1 M			
			Renal	11.1 M			
			Bd Wt	11.1 M			
33	Rat (Sprague-Dawley)	63 d ad lib (W)	Hemato	0.9			Hubermont et al. 1976 Pb(NO3)2
34	Rat (Long- Evans)	90 d ad lib (W)	Bd Wt	38 M			*Kala and Jadhav* 1995a PbAc
			Other	38 M			
35	Rat (NS)	20-30 d 1x/d ad lib (W)	Hepatic	0.005	0.05	(decreased RNA, glycogen; pyknosis of Kupffer cells; increased liver weight)	Krasovskii et al. 1979 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
36	Rat (NS)	6-12 mo ad lib (W)	Hemato	0.0015	0.005 (impaired heme synthesi assessed by increased excretion of ALA and porphobilinogen)		Krasovskii et al. 1979 PbAc
			Hepatic	0.0015	0.005 (decreased glycogen, RNA, sulfhydryl groups, alterations in activities of oxidizing enzymes)		
37	Rat (Long- Evans)	18 d 1x/d (GW)	Hemato	6.4	19.2 (decreased hematocrit)		Overmann 1977 PbAc
38	Rat (Long- Evans)	159 d ad lib (W)	Cardio	0.03 F	0.3 F (increased systolic blood pressure)		Perry and Erlanger 1978 PbAc
39	Rat (Sprague-Dawley)	14 - 50 ad lib (W)	Bd Wt			502 M (24% reduction in body weight gain)	Ronis et al. 1996 PbAc
			Other		502 (17-20% reduction in water intake)		

Table 2-4. Levels of Significant Exposure to Lead - 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
40	Rat (Fischer- 344)	10 wk ad lib (W)	Hemato		14.6 M (decreased erythrocyte ALAD activity and ZPP/heme ratio; increased urinary coproporphyrins		Simmonds et al. 1995 PbAc
41	Rat (NS)	20 wk 5 x/wk (GW)	Bd Wt	0.64			Singh 1993 PbAc
			Other	0.64			
42	Rat (Porton)	4 mo 1 x/d (G)	Hepatic		64 F (significant reduction in hepatic AST, ALT and AP activities)		Singh et al. 1994 PbAc
43	Rat (Buffalo)	7 wk 1-2 x/wk (G)	Cardio			5 M (atrophy of the elastic fibers of the aorta)	Skoczynska et al. 1993 PbAc
			Hepatic		5 M (24% increase in serum triglycerides)		
			Bd Wt	20 M			
44	Rat (Wistar)	2-3 mo 7 d/wk ad lib (W)	Renal	414		828 M (proximal tubular dysfunction; increased urinary excretion of B2- microglobulin)	Vyskocil et al. 1989 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
45	Rat (Wistar)	2-4 mo ad lib (W)	Renal	81 F	320 F (tubular dysfunction as indicated by 2-3-fold increase in urinary excretion of B2-microglobulin)		Vyskocil et al. 1995; PbAc
			Bd Wt	320 F			
			Other	81 F	320 F (water intake reduced by half)		
46	Rat (Wistar)	7-8 wk 7 d/wk (F)	Hemato		318 M (decreased hematocrit)		Walsh and Ryden 1984; PbAc
			Renal		318 M (increased kidney weight)		
			Bd Wt		318 M (18% reduction in body weight gain)		
47	Rat (Wistar)	13 wk ad lib (W)	Bd Wt		77 M (15% reduction in final body weight)		Yokoyama and Araki 1992; PbAc
	Immunological/Lymphoreticular						
48	Rat (Fischer- 344)	31 d (W)		17	42 (decrease in blood total leukocyte count in offspring)		Miller et al. 1998; PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
Neurological							
49	Monkey (Rhesus)	344-362 d 7 d/wk 1x/d (F)				0.3 (deficit in reversal learning during exposure and 3 years after exposure ceased)	Bushnell and Bowman 1979b PbAc
50	Monkey (Rhesus)	357 d (2 d at 10mg/kg, 12 d at 3 mg/kg, 343 d at 0.7 mg/kg) 1x/d (G)				0.7-10 (impaired open field behavior, behavioral alterations)	Ferguson and Bowman 1990 PbAc
51	Monkey (Cynomolgus)	200 d 5 d/wk 1x/d (GW)		0.05		0.1 (impaired spatial discrimination reversal task at 9-10 years of age)	Gilbert and Rice 1987 PbAc
52	Monkey (Rhesus)	174 d (2 d at 10 mg/kg, 12 d at 3 mg/kg, 160 d at 0.7 mg/kg) 1x/d (GW)			0.7-10 (lower muscle tonus; decreased visual attentiveness)		Levin et al. 1988 PbAc
53	Monkey	200 d 5 d/wk 1x/d (GW)			0.05 (impaired nonspatial discrimination at 3 years of age)		Rice 1985b PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
54	Rat (NS)	35 d ad lib (W)			1.6 M (reduced radial maze accuracy)		Bushnell and Levin 1983 PbAc
55	Rat (Long- Evans)	>50 d ad lib (W)			4.2 M (increased sensitivity to muscarinic cholinergic agonists)		Cory-Slechta and Pokora 1995 PbAc
56	Rat (Wistar)	335 d ad lib (W)			9.5 M (increased fixed interval response rates to lever press)		Cory-Slechta et al. 1983 PbAc
57	Rat (Long- Evans)	186 d ad lib (W)			2.1 M (higher response rate for operant learning tests)		Cory-Slechta et al. 1985 PbAc
58	Rat (Long- Evans)	21 d (W)			8.3 (increased sensitivity of D2-D3 receptor subtype to dopamine agonists)		Cory-Slechta et al. 1992 PbAc
59	Rat (Long- Evans)	90 d ad lib (W)			2.2 M (reduction in dopamine in nucleus accumbens and in serotonin in brain stem and frontal cortex)		Kala and Jadhav 1995a PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
60	Rat (Long- Evans)	90 d ad lib (W)			4 M (reduced basal and potaddium induced release of dopamine from the nucleus accumbens)		Kala and Jadhav 1995b PbAc
61	Rat (NS)	6-12 mo ad lib (W)		0.0015	0.005 (disruption of conditioned responses and motor activity)		Krasovskii et al. 1979 PbAc
62	Rat (Wistar)	112 d ad lib (W)		14.3 M			Massaro and Massaro 1987 PbAc
63	Rat (Long- Evans)	18 d 1 x/d (GW)		6.4		19.2 (increased motor activity and operant delayed response; impaired motor coordination)	Overmann 1977 PbAc
64	Rat (NS)	20 wk 5 x/wk (GW)			0.64 (altered normal developmental pattern of proteins in neurons of young exposed prenatally and continued postnatally)		Singh 1993 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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 (NS)	10 wk 5 d/wk 1x/d (G)			0.64 (altered levels of neurotransmitters in the brain after pre- and postnatal exposure)		Singh and Ashraf 1989 PbAc
66	Rat (NS)	10 wk 5 d/wk 1x/d (G)		0.64			Singh and Ashraf 1989 PbAc
67	Rat (Long- Evans)	21 d (W)			8.3 (increased number of D2 dopaminergic receptors in striatum and nucleus accumbens)		Widzowski et al. 1994 PbAc
68	Rat (Wistar)	15 wk ad lib (W)			89.6 M (decrease in motor nerve conduction velocity)		Yokoyama and Araki 1986 PbAc
69	Rat (Wistar)	13 wk ad lib (W)			77 M (decreased slow axonal transport of proteins)		Yokoyama and Araki 1992 PbAc
	Reproductive						
70	Rat (Wistar)	9 wk 7 d/wk 1x/d (GW)			0.19 M (decreased number of spermatozoa)		Barratt et al. 1989 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
71	Rat (albino)	60 d ad lib (W)		22 M	45 M (partial inhibition of spermatogenesis)	90 M (testicular atrophy, cellular degeneration)	Chowdhury et al. 1984 PbAc
72	Rat (NS)	312 d 7 d/wk ad lib (W)		34			Fowler et al. 1980 PbAc
73	Rat (NS)	30 d 1x/d (G)			0.013 M (increased prostate weight)	0.26 M (impotence; hyperplasia; increase prostate weight)	Hilderbrand et al. 1973 PbAc
					0.014 F (irregular estrus cycles)	0.28 F (ovarian cysts; persistent vaginal estrus)	
74	Rat (Sprague-Dawley)	63 d ad lib (W)		0.9 F			Hubermont et al. 1976 Pb(NO3)2
75	Rat (NS)	6-12 mo ad lib (W)		0.0015 M	0.05 M (decreased activity of AIDH, SDH, NAD, and NADPH-diaphorase in spermatogenic epithelium and swelling of follicular epithelial cells in males)		Krasovskii et al. 1979 PbAc
76	Rat (NS)	20-30 d ad lib (W)		0.0015	0.005 M (dystrophy of Leydig cells)	0.05 M (decreased motility of spermatozoa, acid phosphatase activity increased)	Krasovskii et al. 1979 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
77	Rat (Sprague-Dawley)	14 - 50 ad lib (W)				502 (decreased testicular weights; delayed vaginal opening and disruption of estrus cycling)	Ronis et al. 1996 PbAc
78	Rat (Sprague-Dawley)	Gd 5-21 PNd 21-85 ad lib (W)			42 (reduced plasma testosterone and 17B-estradiol at birth)		Ronis et al. 1998b, 1998c PbAc
79	Rat	30 d ad lib (W)			40 (decreased LH and prolactin levels)		Sourgens et al. 1987 PbAc
80	Mouse (NMRI)	12 wk 7 d/wk 1x/d (W)				141 M (decreased number of implantations)	Johansson and Wide 1986 PbCl2
81	Mouse (NMRI)	6 wk ad lib (W)		176 F			Kristensen et al. 1995 PbCl2
	Developmental						
82	Monkey (Rhesus)	Gd 1-165 165 d (W)		5.7			Bushnell and Bowmann 1979a PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
83	Monkey (Macaca fascicularis)	Gd 1-165 195-210 d 1x/d (GW)				3 F (deficit in form discrimination at 6-18 months and in response to inhibition at 19-29 months in offspring)	Hopper et al. 1986 Pb(NO3)2
84	Monkey (Rhesus)	Gd 1-165 8.5 mo ad lib (W)		3.8			Levin and Bowman 1983 PbAc
85	Rat (Sprague-Dawley)	34 d Gd 16-21 PND 1-28 ad lib (W)				166 (30-40% reduction in ChAT activity in septum and hippocampus from pups and 30-40% decrease in cholinergic muscarinic receptors in septum)	Bielarczyk et al. 1994 PbAc
86	Rat (CD)	56 d ad lib (W)			25 (delayed synthesis of cytochrome C in cerebral cortex in male pups neonatally exposed)		Bull et al. 1979 PbCl2
87	Rat (Sprague-Dawley)	Gd 1-21 105-115 d ad lib (W)				3.5 (suppression of delayed hyper-sensitivity response and lymphocyte responsiveness to mitogen stimulation; decreased thymic weight in pups)	Faith et al. 1979 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
88	Rat (NS)	Gd 1-21 312 d ad lib (W)		0.07	0.7	(elevated kidney weight, cytomegaly in male pups)			Fowler et al. 1980 PbAc
89	Rat (CD)	201-291 d ad lib (W)		0.7	3.5	(delays in vaginal opening in pups)	7	(delayed righting reflex in pups)	Grant et al. 1980 PbAc
90	Rat (Sprague-Dawley)	70 d (W)			38	(decreased body weight and tail length in pups)			Hamilton and O'Flaherty 1994 PbAc
91	Rat (Wistar)	Gd 1-21 ad lib (W)			0.45	(decreased erythrocyte ALAD activity in pups; lower fetal weights)			Hayashi 1983 PbAc
92	Rat (Sprague-Dawley)	63 d ad lib (W)		0.09	0.9	(decreased ALAD activity, increased protoporphyrins in pups)			Hubermont et al. 1976 Pb(NO3)2
93	Rat (CD)	84-91 d ad lib (W)		0.7	3.5	(delayed vaginal opening)			Kimmel et al. 1980 PbAc
94	Rat (Sprague-Dawley)	Gd 1-21 105-112 d 1x/d (W)					2.24	(immune suppression; decreased thymus weight in pups)	Luster et al. 1978 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
95	Rat (CD)	56 d ad lib (W)					28	(delayed cortical development in pups)	McCauley et al. 1979 PbCl2
96	Rat (Long- Evans)	Gd 1-21 41 d 1x/d (GW)		48	64	(decreased fetal weight)			Miller et al. 1982 PbAc
97	Rat (Sprague-Dawley)	138-145d two gen (W)					0.7	(impaired righting reflex in pups)	Reiter et al. 1975 PbAc
98	Rat (Wistar)	77 d mat gest lact ad lib (W)		18	36	(increased activity in open field; failure to habituate to environment)			Rodrigues et al. 1993 PbAc
99	Rat (Wistar)	94 d mat gest lact ad lib (W)			17.5	(increased relative kidney weight in 6-month-old rats; increased ALAD reactivation index in kidney from 6-month-old rats)			Rodrigues et al. 1996 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
100	Rat (Sprague-Dawley)	Gd 5-21 Ld 1-21 Pd 21-85 ad lib (W)				502 (19% incidence of stillbirth vs 2% in controls; reduced weight gain of pups; decreased serum testosterone)	Ronis et al. 1996 PbAc
101	Rat (Sprague-Dawley)	Gd 5-21 PNd 21-85 ad lib (W)		42	126 M (reduced birth weight, crown-to-rump length, and anogenital distance)	377 (28% rate of stillbirth compared to 4% in controls)	Ronis et al. 1998b, 1998c PbAc
102	Rat (Wistar)	3 wk 7 d/wk ad lib (W)				15 (increase in volume of mossy fiber zone, granule cell layer, and commissural association zone in hippocampus of offspring)	Slomianka et al. 1989 *PbAc*
103	Rat (Sprague-Dawley)	Gd 1-21 56 d ad lib (W)				28 (slower extinction of acquired response when reward not present relative to controls)	Taylor et al. 1982 PbAc
104	Rat (Charles River)	*Gd 1-21* 5 mo (W)			2.2 *(inhibit renin synthesis* and release)		Victery et al. 1982a PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
105	Mouse (HET)	Gd 1-21 41 d ad lib (W)				608	(altered measures of square crossing and standups in open field, and in time to return to home cage)	Draski et al. 1989 PbAc
106	Gn Pig (NS)	Gd 22-52 Gd 22-62 (GW)				5.5	(reduced levels of gonadotropin-releasing hormone and somatostatin in hypothalamus from 52- and 62-day-old fetuses)	Sierra and Tiffany-Castiglioni 1992 PbAc
107	Gn pig (NS)	Gd 22 to Gd 52 or Gd 62 1x/d (GW)				5.5	(decrease in the neuroglial enzymes GPDH and glutamine synthetase, decreased blood ALAD and increased ZPP levels in pups and dams)	Sierra et al. 1989 PbAc
CHRONIC EXPOSURE								
Systemic								
108	Monkey (Rhesus)	9 yr (F)	Ocular		4 (decrease tyrosine hydroxylase in retinal cells; indication of alterations in cell wiring)			Kohler et al. 1997 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
109	Monkey (Rhesus)	1 yr 7 d/wk 1x/d (F)	Hemato	0.57			Mele et al. 1984 PbAc
			Bd Wt	0.57			
110	Monkey (Macaca fascicularis)	19-14 yr (C)	Hemato	2			Rice 1996 PbAc
			Bd Wt	2			
111	Rat (NS)	2 yr ad lib (F)	Hemato	0.9	3.1 (decreased ALAD activity)		Azar et al. 1973 PbAc
			Bd Wt	27	56.5 (unspecified decrease in weight gain)		
112	Rat (Sprague-Dawley)	18 mo 7 d/wk 1x/d (W)	Cardio	1.4 M	2.8 M (increased systolic and diastolic blood pressure)		Carmignani et al. 1988a PbAc
			Hepatic	5.6 M			
			Renal	5.6 M			
113	Rat (Sprague-Dawley)	76 wk ad lib (W)	Renal			371 M (necrotic & dilated cortical tubules, tubular protein casts)	Koller et al. 1985 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
114	Rat (Long- Evans)	<18 mo 7 d/wk 1x/d (W)	Cardio		0.014 F (increase in systolic blood pressure)		Perry et al. 1988 PbAc
			Bd Wt	0.71 F			
115	Dog (Beagle)	2 yr ad lib (F)	Hemato	1.25	2.5 (decreased ALAD activity)		Azar et al. 1973 PbAc
			Renal	2.5	12.5 (cytomegaly in males)		
			Bd Wt	12.5			
Neurological							
116	Monkey (Rhesus)	365 d (G)		0.7			Ferguson et al. 1996 PbAc
117	Monkey (Rhesus)	1 yr 7 d/wk 1x/d (F)				0.21 (reversal learning deficit; electrophysiological changes in auditory process)	Laughlin et al. 1983 PbAc
118	Monkey (Rhesus)	1 yr 7 d/wk ad lib (F)		0.64			*Levin and* Bowman 1989 PbAc
119	Monkey (Rhesus)	gestation to 9.75 yr (F)			4 (increased wave latency of brain stem auditory evoked potentials)		Lilienthal and Winneke 1996 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
120	Monkey (Rhesus)	1 yr 7 d/wk 1x/d (F)			0.19 (deficit in fixed interval schedule)		Mele et al. 1984 PbAc
121	Monkey (Rhesus)	9 yr (F)			7 (decrease content of S100 protein in hippocampal glia cells)		Noack et al. 1996 PbAc
122	Monkey (Cynomolgus)	200-270 d 7 d/wk 1x/d (G)				0.05 (impaired operant learning)	Rice 1985b PbAc
123	Monkey (Rhesus)	7-8 yr 1 x/d (C)				1.5 (altered performance on a fixed-interval-fixed-ratio schedule of reinforcement at age 7-8 years)	Rice 1992 PbAc
124	Monkey (Macaca fascicularis)	13 yr (C)			2 (increased pure tone hearing thresholds)		Rice 1997 PbAc
125	Monkey (Macaca fascicularis)	15-18 yr (F)			0.5 (slight increase in vibration threshold)		Rice and Gilbert 1995 PbAc
126	Monkey (Macaca fascicularis)	7-8 yr 5 d/wk 1x/d (C)				0.05 (impairment in delayed alternation behavioral task)	Rice and Karpinski 1988 PbAc

Table 2-4. Levels of Significant Exposure to Lead - 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
127	Dog (Beagle)	2 yr 7 d/wk ad lib (F)		12.5			Azar et al. 1973 PbAc
Reproductive							
128	Monkey (Cynomolgus)	10 yr 1 x/d (C)			1 F (decreased serum level of luteinizing and follicle stimulating hormones, and estradiol)		Foster 1992 PbAc
129	Monkey (Cynomolgus)	10 yr 1 x/d (C)			1 M (disrupture of general architecture of seminiferous epithelium)		Foster et al. 1998 PbAc
130	Monkey (Rhesus)	75 mo 5 d/wk (W)			1.3 F (impaired menstrual cycle)		Franks et al. PbAc
Cancer							
131	Rat (NS)	2 yr 7 d/wk ad lib (F)				27 (CEL: 5/50 renal tubular adenomas in males)	Azar et al. 1973 PbAc
132	Rat (Sprague-Dawley)	76 wk *ad lib* (W)				371 M (CEL: renal tubular *carcinomas in 13/16)*	Koller et al. 1985 PbAc

Table 2-4. Levels of Significant Exposure to Lead - Oral (continued)

Key to[a] figure	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)		
133	Mouse (Swiss)	2 yr ad lib (F)				83.2	(CEL: renal tubular adenomas and carcinomas in 7/25)	Van Esch and Kroes 1969 PbAc

[a]The number corresponds to entries in Figure 2-2.

ad lib = ad libitum; ALA = aminolevulinic acid: ALAD = aminolevulinic acid dehydratase; ALA-S = delta-aminolevulinic acid synthetase; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; Bd Wt = body weight; (C) = capsule; Cardio = cardiovascular; CEL = cancer effect level; ChAT = choline acetyltransferase; d = day(s); F = female; (F) = food; (G) = gavage; Gd = gestational day; gen = generation; GPDH = glucose-6-phosphate dehydrogenase; (GW) = gavage in water; Hemato = hematological; lact = lactation; Ld = lactational day; LD_{50} = lethal dose, 50% kill; LH = luteinizing hormone; LOAEL = lowest-observable-adverse-effect level; M = male; mat gest = mating gestation; mo = month(s); multi gen = multigenerational; NOAEL = no-observable-adverse-effect level; NS = not specified; Pd = postnatal day; RBC = red blood cell; RNA = ribonucleic acid; (W) = water; wk = week(s); yr = year(s); x = times; ZPP = zinc protoporphyrin

Figure 2-2. Levels of Significant Exposure to Lead - Oral

Acute (≤14 days)

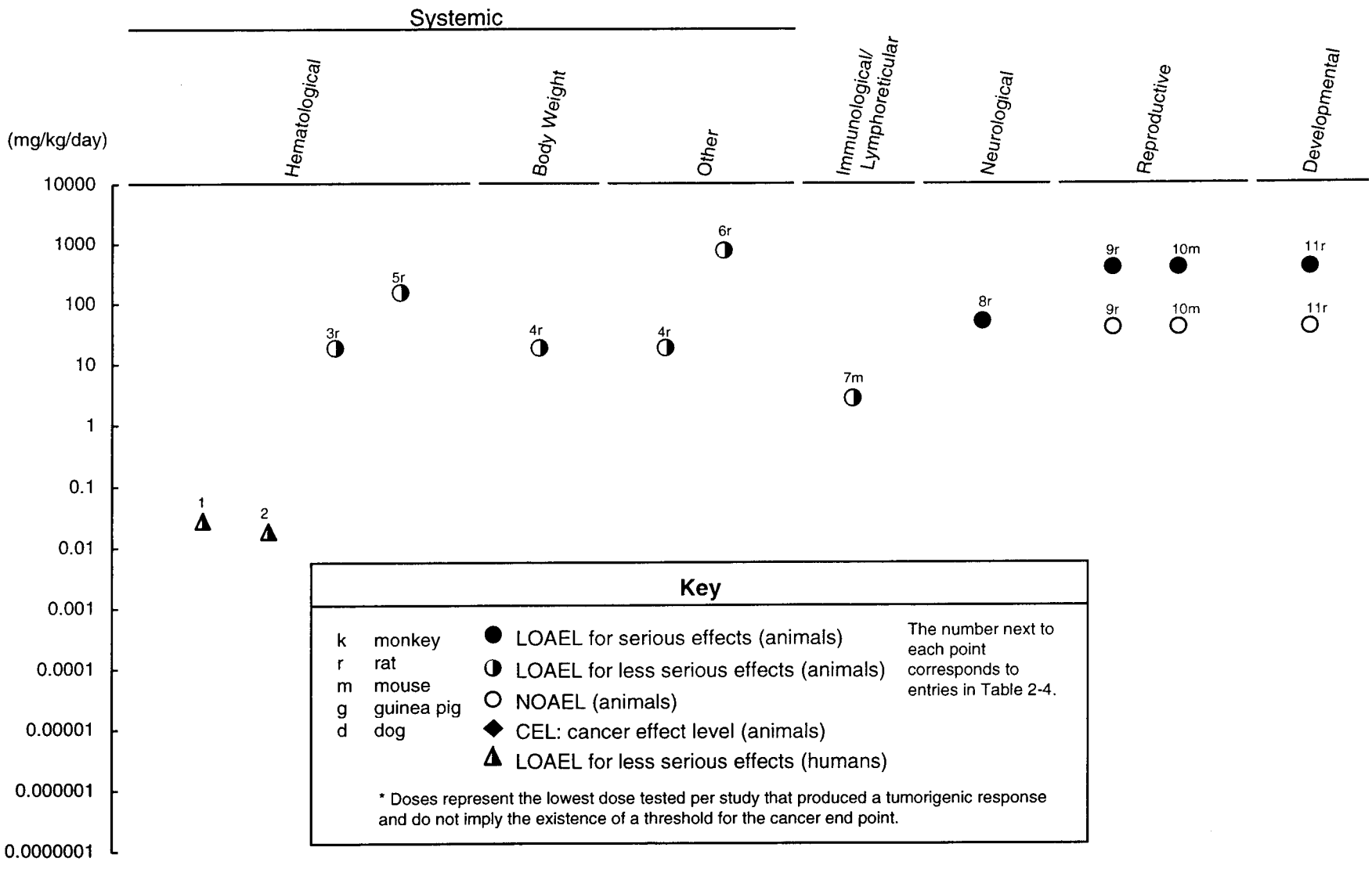


Figure 2-2. Levels of Significant Exposure to Lead - Oral (cont.)

Intermediate (15-364 days)

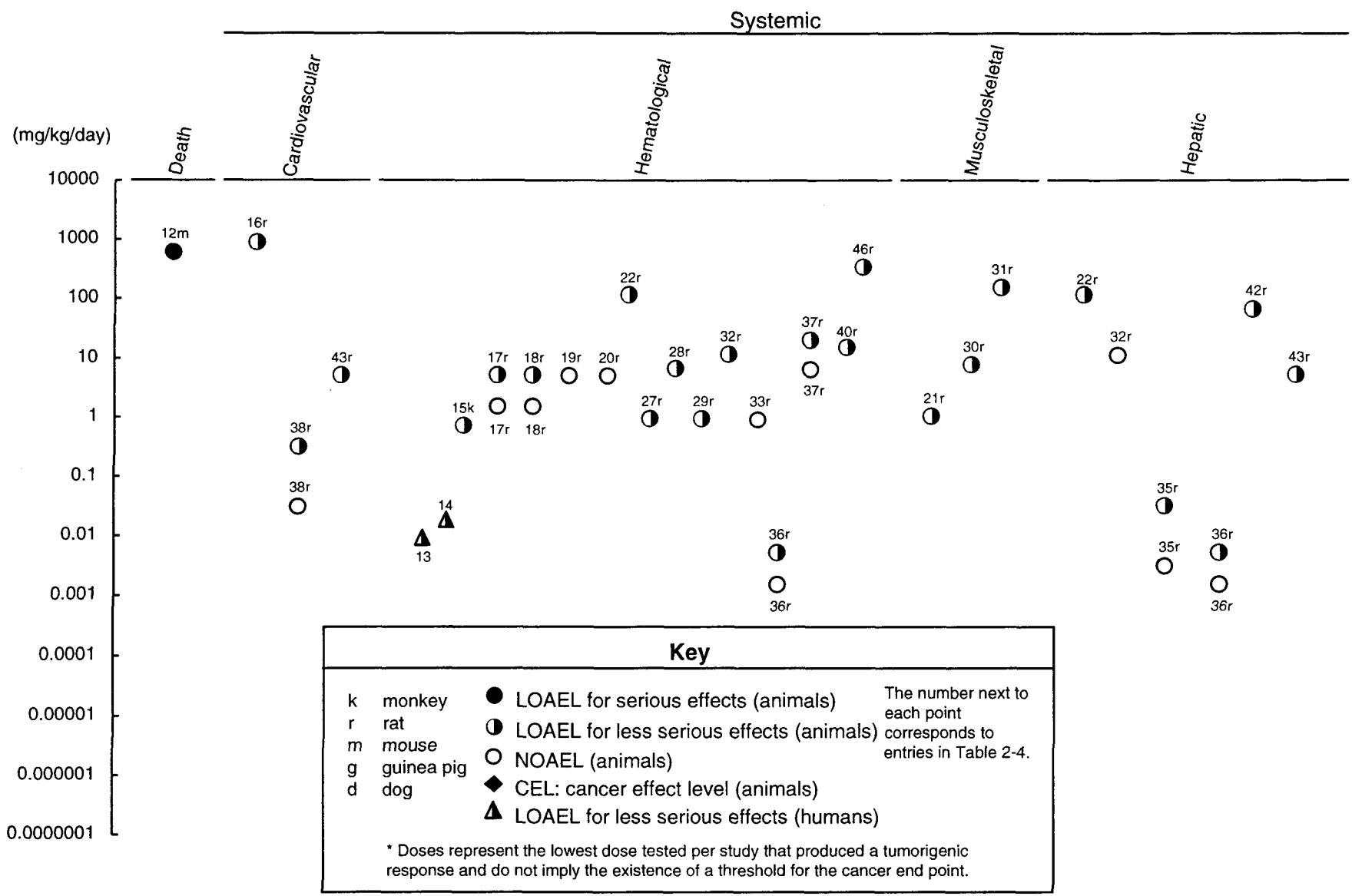


Figure 2-2. Levels of Significant Exposure to Lead - Oral (cont.)

Intermediate (15-364 days)

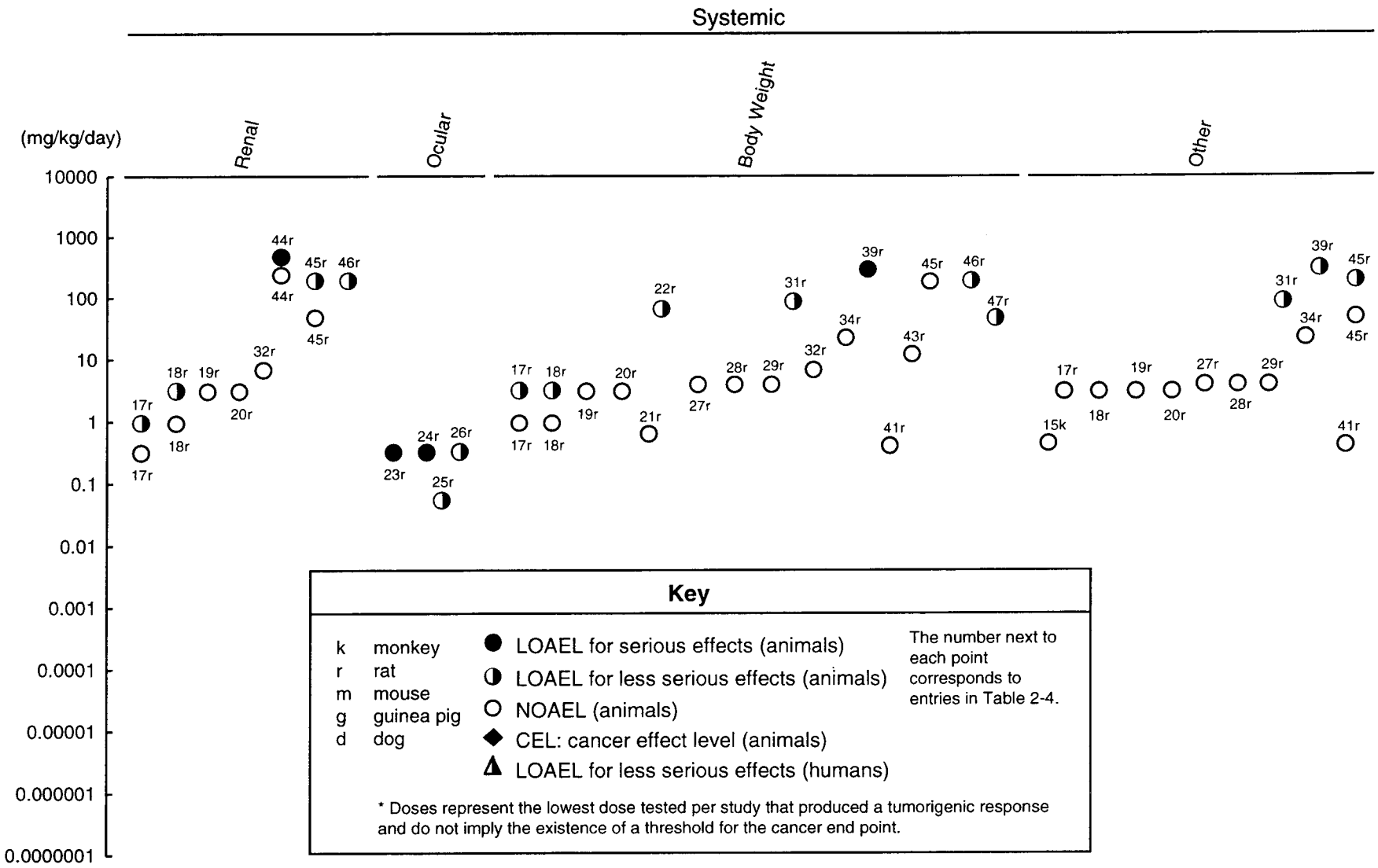


Figure 2-2. Levels of Significant Exposure to Lead - Oral (cont.)

Intermediate (15-364 days)

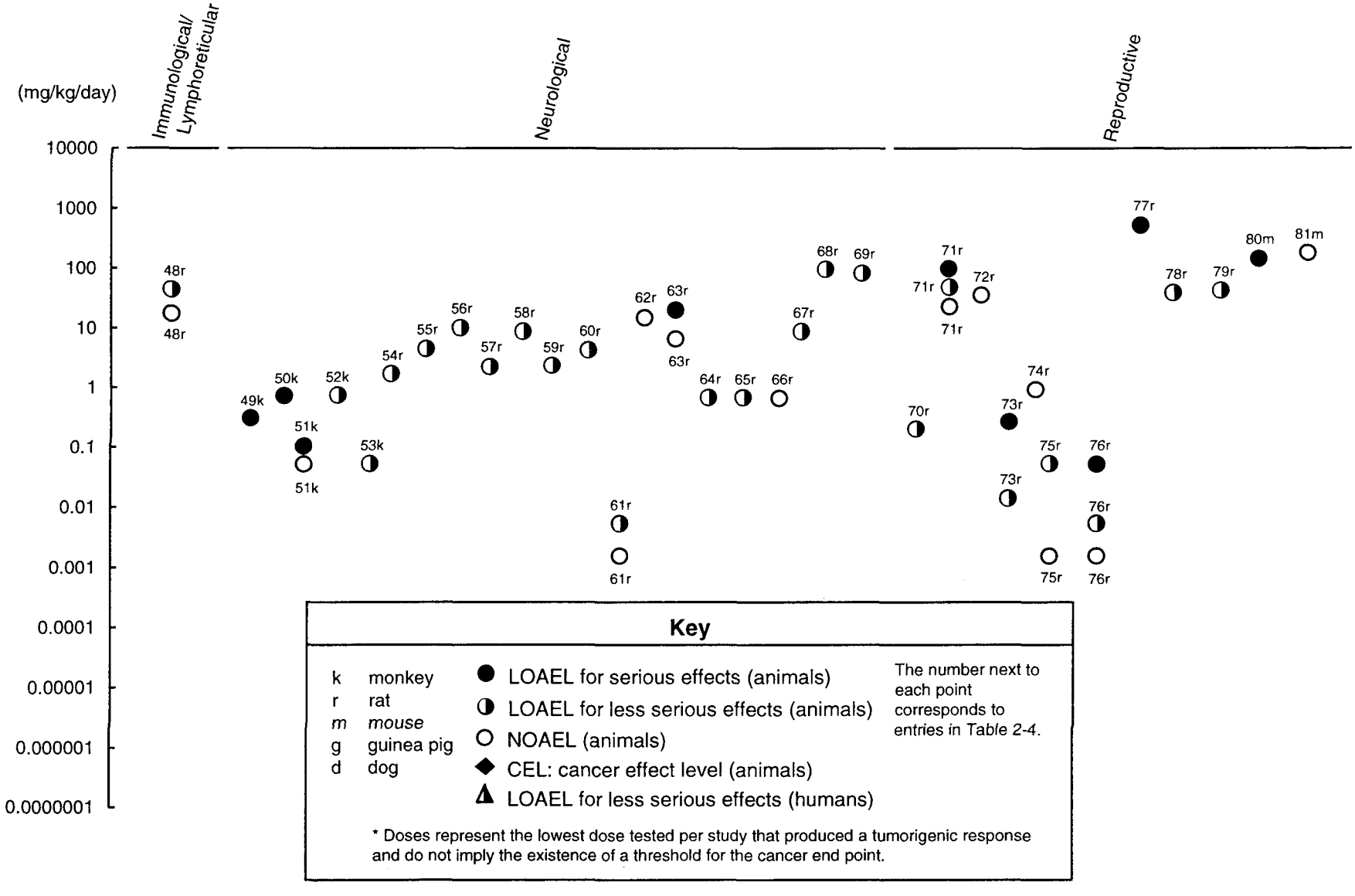


Figure 2-2. Levels of Significant Exposure to Lead - Oral (cont.)

Intermediate (15-364 days)

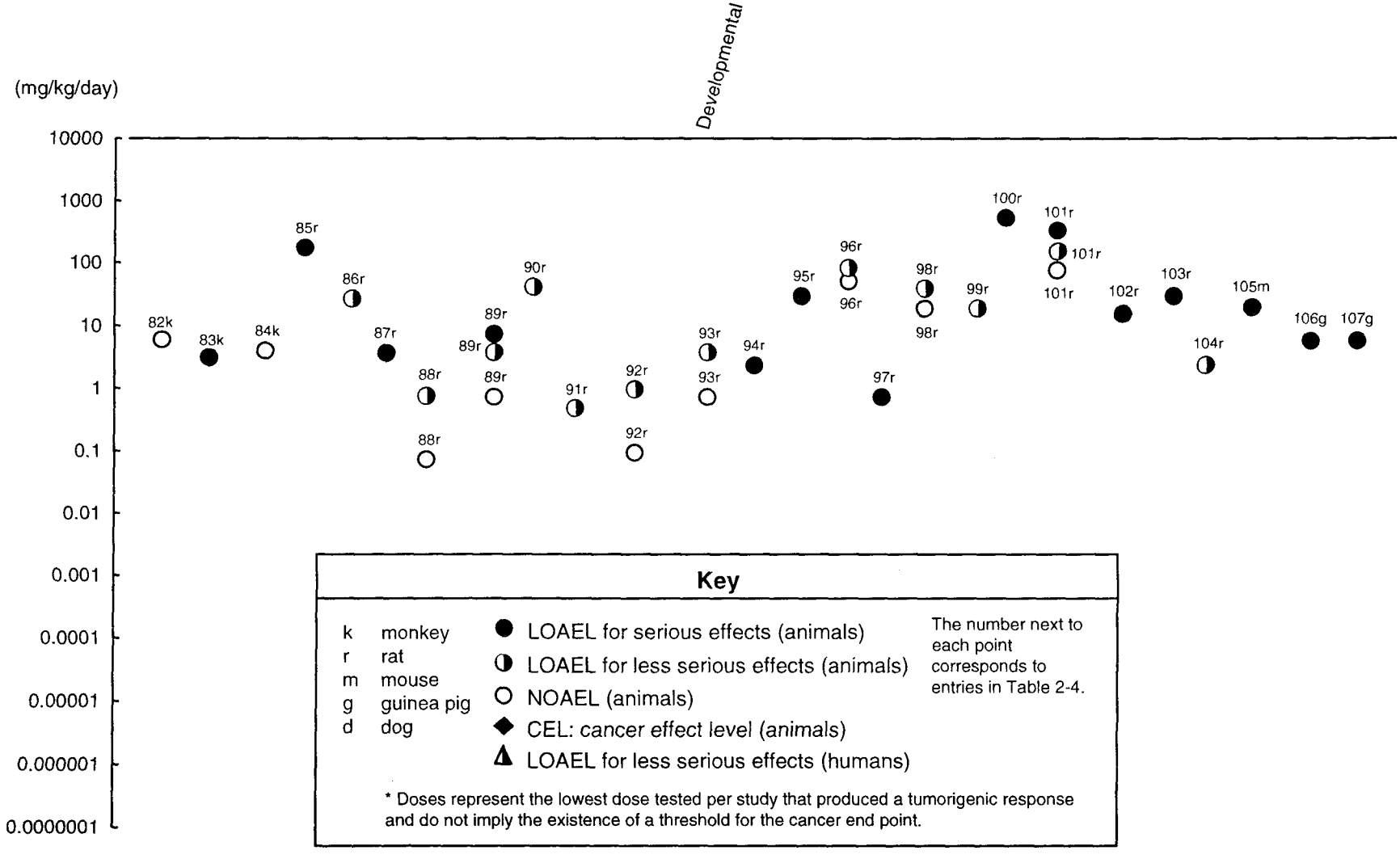
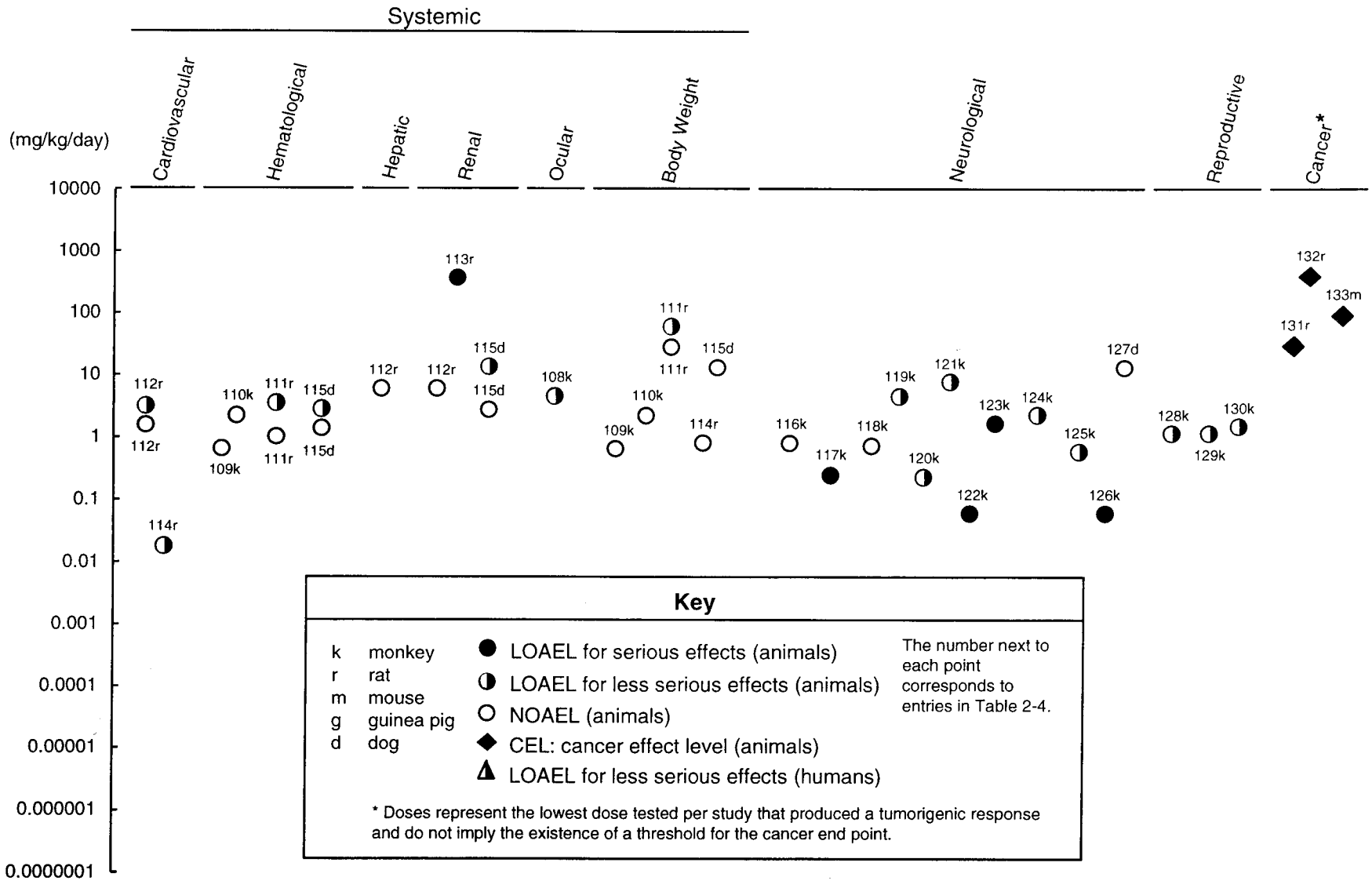


Figure 2-2. Levels of Significant Exposure to Lead - Oral (cont.)

Chronic (≥365 days)



of 182/138 (systolic/diastolic) as compared with 128/98 in controls (Iannaccone et al. 1981) when anesthetized with pentobarbital. The mean PbB level of the treated group was 38.4 µg/dL. Male rats administered lead acetate at 5 or 25 ppm lead in the drinking water for 5 months beginning *in utero* (PbB levels of 5.6 and 18.2 µg/dL, respectively) did not develop hypertension, although plasma renin activity was increased at 25 ppm (Victery et al. 1982b). However, exposure of male rats to 100 ppm lead as lead acetate in drinking water for 6 months beginning *in utero* resulted in a 17-mm Hg increase in blood pressure after 3.5 months of exposure as compared to the control animals when unanesthetized. No change in blood pressure was observed in rats administered 500 ppm lead. It should be noted that kidney effects (e.g., increased kidney weight and intranuclear inclusion bodies) were observed at 100 ppm and/or 500 ppm (Victery et al. 1982a). In a more recent study, administration of 100 ppm in the drinking water for 12 weeks to rats resulted in an increase in mean blood pressure from approximately 107 mm Hg to about 140 mm Hg (Ding et al. 1998). Interestingly, in this study PbB levels in the lead-exposed rats (3.2 µg/dL), while significantly higher than in controls (<1.0 µg/dL), were much lower than those reported in other studies that exposed rats to similar or lower lead concentrations in the drinking water. Also in this study, administration of a scavenger of reactive oxygen species or pharmacological manipulations that increase the blood concentration of the vasodilator nitric oxide, caused a fall blood pressure towards control values. Based on their results, Ding et al. (1998) suggested that hypertension in lead-exposed rats is related to both diminished nitric oxide and increased reactive oxygen species.

An increase in systolic blood pressure was observed in rats at a very low exposure level (1 ppm lead, as acetate, in the drinking water for 159 days), but the dietary and drinking water content of essential and nonessential metals was abnormally low, and the low-contamination quarters in which the rats were housed also limited their exposure to essential and nonessential metals (Perry and Erlanger 1978). These conditions, which result in greater absorption of lead and effects at lower lead intakes than when the diet is less restricted and the living quarters less isolated, may not be relevant to human exposure. Increases in blood pressure at low exposure levels have been demonstrated in other studies. For example, rats administered 0.1 and 1.0 ppm lead acetate in drinking water beginning at weaning through 18 months of age exhibited an approximate 14 mm Hg elevation in blood pressure from 3 months (1 ppm) or 12 months (0.1 ppm) through the entire 18 months of exposure (Perry et al. 1988). No obvious signs of toxicity were observed in these animals.

Low-level, chronic-duration exposure of rats to lead (30 ppm lead acetate in the drinking water) for 18 months resulted in a 10–15 mm Hg increase in both systolic and diastolic blood pressure without any

change in heart rate or histopathological evidence of damage to the kidney, heart, brain, aorta, or liver (Carmignani et al. 1988a). However, lead exposure increased animal responsiveness to stimulation of α and β receptors, altered the renin-angiotensin system, perhaps through inhibition of the renin-angiotensin converting enzyme, and altered the cyclic adenosine monophosphate (cAMP)-dependent contractile processes in both myocardium and vascular myocells. Please refer to Section 2.4 for a more complete discussion of the proposed mechanisms for lead-induced hypertension.

Cardiovascular effects other than effects on blood pressure have also been observed in laboratory animals following ingestion of lead. Male rats given 1% (10,000 ppm) lead acetate in their drinking water from 6 to 12 weeks of age had changes in the myocardium (including myofibrillar fragmentation and separation with edema fluid), dilation of the sarcoplasmic reticulum, and mitochondrial swelling (Asokan 1974). PbB levels in these rats averaged 112 µg/dL versus 5 µg/dL in controls. Administration by gavage of 35 mg lead/kg as lead acetate twice per week for 7 weeks (5 mg/kg/day) to rats resulted in atrophy of the elastic fibers of the aorta (Skoczynska et al. 1993). Mean PbB levels in controls were 4.6 µg/dL compared with 16.8 µg/dL in the lead-treated rats.

The highest NOAEL values and all reliable LOAEL values for each study for cardiovascular effects are recorded in Table 2-4 and plotted in Figure 2-2.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans or animals after oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of the gastrointestinal effects of lead in humans after multi-route exposure.

Hematological Effects. As discussed in Section 2.2.1.2, lead has long been known to affect heme biosynthesis by affecting the activities of several enzymes in the heme biosynthetic pathway. The mechanisms for these effects are discussed in detail in Section 2.4. Two experimental studies of the effects of oral exposure to lead on heme synthesis in humans were available. Two groups of five women and one group of five men who ingested lead acetate at 0.02 mg lead/kg/day every day for 21 days experienced decreases in erythrocyte ALAD by day 3 of lead ingestion (Stuik 1974). The decreases became maximal by day 14 and then remained constant through day 21. An increase in EP occurred in the women, but not in the men, starting after 2 weeks of ingestion. PbB levels were approximately 15 µg/dL before exposure and increased to approximately 40 µg/dL during exposure. Increased EP was observed in five men at a higher dosage, 0.03 mg lead/kg/day (which produced a mean PbB level of 46 µg/dL), starting after 2

weeks of lead ingestion (Stuik 1974). Similar results were reported by Cools et al. (1976) for 11 men ingesting lead acetate at an initial dosage of 0.03 mg lead/kg/day, which was decreased to 0.02 mg lead/kg/day or less as necessary to maintain a PbB level of 40 µg/dL; the mean pre-exposure PbB level was 17.2 µg/dL.

Limited information was located regarding hematological effects in animals after acute oral administration of lead. A significant decrease in erythrocyte ALAD activity was observed in rats administered lead acetate in the drinking water at a dose of approximately 146 mg lead/kg/day for 6 days (Simmonds et al. 1995). PbB levels reached a concentration of 44 µg/dL in 24 hours and remained within 10 µg/dL of that value throughout the exposure period. The results of this study also suggested that erythrocyte ALAD is highly sensitive to lead, but it is not a good indicator of low-level exposure corresponding to PbB levels below 25 µg/dL.

Intermediate-duration studies in animals indicate that adverse hematological effects (i.e., decreased hematocrit, impaired heme synthesis) occur following oral exposure (Dieter et al. 1993; Flora et al. 1993; Freeman et al. 1996; Hayashi et al. 1993; Krasovskii et al. 1979; Overmann 1977; Simmonds et al. 1995; Walsh and Ryden 1984). The lowest dose at which these effects are seen depends on the route of exposure, the nature of the end point studied, and the chemical form of lead. For example, decreases in hematocrit were observed in rats that received 19.2 mg lead/kg/day (as acetate) by gavage (Overmann 1977), but this effect was not seen until a dose of 318 mg lead/kg/day (as acetate) was administered to rats in their daily diet (Walsh and Ryden 1984). Rats that received up to 34 mg lead/kg/day as lead acetate in their drinking water exhibited no adverse effects on hematocrit (Fowler et al. 1980; Victery et al. 1982b). However, evidence of impaired heme synthesis (increased urinary ALA and coprophobilinogen) was observed in rats that received 0.01 mg lead/kg/day as lead acetate in their drinking water for 6–12 months (Krasovskii et al. 1979). A similar correlation between exposure to lead in the drinking water as lead acetate and increased urinary ALA was observed by Fowler et al. (1980) and Flora et al. (1993). Increased urinary ALA and erythrocyte ZPP were also correlated with increasing doses of lead in rats receiving 0, 1.67, or 6.35 mg lead/kg/day in their drinking water (Cory-Slechta 1990b). The increase was observed earlier in the course of the study in older rats. Dieter et al. (1993) found that urinary excretion of ALA was significantly increased in rats by lead administered in the diet for 30 days as acetate or oxide at a dose of about 5 mg lead/kg/day, but not by an equivalent lead dose from lead sulfide or a lead ore concentrate. Similar results were obtained by Freeman et al. (1996) regarding a decrease in blood ALAD activity; the greatest inhibition was seen with lead acetate, followed by lead sulfide and lead-contaminated soil.

Adverse hematological effects have been noted in chronic-duration studies, as well. The severity of the effects seems to be dose-related. For example, dose (blood lead)-effect information for heme synthesis and hematological effects is available; rats and dogs were fed lead acetate in the diet for 2 years (Azar et al. 1973). In rats, lead produced no effects at 10 ppm (PbB level, 11.0 µg/dL; not elevated above controls), significant inhibition of ALAD at $50 ppm (PbB level $18.5 µg/dL), significant increase in urinary ALA at $500 ppm (PbB level $77.8 µg/dL), and slight but significant decreases in hemoglobin concentration and hematocrit at $1,000 ppm (PbB level $98.6 µg/dL). In dogs, lead produced no effects at #50 ppm (PbB level #31.5 µg/dL), significant inhibition of ALAD at $100 ppm (PbB level $42.5 µg/dL), and no effect on urinary ALA, hemoglobin, or hematocrit at any exposure level (highest exposure level = 500 ppm, PbB level = 75.8 µg/dL). Control PbB levels were 12.7 and 16.4 µg/dL in the 2 rat groups and 15.8 µg/dL in the dogs.

Studies in animals indicate that the effects of lead on heme synthesis occur in many tissues and that the time courses of these effects depends on the tissue, exposure duration, and the chemical and animal species administered. Oral exposure of rats to lead acetate increased liver ALAS activity in a single dose study (Chmielnicka et al. 1994), decreased liver ALAS activity in a chronic study (Silbergeld et al. 1982), increased spleen ALAS activity (Silbergeld et al. 1982), increased kidney ALAS activity in a single dose study (Chmielnicka et al. 1994), decreased kidney ALAS activity in a chronic study (Fowler et al. 1980), decreased brain (Gerber et al. 1978), liver, and spleen (Silbergeld et al. 1982) ALAD activity, and decreased kidney ferrochelatase activity along with mitochondrial injury and disturbance of mitochondrial function (Fowler et al. 1980). A lifetime exposure study in monkeys conducted a comprehensive evaluation of hematological and blood chemistry parameters at various times (Rice 1996). The monkeys were exposed continuously to lead acetate at dose levels of 50, 100, 500, or 2,000 µg lead/kg/day for up to 14 years. Additional groups were exposed to 1,500 µg lead/kg/day according to 4 dosing regimens to assess the effects of lead during development. PbB levels were dose-related and ranged between 10 and 90 µg/dL. Some differences (although within the normal range) observed between treated and controls included a decreased lymphocyte count in the 50 and 100 µg/kg/day groups at both 7 and 11 years of age and in the 2,000 µg/kg/day group at 11 years of age; decreased hematocrit and hemoglobin in the 2,000 µg/kg/day group at 7 (PbB 25 µg/dL) and 11 years (PbB 90 µg/dL) of age, and decreased hemoglobin at 6 years of age in a 1,500 µg/kg/day group that began exposure at 300 days old.

The highest NOAEL values and all reliable LOAEL values for each study for hematological effects are recorded in Table 2-4 and plotted in Figure 2-2.

Musculoskeletal Effects. Several case reports of individuals who experienced high exposures to lead either occupationally or through the consumption of illicit lead contaminated whiskey described the occurrence of a bluish-tinged line in the gums (Eskew et al. 1961; Pagliuca et al. 1990). The etiology of this "lead line" has not been elucidated. This effect has also been observed in workers exposed to high lead levels who had exposures via dust or fume. Individuals having high exposures to lead have also been reported to complain of muscle weakness, cramps, and joint pain (Holness and Nethercott 1988; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990).

Only a few studies have explored the effects of oral lead exposure on bone growth and metabolism in animals (Escribano et al. 1997; Gonzalez-Riola et al. 1997; Hamilton and O'Flaherty 1994,1995; Gruber et al. 1997). These limited data, all from intermediate duration studies of rats, indicate that oral lead exposure may impair normal bone growth and remodeling as indicated by decreased bone density and bone calcium content, decreased trabecular bone volume, increased bone resorption activity and altered growth plate morphology. Weanling female rats were exposed to 250 or 1,000 mg lead/L of lead acetate (approximately 38 or 152 mg lead/kg/day) in drinking water for 49 days; the rats were mated and exposure continued through parturition and lactation (approximately an additional 39 days) (Hamilton and O'Flaherty 1994). PbB concentrations after 49 days of exposure to lead were 40 µg/dL in rats exposed to 250 mg lead/L and 74 µg/dL in rats exposed to 1,000 mg lead/L. Tibial calcium and phosphorus levels in dams were decreased 20% relative to controls not supplemented with lead. In pups, body weight and tail length were depressed at both lead exposure levels and tibial growth plate width was increased by approximately 10% in high lead exposure group. The latter effect may represent retardation of bone mineralization in the pups. Enhanced calcification and decreased alkaline phosphatase activity of implanted demineralized bone matrix was observed in male rats exposed to 1,000 mg lead/L lead acetate in drinking water for 26 days (approximately 145 mg lead/kg/day) (Hamilton and O'Flaherty 1995). In female rats exposed to food supplemented with 17 mg lead acetate/kg food (approximately 1 mg lead/kg/day) for 50 days, femur trabecular bone mass and thickness of the growth cartilage were decreased (Escribano et al. 1997; Gonzalez-Riola et al. 1997). In male rats exposed to 100 mg/L lead acetate in drinking water (approximately 7.7 lead/kg/day) for one year, bone density decreased as did bone calcium content and trabecular bone volume; increased bone resorption activity was evident from increased osteoid coverage of trabecular surfaces and increased osteoclast presence in trabecular lacunae. These changes were evident after 3–12 months of exposure and at PbB concentrations of 20–30 µg/dL (Gruber et al. 1997).

The highest NOAEL values and all reliable LOAEL values for each study for musculoskeletal effects are recorded in Table 2-4 and plotted in Figure 2-2.

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of hepatic effects in humans following multi-route exposure to inorganic lead.

Liver toxicity, as evidenced by alterations in the incorporation of lysine into liver proteins, was observed in rats administered 192 mg lead/kg/day by gavage as lead acetate for 9 weeks (Barratt et al. 1989). No effects were observed at 21 mg lead/kg/day. However, the toxicological significance of this finding is not known because neither serum enzymes nor histopathological evaluations were performed.

Intermediate-duration exposure to 0.01 mg lead/kg/day as lead acetate in the drinking water of rats resulted in increased liver weight, decreases in RNA and glycogen, pycnosis of Kupffer cells, and decreased enzyme activity (e.g., lactate dehydrogenase) (Krasovskii et al. 1979). In other studies in rats, significant reductions in the activities of hepatic aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (AP) were seen following treatment for 4 months with daily gavage doses of 64 mg lead/kg/day as lead acetate (Singh et al. 1994), but no effect was observed on the serum activities of these enzymes after administration of 11 mg lead/kg/day (acetate) in the water for 20 days (Hayashi et al. 1993). Singh et al. (1994) attributed the decrease in hepatic enzyme activity to lead-related liver injury.

The effects of lead exposure on blood lipids was investigated in rats treated by gavage for 7 weeks with 5 or 20 mg lead/kg/day (as acetate) (Skoczynska et al. 1993). PbB levels were 16.8 and 32.4 µg/dL in the low- and high-dose groups, respectively. Treatment with lead significantly decreased total cholesterol and increased serum triglycerides in a dose-related fashion, decreased HDL-cholesterol in the high dose group, and did not significantly alter serum lipid peroxide level or blood superoxide dismutase activity. However, rats treated with lead in drinking water that provided a dose of approximately 109 mg lead/kg/day for 4 weeks had a significant increase in hepatic lipid peroxidation (Flora et al. 1993); PbB levels were not provided in this study.

The highest NOAEL values and all reliable LOAEL values for each study for hepatic effects are recorded in Table 2-4 and plotted in Figure 2-2.

Renal Effects. Ingestion of drinking water containing lead was found to be associated with evidence of renal insufficiency in humans (Campbell et al. 1977). Lead concentrations in drinking water were compared to PbB concentrations in 283 residents who ingested this water for a mean of 21.5 years. A highly significant correlation was found for these two parameters. In addition, elevated PbB concentrations were associated with renal insufficiency, reflected as raised serum urea concentrations and hyperuricemia. No renal biopsies were performed.

Information is available on the renal toxicity of ingested lead in several species, including rats, dogs, monkeys, and rabbits. The results indicate that histopathological changes in the kidneys of lead-treated animals are similar to those in humans (see Section 2.2.1.2). Reduced glomerular filtration rates and aminoaciduria were reported in some of the animal studies. Key animal studies on lead-induced renal toxicity will be discussed below.

Dose (blood lead)-effect data are available in the study by Fowler et al. (1980). Rats exposed to lead acetate in the drinking water through the dams during gestation and lactation and then directly until 9 months of age had the following external exposures (ppm lead), internal exposures (µg lead/dL in blood), and renal effects: 0 ppm (controls), 5 µg/dL, no lesions; 0.5 ppm, 4.5 µg/dL, no lesions; 5 ppm, 11 µg/dL, cytomegaly; 50 ppm, 26 µg/dL, cytomegaly, intranuclear inclusion bodies, and swollen mitochondria; 250 ppm, 67 µg/dL, cytomegaly, intranuclear inclusion bodies, swollen mitochondria, and hemosiderin. These effects occurred in the proximal tubule cells; no lesions were seen in the glomeruli. No evidence of interstitial reaction or of tumor formation was seen. Using a similar exposure protocol, Rodrigues et al. (1996) reported that the ALAD reactivation index by dithiothreitol (a sensitive index of lead toxicity) was increased in the kidneys of 6-month-old rats that had a PbB concentration of 42 µg/dL.

Similar results were obtained by Vyskocil et al. (1989) who studied the effects of administration of lead acetate in the drinking water for 2–3 months on renal function in male Wistar rats. Administration of approximately 414 mg lead/kg/day (PbB, 105 µg/dL) was without effect. An increase in the urinary excretion of $\beta_{2\mu}$-globulin was seen in the animals that received 828 mg lead/kg/day (PbB, 196 µg/dL). Animals treated with 1,660 mg lead/kg/day (PbB, 320 µg/dL) exhibited increased urinary excretion of $\beta_{2\mu}$-globulin, glucose, total proteins, lysozyme, and lactate dehydrogenase (LDH) levels. Examination of the kidneys revealed no treatment-related changes in the 414 mg/kg/day group, and morphological changes primarily in the epithelial cells of the proximal tubules in the 828 and 1,660 mg/kg/day groups that were characterized by intranuclear inclusion bodies and enlarged nuclei. Hyperplasia and flattening of the

proximal tubular epithelium were also observed. Based on these results, exposure to lead acetate at levels of $828 mg lead/kg/day in the drinking water results in proximal tubular dysfunction in rats. In a more recent publication, the same group of investigators repeated the study in female Wistar rats and the results were essentially the same (Vyskocil et al. 1995). As seen in male rats, urinary excretion of $\beta_{2\mu}$-globulin was the most sensitive marker of kidney toxicity. Another intermediate-duration study in male Fischer 344 rats reported kidney effects at much lower estimated doses than those used by Vyskocil et al. (1989, 1995). In this study, lead acetate was administered in the food at doses of approximately 0.5, 1.5, or 5 mg lead/kg/day for 30 days (Dieter et al. 1993). High-dose rats exhibited mild-to-moderate enlargement of nuclei in the renal tubules, particularly in the outer stripe of the adrenal medulla. Mean PbB level in these rats was about 80 µg/dL after 30 days of exposure. Similar results were observed with the same dietary levels of lead oxide. However, no such effects were seen when the rats were treated with lead sulfide or a lead ore concentrate from Skagway, Alaska; maximum PbB levels were below 15 µg/dL in these groups. The results suggested that systemic toxicity is determined by the bioavailability of the lead species.

Histopathological changes were noted in the kidneys of rats administered lead acetate in the drinking water for 76 weeks at lower doses (Koller et al. 1985). These changes, which were observed at a dose of 37 mg/kg/day, a dose much lower than that used by Vyskocil et al. (1989), included necrotic and dilated cortical tubules, tubular protein casts, areas with large nuclei and fibrous connective tissue, and large intranuclear inclusion bodies in the enlarged epithelial cells of the cortex near the cortical-medullary junction.

The highest NOAEL values and all reliable LOAEL values for each study for renal effects are recorded in Table 2-4 and plotted in Figure 2-2.

Endocrine Effects. No studies were located regarding endocrine effects in humans or animals after oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of endocrine effects of lead in humans after multi-route exposure to lead.

Dermal Effects. No studies were located regarding dermal effects in humans or animals after oral exposure to inorganic lead.

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to inorganic lead.

Long-term scotopic visual system deficits have been observed in laboratory animals following low-level lead exposure during early postnatal development (Fox et al. 1982). To determine whether this was due to an effect of lead on the central nervous system or a direct effect of lead on the eye, a series of experiments were performed by Fox and coworkers to determine the effects of low-level lead exposure on ocular function during early postnatal development in rats (Fox and Chu 1988; Fox and Farber 1988; Fox and Rubinstein 1989). In the first study, timed-pregnant hooded rats were administered 0.2% lead acetate in the drinking water from day of birth (day 0) through lactation (day 21). The authors state that results from previous studies show that rat pups receive 0.5 mg/kg/day of lead through the milk under such an exposure regimen. At weaning the animals were transferred to standard laboratory chow and maintained until 90 days of age. At this point, acute (single flash) electroretinograms (ERG) and cyclic nucleotide metabolism studies were conducted. The PbB levels in the lead-exposed pups were 59 µg/dL at 21 days of age and 7 µg/dL at 90 days of age. The results of the single-flash ERGs indicated that lead exposure caused a significant decrease in amplitude, a significant increase in latency, and a significant decrease in sensitivity in various waveforms suggesting that low-level lead exposure during postnatal development has a selective detrimental effect on the rods of the retina. The authors speculated on the mechanism of such a change. One possibility is that lead alters cyclic nucleotide metabolism such that the activity of the sodium channels in the rods is changed. To investigate this possibility, cyclic nucleotide content and the activity of the enzymes associated with their metabolism were measured. A significant increase in cyclic guanosine monophosphate (cGMP), but not cyclic adenosine monophosphate (cAMP) was found in both light- and dark-adapted lead-exposed animals as compared to the controls. This increase in cGMP content was in turn found to be associated with decreased cGMP-phosphodiesterase (PDE) activity (Fox and Farber 1988). In a subsequent study, it was found that the rod sensitivity and range of dark adaptation were decreased after developmental exposure to 0.08 and 0.5 mg lead/kg/day and that the rate of dark adaptation was decreased only at the 0.5 mg lead/kg/day level (Fox and Katz 1992). The authors suggested that the reduced rod sensitivity was due to an increased rod depolarization, which in turn was caused by increased intracellular sodium.

A similar exposure regimen was employed in the second study (Fox and Chu 1988) to study the effects of low-level lead exposure on the ultrastructure and quantitative histology of the retina during early postnatal development in rats. At weaning the animals were transferred to standard laboratory chow and maintained until 90 days of age. At this point, the animals were sacrificed, and the retinas were removed for light and electron microscopic analysis. The authors found that there was a selective degeneration of rod (but not cone) photoreceptor cells in the lead-exposed rats, leading to an overall loss of 20% of rod cells.

Degeneration occurred more in the inferior than the superior retina, and more in the posterior than the peripheral retina. The outer and inner nuclear layers were also reduced in thickness in the lead exposed-rats. General retinal damage was evidenced by the accumulation of glycogen particles in the lead-exposed rats. These results support the hypothesis posed by Fox and Farber (1988) that lead exposure during postnatal development has a selective detrimental effect on the rods of the retina.

In the third study, rats were exposed in the same manner as the two previous studies to evaluate the effects of low-level lead exposure on retinal sensitivity, rhodopsin content, and rod outer segment length throughout the first year of life in rats exposed during early postnatal development (Fox and Rubinstein 1989). The authors found that retinal sensitivity and rhodopsin content in the lead-exposed rats were decreased at all ages tested. There was no change in the λ_{max} of the rhodopsin in the lead-exposed animals as compared to the control animals. Histological evaluation revealed that there was a decrease in rod outer segment length coupled with a selective loss of 20% of the rod cells which would account for the decrease in rhodopsin content in the lead-exposed rats. The results also indicate that most of these effects occur within the first 30 days of life, although the changes remain throughout the first year. In a subsequent study from this series, Fox et al. (1997) compared the effects observed in rats exposed via dam's milk with those seen in exposed adults. The result showed that developing and adult retinas exhibited qualitatively similar structural and functional alterations, but developing retinas were much more sensitive, and in both cases alterations in retinal cGMP metabolism was the underlying mechanism leading to lead-induced ERG deficits and rod and bipolar cell death. Taken together, the results of these studies strongly suggest that lead exposure during postnatal development has a selective detrimental effect on the rods of the retina in rodents.

Retinal effects have also been reported in other species exposed to lead. For example, monkeys were fed a diet containing 350 ppm or 600 ppm lead acetate in the diet for over 9 years (Kohler et al. 1997). This diet provided approximately 4 or 7 mg lead/kg/day and resulted in PbB levels of about 38 µg/dL and 55 µg/dL when the monkeys were 9 years old. The treatment period was followed by a 35-month period of lead-free diet, during which time, PbB lead levels declined to nearly those of untreated monkeys. Treatment with lead resulted in a dose-related decrease in tyrosine hydroxylase (TH, rate-limiting enzyme in catecholamine synthesis) content in neurons of the retina. Treated animals also showed a reduced number of ascending fibers in the inner nuclear layer and of dense staining fibers in sublayer 1 of the inner plexiform layer. The results showed that lead treatment during development can produce long-lasting effects that persist long after PbB levels had return near background levels.

The LOAELs from these studies are recorded in Table 2-4 and plotted in Figure 2-2.

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of effects of lead on growth in humans after multi-route exposure to lead.

Several studies provide information regarding body weight effects of lead in animals (Dieter et al. 1993; Freeman et al. 1996; Hamilton and O'Flaherty 1995; Hayashi et al. 1993; Kala and Jadhav 1995a; Skoczynska et al. 1993; Yokoyama and Araki 1992). Most of these studies were conducted in rats, are of intermediate-duration exposure, and used various media to administered the lead.

Weanling female rats exposed to 250 ppm lead acetate in the water for 10 days exhibited an approximately 19% decrease in body weight gain during the exposure period (Minnema and Hammond 1994). This concentration of lead in the water provided an estimated dose of 17.5 mg lead/kg/day and doubled the blood ZPP levels in the treated rats. As indicated below, the reduced growth was due to a decrease in food intake, which in turn was due to a reduction in feeding time.

In intermediate-duration studies in which lead acetate was administered in the drinking water, the lowest LOAEL was approximately 77 mg lead/kg/day for a 15% decrease in final body (Yokoyama and Araki 1992). Since this was the only dose level tested, it is possible that the true LOAEL was actually lower than 77 mg/kg/day. However, a different 90-day study, also with lead acetate in drinking water reported a NOAEL for body weight of approximately 38 mg lead/kg/day (Kala and Jadhav 1995a). Two studies of similar design in which lead was administered mixed in the food provided conflicting results. Freeman et al. (1996) reported a NOAEL for body weight effects in male Fischer 344 rats of 6.4 mg lead/kg/day, as lead acetate, sulfide, and lead-contaminated soil in a 44-day feeding study. Dieter et al. (1993), however, reported a 14–20% decrease in body weight gain in male Fischer 344 rats at a dietary level of 5 mg lead/kg/day also as lead acetate in a 30-day study. The findings of Freeman et al. (1996) regarding the lead sulfide and lead-contaminated soil are consistent with results of Dieter et al. (1993) who found no body weight effects also for the sulfide and for a lead ore at dietary levels of 5 mg lead/kg/day. A NOAEL of 20 mg lead/kg/day was identified in a study in which lead acetate was administered by gavage once or twice per week for 7 weeks (Skoczynska et al. 1993).

Lifetime exposure (up to 14 years) of monkeys to doses of 50–2,000 µg lead/kg/day did not affect body weight gain (Rice 1996). PbB levels throughout the study were dose-related and during the growth period were always below 40 µg/dL.

The highest NOAEL values and all reliable LOAEL for each study for body weight effects are recorded in Table 2-4 and plotted in Figure 2-2.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after oral exposure to inorganic lead. See Section 2.2.1.2 for a discussion of other systemic effects of lead in humans after multi-route exposure to lead.

Significant decreases in both food and water intakes were reported in weanling female rats administered 250 ppm lead acetate in the drinking water (approximately 17.5 mg Pb/kg/day) for 10 days (Minnema and Hammond 1994). The reduction in food intake resulted in reduced body weight gain. In turn, reduced food intake was due to decreased feeding time. The average number of meals in either the light or dark phase was not significantly altered by treatment with lead (Minnema and Hammond 1994). Food consumption was also reduced in male rats administered lead in the drinking water at a concentration that provided approximately 145 mg lead/kg/day for 14 days (Hamilton and O'Flaherty 1995).

Two intermediate-duration studies in rats in which lead was administered mixed in the food as acetate, oxide, sulfide, and lead contaminated soil identified NOAELS of 5 mg lead/kg/day (Dieter et al. 1993) and 6.4 mg lead/kg/day (Freeman et al. 1996) for food intake for all lead forms tested. These doses were the highest doses tested. A 90-day study in rats reported no effects of lead exposure on water intake in rats administered doses of approximately 38 mg lead/kg/day as acetate via drinking water (Kala and Jadhav 1995a). In contrast, rats given a much higher dose of lead acetate in the water (0.6% corresponding to approximately 502 mg lead/kg/day) for 14–50 days showed a 17–20% decrease in water intake (Ronis et al. 1996).

Depression of plasma levels of 1,25-dihydroxyvitamin D was observed in rats fed 0.82% lead in the diet as lead acetate for 7–14 days (Smith et al. 1981). High calcium diets protected against this effect. An additional finding was that lead blocked the intestinal calcium transport response to exogenous 1,25-dihydroxyvitamin D but had no effect on bone response to the vitamin D hormone. Although the lead exposure and resulting PbB levels ($174 µg/dL) were high in this study, the results provide support for the

disturbances in vitamin D metabolism observed in children exposed to high levels of lead (described in Section 2.2.1.2).

The highest NOAEL values and all reliable LOAEL for each study for other effects are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.3.3 Immunological Effects

No studies were located regarding immunological effects in humans after oral exposure to inorganic lead. See Section 2.2.1.3 for a discussion of immunological effects of lead in humans after multi-route exposure to lead.

Low-level exposure of rats to lead has resulted in adverse effects on both the humoral and cellular components of the immune system. Prenatal and postnatal exposure of rats to 2.24 mg lead/kg/day as lead acetate in the drinking water (indirectly through the dams and then directly) until testing at 35–45 days of age resulted in a mean PbB level of 29.3 µg/dL and marked depression of antibody responses to sheep red blood cells, decreased serum IgG (but not IgA or IgM) levels, decreased lymphocyte responsiveness to mitogen stimulation, impaired delayed hypersensitivity reactions, and decreased thymus weights as compared with controls. The 2.24 mg lead/kg/day dose was the lowest level tested (Faith et al. 1979; Luster et al. 1978). Evidence of a modulatory effect of lead on immune parameters assessed in young rats exposed *in utero* (and possibly via mothers's milk) was recently presented by Miller et al. (1998). In that study, pregnant rats were exposed to lead acetate in the drinking water during breeding and pregnancy. The estimated doses were 11, 28, and 56 mg lead/kg/day and resulted in corresponding PbB levels of 39.4, 70.8, and 112.0 µg/dL during pregnancy and lactation. Immune function was assessed in the offspring at 13 weeks of age and in the dams at 7–8 weeks postpartum. At these times, PbB levels in the dams was approximately 12 µg/dL and in offspring, 0.68–2.63 µg/dL. Results from a comprehensive battery of tests showed no significant effects in lead-exposed dams. However, alterations were observed in the offspring and included elevated macrophage cytokine and effector function properties and depressed cell-mediated immune function in the mid-dose group, decreased interferon-γ levels in the high-dose group, and increased serum IgE levels in the low-dose group. Also, total leukocyte counts were significantly decreased in the mid- and high-dose young, but analyses of subpopulation distribution revealed no significant treatment-related effects. These findings indicate that exposure *in utero* may result in

alterations in immune parameters that persist beyond the exposure period. The lack of effects seen in dams may have reflected less vulnerability and/or that the effects were transient.

Other investigators have been unable to demonstrate lead-induced effects on various components of the immune system in laboratory animals. The effects of lead exposure of varying duration on natural killer cell and T-lymphocyte function were investigated in rats. Male Alderly Park rats received lead as lead acetate in the drinking water at lead concentrations equivalent to 14.3 and 143 mg lead/kg/day for 1–8 weeks (Kimber et al. 1986a). Every week starting at 1 week of exposure, two rats were killed and the spleens and thymus glands were removed. PbB concentrations were <9 µg/dL in the control animals, 5–14 µg/dL in the low-dose animals, and 15–45 µg/dL in the high-dose animals. The activity of ALAD was also measured as an indicator of lead toxicity and was substantially inhibited (27% and 43% inhibition for the low-dose and high-dose animals, respectively). Lead exposure had no effect on the weight of the spleen or thymus. There was no difference between the control and lead-exposed natural killer cells with respect to cytotoxic capacity or interferon-induced potentiation of cytotoxic activity. Furthermore, there was no effect of lead on the proliferative response of T-lymphocytes to phytohemagglutinin. Thus, it appears that exposure to lead at levels that inhibit ALAD has no effect on certain components of the cellular immune function (e.g., natural killer cells and T-lymphocytes). However, the conclusions that can be reached based on the results of the Kimber et al. (1986a) study are limited in that only two animals were examined per time point.

An additional study reported that oral lead exposure had no significant effect on local and systemic immune function following intratracheal, intraperitoneal, or intravenous immunization with sheep red blood cells in mice (Hillam and Ozkan 1986). The mice were administered 2.6 mg lead/kg/day as lead nitrate by gavage once. The following parameters of immune function were measured in the immunized, lead-exposed mice: differential and total leukocyte counts (measure of systemic cellular immune function), hemagglutination titers (measure of systemic humoral immune function), and antibody forming cells (AFC) counts in the thoracic lymph nodes and the spleen (measure of both local and systemic immune function). Splenic and thymic organ weights were also determined, as well as tissue lead content. Lead content was similar to the controls in all tissues. Both splenic and thymic weights were significantly decreased in the lead-exposed animals as compared to the controls. Total leukocyte count was significantly decreased in the lead-exposed animals, but no change in the differential leukocyte counts was observed. Intraperitoneal immunization did not result in a significant decrease in the antibody titers of the lead-exposed animals as it did when mice were exposed by inhalation for 28 days. Regardless of the route

of immunization, oral administration of lead did not affect the number of AFCs in either the spleen or the thoracic lymph node. Based on the fact that the concentration of lead in tissues and in blood did not differ between treated an control mice, the absence of significant immunological effects in the treated mice is not totally unexpected.

A LOAEL for immunological effects is recorded in Table 2-4 and plotted in Figure 2-2.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to inorganic lead. See Section 2.2.1.4 for a discussion of neurological effects of lead in humans after multi-route exposure to lead.

The literature on the neurobehavioral effects of oral exposure to lead in animals is extensive. Only those studies considered key to clarifying human health issues will be presented here. High levels of exposure to lead produce encephalopathy in several species, but blood lead data for this effect are generally not available.

A number of histopathological studies of lead's effects on the nervous system of rats treated during early postnatal life with lead acetate or carbonate in the drinking water or diet through their dams or directly, for #3 weeks, have shown a variety of adverse effects at PbB levels ranging from 258 to 400 µg/dL. These effects include reductions or delays in the development of the hippocampus or other hippocampal changes (Alfano and Petit 1982; Alfano et al. 1982; Slomianka et al. 1989), reductions or delays in the development of the cerebral cortex (Petit and LeBoutillier 1979), reductions in the number and size of axons in the optic nerve of mice (Tennekoon et al. 1979), and demyelination of peripheral nerves (Windebank et al. 1980). Cytoarchitectural changes have also been noted in limited studies of the eyes of monkeys chronically exposed to lead beginning at or shortly after birth (Reuhl et al. 1989).

A number of neurochemical changes have been observed in the brains of rats exposed both pre- and post-natally to lead (Singh and Ashraf 1989). Pregnant rats were administered lead acetate by gavage in saline 5 times per week after day 14 of gestation at a dose of 0.64 mg lead/kg/day. After birth, pups were given 0.64 mg lead/kg/day by gavage 5 days per week for 10 weeks. Brain norepinephrine and γ-aminobutyric acid (GABA) levels and glutamic acid decarboxylase (GAD) activity were decreased, and brain glutamate, glutamine + asparagine, tyrosine levels, and monoaminooxygenase (MAO) activity were increased in the

lead-exposed rats. Brain ammonia, alanine, aspartic acid, and dopamine were not affected. Brain uptake values for glutamine were significantly increased. Similar results were observed in pups exposed to 0.64 mg lead/kg/day, 5 days per week for 10 weeks when exposure was initiated 5 days postnatally, but not when initiated at 5 weeks postnatally. Brain lead levels were similar in the three exposure scenarios. In a more recent study, it was reported that prenatal exposure to lead, that continued for 20 weeks after birth resulted in altered normal developmental pattern of protein in neurons from the central nervous system (Singh 1993). The effects were not observed in rats exposed only as adults; however, brain lead levels were similar in the two groups. These results suggest that the rapidly developing rat brain may be more susceptible to the neurotoxic effects of lead than the brains of older rats. Kala and Jadhav (1995a) reported changes (increases and decreases) in the levels of several neurotransmitters and their metabolites in various areas of the rat brain following 90-day exposure to lead acetate in the drinking water. The most significant was a decrease in dopamine in the nucleus accumbens with the lowest lead dose tested, approximately 2.2 mg/kg. These changes were observed at PbB concentrations in the 10–19 µg/dL range. In a subsequent study, the same group of investigators reported that both the basal and potassium-induced release of dopamine in the nucleus accumbens were significantly reduced as a result of lead treatment (Kala and Jadhav 1995b) and suggested that lead may decrease the availability of dopamine in the neurons, interfere with calcium-mediated transmitter release at the site, and/or interfere with autoreceptor processes.

The effect of lead on the distribution of calcium binding proteins in the hippocampus from monkeys was recently examined by Noack et al. (1996). Monkeys were treated for 9 years (exposure beginning *in utero*) with lead in the diet at a concentration that provided approximately 4 or 7 mg lead/kg/day and resulted in PbB levels of about 38 and 55 µg/dL, respectively, at 9 years of age. After a 32-month period of lead-free diet, PbB levels, while still higher than in unexposed monkeys, had decreased considerably. Immuno-histochemical examination of the hippocampus revealed no significant differences in the pattern of distribution of three high-affinity calcium binding neuronal proteins, but there was a marked decrease in the immunoreactivity of the glial protein S100 in the high-dose group. The results were interpreted as confirming the hypothesis that glial cells are the main target of lead toxicity in the central nervous system.

Recent studies have focused on neurobehavioral effects of exposure of the developing organisms to lead. Studies concerned primarily with the effects of prenatal exposure are presented in the section on developmental effects (Section 2.2.3.6), while studies concerned primarily with postnatal exposure are discussed here.

Investigations of the development of motor function and reflexes in rats have shown effects at PbB levels of $59 µg/dL. Male rats were treated with lead acetate at 45, 90, or 180 mg lead/kg/day by gavage on postnatal days 3–21 (Kishi et al. 1983). The air righting reflex was significantly delayed at all doses. Eye opening was accelerated at the lowest dose tested, which produced a mean PbB level of 59 µg/dL. Rotorod performance at postnatal days 53–58 was significantly impaired at the highest dose, which produced a mean PbB level of 186 µg/dL. An adverse effect of lead on rotorod performance at postnatal days 30–70 was noted in rats treated by gavage on days 3–21 of age with 19.2 mg lead/kg/day as lead acetate, which resulted in a mean PbB level of 174 µg/dL, but no effect was noted in rats treated with 6.4 mg lead/kg/day as lead acetate, which resulted in a mean PbB level of 33 µg/dL (Overmann 1977). Thus, neonatal lead exposure produced behavioral effects without causing adverse effects on growth or overt signs of poisoning.

Several studies have reported effects on performance in learning tasks in rats with PbB levels of <30 µg/dL. The lowest external exposure level that was significantly associated with a behavioral effect in rats was reported by Bushnell and Levin (1983). The authors found that exposure of rats starting at postnatal day 21 (postweaning) to drinking water at 1.6 mg lead/kg/day for 35 days produced a decrease in spontaneous alternation in a radial arm maze. Although the PbB level was not measured, the mean brain lead level on the day following termination of exposure was 0.05 µg/g. The effects of neonatal exposure to lead on complex maze learning were studied in male Wistar rats. The rats were administered 50 mg lead/kg/day as lead acetate in water by gavage on postgestation days 9, 12, 15, and 18, or 14.3 mg lead/kg/day in the drinking water for 112 days beginning on postgestation day 21 (Massaro and Massaro 1987). Two control groups were included: a vehicle (sodium acetate) control group and an untreated control group. The animals began extensive maze training on day 31 or 143 postpartum and were tested on days 41–45 or 153–157. The parameter studied was latent learning: the animals were trained to run the maze or explore an open field in a satiated condition and in the absence of any positive or negative reinforcement (known as the free exploration phase). Experienced animals as well as unexperienced animals are then placed in the maze following food deprivation. The measure of latent learning is the performance of the experienced animals compared to that of the inexperienced animals. There was no difference between the controls and the lead-exposed animals with respect to activity during the free exploration phase. However, during the food deprivation trial in the maze, the animals exposed to lead during the early postgestation period made significantly more errors, whereas the young adults exposed for 112 days did not. These results indicate that in animals lead exposure alters the ability to transfer

information from a previous learning experience in this experimental paradigm but that this effect is not seen in the young adult.

Other types of tests have also revealed behavioral changes in rats exposed to low levels of lead. For example, weaning rats exposed to lead in the drinking water for 90 days at a concentration that provided 0.47–0.72 mg lead/kg/day and that resulted in PbB levels of 15 µg/dL exhibited in a significant delay in learning a task (Jadhav and Areola 1997). However, no such impairment was seen in rats that had a PbB concentration of 6 µg/dL. Significant effects were noted in rats exposed after weaning and throughout the course of the experiment to lead acetate at 2.1 mg lead/kg/day in their drinking water, which resulted in PbB levels of 15–20 µg/dL (Cory-Slechta et al. 1985). The lead-exposed rats had a significantly higher response rate and a significantly shorter interval between bar-press responses on a fixed-interval operant schedule of food reinforcement. Similar results were obtained at higher exposure levels in a series of earlier studies (Cory-Slechta and Thompson 1979; Cory-Slechta et al. 1981, 1983), even when the operant schedule or contingency for reinforcement was rather different. According to EPA (1986a), a tendency in lead-treated rats to respond more rapidly (higher response rate, shorter inter-response times, shorter response latency) or to respond even when inappropriate (such as when no reward is provided for responses or when reward is specifically withheld for responding) has been reported in many other studies as well, frequently at PbB levels of <30 µg/dL at the time of testing. A two-lever operant food-reinforced drug discrimination paradigm was also used to examine the effects of lead exposure on the ontogeny of dopaminergic systems in rats (Cory-Slechta et al. 1992). In this study the dams were exposed to lead acetate in the drinking water (approximately 8.3 or 29.2 mg lead/kg/day) from postnatal day 1 until day 21; this resulted in the pups being exposed to lead only through maternal milk. PbB in the low- and high-dose pups at 21 days of age was 16 µg/dL and 34 µg/dL, respectively; however, at the time behavioral training began it had declined below the detection limit of 5 µg/dL. The effect of exposure to lead was manifested as a left-shift of the sensitivity dose-effect curve for discrimination of various doses of the D2 agonist quinpirole and was consistent with an increased sensitivity of subtype D2 dopaminergic receptors to dopamine agonists. The lead-induced supersensitivity represented a D2 autoreceptor rather than a postsynaptic receptor supersensitivity. The results further suggested that functional supersensitivity is a permanent effect of postnatal exposure since both blood and lead levels were negligible at the time training began. Results from further studies by the same authors suggested that the increased D2 sensitivity may be due to a facilitated D2 receptor number, particularly in the nucleus accumbens (Widzowski et al. 1994). Evidence of increased sensitivity of muscarinic cholinergic receptors in the central nervous system as a result of exposure to lead has also been presented (Cory-Slechta and Pokora 1995). A recent study from

the same group of investigators showed that exposure of rats to lead in the drinking water for 12 months from weaning selectively decreased dopamine binding sites in the nucleus accumbens (mesolimbic dopamine system and not in the dorsal striatum (nigrostriatal dopamine system) (Pokora et al. 1996). These changes were seen primarily in D2 receptors and in the dopamine transporter and after as little as 2 weeks of 150 ppm lead exposure (this resulted in a PbB level of 29 µg/dL at 8 months). Effects of a 50 ppm exposure with corresponding PbB levels of approximately 16 µg/dL were observed after 12 months of exposure.

Many studies have suggested that the N-methyl-D-aspartate (NMDA) receptor play a role in the lead-induced neurobehavioral alterations in rodents (Cory-Slechta 1995a; Cory-Slechta et al. 1997b, 1997c). To test this hypothesis, extensive use has been made of neuropharmacological tools. For example, in rats, lead has been shown to decreases MK-801 binding throughout the brain (MK-801 is a noncompetitive NMDA receptor antagonist); decreases in MK-801 binding suggest a hypoglutamatergic function. Some studies have suggested that lead inhibits NMDA receptor binding through the zinc allosteric site, which modulates receptor binding (Cory-Slechta 1995a; Guilarte et al. 1995). Studies have also shown that treatment of adult rats with lead results in alterations in the NMDA receptor complex function similar to those seen after treatment postnatally or postweaning, but only after administration of doses that result in PbB levels 2–3 times higher (>40 µg/dL) than with exposures earlier in life (Cory-Slechta 1995b, 1997a; Cory-Slechta et al. 1997d).

Impairment has also been reported at low blood lead levels in other types of behavior/learning studies in rats. In a test of spatial discrimination, rats were exposed to lead acetate at 745 mg lead/kg/day in the diet indirectly via administration to their dams through gestation and lactation and then directly until testing (at 100 and 200 days of age) (Winneke et al. 1977). The lead-exposed rats were slower to learn the discrimination than were controls. Their PbB levels at postnatal day 16 averaged 26.6 µg/dL and the levels at 190 days averaged 28.5 µg/dL.

The results from a study in rodents demonstrated that lead (at PbB levels <30 µg/dL) has a selective effect on learning that is distinct from non-specific performance changes. Male Long-Evans rats were exposed to lead as lead acetate in drinking water from weaning through the completion of the experiment (Cohn et al. 1992). At 55 days of age they were trained to respond on a multiple repeated acquisition (RA) and performance (P) schedule. Each animal went through 80 daily sessions after training was complete. The RA component required the learning of a new three-member sequence of lever pushes each session, and

the P component remained constant across sessions. Correct completion of each sequence was rewarded with a food pellet, and mistakes resulted in "time-outs" during which the chamber lights were off and pushing the lever was without consequence. The authors reported that the learning component (i.e., the RA) was selectively affected in the lead-exposed animals. The P component was unaffected, indicating that the differences observed in the RA component were not due to a nonspecific effect on the ability to press the lever. The errors committed by the lead-exposed animals in the RA component appeared to be due either to perseverative responding on sequences similar to the P component sequence or perseverative responding on a single lever; both types of behavior prohibited the ability to learn new sequences that were unlike the P component sequence. The possibility that the reduced accuracy in the RA component of the lead-exposed rats was due simply to some sort of impairment in their ability to attend to stimuli indicating the transition from the P to the RA component of a session was eliminated by adding additional stimuli which were without effect. PbB levels measured after 60 sessions were 2.8±1.0, 25.1±4.1, and 73.5±5.7 µg/dL for the 0-, 50-, and 250-ppm groups, respectively. No clinical signs of toxicity (if any) or body weight were reported, but previous studies by these authors had shown that these PbB levels were not associated with body weight changes (Cory-Slechta et al. 1985).

Several studies are available on the effects of postnatal lead exposure on a number of behavioral tests in monkeys. For example, four rhesus monkeys (2 male and 2 female) were exposed to lead as lead acetate trihydrate according to the following regimen: 2 doses of 10.0 mg lead/kg were administered to the monkeys on day 8 or 9 and again on day 29 or 30 after birth by nasogastric intubation in distilled water (Levin et al. 1988). From day 9 to day 29 they received 0.7 mg lead/kg/day in their milk formula, and for 12 days after the second dose of 10 mg lead/kg, they received daily doses of 3.0 mg lead/kg/day. For the rest of the first 6 months after birth they were administered 0.7 mg lead/kg/day in the milk formula. Four (two males and two females) rhesus monkeys receiving equiionic doses of sodium acetate served as controls. This treatment regimen was supposed to mimic the temporal pattern of blood levels ("pulse chronic") seen in children. Blood lead levels, ZPP, hematocrit, and body weight were measured. The control monkeys had mean PbB levels of 4.1–7.9 µg/dL during the first 6 months. The lead-exposed monkeys had mean PbB levels of 25.5 µg/dL during the first 4 weeks, which increased to between 33.1 and 42.9 µg/dL during the first 6 months. PbB levels peaked at 55.8 µg/dL 5 weeks after birth. The following behavioral tests were conducted in an attempt to identify early predictors of later cognitive impairment resulting from postnatal lead exposure: (1) the early infant behavioral scale (conducted during the first 6 weeks after birth) to screen the development of a broad range of behavioral responses including orientation, muscle tonus, motor maturity, temperament, and quieting abilities; (2) the Piagetian object

permanence test (conducted at 14 days of age) to serve as an early measure of cognitive function during the sensorimotor stage of development; and (3) the visual exploration test to assess delayed spatial alternation performance which suggest deficits in visual attention. The lead-exposed infants were more agitated and had lower muscle tonus in the early infant behavior test. All other parameters in this test were not significantly affected by lead exposure. There was also no difference between the lead-exposed monkeys and the controls in the Piagetian object permanence test. Some aspects of the visual exploration test were affected by lead exposure; these changes were suggestive of decreased visual attentiveness in the lead-exposed monkeys. Based on these results, these tests may serve as both indices of behavioral dysfunction during postnatal lead exposure, and to predict later lead-induced cognitive dysfunction (Levin et al. 1988).

Studies of the effects of lead on learning in monkeys are also available. Perinatal exposure to lead nitrate (3 mg lead/kg/day) resulted in significant behavioral deficits in the offspring of *Macaca fascicularis* at maternal gestational PbB concentration of 30–70 µg/dL with no signs of maternal toxicity (Hopper et al. 1986). The infant monkeys showed deficits in form discrimination performance (6–18 months age), and in response inhibition performance (19–29 months of age). Persistent deficits in form discrimination up to 18 months following the termination of exposure suggests that lead-induced behavioral deficits may be permanent. Other investigators have used discrimination reversal tasks to detect impaired learning in monkeys treated orally with lead acetate (Bushnell and Bowman 1979b, 1979c; Laughlin et al. 1983; Levin and Bowman 1983; Mele et al. 1984). Discrimination reversal tasks require the subject to correctly respond to one of two stimuli to get a reward and then, once the task has been mastered, to make the reverse discrimination (i.e., respond only to the cue formerly unpaired with reward). In these studies, monkeys administered lead acetate orally from birth at low or high levels (0.2 or 0.88 mg lead/kg/day) that produced PbB levels of $32 µg/dL for 5 months to 1 year were consistently slower in reversal and other learning tasks (Bushnell and Bowman 1979a; Laughlin et al. 1983; Levin and Bowman 1983) even when exposure was terminated at 1 year and the monkeys were tested again at 33 months (Mele et al. 1984) and 49–55 months of age (Bushnell and Bowman 1979b). No effects were seen on body weight, growth rate, hematocrit, or general health. The monkeys tested at 49–55 months of age had PbB levels of 4 µg/dL for controls, 5 µg/dL for the low-lead group, and 6 µg/dL for the high-lead group, as compared with average and peak PbB levels during the year of treatment of 4 and 12 µg/dL for controls, 32 and 70 µg/dL for the low-lead group, and 65 and 134 µg/dL for the high-lead group (Bushnell and Bowman 1979b, 1979c). Additional evidence was provided by Ferguson and Bowman (1990) in a study on rhesus monkeys where postnatal exposure to varying doses of lead (0.7–10 mg/kg/day) resulted in behavioral alterations such as longer latency to enter the open field and increased activity and retarded habituation while in the open field.

These effects were observed 3 years after cessation of exposure although blood levels were similar to controls (#5 µg/dL); the PbB levels averaged 36 µg/dL for the first year of age. Evaluation of these monkeys at 7 years of age revealed that the open field behavioral alterations previously reported were greatly diminished or no longer present (Ferguson et al. 1996). Latency to enter an open field was marginally increased in the lead-treated monkeys, but levels of environmental exploration were comparable to controls. Although these studies were well conducted, it is difficult to determine a dose-response relationship given the unorthodox exposure regimen.

The above findings were supported and extended by other investigators (Gilbert and Rice 1987; Rice 1984, 1985b; Rice and Gilbert 1985; Rice and Karpinski 1988; Rice and Willes 1979; Rice et al. 1979). These studies demonstrated impaired learning ability on operant conditioning tasks and discrimination reversal tasks and extended the dose-response observations to lower blood lead levels. Monkeys were given lead (as lead acetate) orally, 5 days a week, from birth throughout the duration of the studies; doses ranged from 0.05 to 2.0 mg lead/kg/day. Deficiencies in discrimination reversal and/or operant learning were noted in the first 9 months and at 3–4 years with the highest dosage, and at 421 days through 3.5 years at 0.5 mg lead/kg/day (Rice 1984; Rice and Willes 1979; Rice et al. 1979). Peak and steady-state PbB levels were 115 and 33 µg/dL for the 2.0-mg/kg group and 55.3 and 32.8 µg/dL for the 0.5-mg/kg group. Even at the lowest dosages, 0.05 and 0.1 mg lead/kg/day, the monkeys performed significantly less well in learning discrimination reversals at 3–4 years of age, in learning a delayed alternation task at 6–7 years of age, and in learning discrimination reversals in the presence of irrelevant cues at 9–10 years of age (Gilbert and Rice 1987; Rice 1985b). In this series of studies on the same monkeys, peak and steady-state PbB levels were 15 and 11 µg/dL, respectively, for the 0.05-mg/kg group and 25 and 13 µg/dL, respectively, for the 0.1-mg/kg group (Gilbert and Rice 1987; Rice 1985b).

In addition to the confirmation of the observation that lead-treated monkeys were impaired in their ability to learn discrimination reversal tasks, notable findings were the tendency of lead-treated monkeys to respond excessively or inappropriately (e.g., with more responses than controls during time-outs) in operant schedules when responses were not rewarded (Rice et al. 1979). In addition, lead-treated monkeys were also slower to learn reinforcement schedules which required a low rate of responding (Rice and Gilbert 1985), tended to have higher response rates and shorter inter-response times on fixed-interval operant schedules, and made more perseverative errors on operant matching-to-sample tasks which required them to direct their responses according to stimulus colors (Rice 1984). These characteristic findings are similar to those seen in rats as discussed previously. No overt signs of toxicity were observed in the monkeys. In

experiments conducted in separate groups of monkeys, in which the animals were exposed to lead (1.5 mg/kg/day) either continuously for 7–8 years, only during infancy, or only as adults, it was found that all three groups exhibited altered performance on a fixed-interval-fixed-ratio schedule of reinforcement when tested at age 7–8 years (Rice 1992). These results suggested that exposure to lead during infancy is not necessary for the altered adult performance, and also that exposure only during infancy is sufficient to produce the effect.

Simple visual reaction time has proven not to be as sensitive an indicator of lead-induced neurotoxicity as some of the other behavior paradigms discussed above. Adult monkeys were tested in a simple visual reactive time task (Rice 1988). Seven cynomolgus monkeys (three female controls and two lead-treated monkeys of each sex) were used in this study. The lead-treated monkeys received 0.5 mg/kg/day of lead from birth into adulthood. The exact mode of administration was not specified. This study was conducted when the monkeys were approximately 7 years of age. PbB levels increased from birth to 53 µg/dL by 100 days of age, were stable at this level until 200 days of age, and then restabilized at a concentration of 33 µg/dL. The monkeys were trained to perform a simple visual reaction time task using delays between 1 and 13 seconds. There were no differences in performance between the control and treated monkeys. Based on these results the authors concluded that this simple paradigm used to measure reaction time was not a sensitive indicator of lead toxicity. These authors had previously demonstrated performance deficits in the same group of monkeys using different behavioral tasks.

Long-term administration of lead has also resulted in neurological effects other than neurobehavioral. For example, monkeys (Macaca fascicularis) treated for a lifetime with 0.5 mg lead/kg/day exhibited a slight decrease in vibration sensitivity (increased threshold to stimuli) when tested at the age of 18 years (Rice and Gilbert 1995). The results in a group treated with a 2 mg lead/kg/day dose, however, were equivocal in that only 2 of 6 monkeys showed clear impairment. In a more recent publication, Rice (1997) showed that lifetime treatment with 2 mg lead/kg/day increased thresholds for pure tones in 3 of 6 monkeys, higher frequencies tended to be more affected. At the time of testing at the age of 12–13 years, the PbB levels ranged between 70 and 150 µg/dL; up to age 10–11 years, PbB concentrations were stable at about 30 µg/dL. The results of increased hearing thresholds is consistent with results reported in humans (Schwartz and Otto 1991). Lilienthal and Winneke (1996) reported increased latencies of waves of the brain stem auditory evoked potentials in monkeys chronically exposed to 4 or 7 mg lead/kg/day, as lead acetate, in the diet. Exposure was began *in utero* and continued until the animals were about 9.7 years old.

This altered response was still present when the monkeys were retested 18 months after treatment with lead had ceased, at which time the PbB concentration had declined to nearly normal values.

Electrophysiological studies have reported effects at higher blood lead levels than have the neurobehavioral studies presented above. Suckling rats whose dams were given 152.9 mg lead/kg/day as lead acetate in their drinking water had significant alterations in the visual evoked responses (VERs) and decreased scotopic visual acuity at postnatal day 21, at which time their PbB levels averaged 65 µg/dL (Fox et al. 1977). Effects on the nervous system were persistent; decreases in visual acuity and spatial resolution were observed at 90 days of age in rats exposed only from birth to weaning as noted above (Fox et al. 1982). Further investigations by this laboratory on the effects on the eye of pre- and postnatal exposure of rats to lead are discussed in Section 2.2.3.2.

Similarly, changes in nerve conduction velocity (NCV) have also been used as indicators of lead-induced neurotoxicity (see Section 2.2.1.4), and these effects also occur at higher blood lead levels than those at which neurobehavioral effects are observed. The effects of lead exposure on motor NCV were evaluated in rats administered lead acetate in the drinking water for 15 weeks at the following doses: 0, 89.6, 448, 896, and 1,792 mg lead/kg/day (Yokoyama and Araki 1986). Body weight, blood lead levels, and nerve lead levels were measured at the termination of the exposure period. Maximal motor NCV of the left sciatic nerve was measured in ether anesthetized rats after 15 weeks of exposure to lead. NCV was significantly decreased in the 89.6 mg lead/kg/day group as compared to the controls (46.8 meters/second versus 51.2 meters/second). This decrease was roughly dose-dependent, although a wide range of NCVs were observed at each dose. NCV was significantly correlated with PbB levels in all treated groups, but did not correlate with nerve lead levels or body weight. The authors concluded that PbB level is a better indicator of the effect of lead on NCV because it reflects the "active" lead in the peripheral nerves, whereas the nerve lead level may represent an "inactive" form of lead. Yokoyama and Araki (1992) also reported that exposure to lead (approximately 77 mg lead/kg/day in the drinking water for 13 weeks) induced a decrease in slow axonal transport of proteins in the sciatic nerve of rats. The mean PbB concentration in the treated and controls animals was 153 µg/dL and 9 µg/dL, respectively.

The highest NOAEL values and all reliable LOAEL values for each study for neurological effects are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.3.5 Reproductive Effects

According to EPA (1986a), lead was used in preparations sold as abortifacients in Britain around the turn of the century. These preparations were apparently effective at levels that produced marked signs of lead poisoning in the women. The available studies were methodologically inadequate and did not provide dose-effect information. Evidence for adverse reproductive outcomes in women with obvious lead poisoning is of little help in defining the effects of lead at much lower exposure levels.

An adverse effect of lead on pregnancy rate has been noted in some animal studies (Kennedy et al. 1975). Acute-duration gavage administration of 390 mg lead/kg/day as lead acetate to rats resulted in a sharp decrease in pregnancy rates. This effect was not noted at 39 mg lead/kg/day. The study limitations include a lack of measurement of blood lead levels and lack of statistical analysis of pregnancy incidence. A decrease in the number of implantations was noted in untreated female mice that were mated to males that had been treated with 141 mg/kg/day lead chloride in the drinking water for 3 months (Johansson and Wide 1986). A more recent study in mice found no effects of administration of lead chloride in the drinking water on fertility in mice (Kristensen et al. 1995). Females (F0) received approximately 176 mg lead/kg/day for 6 weeks before mating. This resulted in a median PbB concentration of 68 µg/dL (0.8 µg/dL in controls) during the second week of pregnancy. F_1 females were continuously bred to untreated males for 6 months. The results showed that treatment with lead had no significant effects on number of litters, number of offspring, median number of offspring, median number of litters, median litter size, and median number of days between litters. Moreover, ovarian weight was not altered and neither were the number of small, medium, or large follicles/F_1, or number of corpora lutea/F_1.

No treatment-related effects on reproductive indices were noted in rats exposed to up to 0.9 mg lead/kg/day as lead nitrate in the drinking water 3 weeks before mating, during gestation, and during lactation (Hubermont et al. 1976). However, other animal studies have reported lead-induced damage to the ovaries and testes. Such effects of lead were examined by Hilderbrand et al. (1973), who reported that oral dosing with low dose levels of lead acetate, 0.014 and 0.26 mg lead/kg/day for 30 days produced PbB levels of 30 and 53 µg/dL, respectively; these were higher than levels found in the study by Grant et al. (1980). Irregular estrous cycles occurred at both treatment levels, and ovarian follicular cysts with reductions in numbers of corpora lutea occurred at the higher level. Male rats treated orally with lead acetate (0.013 and 0.26 mg lead/kg/day) in the same manner had PbB levels of 19 and 30 µg/dL, respectively, and had

testicular damage at the higher exposure level, with increased prostate weight at the lower level. No details regarding the strain of rats used were provided.

In a later study of lead effects on male reproductive tract, Chowdhury et al. (1984) found testicular atrophy and cellular degeneration in male rats given lead acetate in drinking water at 90 mg lead/kg/day for 60 days. PbB levels averaged 142.6 µg/dL. At a lower exposure level of 45 mg lead/kg/day and mean blood lead level of 71.7 µg/dL, the seminiferous tubular diameter and spermatic count were reduced. No significant changes were seen at 22 mg lead/kg/day and a PbB level of 54.0 µg/dL. The study is limited by the lack of determination of whether the partial inhibition of spermatogenesis seen at 45 mg lead/kg/day was a transitional effect. Treatment of male rats with a dose of approximately 6.4 mg lead/kg/day as lead acetate for 3 months resulted in altered spermatogenesis as reflected as a decrease in the number of all types of germinal cells, and decreases in seminiferous tubular diameters and in the germinal height of the tubules (Kaushal et al. 1996). These effects were less marked with higher doses, but were consistent with a higher accumulation of lead in the testis with the lowest dose tested, 6.4 mg/kg/day. PbB levels, however, were increased in a dose-related manner, 11.8 µg/dL with the lowest dose level versus 72.9 µg/dL with the highest dose level tested, 127.4 mg/kg/day. Relative testis weight was also maximally decreased in the low-dose animals.

Decreases in sperm motility and increased acid phosphatase activity were reported to result from oral administration of 0.05 mg/kg lead in drinking water to male rats for 20–30 days in a study from the former U.S.S.R. (Krasovskii et al. 1979). Dystrophic changes of the Leydig cells were reported in gonadal tissues of rats exposed to doses as low as 0.005 mg lead/kg/day. The weaknesses of the study include absence of data on the strain and number of rats used, and the fact that PbB levels were not reported.

Male rats exposed to lead acetate in drinking water through the dams during gestation and lactation and then directly until 9 months of age exhibited no significant effects on sperm count or sperm morphology (Fowler et al. 1980). The PbB levels in these animals ranged from 4.5 to 67 µg/dL. Rats administered 0.19 mg lead/kg/day as lead acetate by gavage for 9 weeks exhibited a significant reduction in the number of spermatozoa within the cauda epididymis. At 192 mg lead/kg/day, the number of abnormal spermatozoa increased significantly, but a decrease in the number of spermatozoa was not significant. No adverse effects were noted in the testes. The results of this study indicate that lead affected spermatozoa after release from the germinal epithelium which was possibly protected from the effects of lead by the blood-testes barrier (Barratt et al. 1989).

Lifetime exposure of male cynomolgus monkeys to lead at dose levels that resulted in mean PbB of 10 µg/dL (range, 6–20 µg/dL) or 56 µg/dL (range, 22–148 µg/dL) did not alter circulating levels of testosterone nor affected parameters of semen quality such as sperm count, viability, motility, and morphology (Foster et al. 1996). However, there were treatment-related changes in sperm chromatin structure, as revealed by flow cytometric analysis. These analyses were conducted over a period of one year when the monkeys were 15–20 years old. According to Foster et al. (1996), the results suggest that flow cytometric analysis of monkey sperm provides a more sensitive measure of toxicant-induced effects on semen quality than measures such as sperm concentration, viability, and motility. Also, the observed changes occurred at blood lead concentrations relevant to the human population. More recently, the same group of investigators also reported on the effects of lead on reproductive parameters of monkeys exposed from postnatal day 300 to 10 years of age (postinfancy) and from postnatal day 0 to 400 (infancy) (Foster et al. 1998). A lifetime exposure group was also included. Endpoints evaluated included testis ultrastructure, semen analysis, and hormone assays. PbB levels in lifetime and postinfancy exposed monkeys were approximately 35 µg/dL compared to <1.0 µg/dL in controls and infancy exposed animals. Relative to controls, absolute and relative testis weight was higher in lead-treated monkeys, but the difference was not statistically significant. Circulating concentrations of follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone were not altered by treatment with lead. Semen characteristics were not affected by treatment with lead. Electron microscopy of the testis revealed disrupture of the general architecture of the seminiferous epithelium that involved Sertoli cells, basal lamina, and spermatids in the groups exposed for lifetime and during infancy, with equal severity. No such alterations were seen controls or in the postinfancy exposure group. The results showed that lead exposure in monkeys during infancy can induce testicular alterations that persist in later life when blood lead concentrations had decreased considerably.

Exposure of female rhesus monkeys to 1.3 or 5 mg lead/kg/day as lead acetate in their drinking water for 75 months resulted in reduced circulating concentration of progesterone, suggesting impaired luteal function; however, treatment with lead did not prevent ovulation (Franks et al. 1989). The monkeys also exhibited longer and more variable menstrual cycles and shorter menstrual flow. PbB levels attained in the monkeys in this study were 70 µg/dL. Female cynomolgus treated daily for up to 10 years with gelatin capsules containing lead acetate, which provided approximately 1 mg lead/kg/day, had significantly suppressed circulating levels of luteinizing hormone (LH), follicle stimulating hormone (FSH), and estradiol (Foster 1992). However, circulating progesterone concentrations were not significantly affected by lead treatment. In these monkeys, PbBs were approximately 35 µg/dL, half those observed in the

monkeys studied by Franks et al. (1989). The results of these studies suggested that impaired luteal function induced by relatively high PbB levels is secondary to lead-induced suppression of circulating FSH concentrations.

Pre- and postnatal exposure of female animals to lead can affect pubertal progression and hypothalamic-pituitary-ovarian-uterine functions in offspring. The administration of lead acetate in drinking water to rats, both indirectly through the dams during gestation and lactation and then directly, produced no effects on female offspring exposed to 0.7 mg lead/kg/day but delayed the vaginal opening in females exposed to $3.5 mg lead/kg/day (Grant et al. 1980); these females were not retarded in their growth. Similar effects were also reported in dams receiving lead acetate prior to breeding (Kimmel et al. 1980). This effect was dose-dependent. Exposure of male and female rats prepubertally (age 24 days to 74) to lead acetate in the drinking water (approximately 502 mg lead/kg/day) resulted in significant reduction in testis weight and in the weight of secondary sex organs in males and in delayed vaginal opening and disruption of estrus cycle in females (Ronis et al. 1996). However, these effects were not observed in rats exposed postpubertally (day 60–74 in males, 60–85 in females). Mean PbB concentrations in rats exposed prepubertally and postpubertally were 57 and 31 µg/dL, respectively. In the same study, Ronis et al. (1996) also exposed a group of rats beginning during gestation, and continuing through lactation and postpubertally. In this group, the effects were much more severe than in the rats exposed only pre- or postpubertally, and were consistent with the much higher blood lead concentrations achieved in the offspring, approximately 316 µg/dL (see also under Developmental Effects). In follow-up studies, Ronis et al. (1998a, 1998b, 1998c) found that prenatal lead exposure (0.15% or 0.45% lead acetate in drinking water; approximately 126 or 377 mg lead/kg/day) that continued until adulthood (85 days old) delayed sexual maturation in male and female pups in a dose-related manner. PbB levels in the pups between the ages of 21 and 85 days ranged from 103–192 µg/dL and 238–388 µg/dL in the two dosage groups. Measures of adult reproductive physiology were less sensitive to lead exposure. According to Ronis et al. (1998b, 1998c), these findings are consistent with a suppression of the normal sex steroid surges that occur at birth and during puberty and suggested a site of lead action at the hypothalamic-pituitary unit. Also, the normalization of reproductive parameters post-puberty suggested a transient rather than permanent defect.

An effect of lead on central regulation of endocrine functions through the hypothalamus-pituitary axis has also been observed in adult animals. Following exposure to 40 mg lead/kg/day administered as lead acetate in drinking water, histopathological examination of the gonads and thyroid gland and measurements of serum testosterone, 17β-estradiol, FSH, LH, prolactin, TSH, T_3, and T_4 were conducted. No changes were

seen at the 40- and 81-mg/kg/day dose levels. No lead uptake was noted in the gonads. However, the lowest dose was sufficient to reduce serum prolactin and LH levels significantly (Sourgens et al. 1987).

The highest NOAEL for reproductive effects in rats and mice and all reliable LOAELs for reproductive effects in rats, mice, and monkeys are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to inorganic lead. See Section 2.2.1.6 for a discussion of developmental effects in humans after multi-route exposure to lead.

Twenty-three teratogenicity studies in which lead compounds (acetate or nitrate) were administered in the drinking water or feed or by gavage to rats and mice have shown no evidence that lead causes malformations, but some evidence that lead causes fetotoxic effects. The following discussion is based on the teratogenicity studies most relevant to current concerns for human prenatal exposure along with studies concerned primarily or exclusively with the neurobehavioral effects of prenatal exposure to lead.

In rodents, a greater proportion of nervous system development takes place postnatally than in humans. Accordingly, rodent studies of developmental neurobehavioral toxicity that extend exposure into the early postnatal period are probably more analogous to human prenatal exposure than are rodent studies that use only prenatal exposure.

Following oral administration of lead acetate at doses up to 64 mg lead/kg/day to rats before breeding and throughout pregnancy, the only effect seen was fetal stunting at the high dose (Miller et al. 1982). However, the lack of effect on fetal brain and litter size indicated that lead exposure failed to influence development in rats. Maternal PbB values ranged from 80 to 92 µg/dL prior to mating and from 53 to 92 µg/dL during pregnancy. Pretreatment and control PbB levels averaged 6–10 µg/dL. Similar results were obtained in rats administered up to 390 mg/kg/day by gavage on gestation days 6–16. Fetotoxicity (retarded skeletal development) was evident at the high dose, a dose that was maternally toxic as well (Kennedy et al. 1975). Treatment of rats with 0.6% lead acetate (estimated dose of 502 mg lead/kg/day) in the drinking water on gestation days 5–21 resulted in 19% incidence of stillbirth compared to 2% observed in a control group (Ronis et al. 1996). In subsequent studies using a similar experimental protocol, the same group of investigators reported that treatment of rats with 0.45% lead acetate (approximately 377 mg

lead/kg/day) in the drinking water on gestation days 5–21 resulted in 28% incidence of stillbirth (Ronis et al. 1998b). The mean PbB level in the pups at birth in this exposure group was 197 µg/dL. Exposure to 0.15% lead acetate resulted in significant decreases in birth weight in males, crown-to-rump length in males, and anogenital distance in both males and females. Pups up to age 85 days that drank water containing 0.45% lead acetate showed a significant reduction in growth rate during the prepubertal and pubertal period; growth rates during ages 55 and 85 days were similar to control rates. Lower exposure concentrations (0.15% and 0.05% lead acetate) did not alter growth rates significantly (Ronis et al. 1998c). The authors suggested that the reduced growth may have been caused by lead-induced effect on growth hormone secretion, and this was confirmed after measuring a number of endocrine and biochemical parameters known to be growth hormone-dependent.

Neurodevelopmental endpoints were assessed in the offspring of rats exposed to lead acetate at 448 mg lead/kg/day in the drinking water prior to mating and throughout gestation (Rabe et al. 1985). The pups were transferred to unexposed foster dams on the second day after birth. Mean PbB levels were 98 µg/dL at day 1 and 20 µg/dL at day 16 of age in pups from treated dams and approximately 10 µg/dL at both ages in pups from control dams. Body weights were reduced in treated pups relative to controls at birth but not at 30 days of age. Neurobehavioral function (surface righting and negative geotaxis reflexes, spatial discrimination, and reversal in T-maze), tested in the pups at 17 days of age, was not affected by prenatal lead treatment. In a study conducted on Binghamton Heterogeneous Stock mice by Draski et al. (1989), dams received lead acetate (608 mg lead/kg/day) in their drinking water during gestation; at birth, litters were cross-fostered so as to receive postnatal exposure to lead acetate. The PbB level in treated dams was 100 µg/dL (versus <10 µg/dL in controls); in pups the levels ranged from 76 to 130 µg/dL (versus 3–6 µg/dL in controls) during postnatal days 5–15. The open field test and time to return to home cage showed changes in behavioral patterns of pups depending on the developmental stage during which the dams were exposed, as well as age and conditions when tested. Open field behavior was also evaluated in 6-month-old rats that had been exposed to lead acetate *in utero*, during lactation, and through their drinking water (Rodrigues et al. 1993). The daily doses of lead were approximately 18, 36, and 146 mg/kg/day, which resulted in corresponding PbB concentrations of 51, 67, and 169 µg/dL. Treatment with lead resulted in an altered activity pattern in the mid- and high-dose groups consisting in increased activity in the open field and failure to habituate to the environment.

The different aspects of a study of prenatal, postnatal, and long-term exposure of rats to lead were presented by Kimmel et al. (1980) and Grant et al. (1980). The well-conducted study by Kimmel et al. (1980)

provided a variety of relevant dose-effect data. In this study, female rats were exposed to lead acetate in the drinking water at 0.07, 0.7, 3.5, 7, and 35 mg lead/kg/day from weaning through mating, gestation, and lactation. The pups were weaned onto the same drinking water solutions as their dams received. In addition, some of the dams were killed at day 21 or 22 of gestation for evaluation of the fetuses and uteri. Toxicity to the dams (dose-related slight depression of body weight and delay in time of vaginal opening) was seen at $3.5 mg/kg/day. Exposure to lead did not affect the ability of females to conceive, to carry a normal litter to term, or to deliver offspring. No significant differences in indices of embryo- or fetotoxicity or teratogenicity were seen in treated groups relative to controls. Length of gestation and birth weights were unaffected, but mean crown-rump length of 1-day-old female pups in the 35-mg/kg/day group was significantly shorter than in controls. Median PbB levels just prior to mating and at day 21 of gestation were 1 and 4 µg/dL for controls, 9 and 12 µg/dL for the 0.7-mg/kg/day group, 20 and 23 µg/dL for the 3.5-mg/kg/day group, 24 and 35 µg/dL for the 7-mg/kg/day group, and not reported for the 35-mg/kg/day group (Kimmel et al. 1980).

Significant delays in vaginal opening in female pups of groups receiving $3.5 mg lead/kg/day and significant delays in the development of surface and air righting reflexes in pups receiving 7 or 35 mg lead/kg/day were reported by Grant et al. (1980). PbB levels of the pups at 1 and 11 days were 4 and 3 µg/dL for controls, 37 and 22 µg/dL for 3.5-mg/kg/day pups, 57 and 35 µg/dL for 7-mg/kg/day pups, and not reported for 35-mg/kg/day pups. In comparing the results of this study with results of the study by Rabe et al. (1985), in which no effects on the development of reflexes were seen at a much higher level of lead in the drinking water, it should be noted that exposure to lead in the Rabe et al. (1985) study ceased shortly after birth, but in the Grant et al. (1980) study exposure to lead continued through the time of testing.

Delays in the development of the righting reflex were observed by Reiter et al. (1975) in rat pups whose dams were exposed to lead acetate at concentrations of 0.7 and 7 mg lead/kg/day in their drinking water throughout gestation and lactation. Eye opening was delayed at the higher exposure level. Blood lead levels were not determined.

In assessing the behavioral responses of rat pups, Taylor et al. (1982) found that exposure of female rats, prior to mating and through gestation and lactation, to lead acetate (28 and 56 mg lead/kg/day) in the drinking water did not result in significant differences in the pups' acquisition of a response when tested at 11 days of age, but did result in significantly slower extinguishing of the response when the reward was no

longer provided. PbB levels at 21 days of age were 3.7 µg/dL in controls, 38.2 µg/dL in the low-exposure group, and 49.9 µg/dL in the high-exposure group. Jett et al. (1997) showed that treatment of rats with 250 ppm lead acetate in the diet beginning 10 days prior to breeding and continued during gestation and lactation resulted in impaired learning of a swim task in the pups when tested at 21 days of age, but not at 56 or 91 days of age. PbB levels were not provided, but lead concentrations in the hippocampus of treated pups was 41–47% lower at age 56 and 91 days than at age 21 days. The authors stated that the age-dependent differences in performance may be due both to developmental differences of lead effect on neuronal targets, and the concentration of lead achieved at the site of action.

Neurobehavioral effects in infant monkeys were examined by Bushnell and Bowman (1979a) and Levin and Bowman (1983) who treated adult female monkeys orally with lead acetate at 1.9 and 3.8 mg lead/kg/day prior to mating and throughout gestation. PbB levels at birth were 5, 30, and 55 µg/dL in control (n=5), low-lead (n=3), and high-lead (n=4) groups, respectively. Treatment of the mothers produced no changes in early social behavior of their infants and no differences in learning ability, relative to controls, when the offspring were tested on a search task at 4–5 years of age. However, the dosing was administered over variable dose ranges throughout the study, which indicates metabolic differences in maintaining the blood lead levels. A recent study reported prolonged deficits in learning and motor functions in monkeys tested between the ages of 3 and 7 years and that were exposed to lead *in utero* (Newland et al. 1996). During exposure, maternal PbB concentrations ranged from 21 to 70 µg/dL.

Histological changes have been reported in the brains of rat pups at much higher blood lead levels than those reported above. Administration of lead chloride (28 mg lead/kg/day) in drinking water to pregnant rats during gestation and lactation was reported to produce a less mature synaptic profile in the cerebral cortex of the pups at postnatal day 15 (McCauley et al. 1979) and a 30% reduction in synaptic density in the cerebral cortex at postnatal day 15 but not day 21 (McCauley et al. 1982). PbB levels were 80 µg/dL at birth. Although the authors reported a dose-dependent increase in blood lead levels in pups from the 4.2 and 28 mg/kg/day groups, the synaptic counts were measured only for pups from the high-dose group.

In rats exposed to lead during gestation and through postnatal day 28 via breast milk there was a 30–40% reduction in the cholinergic marker choline acetyltransferase activity (ChAT) in the septum and hippocampus relative to controls (Bielarczyk et al. 1994). At this time, the PbB concentration in the pups was approximately 20–22 µg/dL compared with 2–3 µg/dL in controls. This was paralleled by a reduction in muscarinic cholinergic receptor binding in the septum, but not in the hippocampus. This suggested

preferential vulnerability of septal cholinergic neurons to low-level lead exposure. Results from a follow-up study with extended observation period showed that early lead exposure causes long-lasting cholinergic deficits which induce secondary responses in the hippocampus resembling compensatory changes observed following surgical cholinergic denervation of the hippocampus in adult animals (Bielarczyk et al. 1996; Bourjeily and Suskiw 1997).

Decreased numbers of dendritic spines and malformed spines in brain parietal cortex were observed at postnatal day 30 in rat pups whose mothers were administered 256–480 mg lead/kg/day as lead acetate in drinking water during gestation and lactation (Murray et al. 1978). PbB levels were not reported.

Gestational exposure of guinea pigs to 5.5 or 11 mg lead/kg/day produced dose-dependent alterations of neuroglial enzymes (glutamine synthetase and glycerol-3-phosphate dehydrogenase) and changes in trace metal levels (Sierra et al. 1989). PbB levels in dams and fetuses associated with these changes were within the range of 10–30 µg/dL lead. However, the authors did not examine for histopathological alterations in neural tissue. The same group of investigators examined the effects of gestational exposure on the levels of gonadotropin-releasing hormone (GRH) and somatostatin (ST) in the hypothalamus of guinea pig fetuses (Sierra and Tiffany-Castiglioni 1992). Dams were exposed on gestation days 22–52 or 22–62. The doses of lead were 0 (controls), 5.5, or 11 mg lead/kg/day and on gestation day 62 resulted in PbB levels in the dams of 1.5, 22.2, and 39 µg/dL, respectively. PbB levels in the fetuses were similar to those of the dams. Exposure to lead significantly reduced in a dose-related manner the hypothalamic levels of GRH and ST in both fetuses and dams.

Some studies have investigated the effects of prenatal exposure to lead on heme metabolism. Hubermont et al. (1976) administered lead nitrate at concentrations of 0.009, 0.09, and 0.9 mg lead/kg/day in drinking water to female rats before mating, throughout gestation, and during lactation. PbB levels in the dams and pups that received 0.9 mg lead/kg/day group were 68 and 42 µg/dL, respectively. An increase in free tissue porphyrins and a decrease in blood ALAD activity were seen in the pups that received 0.9 mg lead/kg/day, as compared with controls. The study did not examine the long-term hematological effects of lead. An increase in free erythrocyte protoporphyrins was also observed in 1-week-old rats exposed to lead acetate *in utero* (gestation days 1–21) and via maternal milk for 7 days; no such effect was seen in 1-day-old pups after similar gestational exposure (Bogden et al. 1995). Interestingly, the PbB concentration in the 1-day-old pups was higher (72.5 µg/dL) than in the 7-day-old pups (51.8 µg/dL).

Effects at even lower external and internal exposure levels were reported by Hayashi (1983). Lead acetate at 0.7 mg lead/kg/day in the drinking water of rats for the first 18 or 21 days of pregnancy resulted in decreased ALAD activity in the fetal and maternal erythrocytes and increased ALAD activity in fetal but not maternal liver. Fetal, but not maternal, hematocrits and hemoglobin levels were decreased in the group treated for 21 days. Fetal PbB levels were 27 µg/dL and 19 µg/dL in the 18-day and the 21-day treated groups, respectively. Maternal PbB levels were approximately 4 µg/dL in treated and control groups. The study is limited by the use of one dose level, which precluded assessment of dose response.

Adverse kidney effects have been reported in rats exposed to lead during development (Fowler et al. 1980). Also, alterations in immune function have been observed in young rats exposed to lead perinatally (Faith et al. 1979; Luster et al. 1978). These studies are discussed in more detail in Sections 2.2.3.2 and 2.2.3.3.

The highest NOAEL values and all reliable LOAEL values for each study for developmental effects are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.3.7 Genotoxic Effects

Eleven male volunteers aged 20–30 years ingested lead acetate for 49 days. PbB levels were kept at approximately 40 µg/dL. The frequency of chromosome aberrations was assayed after lymphocyte culture for 72 hours and found to be no different from that of 10 controls. The lymphocytes from lead-exposed subjects did show a higher mitotic activity (Bulsma and DeFrance 1976).

Intermediate-duration exposures of mice to lead in the diet resulted in slight increases in chromatid gaps, but no significant increases in any class of serious chromosome aberrations (Jacquet et al. 1977). Cytogenetic analysis was performed on bone marrow cells of Wistar rats exposed to 500 ppm lead acetate in drinking water for 6 weeks. Although there was a marked increase in chromosome pulverization and erosion, there was no increase in the frequency of chromosomal aberrations. Sister chromatid exchanges were slightly, but significantly, increased over controls (Kowalska-Wochna et al. 1988).

Monkeys given daily doses of 1 or 5 mg of lead by intubation for 12 months showed only minor chromosome aberrations such as chromatid and chromosome gaps and fragments at the beginning of the experiment. After 7 months of exposure, more severe aberrations (translocations and dicentrics) appeared in the lymphocytes. However, no statistically significant difference in severe aberrations between the

exposed monkeys and the controls was ever seen. Lead treatment did produce a significant increase in the number of gaps, but this was not related to dose or to measured blood lead level (Jacquet and Tachon 1981). An earlier chronic study on monkeys given lead acetate in the diet 6 days a week for 16 months showed that severe chromosome abnormalities occurred only in animals given a calcium-deficient diet (Deknudt et al. 1977).

Other genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding cancer in humans after oral exposure to inorganic lead. See Section 2.2.1.8 for a discussion of cancer in humans following multi-route exposure to lead.

The available data on the carcinogenicity of lead following ingestion by laboratory animals indicate that lead acetate and lead phosphate are carcinogenic, and that the most common tumor is renal. However, the extremely high cumulative doses of lead used in these studies are difficult to extrapolate to low-level exposure in humans, and thus do not provide a sufficient basis for quantitative risk assessment (see Section 2.5). In addition, it is possible that the high doses required to induce renal tumors may themselves have produced a carcinogenic effect that was independent of any direct effect of lead as a result of nonspecific tissue damage. Furthermore, the relevance of male rat kidney tumors induced by some chemicals to humans has been questioned (EPA 1991c). It is not known whether the mechanism by which lead induces tumors in the rat kidney involves the same or similar species-specific proteins ($\alpha_{2\mu}$-globulin) identified in the recent studies of other substances, such as unleaded gasoline (see Section 2.9.3 for a discussion of ongoing research designed to answer this question).

The most comprehensive set of studies was performed by Azar et al. (1973), who administered lead acetate to rats for 2 years. Renal tumors occurred in 5 of 50 male rats that received 27 mg lead/kg/day, in 10 of 20 males that received 56.5 mg lead/kg/day, and in 16 of 20 males and 7 of 20 females that received 105 mg lead/kg/day. No renal tumors were observed in the control groups or in rats administered 0.9–7 mg lead/kg/day. Limitations of this study were likelihood of environmental contamination from lead in the air or drinking water was not mentioned, and the strains of rats used were not specified. Body weight gain in the two highest dose treatment groups was reported to be depressed, but no details were given regarding this finding.

Male Sprague-Dawley rats were administered lead acetate equivalent to 37 mg lead/kg/day in their drinking water for 76 weeks as part of a study to determine interactions between sodium nitrite, ethyl urea, and lead. There were no kidney tumors in the 10 control rats. Renal tubular carcinomas were found in 13 (81%) of the 16 treated rats. Three of these tumors were detected at 72 weeks and the remaining were found at terminal necropsy (Koller et al. 1985).

An increased incidence of renal tumors (7 out of 25 combined adenomas and carcinomas) was observed in male Swiss mice fed 0.1% basic lead acetate in the diet for 2 years (Van Esch and Kroes 1969). No renal tumors were found in the control animals. One female in the 1.0% treatment group had a renal tumor. The authors attributed the low tumor incidence in the 1.0% group to early mortality. The cancer effects levels described above are recorded in Table 2-4 and plotted in Figure 2-2.

2.2.4 Dermal Exposure

No studies were located regarding the following effects in humans or animals after dermal exposure to inorganic lead. See Section 2.2.1 for a discussion of these effects in humans following multi-route exposure to lead:

2.2.4.1 Death

2.2.4.2 Systemic Effects

2.2.4.3 Immunological Effects

2.2.4.4 Neurological Effects

2.2.4.5 Reproductive Effects

2.2.4.6 Developmental Effects

2.2.4.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.4.8 Cancer

No adequate studies were located regarding cancer in humans or animals after dermal exposure to inorganic lead. See Section 2.2.1.8 for a discussion of cancer in humans following multi-route exposure to lead.

2.3 TOXICOKINETICS

The absorption, distribution, metabolism, and elimination of lead has been extensively studied in both animals and humans. While some of the precise pharmacokinetic mechanisms that control these physiological processes are unknown, available data can be used to quantify the uptake and disposition of lead in the human body for various populations of children and adults. Lead absorption is influenced by the route of exposure, chemical speciation, the physicochemical characteristics of the lead and exposure medium, and the age and physiological states of the exposed individual (e.g., fasting, nutritional calcium and iron status). The primary sites for inorganic lead absorption are the gastrointestinal and respiratory tracts. The bioavailability of ingested soluble lead in adults may vary from less than 10% when ingested with a meal to 60–80% when ingested after a fast. Nonlinear relationships observed between uptake and blood lead concentrations may be explained by both capacity-limited absorption in the gastrointestinal tract, and capacity-limited binding of lead with red blood cells. Immediately following absorption, lead is widely distributed to blood plasma and soft tissues, then it redistributes and accumulates in bone. Bone lead accounts for approximately 73% of the total body burden in children, increasing to 94% in adults due to changes in bone turnover rates with age. Therefore, kinetic behavior of lead in humans is determined largely by the mechanisms by which lead is exchanged between blood plasma and bone surfaces, processes of bone growth and resorption, and heteroionic exchange processes in the kidney and intestines. Age-dependence of lead kinetics is reflected by greater absorption efficiency, bone turnover rates, and excretion efficiency in children compared with adults. Transplacental transfer of lead has been demonstrated based on measurements of lead in umbilical cord blood in humans, as well as tissue concentrations in offspring of mice. In addition, studies in suckling mice and rats suggest that as much as one-third of the maternal dose of lead can be transferred to mother’s milk during periods of lactation.

Inorganic lead ions are not known to be metabolized in the body but they are complexed by macromolecules. Lead that is not retained in the body is excreted principally by the kidney as salts or through biliary clearance into the gastrointestinal tract in the form of organometallic conjugates. Excretion rates measured in infants, children, and adults are highly variable, although available data suggest that the fraction of absorbed lead that is retained in humans decreases with age. In addition, acute and chronic lead exposure studies in mice, rats, and non-human primates show that, in general, there is greater excretion of lead in feces than in urine due to the high molecular weights of lead conjugates. Exhalation is a major route of excretion following inhalation exposure of organic lead in humans.

A number of mathematical pharmacokinetic models for lead have been proposed to explain and predict physiological processes, including intercompartmental lead exchange rates, retention of lead in various pools, and relative rates of distribution among the tissue groups. A physiologically based pharmacokinetic (PBPK) model developed by O'Flaherty (1993, 1995a) simulates lead absorption and disposition as a function of age-specific anatomical and physiological variables. Compartmental pharmacokinetic models, including the IEUBK Model for lead in children (EPA 1994a, 1994b) and the Leggett Model (Leggett 1993), simulate the same general processes, although transfer rate constants and kinetic coefficients may not have precise physiological correlates. All three models have been calibrated, to varying degrees, against empirical physiological data on animals and humans, and on blood lead concentrations observed in exposed populations of children and adults. Only the IEUBK model is used to estimate the probability distribution of blood lead concentrations in children potentially exposed to lead via multiple exposure pathways at hazardous waste sites. Efforts are currently in progress to fully assess the degree to which the IEUBK Model accurately simulates blood lead distributions in populations of children who are exposed to lead at hazardous waste sites. The O'Flaherty and Leggett models have accurately reproduced adult blood lead concentrations, and may be modified to reflect changes in toxicokinetics of lead associated with pregnancy, aging, or disease states.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Inorganic Lead. Prior to the actual absorption of lead by the lungs, some fraction of inhaled airborne lead must be deposited in the respiratory tract. The rate of deposition of particulate airborne lead in adult humans is approximately 30–50% and is modified by factors such as particle size and ventilation rate (EPA 1986a). Once deposited in the lower respiratory tract, particulate lead is almost completely absorbed, and all chemical forms of lead also seem to be absorbed (EPA 1986a; Morrow et al. 1980). After subjects breathed lead chloride, with a mass median aerodynamic diameter (MMAD) of 0.26 μm, and lead hydroxide, with an MMAD of 0.24 μm, through a standard respiratory mouthpiece for 5 minutes, 23% and 26%, respectively, of the aerosol was deposited in the lungs and respiratory tract (Morrow et al. 1980). A multiple linear regression model used to predict PbB concentrations in 44 adult males exposed to particulate airborne lead showed a 25% stronger relationship (r^2 increased from 0.36 to 0.45) between air lead and PbB when particles smaller than 1 μm were assumed to undergo greater rates of deposition and absorption in the lungs than larger particle (Hodgkins et al. 1991).

Absorption is suggested by elevated PbB concentrations in subjects who were continuously (23 hours per day) exposed to 0.0032–0.011 mg lead/m^3 for 18 weeks (the species of lead to which the subjects were exposed was not specified) (Griffin et al. 1975b). Elevated blood and urinary lead concentrations were also found in volunteers exposed to 0.15 mg lead/m^3 for 7.5 hours per day, 5 days per week for 16–112 weeks (Kehoe 1987). PbB concentrations as high as 45 µg/dL were observed in one subject exposed at that rate for 2 years. Daily lead absorption of 14 µg was reported for five male volunteers who inhaled ambient air (0.002 mg lead/m^3) (Rabinowitz et al. 1977). No lead was found at autopsy in the lung tissues of occupationally exposed lead workers (Barry 1975) and nonoccupationally exposed subjects (Gross et al. 1975), but the analytical techniques at the time may have not be sensitive enough to detect lead. In contrast, Gerhardsson et al. (1995b) showed the presence of lead in the lungs from 32 deceased smelter workers.

Organic Lead. Following a single exposure to vapors of tetraalkyl lead compounds (approximately 1 mg/m^3 breathed through a mouthpiece, 10–40 breaths of approximately 1 L volume) in four male subjects, 37% and 51% of inhaled tetraethyl and tetramethyl lead, respectively, were initially found in the respiratory tract, but a considerable percentage of these volatile compounds was lost through exhalation (Heard et al. 1979). Approximately 60–80% of the deposited tetraalkyl lead was absorbed by the lungs. In a case report of a 22-year-old male exposed to tetramethyl lead, absorption was evident because of elevated urinary lead levels for 4 days after exposure (Gething 1975).

Limited experimental data suggest that inhaled lead, whether organic or inorganic, is absorbed rapidly by animals (EPA 1986a). Female Wistar rats breathed total lead concentrations of 0.01 mg lead/m^3 as tetraethyl lead in the form of aerosolized leaded gasoline labeled with lead-210 (^{210}Pb) tracer for 30–45 minutes; 1 hour later, lead clearance in the lungs was 30% and the majority of the particles were 0.1–0.5 µm in diameter (Boudene et al. 1977). Immediately after nose-only breathing of engine exhaust aerosols containing 6 mg lead/m^3 as lead-203 (^{203}Pb)-labeled tetraethyl lead for 40 or 60 minutes, 25% of the dose was accounted for in tissues other than the lung and gastrointestinal tract in rats (Morgan and Holmes 1978). Initially, the lead content in lungs decreased quite rapidly; only 7.5% of the dose was retained in the lungs after 48 hours, followed by a slower decline in which less than 2% of the dose remained in the lungs after a week. The lung had the lowest tissue lead content in rats and rhesus monkeys who inhaled 0.0215 mg lead/m^3 continuously (22 hours per day) for a year (Griffin et al. 1975b).

2.3.1.2 Oral Exposure

The extent and rate of gastrointestinal absorption are influenced by physiological states of the exposed individual (e.g., age, fasting, nutritional calcium and iron status) and physicochemical characteristics of the medium ingested (e.g., particle size, mineralogy, solubility, lead species). Although there were limited data, gastrointestinal absorption of lead appears to be higher in children than in adults. Estimates derived from dietary balance studies conducted in infants and children (ages 2 weeks to 8 years) indicate absorption of approximately 40–50% of ingested lead (Alexander et al. 1974; Ziegler et al. 1978). In adults, estimates of absorption of ingested water-soluble lead compounds (e.g., lead chloride, lead nitrate, lead acetate) range from 20 to 70% in fasted subjects and 3–15% in fed subjects; fasted/fed ratios range from 0.04 to 0.2 (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980). Mineral content is one contributing factor to the lower absorption of lead when lead is ingested with a meal; in particular, the presence of calcium and phosphate in a meal will depress the absorption of ingested lead (Blake et al. 1983; Blake and Mann 1983; Heard and Chamberlain 1982). Data available on lead absorption between childhood and adulthood ages are very limited. While no absorption studies have been conducted on subjects in this age group, the kinetics of the change in stable isotope signatures of blood lead in mothers and their children as both come into equilibrium with a novel environmental lead isotope profile, suggest that children ages 6–11 years and their mothers may absorb a similar percentage of ingested lead (Gulson et al. 1997).

Studies in experimental animals provide additional evidence for an age-dependency of gastrointestinal absorption of lead. The rat pup absorbs 40–50 times more lead via the diet than does the adult rat (Forbes and Reina 1972; Kostial et al. 1978). In rats receiving an oral dose of 1 mL lead-212 (^{212}Pb)-labeled tracer, absorption was approximately 74–89% for animals 16–22 days of age, 15–42% in animals 24–32 days old, and only 16% at 89 days old (Forbes and Reina 1972). A single dose of lead resulted in 52% absorption in 1–2-week-old suckling rats compared to 0.4% in adults (Kostial et al. 1978). Age differences in absorption rate were evident in rat pups who had slightly higher tissue levels than adult rats following a single gavage dose of 1 or 10 mg lead/kg as lead acetate (Aungst et al. 1981). Absorption was 37.9% for young monkeys versus 26.4% in adults following a single radiolabeled gavage dose of 6.37 mg lead/kg as lead acetate (Pounds et al. 1978). This age difference in absorption rate may be due, in part, to dietary differences and to physiological differences between the immature and mature intestine (EPA 1986a).

Lead absorption in children is affected by nutritional iron status. Children who are iron deficient have higher blood lead concentrations than similarly exposed children who are iron replete, which would suggest that iron deficiency may result in higher absorption of lead or, possibly, other changes in lead biokinetics that would contribute to lower blood lead concentrations (Mahaffey and Annest 1986; Marcus and Schwartz 1987). Evidence for the effect for iron deficiency on lead absorption has been provided from animal studies. In rats, iron deficiency increases the gastrointestinal absorption of lead, possibly by enhancing binding of lead to iron binding proteins in the intestine (Barton et al. 1978; Morrison and Quatermann 1987).

Dietary calcium intake appears to affect lead absorption. An inverse relationship has been observed between dietary calcium intake and blood lead concentration in children, suggesting that children who are calcium deficient may absorb more lead than calcium replete children (Mahaffey et al. 1986; Ziegler et al. 1978). An effect of calcium on lead absorption is also evident in adults. In experimental studies of adults, absorption of a single dose of lead (100–300 µg lead chloride) was lower when the lead was ingested together with calcium carbonate (0.2–1 g calcium carbonate) than when the lead was ingested without additional calcium (Blake and Mann 1983; Heard and Chamberlain 1982). A similar effect of calcium occurs in rats (Barton et al. 1978). In other experimental animal models, absorption of lead from the gastrointestinal tract has been shown to be enhanced by dietary calcium depletion or administration of vitamin D (Mykkänen and Wasserman 1981, 1982).

Absorption of lead may increase during pregnancy. An increase in lead absorption may contribute, along with other mechanisms (e.g., increased mobilization of bone lead), to the increase in PbB concentration that has been observed during the later half of pregnancy (Gulson et al. 1997; Lagerkvist et al. 1996; Schuhmacher et al. 1996).

Lead absorption in humans may be a capacity limited process, in which case, the percentage of ingested lead that is absorbed may decrease with increasing rate of lead intake. Studies, to date, do not provide a firm basis for discerning if the gastrointestinal absorption of lead is grossly linear or non-linear. Numerous observations of non-linear relationships between PbB concentration and lead intake in humans provide further support for the existence of a saturable absorption mechanism or some other capacity limited process in the distribution of lead in humans (Pocock et al. 1983; Sherlock et al. 1984, 1986). However, in immature swine that received oral doses of lead in soil, lead dose-blood lead relationships were non-linear; whereas, dose-tissue lead relationships for bone, kidney and liver were linear. The same pattern

(nonlinearity for PbB and linearity for tissues) was observed in swine administered lead acetate intravenously (Casteel et al. 1997). These results suggest that the non-linearity in the lead dose-PbB relationship may derive from an effect of lead dose on some aspect of the biokinetics of lead other than absorption. Evidence from mechanistic studies for capacity-limited processes at the level of the intestinal epithelium is compelling, which would suggest that the intake-uptake relationship for lead is likely to be non-linear; these studies are discussed in greater detail in Section 2.4.1.

The absorption of lead in soil is less than that of dissolved lead, but is similarly depressed by meals. Adult subjects who ingested soil (particle size less than 250 μm) from the Bunker Hill NPL site absorbed 26% of the resulting 250 μg/70 kg body weight lead dose when the soil was ingested in the fasted state and 2.5% when the same soil lead dose was ingested with a meal (Maddaloni et al. 1998). There are no reported measurements of the absorption of soil-borne lead in infants or children. Additional evidence for a lower absorption of soil-borne lead compared to dissolved lead is provided from studies in laboratory animal models. In immature swine that received oral doses of soil from one of four NPL sites (75 or 225 μg Pb/kg body weight), bioavailability of soil-borne lead ranged from 50% to 82% of that of a similar dose of highly water soluble lead acetate (Table 2-5) (Casteel et al. 1997; EPA 1996a, 1996b, 1996c). If the relative bioavailability of soil-borne lead (soil/acetate) in immature swine is indicative of the relative bioavailability in human children, and if the absolute bioavailability of water soluble lead in humans children is 50%, as the Alexander et al. (1974) and Ziegler et al. (1978) studies would suggest, then the absolute bioavailability of soil-borne lead in human children predicted from the swine studies would range from 25 to 41%. In fasted rats, absorption was estimated at 42 and 2% following single oral administration of 1 and 100 mg lead/kg, respectively, as lead acetate (Aungst et al. 1981). Fed rats were administered lead in soil from mine waste over a 30-day period, and relative bioavailability compared to that of lead acetate was estimated from measurements of blood lead concentration (Freeman et al. 1992). For one test soil, relative bioavailability estimates for samples having lead concentrations of 1.62 and 4.05 ppm were 18.1 and 12.1% in males and 25.7 and 13.8% in females for average lead dosages of 1.13 and 3.23 mg Pb/kg/day in males, and 1.82 and 4.28 mg Pb/kg/day in females (1.62 and 4.05 ppm Pb), respectively. For a second test soil, relative bioavailability estimates for samples having lead concentrations of 78.2 and 19.5 ppm were 19.6 and 21.5% in males and 26.8 and 22.1% in females for average lead dosages of 5.13 and 12.1 mg Pb/kg/day in males and 7.39 and 23.2 mg Pb/kg/day in females, respectively. In a subsequent follow-up study, absolute bioavailability of ingested lead acetate in rats was estimated to be 15% based on measurements of blood lead concentrations after oral or intravenous administration of lead acetate (Freeman et al. 1994). Based on this estimate, the absolute bioavailability of lead in the soils from the

Table 2-5. Relative Bioavailability of Lead in Various Samples of Soil from Hazardous Waste Sites as Assessed in Immature Swine

Site Site type	Smuggler Mountain, CO (Mining)		Palmerton, PA (Smelter)		Jasper County, MO (Smelter)			*Murray Smelter, UT* (Smelter)	
Sample location	Berm	Residential	Location 2	Location 4	HL Smelter	LL Yard	HL Mill	Slag	Soil
Mean Pb concentration (ppm)	142	3870	3230	2150	10800	4050	6940	11500	3200
Relative Bioavailability (% of Lead Acetate)									
Blood AUC	0.56	0.58	0.74	0.58	0.56	0.78	0.82	0.55	0.67
Tissue	0.75	0.72	0.46	0.42	0.66	0.86	0.70	0.47	0.84
Mean	0.66	0.65	0.60	0.50	0.61	0.82	0.76	0.51	0.76
*Absolute Bioavailability (estimated)**	0.33	0.32	0.30	0.25	0.30	0.41	0.38	0.25	0.38
Soil Lead Characterization (% of Total Lead)									
Anglesite	6.6		6.0	4.0					
Cerrusite	61.7	64.2			32.1	81.0	57.0		14.0
Fe-Pb Oxide	9.1	7.4							
Fe-Pb Silicate					11.5		8.1		
Fe-Pb Sulfate	4.7	4.6							
Galena	12.0	17.1				7.6		9.2	20.0
Mn-Pb Oxide	4.5	5.1	66.1	65.8			8.7		
Native Lead					22.2				
Pb Phosphate			24.4		21.1	6.0	7.4		
Pb Vanidate				17.7					
Pb-As Oxide								5.7	29.4
Pb-Metal Oxide				7.0					
PbO							6.5	68.7	26.6
PbSi									
Slag					4.3			7.0	6.4
TOTAL	98.6	98.4	96.5	94.5	91.2	94.6	87.7	90.6	96.4

*Assuming 50% absorption of fully soluble form of lead (e.g., lead acetate) dissolved in water.
Bioavailability was assessed from measurement of the area under the curve (AUC) of whole blood lead concentration vs time (Blood AUC) or from measurements of the lead concentrations in bone, kidney or liver (the arithmetic mean of the three tissues is shown in the table). Data are from Casteel et al. (1997) and EPA (1996a, 1996b, 1996c).

Freeman et al. (1992) study was estimated to be 2.7% (Freeman et al. 1994). In rats that received diets containing 17–127 mg lead/kg for 44 days in the form of lead acetate, lead sulfide, or lead-contaminated soil, bone and tissue lead levels increased in a dose-dependent manner (Freeman et al. 1996). Estimated bioavailability of lead sulfide was approximately 10% that of lead acetate. Bioavailability of lead in soil from the California Gulch NPL site (Freeman et al. 1996), a former mining site, decreased with increasing soil lead concentration in the diet and ranged from 7 to 28% of that of lead acetate. The predominant forms of lead in the NPL site soil were identified as: iron-lead oxide (40%), manganese-lead oxide (16%), lead phosphate (13%), "slag" (12%) and iron-lead sulfate (10%). The addition of "uncontaminated soil" (having a lead concentration of 54±3 mg lead/kg soil) to diets containing lead acetate decreased the bioavailability of lead acetate by approximately 76%. In adult mice, absorption was 14% in fasted mice versus 7.5% in fed mice 4 hours after an oral gavage dose of 0.003 mg lead/kg as lead acetate (Garber and Wei 1974). However, no difference in absorption (4–5%) was observed in fasted and nonfasted mice receiving 2 mg lead/kg.

Particle size also influences the degree of gastrointestinal absorption (EPA 1986a; Grobler et al. 1988). An inverse relationship was found between diets containing metallic lead of particle sizes #250 µm and absorption in rats (Barltrop and Meek 1979). There was a 2.3-fold increase in tissue lead concentration when animals ingested an acute dose of 37.5 mg/kg with a particle size of <38 µm (diameter) compared to a particle diameter of 150–250 µm (Barltrop and Meek 1979). Dissolution kinetics experiments with lead-bearing mine waste soil suggest that surface area effects control dissolution rates for particles sizes of <90 µm diameter; however, dissolution of 90–250 µm particle size fractions appeared to be controlled more by surface morphology (Davis et al. 1994). Similarly, Healy et al. (1982) found that the solubility of lead sulfide in gastric acid *in vitro* was much greater for particles of 30 µm diameter than particles of 100 µm diameter.

2.3.1.3 Dermal Exposure

Inorganic Lead. Limited information is available regarding absorption after dermal exposure in humans. Dermal absorption of inorganic lead compounds is reported to be much less significant than absorption by inhalation or oral routes of exposure, because of the greatly reduced dermal absorption rate (EPA 1986a). Following skin application of ^{203}Pb-labeled lead acetate in cosmetic preparations (0.1 mL of a lotion containing 6 mmol lead acetate/L or 0.1 g of a cream containing 9 mmol lead acetate/kg) to 8 male volunteers for 12 hours, absorption was #0.3%, but expected to be 0.06% during normal use of such

preparations (Moore et al. 1980). Most of the absorption took place by 12 hours of exposure. A study suggests that lead, applied to the skin as lead acetate or lead nitrate, was rapidly absorbed through the skin and was detected in sweat, blood, and urine within 6 hours of application (Stauber et al. 1994). In this study, 4.4 mg of lead equivalent was applied to the skin under a covered wax/plastic patch on the forearms of human subjects; of the applied dose, 1.3 mg of lead was not recovered from skin washings. The amount that actually remained in (or on) the skin and the mass balance of the fate of this lead was not determined; it may have been absorbed or eliminated from the skin by exfoliation of epidermal cells. Thus, while this study provides evidence for dermal absorption of lead, it did not quantity the fraction of applied dose that was absorbed. The quantitative significance of the dermal absorption pathway as a contributor to lead body burden remains an uncertainty. The wax/plastic patch provided a means by which the lead compounds could permeate or adhere to the skin. The effect of concentration in aqueous solution may cause skin abrasion through enhanced acidity since the lead ion is acidic. Abraded skin is known to promote subsequent higher lead penetration.

Limited information was located regarding dermal absorption of inorganic lead in animals. An early study reported that lead acetate was absorbed from the clipped skin of rats, as determined by an increase in the concentration of lead in the kidneys relative to controls (Laug and Kunze 1948). It was further shown in that study that mechanical injury to the skin significantly increased the penetration of lead and that the penetration of lead from lead arsenate was significantly less than from lead acetate.

Organic Lead. Tetraalkyl lead compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931; Laug and Kunze 1948). A 0.75-mL amount of tetraethyl lead, which was allowed to spread uniformly over an area of 25 cm^2 on the abdominal skin of rabbits, resulted in 10.6 mg of lead in the carcass at 0.5 hours and 4.41 mg at 6 hours (Kehoe and Thamann 1931). Tetraethyl lead was reported to be absorbed by the skin of rats to a much greater extent than lead acetate, lead oleate, and lead arsenate (Laug and Kunze 1948). The rank order of absorption rates through excised skin from humans and guinea pigs was as follows: tetrabutyl lead >lead nuolate > lead naphthalene > lead acetate > lead oxide (nondetectable) (Bress and Bidanset 1991).

2.3.2 Distribution

2.3.2.1 Blood and Other Soft Tissues

Inorganic Lead. Once absorbed, inorganic lead appears to be distributed in essentially the same manner regardless of the route of absorption (Kehoe 1987). This implies that a common lead transport system is involved. Therefore, the distribution and body burden of absorbed lead for all routes is discussed in one section. The body burden of a particular chemical is the total amount of that chemical found in the body. The distribution of lead in the body is initially dependent on the rate of delivery by the bloodstream to various organs and tissues. A subsequent redistribution may then occur, based on the relative affinity of tissues for the element and its toxicodynamics there (EPA 1986a). With consistent exposure for an extended period, a steady state of intercompartmental distribution is achieved; however, fluctuation can occur when short-term exposure is superimposed on the long-term uptake pattern (EPA 1986a).

The distribution of lead in humans has been well characterized. In general, the distribution of lead appears to be similar in children and adults, although a larger fraction of the lead body burden of adults resides in bone (See Section 2.3.3 for further discussion). Lead in blood is primarily in the red blood cells (99%) rather than the plasma (DeSilva 1981; EPA 1986a; Everson and Patterson 1980; Hursh and Suomela 1968). Most of the lead found in red blood cells is found bound within the cell rather than the erythrocyte membrane. Within the cell, 50% of lead is bound to hemoglobin A_2 (EPA 1986a). Another 5% is bound to a 10,000-dalton molecular-weight fraction, approximately 20% to a much heavier molecule, and about 25% is considered "free" or bound to lower weight molecules (EPA 1986a; Raghavan and Gonick 1977). Fetal hemoglobin appears to have a higher affinity for lead than adult hemoglobin (Ong and Lee 1980c).

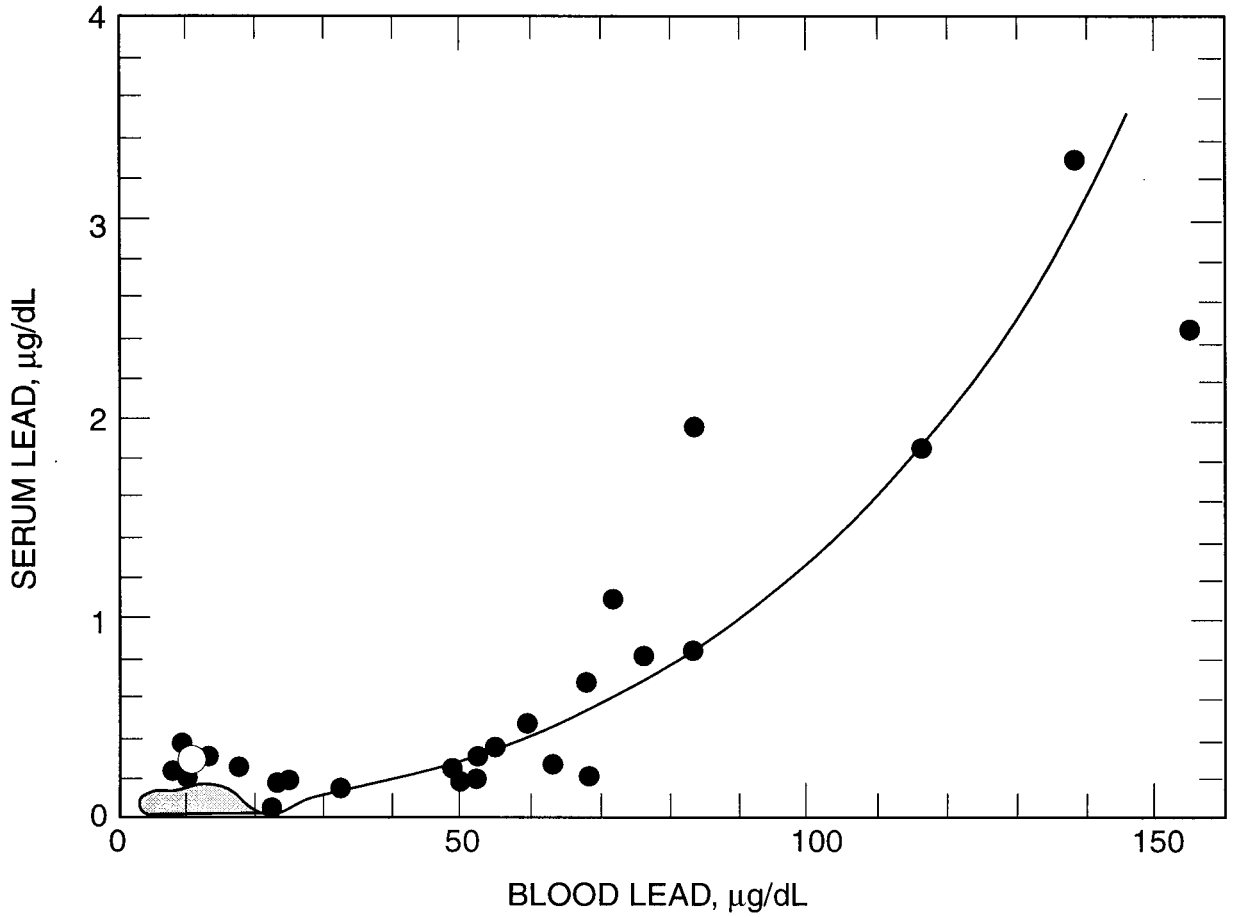
Absorbed lead is distributed in various tissue compartments. Several models of lead pharmacokinetics have been proposed to characterize such parameters as intercompartmental lead exchange rates, retention of lead in various pools, and relative rates of distribution among the tissue groups. See Section 2.3.5 for a discussion of the classical compartmental models and physiologically based pharmacokinetic models (PBPK) developed for lead risk assessments.

In adult volunteers exposed to 0.0032–0.011 mg lead/m^3 (species of lead not specified) continuously for 18 weeks, blood lead levels increased for about 12 weeks then leveled off between 27 and 37 µg/dL (Griffin et al. 1975b). Lead content in blood declined after cessation of exposure, returning to pre-exposure levels

by 5 months. The half-life of lead in adult human blood has been measured as 36 days by Rabinowitz et al. (1976) and 28 days by Griffin et al. (1975b). Under steady-state conditions, 96–99% of blood lead is associated with the erythrocytes *in vivo* (Boudene et al. 1977; Castellino and Aloj 1964; DeSilva 1981; Everson and Patterson 1980; Kehoe 1987; Lloyd et al. 1975; Morgan et al. 1977). Within 1 hour following the inhalation of tetramethyl lead, 61% and 39% of the inhaled dose was detected in the red blood cells and plasma, respectively (Heard et al. 1979). Over 50% of this erythrocyte lead pool is bound to hemoglobin, with lesser amounts bound to other proteins (Bruenger et al. 1973; Simons 1986). However, the ratio of plasma lead to red blood cell lead was strongly correlated among 75 mother-newborn pairs, suggesting that the partitioning of lead between plasma and red blood cells may not differ greatly between adults and children (Cavalleri et al. 1978).

The relationship between the fractions of lead distributed in human erythrocytes and plasma has been described by Manton and Cook (1984) in patients with neurological disease and in control subjects including cases of plumbism. At blood lead levels #40 µg/dL, blood lead and serum lead levels increase linearly in a positive fashion; at higher blood lead levels, they assume a curvilinear relationship (Figure 2-3). The ratio of lead in plasma to that in whole blood increases dramatically at blood lead levels >40 µg/dL. *In vitro* data of the partitioning of PbB between erythrocytes and plasma show a positive linear correlation at PbB levels #100 µg/dL and deviation from linearity above that value (Clarkson and Kench 1958). The departure from linearity of this relationship *in vivo* at PbB levels >40 µg/dL may be caused by altered cell morphology at high blood lead levels, resulting in a reduced availability or stability of lead binding sites in the erythrocytes (EPA 1986a; Gonick et al. 1985; Raghavan et al. 1980). The low concentrations of lead in plasma, relative to red blood cells, has made it extremely difficult to accurately measure plasma lead concentrations in humans, particularly at low PbB concentrations (i.e., less than 20 µg/dL). More recent measurements have been achieved with inductively coupled mass spectrometry (ICP-MS), which has a higher analytical sensitivity than earlier atomic absorption spectrometry methods. Using this analytical technique, a curvilinear relationship between plasma and blood lead concentrations has been demonstrated in adults (118 active lead industry workers and 25 retired workers) whose PbB concentrations were 1– 93 µg/dL: log plasma (µg/L)= 0.00225 x blood (µg/L) – 0.58; this relationship describes a plasma/blood lead concentration ratio of approximately 0.4 at PbB concentrations between 10 and 30 µg/dL, and ratios increasing to 3.5% at PbB concentrations between 30 and 90 µg/dL (Berdahl et al. 1997; Berdahl and Skerfving 1997). Similar ratios have been reported for serum and blood; serum lead concentrations were estimated to be 1–2% of PbB concentration in adults (49 lead industry workers) whose

Figure 2-3. Curvilinear Relationship of Human Serum Lead to Blood Lead



Source: Derived from Manton and Cook 1984

Note: Cross-hatched area represents several overlapping points

blood lead concentrations were 16–55 µg/dL: plasma (µg/L) = 0.0206 x blood (µg/L) - 1.58 (Cake et al. 1996).

PbB concentrations have been observed to decrease in the early stages of pregnancy and increase during the latter stages of pregnancy. The mechanism for these changes are not understood; however, increased mobilization of bone lead during pregnancy may contribute to part of the increase (Gulson et al. 1997; Lagerkvist et al. 1996; Schuhmacher et al. 1996). Increased blood volume and hemodilution may contribute to the decrease observed the first half of pregnancy, whereas, increased absorption of lead during pregnancy or decreased elimination may also occur, although evidence for this is limited (Gulson et al. 1997; Franklin et al. 1997).

Autopsies of occupational workers showed that the lead content in lungs and liver was elevated compared to control levels (Gerhardsson et al. 1986a). Gerhardsson et al. (1995b) showed that in 32 deceased smelter workers with known lead exposure history, the major soft tissue organs of lead accumulation were, in decreasing order: liver > kidney > lungs > brain. Autopsies of nonoccupational subjects revealed that males had higher lead content in tissues compared to females; however, sex differences in lead levels were not observed in tissues of children (Barry 1975; Treble and Thompson 1997). Autopsies of 41 men ages 18–80 years showed no relationship between blood lead concentrations and lead concentrations in reproductive organs (Oldereid et al. 1993). In most soft tissues (including brain), lead does not appear to accumulate as a function of age in humans over 20 years old (Barry 1975, 1981; Gross et al. 1975; Treble and Thompson 1997), but these data are based on limited sample size. Selective accumulation of lead has been observed in the hippocampus in both children and adults (EPA 1986a). However, this selective concentration of lead in hippocampus may be an artifact of the use of dry rather than wet weights in the analyses (Widzowski and Cory-Slechta 1991).

In animals, lead is widely distributed to soft tissues initially then redistributes and accumulates in bones. In general, the liver, lungs, and kidneys of rats showed the highest tissue lead concentrations immediately after acute exposure by inhalation (Boudene et al. 1977; Morgan and Holmes 1978), oral (Aungst et al. 1981), dermal (Kehoe and Thamann 1931; Laug and Kunze 1948), and intravenous routes (Castellino and Aloj 1964). The lead content in the bones gradually increased while levels in soft tissues began to decline and stabilize (Kehoe and Thamann 1931; Keller and Doherty 1980b). In a 12-month continuous inhalation exposure to 0.0215 mg lead/m^3 (species of lead not specified) in rats, lead content in kidney, liver, and lungs were increased at 6 and 12 months (Griffin et al. 1975b). The bone had the highest concentrations of lead.

Lead concentration in the lung increased the least. Following the end of exposure, tissue levels declined except in the bone. A similar distribution pattern was observed in mice following intermediate exposure to lead nitrate (Kozlowski and Wojcik 1987). In rats exposed to 5 or 50 ppm lead acetate via drinking water (approximately 1.7 or 17 mg lead/kg/day) for 90 days the distribution of lead in the high-dose group was in descending order: kidney > brain > spleen > prostate > heart > testis and liver (Areola et al. 1999). In the low-dose group, significant lead accumulation was seen only in the brain and kidney. In most organs, the lead concentration was highest 2 weeks after dosing began and subsequently declined. In the brain, lead increased gradually over the 90-day dosing period. PbB in the low-dose group was similar to untreated controls over the duration of the experiment (1–2 µg/dL), whereas in the high-dose group it rose gradually to a maximum of about 16 µg/dL at the termination of the study.

The effects of aging on the tissue distribution of lead acetate were studied in male Fischer 344 rats; the compound was administered in drinking water to juvenile (21-day-old), adult (8-month-old), and old (16-month-old) rats (Cory-Slechta 1990b; Cory-Slechta et al. 1989). Animals received 0, 1.27, and 6.37 mg lead/kg/day for 9.5 months (Cory-Slechta 1990b) or 0 and 4.5 mg lead/kg/day for 11 months (Cory-Slechta et al. 1989). Although the tissue lead distribution pattern (femur > kidneys > liver > brain) was similar for the three groups of animals, age-related increases in distribution were found in the brain and kidneys and a decline in lead content was found in the bones (femur). These age-related changes in tissue concentration may be the result of bone demineralization and redistribution of released lead (Cory-Slechta 1990b). Retention was greater in suckling rats than adults following intraperitoneal exposure; brain levels were higher and kidney levels were lower in the pups (Kostial et al. 1978). One day after administration of the first dose of 50 mg lead/kg as lead acetate by gavage to neonatal rats, lead had accumulated in the liver, kidney, intestine, and intestinal contents (Miller et al. 1983). No lead was found in the blood, bone, or brain. Fifteen days after the first dose, and after the 50-mg/kg dose had been repeated for a total of five administrations, the highest concentration of lead was found in the femur. Brain lead levels had also increased. No accumulation of lead was observed in the lungs, heart, stomach, or spleen over the dosing period. Rat pups (4–8 weeks old) had a 2–3-fold increase in brain lead concentration when oral doses increased by 10-fold from 0.1 to 1 mg lead/kg (Collins et al. 1982). The highest brain lead level in these pups was in the hippocampus.

Transplacental transfer of lead in humans has been demonstrated in a number of studies, and lead has been identified in umbilical cord blood. In the work of Bellinger et al. (1987a), the mean lead concentration in umbilical cord blood from a sample size of $11,000 women was 6.6±3.2 µg/dL. In a study of 236 pregnant

women in Glasgow, Scotland, the geometric mean PbB levels were 14 µg/dL for the mothers and 12 µg/dL in the umbilical cord at birth (Moore et al. 1982). The fetal/maternal PbB concentration ratio based on maternal and umbilical cord blood lead concentrations at delivery, is approximately 0.9 (Abdulla et al. 1997b; Goyer 1990; Graziano et al. 1990; Schuhmacher et al. 1996). Diffusion, associated with fetal blood flow rate, has been proposed as the primary mechanism for transplacental lead transport (Goyer 1990).

A portion of the maternal-to-fetal transfer of lead appears to be related to the mobilization of lead from the maternal skeleton. Analysis for kinetics of changes in the stable isotope signatures of blood lead in pregnant women as they come into equilibrium with a novel environmental lead isotope signature indicate that 9–65% of the lead in blood may derive from the mobilization of bone lead stores (Gulson et al. 1997). Additional evidence for increased mobilization of bone lead into blood during pregnancy is provided from studies in non-human primates and rats (Franklin et al. 1997; Maldonado-Vega et al. 1996). Lead may enhance processes of bone demineralization (and excretion of bone lead to mother's milk) by inhibiting activation of vitamin D, decreasing calcium absorption, and interfering with hormonal regulation of mineral metabolism and bone cell function (Silbergeld 1991). Direct evidence for transfer of maternal bone lead to the fetus has been provided from stable lead isotope studies in cynomolgus monkeys (*Macaca fascicularis*); approximately 7–39% of the maternal lead burden that is transferred to the fetus in this species appears to derive from the maternal skeleton (Franklin et al. 1997). Maternal-to-fetal transfer of lead also has been shown to occur in other animal models, including pigs and rats (Donald et al. 1986b; Jing et al. 1997). Transfer of maternal lead to offspring can also occur during nursing, as indicated from studies in mice and rats (Keller and Doherty 1980a; Palminger Hallén et al. 1995, 1996a, 1996b).

Studies in animal models have shown that maternal lead is distributed to breast milk and can be transferred to offspring during breast feeding. Lead is transferred through breast milk to suckling mouse litters (Keller and Doherty 1980a) and suckling rat litters (Palminger Hallén et al. 1995, 1996a, 1996b) if the mothers are exposed prior to or during lactation. Approximately 25% of the maternal dose was transferred to suckling mice via milk (Keller and Doherty 1980a), and 33% was transferred to suckling rats (Palminger Hallén et al. 1996a, 1996b), suggesting that excretion of lead into milk may represent a significant change in lead pharmacokinetics in humans (both lactating mothers and nursed infants).

Organic Lead. The highest lead levels were reported to be in liver, kidney, spleen, and lungs from autopsies (Gross et al. 1975). In a man and woman who accidentally inhaled a solvent containing 31%

tetraethyl lead (17.6% lead weight to weight [w/w]) (Bolanowska et al. 1967), lead concentrations in the tissues, from highest to lowest, were liver, kidney, brain, pancreas, muscle, and heart. In another incident, a man ingested a chemical containing 59% tetraethyl lead (38% lead w/w); lead concentration was highest in the liver followed by kidney, pancreas, brain, and heart (Bolanowska et al. 1967).

2.3.2.2 Bone

In human adults, approximately 94% of the total body burden of lead is found in the bones. In contrast, bone lead accounts for 73% of the body burden in children (Barry 1975). This large pool of lead in adults can serve to maintain blood lead levels long after exposure has ended (Flemming et al. 1997; Inskip et al. 1996; Kehoe 1987; O'Flaherty et al. 1982; Smith et al. 1996). It can also serve as a source of lead transfer to the fetus when the maternal skeleton is catabolized for the production of the fetal skeleton (Franklin et al. 1997; Gulson et al. 1997).

Lead is not distributed uniformly in bone. Lead will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in cortical and trabecular bone. This would suggest that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Auferheide and Wittmets 1992). Two physiological compartments appear to exist for lead in cortical and trabecular bone, to varying degrees. In one compartment, bone lead is essentially inert, having a half-life of several decades. A labile compartment exists as well that allows for maintenance of an equilibrium of lead between bone and soft tissue or blood (Rabinowitz et al. 1976, 1977). The presence of labile lead may be a more accurate predictor of recent exposure or imminent toxicity than total body or whole blood burdens (EPA 1986a). Although a high bone formation rate in early childhood results in the rapid uptake of circulating lead into mineralizing bone, bone lead is also recycled to other tissue compartments or excreted in accordance with a high bone resorption rate (O'Flaherty 1995a). Thus, most of the lead acquired early in life is not permanently fixed in the bone (O'Flaherty 1995a). In general, bone turnover rates decrease as a function of age, resulting in slowly increasing bone lead levels among adults. An X-ray fluorescence study of tibial lead concentrations in individuals older than 10 years showed a gradual increase in bone lead after age 20 (Kosnett et al. 1994). In 60–70-year-old men, the total bone lead burden may be $200 mg, while children less than 16 years old have been shown to have a total bone lead burden of 8 mg (Barry 1975). However, in some bones (i.e., mid femur and pelvic bone) the increase in lead content plateaus at middle age and then

decreases at higher ages (Drasch et al. 1987). This decrease is most pronounced in females and may be due to osteoporosis. Bone lead burdens in adults are slowly lost by diffusion (heteroionic exchange) as well as by resorption (O'Flaherty 1995a, 1995b).

Evidence for the exchange of bone lead and soft tissue lead stores comes from analyses of stable lead isotope signatures of lead in bone and blood. A comparison of blood and bone lead stable isotope signatures in five adults indicated that bone lead stores contributed to approximately 40–70% of the lead in blood (Smith et al. 1996). During pregnancy, the mobilization of bone lead increases, apparently as the bone is catabolized to produce the fetal skeleton. Analysis for kinetics of changes in the stable isotope signatures of blood lead in pregnant women as they come into equilibrium with a novel environmental lead isotope signature indicate that 9–65% of the lead in blood may derive from the mobilization of bone lead stores (Gulson et al. 1997). The mobilization of bone lead during pregnancy may contribute, along with other mechanisms (e.g., increased absorption), to the increase in PbB concentration that has been observed during the later stages of pregnancy (Gulson et al. 1997; Lagerkvist et al. 1996; Schuhmacher et al. 1996). Additional evidence for increased mobilization of bone lead into blood during pregnancy is provided from studies in non-human primates and rats (Franklin et al. 1997; Maldonado-Vega et al. 1996). Direct evidence for transfer of maternal bone lead to the fetus has been provided from stable lead isotope studies in cynomolgus monkeys (*Macaca fascicularis*) that were dosed with lead having a different stable isotope ratio than the lead to which the monkeys were exposed at an earlier age; approximately 7–39% of the maternal lead burden that is transferred to the fetus in this species appears to derive from the maternal skeleton (Franklin et al. 1997).

2.3.3 Metabolism

Inorganic Lead. Inorganic lead ion in the body is not known to be metabolized or biotransformed (Phase I processes); it does form complexes with a variety of protein and non-protein ligands (see Section 2.4.1). Primarily, it is absorbed, distributed, and then excreted, often in complexed form (EPA 1986a).

Organic Lead. Alkyl lead compounds are actively metabolized in the liver by oxidative dealkylation catalyzed by cytochrome P-450.

Relatively few human studies that address the metabolism of alkyl lead compounds were found in the available literature. The dealkylation, mediated by cytochrome P-450, of alkyl lead compounds is thought to occur in the rat, mouse, and rabbit. This step converts tetraethyl and tetramethyl lead to the triethyl and trimethyl metabolites, respectively, and inorganic lead (Bolanowska 1968; EPA 1986a; Kehoe and Thamann 1931). Further biotransformation of these intermediate metabolites is highly species-specific. Diethyl metabolite was not detected in rats receiving tetraethyl lead (Bolanowska 1968). Trialkyl lead metabolites were found in the liver, kidney, and brain following exposure to the tetraalkyl compounds in workers; these metabolites have also been detected in brain tissue of nonoccupational subjects (Bolanowska et al. 1967; Nielsen et al. 1978). In volunteers exposed by inhalation to 0.64 and 0.78 mg lead/m^3 of ^{203}Pb-labeled tetraethyl and tetramethyl lead, respectively, lead was cleared from the blood within 10 hours, followed by a reappearance of radioactivity back into the blood after approximately 20 hours (Heard et al. 1979). The high level of radioactivity initially in the plasma indicates the presence of tetraalkyl/trialkyl lead. The subsequent rise in blood radioactivity, however, probably represents water-soluble inorganic lead and trialkyl and dialkyl leads that were formed from the metabolic conversion of the volatile parent compounds (Heard et al. 1979).

2.3.4 Excretion

Inorganic Lead. Excretion of lead for all routes of exposure is discussed without subdividing data according to the route of exposure. In humans or animals, any dietary lead not absorbed by the gastro-intestinal tract is eliminated in the feces (EPA 1986a). However, the feces also include an enterohepatic component. Airborne lead that has been swallowed and not absorbed is eliminated in a similar fashion. The lead that is not retained is either excreted by the kidney or excreted through biliary clearance, some in the form of glutathione conjugates, into the gastrointestinal tract (EPA 1986a). For example, ingestion of 0.3–3.0 mg lead as lead acetate in drinking water per day for 16–208 weeks by adult volunteers resulted in excretion of greater than 85% of the ingested lead, of which over 90% was found in the feces (Kehoe 1987). Negligible amounts were eliminated in perspiration.

Urinary excretion of lead was observed at $1.0 mg lead per day after ingesting lead in the drinking water as lead acetate (Kehoe 1987). The urinary lead excretion in men after 3 months of continuous inhalation exposure to 0.011 mg lead/m^3 was approximately 85 µg lead/g urinary solids, which was nearly double the pre-exposure baseline level of urinary excretion (Griffin et al. 1975b). Lead content in feces did not reveal any differences between the exposed and control groups (Griffin et al. 1975b). However, this may have

been due to the relatively low concentration of lead used and the presence of lead in the diet. Moderately exposed workers were shown to have mean levels of lead in urine of 0.05–0.2 mg/L (Robinson 1974). The data suggest that 50–60% of the absorbed fraction of lead in adults in a steady-state condition with regard to lead intake/output was excreted on a short-term basis (Chamberlain et al. 1978; Rabinowitz et al. 1976). The half-life of this short-term fraction was found to be 19 days (Chamberlain et al. 1978). Comparison of data on lead kinetics for children and adults, shows that infants may have a lower total excretion rate for lead (Rabinowitz et al. 1977; Ziegler et al. 1978). Infants from birth to 2 years of age have been shown to retain 31.7% of the total amount of lead absorbed (Ziegler et al. 1978), whereas adults retained only 1% of an absorbed dose of lead (Rabinowitz et al. 1977).

In general, there is a greater excretion of lead in feces than in urine of animals following acute, intermediate, and chronic exposure. Species differences exist in the rate and extent of total lead excretion. Rats excreted 43% of the dose after 5 days (Morgan et al. 1977) and 66% after 8 days (Momcilovic and Kostial 1974). Six days after inhalation of 0.01 mg/m^3 lead for 30–45 minutes in Wistar rats, 40% and 15% of the dose was eliminated in the feces and urine, respectively (Boudene et al. 1977). After rats received an intravenous dose of lead, 45.3% of the administered dose was excreted 6 days postexposure (Castellino and Aloj 1964). Total excretion of lead was 7.29% and 18.3% of a single oral exposure to 6.37 mg/kg as lead acetate in young and adult rhesus monkeys, respectively (Pounds et al. 1978). Three weeks following intravenous administration of lead, Beagle dogs excreted approximately 50% of the dose; 75% of the excreted dose was detected in the feces (Lloyd et al. 1975). Adult mice excreted 62% of injected lead by 50 days; cumulative lead in feces was 25–50% (Keller and Doherty 1980a; Kostial and Momcilovic 1974). Fecal excretion was relatively constant (6% of the dose per day) during the 30-day recovery period in mice fed wheat grain containing 3.38, 83.2, or 171.1 mg lead/kg as lead nitrate for up to 40 days (Kozlowski and Wojcik 1987). However, urinary excretion was not measured. With chronic lead exposure, the average fecal and urinary lead concentrations in rats and rhesus monkeys exposed to 0.0215 mg lead/m^3, 22 hours per day, for a year, were higher than controls, with lead content greater in the feces than in the urine; however, there were high individual variations in the excretion rate (Griffin et al. 1975b).

Lead is also eliminated in the bile (Klaassen and Shoeman 1974). In the rat, excretion occurs in the urine, with greater excretion in the feces following intravenous administration (Castellino and Aloj 1964; Klaassen and Shoeman 1974; Morgan et al. 1977). As the dose increases, the proportion of the lead excreted into the gut via bile increases, then plateaus at 3 and 10 mg/kg (Klaassen and Shoeman 1974). Biliary excretion of

lead is suggested to be a saturable process (Gregus and Klaassen 1986). Excretion of lead in the bile by dogs amounted to approximately 2% of that by rats, and biliary excretion of lead by rabbits amounted to approximately 40% of that by rats (Klaassen and Shoeman 1974).

In rats, excretion of lead was biphasic following intravenous administration, with half-lives of 21 hours for the fast phase and 280 hours for the slow phase (Morgan et al. 1977). Dogs excreted lead in three phases, with half-lives of 12, 184, and 4,951 days (Lloyd et al. 1975). The half-life of the terminal phase of a biphasic elimination curve for mice was 110 days (Keller and Doherty 1980a).

Lead acetate administered at 100 µg lead/g in the drinking water of fasting rats for 3 days resulted in a 2-fold increase in the total mass of lead excreted in feces and urine compared with the same dose rate for fed rats (Hayashi et al. 1993). In addition, the total mass of lead in feces of control animals that were fasted for 3 days resulted in an increase in the mass of lead excreted, suggesting that excretion of lead from other tissues is enhanced during short periods of fasting.

Organic Lead. Urinary lead levels were elevated for 4 days in a man accidentally exposed to an unknown quantity of tetramethyl lead (Gething 1975). Exhalation of the tetraalkyl lead compounds following inhalation exposure is a major route of elimination in humans. At 48 hours postexposure, 40% and 20% of the initially inhaled tetramethyl and tetraethyl lead doses, respectively, were exhaled with low urinary excretion (Heard et al. 1979).

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

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

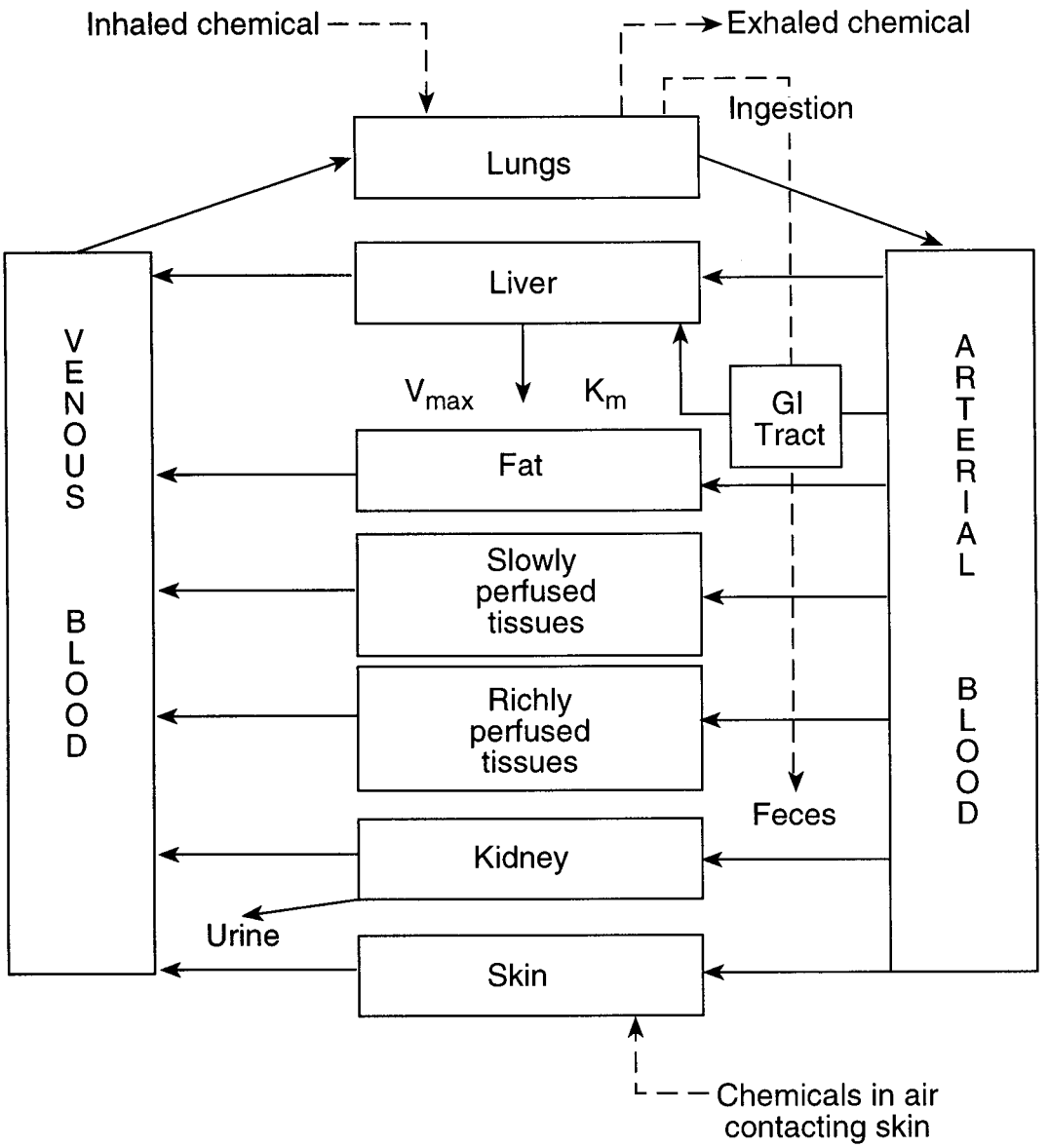
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically-sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 2-4 shows a conceptualized representation of a PBPK model.

Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

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

The fundamental basis for physiological pharmacokinetics is given by Fick's First Law, which states that the rate of diffusion of a solute down a concentration gradient is proportional to the magnitude of the gradient (O'Flaherty 1987). In the general case of modeling the rate of change in the amount of a chemical in blood or tissue, Fick's First Law can be expressed as blood flow rate times the concentration difference according to the following equation:

$$\frac{dM_1}{dt} = V_1 \frac{dC_1}{dt} = k_t(C_1 - C_2)$$

where M_1 is the mass of a chemical in blood, V_1 is the volume of blood, C_1 - C_2 is the concentration difference among blood and tissue fluids, and k_t is the blood flow rate to the tissue (O'Flaherty 1987). Both physiologically based pharmacokinetic models and classical pharmacokinetic models employ first-order mass balance equations of this form with rate constants that have dimensions of flow rate. However, the fundamental distinction between PBPK and classical models is that in PBPK models, the rate constant is a physiologically based parameter (e.g., blood flow in the above equation), whereas in classical pharmacokinetics, precise physiological correlates to model parameters may not exist. In addition to using physiologically based parameters of the test species, mass balance equations for each compartment in a PBPK model also include physicochemical parameters (i.e., partition coefficients and biochemical constants) for each chemical (Gerlowski and Jain 1983). The solution set of mass balance differential equations yields chemical concentrations as a function of time in each compartment/tissue.

PBPK and classical pharmacokinetic models both have valid applications in lead risk assessment. Both approaches can incorporate capacity-limited or nonlinear kinetic behavior in parameter estimates. An advantage of classical pharmacokinetic models is that, because the kinetic characteristics of the compartments of which they are composed are not constrained, a best possible fit to empirical data can be arrived at by varying the values of the parameters (O'Flaherty 1987). However, such models are not readily extrapolated to other species because the parameters do not have precise physiological correlates. Compartmental models developed to date also do not simulate changes in bone metabolism, tissue volumes, blood flow rates, and enzyme activities associated with pregnancy, adverse nutritional states, aging, or

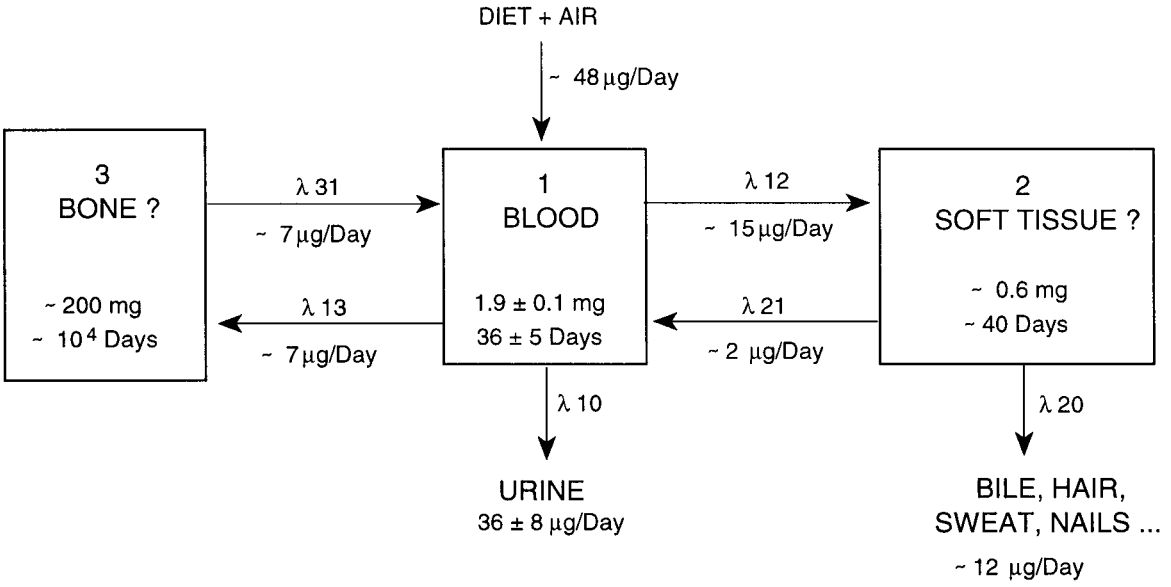
osteoporotic diseases. Therefore, extrapolation of classical compartmental model simulations outside the age and exposure ranges for which they have been calibrated is assumed to be less reliable than for PBPK model simulations (O'Flaherty 1995a).

2.3.5.1 Summary of Physiologically Based and Classical Pharmacokinetic Models.

Early lead modeling applications relied on classical pharmacokinetics. Compartments representing individual organs or groups of organs that share a common characteristic were defined as fluid volumes, or pools, that are kinetically homogeneous. For example, the body could be represented by a central compartment (e.g., blood plasma), and one or two peripheral compartments which may be “shallow” or “deep” (i.e., they may exchange relatively rapidly or relatively slowly with blood plasma) (O'Flaherty 1987). A three-compartment model for lead proposed by Rabinowitz et al. (1976), based on tracer and balance data from five healthy men, identifies the relative proportioning of lead among the bone, blood, and soft-tissue pools (Figure 2-5). The figure shows the lead content and mean half-life of each pool and the rates of lead movement between pools (λ). The blood compartment shows the shortest half-life (36 days), followed by the soft-tissue compartment (40 days), and then by the bone compartment (10^4 days or approximately 27 years). Bone contains most of the total body burden of lead, as discussed in Sections 2.3.2 (Distribution) and 2.4.1 (Pharmacokinetic Mechanisms). Thus, although sequestration by binding to specific metal-binding proteins in liver, kidney, and red blood cells is an important mechanism by which metals are distributed to various soft tissue compartments, physiologically based models for bone-seeking elements such as lead require that bone turnover and metabolism be incorporated into modeling efforts (O’Flaherty 1993).

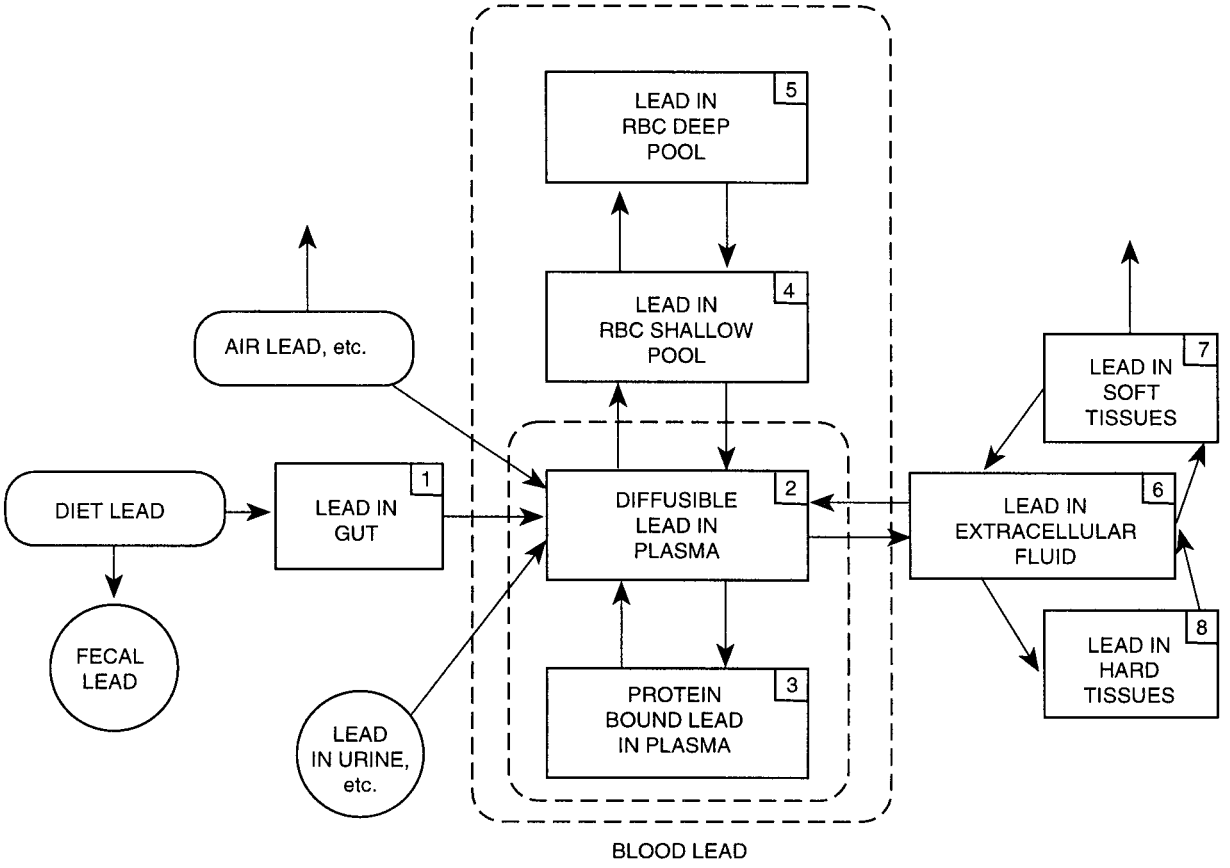
The generation of more recent data on lead pharmacokinetics has allowed for a refinement of this three-compartment model. The proposed multicompartment kinetic model for lead presented in Figure 2-6 addresses the diffusion of lead into bone and such principles as plasma-erythrocyte lead interactions (Marcus 1985a, 1985b, 1985c). For the bone diffusion model, Marcus (1985a) used the lead kinetic parameters generated for the dog. This model, which accounts for the exchange of lead between blood in bone canaliculi and the crystalline bone of the osteon, enables one to predict the effect of a number of parameters (such as diffusion and surface area) on the kinetics of lead in bone. A similar multicompartment model was developed by Marcus (1985c) to describe the kinetics of lead in plasma and erythrocytes. Based on the data collected by DeSilva (1981), Marcus (1985c) incorporated four blood lead compartments into this model: diffusible lead in plasma, protein-bound lead in plasma, a "shallow" erythrocyte pool, and a

Figure 2-5. Lead Metabolism Model



Source: Derived from Rabinowitz et al. 1976

Figure 2-6. A Compartmental Model for Lead Biokinetics with Multiple Pool for Blood Lead



Source: Derived from Marcus 1985a, 1985b, 1985c

"deep" erythrocyte pool (see Figure 2-6). When this model is applied to the data of DeSilva (1981), a curvilinear relationship results between plasma and blood lead levels.

Additional information on lead biokinetics and lead exposures has led to further refinements and expansions of these earlier modeling efforts. Three pharmacokinetic models, in particular, are currently being considered for broad application in lead risk assessment: (1) the O'Flaherty Model, a PBPK model for children and adults (O'Flaherty 1993, 1995a); (2) the Integrated Exposure Uptake BioKinetic (IEUBK) Model for Lead in Children developed by EPA (1994a, 1994b); and (3) the Leggett Model for children and adults (Leggett 1993). Of the three approaches, only the O'Flaherty Model uses physiologically based parameters to describe the volume, composition, and metabolic activity of blood and tissues that determine the disposition of lead in the human body. Both the IEUBK Model and the Leggett Model are classic multicompartmental models; the values of the age-specific transfer rate constants are based on kinetic data from studies in animals and humans, and may not have precise physiological correlates. Thus, the structure and parameterization of the O'Flaherty Model is distinct from both the IEUBK Model and Leggett Model. The models represent the rate of uptake of lead (i.e., amount of lead absorbed per day) as relatively simple functions of lead intake (e.g., uptake = intake x A, or uptake = intake x f[intake]). The values assigned to A or other variables in f[intake] are, in general, age-specific and, in some models, environmental medium-specific. However, the models do not modify the representation of uptake as functions of the many other physiologic variables that may affect lead absorption (e.g., nutritional status). While one can view this approach as a limitation of the models, it also represents a limitation of the data available to support more complex representations of lead absorption.

The IEUBK Model is used to simulate multimedia exposures, uptake, and kinetics of lead in children ages 0 to 7 years; the model is not intended for use in predicting lead pharmacokinetics in adults. The O'Flaherty and Leggett models are lifetime models, whose parameter values are based on experimental information about the uptake and kinetics of lead during infancy, childhood, adolescence, and adulthood. Detailed information describing exposure (e.g., residence-specific environmental lead concentrations, childhood activity patterns) is not readily described by current versions of these models. By contrast, the IEUBK model incorporates detailed exposure and uptake modules to estimate average daily uptake of lead (μg/day) among populations of children potentially exposed via soil and dust ingestion, air inhalation, lead-based paint chip ingestion, tap water ingestion, and diet.

All three models have been calibrated, to varying degrees, against empirical physiological data on animals and humans, and data on blood lead concentrations in individuals and/or populations (EPA 1994a, 1994c; Leggett 1993; O'Flaherty 1993). However, applications in risk assessment require that the models accurately predict blood lead distributions in real populations, in particular the "upper tails"(e.g., 95th percentile), when input to the models consists of data that describe site-specific exposure conditions (e.g., environmental lead concentrations, physicochemical properties of soil and dust). In evaluating models for use in risk assessment, exposure data collected at hazardous waste sites are used to drive model simulations. The exposure module in the IEUBK model enables this type of evaluation to be made. Efforts described by EPA (1994c) are currently in progress to fully assess the degree to which the IEUBK model accurately simulates PbB distributions in populations of children who are exposed to lead at hazardous waste sites.

2.3.5.2 Lead PBPK Model Comparison and Discussion

Several pharmacokinetic models have been developed to predict blood and tissue lead concentrations as a function of multimedia lead exposures. Although the principal adverse health effects of lead have been related to concentrations of lead in blood (see Section 2.2.1), current PbB concentrations may not always be predictive of lead-related behavioral dysfunction and need not be the only measure of adverse health effects of lead. Nevertheless, the empirical basis for a relationship between low levels of lead exposure and behavioral dysfunction largely consists of prospective epidemiological studies relating various indices of dysfunction with PbB concentration. Thus, in this context, PbB concentration has been related to health effects of lead, and this is the main reason that the focus of interest in the models has been on estimating PbB concentrations. Also, the best data with which to calibrate and validate the models has been data relating exposure and/or lead intake to PbB concentration. Thus, there is greater confidence in the validity of the models for estimating PbB concentrations, rather than lead levels in other physiologic compartments.

While these models simulate the transfer of lead between many of the same physiological compartments, they use different methodologies to quantify lead exposure as well as the kinetics of lead transfer among the compartments. As described earlier, in contrast to PBPK models, classical pharmacokinetic models are calibrated to experimental data using transfer coefficients that may not have any physiological correlates. Examples of lead models that use PBPK and classical pharmacokinetic approaches are discussed in the following section, with a focus on the basis for model parameters, including age-specific blood flow rates and volumes for multiple body compartments, kinetic rate constants, tissue dosimetry, and species

extrapolations. The following three pharmacokinetic models for lead are discussed below: (1) the O'Flaherty Model (O'Flaherty 1993, 1995a); (2) the IEUBK Model for Lead in Children (EPA 1994a, 1994b); and (3) the Leggett Model (Leggett 1993).

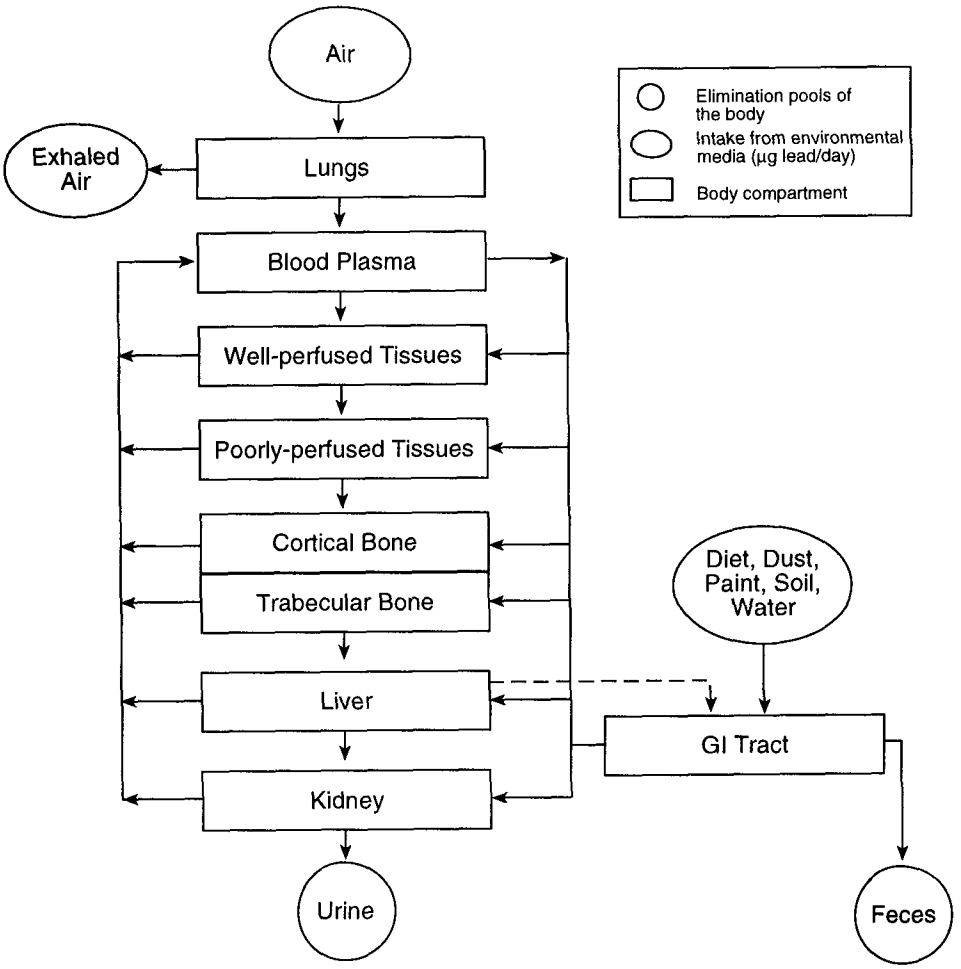
The O'Flaherty Model.

The O'Flaherty Model is a physiologically based pharmacokinetic (PBPK) model of lead uptake and disposition in children and adults (O'Flaherty 1993, 1995a). Figure 2-7 shows a conceptualized representation of the O'Flaherty Model, including the movement of lead from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between blood plasma, liver, kidney, richly-perfused tissues, poorly-perfused tissues, bone compartments, and excretion from liver and/or kidney. A detailed exposure module is not linked to the O'Flaherty Model; rather, lead exposure estimates are incorporated into the model as age-specific point estimates of average daily intake (µg/day) from inhalation, or total ingestion via diet, dust, lead-based paint, soil, and water. The model also simulates both age- and media-specific absorption. Because many of the pharmacokinetic functions are based on body weight and age, the model can be used to estimate PbB concentrations across a broad age range, including infants, children, adolescents, and adults. The model uses physiologically based parameters to describe the volume, composition, and metabolic activity of blood, soft tissues, and bone that determine the disposition of lead in the human body.

Description of the model. The O'Flaherty Model simulates lead absorption and disposition as a function of age-specific anatomical and physiological variables. A central feature of the model is the growth curve, a logistic expression relating body weight to age. The full expression relating weight to age has five parameters (constants), so that it can readily be adapted to fit a range of standardized growth curves for men and women. The values of the five parameters were calibrated (but not optimized) based on comparisons with model predictions and concentrations measurements in empirical studies (O'Flaherty 1991a). Physiologic functions are linked to body weight, to age, or to both, as appropriate.

Bone formation rate is also a critical feature of the model. The model includes three mechanisms of interaction of lead with bone. One is the rapid exchange of lead at all surfaces of the bone in contact with blood, one is incorporation into forming bone and return to the blood with resorbing bone, and the third is a heteroionic exchange process that can be modeled as diffusion throughout the entire bone volume (O'Flaherty 1995b). All three processes are linked to body weight, or the rate of change of weight with age.

Figure 2-7. Compartments and Pathways of Lead Exchange in the O'Flaherty Model



Source: Derived from O'Flaherty 1991b, 1993, 1995a

The physiological parameters required to simulate these processes were first derived for a PBPK model of lead in rats (O'Flaherty 1991a), and include rate of body growth; bone formation rate, net bone volume, volume of rapidly exchanging fraction of bone mineral, and blood flow rate to bone; and bone structure (canaliculi diameter and spacing), in addition to specifying the fractional tissue volumes and blood flow rates to other tissue compartments. Values for many of these growth and bone-related parameters used in the PBPK for humans are given in Table 2-6. In contrast to the values of the plasma/erythrocyte partitioning parameters, the values of the partition coefficients do not greatly influence the whole-body predictions of the model (O'Flaherty 1991a). Parameters describing bone formation rate for children were calibrated based on measured bone calcium accretion rates in healthy children and adolescents using a stable calcium isotope technique (Abrams et al. 1992). Values of allometric exponents less than unity in expressions for liver, kidney, and bone volumes as a function of body weight, mean that these organs occupy a slightly greater fraction of model body weight in children than in adults (O'Flaherty 1991a).

Only a subset of the parameter values in the O'Flaherty model require inputs from the user to simulate blood and tissue lead concentrations. Lead-related parameters for which values can be entered into the model include: fractional absorption from the gastrointestinal tract; partition coefficients for lead in non-bone tissues and in the surface region of bone; maximum capacity and half-saturation concentration for capacity-limited binding in the erythrocyte; elimination clearance; fractional clearance of lead from plasma into forming bone; and the restricted permeability coefficients for lead diffusion within bone, from plasma into bone, and from bone into plasma (O'Flaherty 1991a).

The O'Flaherty Model incorporates exposure routes that are unique to infants and children, including infant formula, and elevated soil and dust ingestion rates (mg/day). Age-specific soil and dust ingestion rates (mg/day) are simulated separately, with the peaks of soil and dust ingestion occurring at ages 3 and 2 years, respectively. The model includes two routes of lead (Pb) intake: ingestion and inhalation. Lead levels in dust, soil, drinking water, infant formula or milk, and air (both ambient and workplace) are inputs to each simulation. Lead intake rates from these media are computed using medium-specific ingestion or respiration rate as a function of age and gender. Soil and dust exposures are modeled as age-specific ingestion only in children (0.3 to 6.5 years); ingestion of dusts and soils by adults is not included in the current version of the model. Soil and dust bioavailability may be specified by the user. Lead intakes from food can also be specified. Values for ambient air Pb concentration and food Pb ingestion rate vary with date of birth, simulating the decline in lead in food and air since 1970 and 1975, respectively. Intake may occur at any age, however fetal exposure is not explicitly addressed in the model. Sequential input files

Table 2-6. Kinetic Constants and Model Parameters in the O'Flaherty Model

Physiological parameters	Parameter value	Units
Partition coefficients for blood		
Maximum binding capacity of erythrocytes	2.7	mg lead/L red cell volume
Half-saturation concentration	0.0075	mg lead/L red cell volume
Partition coefficients for blood/tissue kinetics		
Blood/liver	100	unitless
Blood/kidney	100	unitless
Blood/other rapidly perfused	100	unitless
Blood/bone	1000	unitless
Blood/other slowly perfused	20	unitless
Metabolic constants		
Fractional clearance into forming bone	15,000	L plasma cleared/L bone formed
Permeability coefficient bone/bone	$1x10^{-7}$	cm/day-unit distance
Permeability coefficient bone/plasma	$1x10^{-7}$	cm/day-unit distance
Permeability coefficient plasma/bone	0.08	cm/day-unit distance
Weights		
Newborn (kg)	3.5	kg
Max child (kg)	22	kg
K, logistic growth curve constant	600	unitless
K, logistic growth curve constant	0.017	unitless
Volume, allometric exponents		
Liver	0.85	L
Kidney	0.84	L
Bone	1.02	L
Surface bone	$2.04x10^{-3}$	L
Bone growth[a]		
Bone mass	1.21	kg
A1	0.1	$year^{-1}$
A2	4.6	$year^{-1}$
A3	0.55	$year^{-1}$
Bone structure		
Canicule spacing (μm)	8	micrometers
Canicule surface	$3.1x10^{-4}$	(cm^2/cm length)
Canicule total length	$2.0x10^{9}$	(cm/L bone)

[a] Three-parameter expression relates bone formation rate with body and bone growth, according to: Bone formation = A1 + (A2)(1-EXP(-A3) x (rate of change of bone mass / bone mass).

Source: Derived from O'Flaherty 1993

may be specified to simulate changes in lead levels and intake rates over time. Both chronic and acute exposures may be modeled. Fractional lead absorption from the gastrointestinal tract was modeled as a first-order process.

The O'Flaherty Model simulates the age-dependence of lead kinetics on such factors as absorption efficiency, excretion efficiency, uptake into bone and loss from bone, and partitioning between plasma and red blood cells. The model does not incorporate age, dose rate, or time dependence of lead accumulation in every organ (e.g., kidney) because the complex patterns of lead accumulation in certain tissues are not known (O'Flaherty 1991a) (see Section 2.4.1). However, the basic model structure allows for additional modules to be incorporated, depending on its intended use in risk assessment. For example, additional modules that are currently being developed are a pregnancy model and a model of net bone loss in older women and men.

Risk assessment. The O'Flaherty Model has several potential applications to risk assessments at hazardous waste sites. The model can be used to predict the PbB concentrations in a broad age range, including infants, children, and adults. The model may be modified to simulate the pharmacokinetics of lead in potential sensitive subpopulations, including pregnant women and fetuses, as well as older adults. The model does not contain a detailed exposure module; however, model simulations have been run holding physiological variables fixed and allowing soil and dust lead concentrations to vary in order to estimate the range of environmental lead concentrations that would be expected to yield close correspondence between predicted and observed PbB concentrations (O'Flaherty 1993, 1995a).

The O'Flaherty Model utilizes point estimates for parameter values and yields point estimates as output. It does not contain a probabilistic modeling component that simulates variability; therefore, it is not used to predict PbB probability distributions in exposed populations. Accordingly, the current version will not predict the probability that children exposed to lead in environmental media will have PbB concentrations exceeding a health-based level of concern (e.g., 10 µg/dL). Efforts are currently underway to explore applications of stochastic modeling methodologies to investigate variability in both exposure and biokinetic variables that will yield estimates of distributions of lead concentrations in blood, bone, and other tissues.

Validation of the model. The O'Flaherty Model was initially calibrated to predict blood, bone, and tissue lead concentrations in rats (O'Flaherty 1991a), and subsequently modified to reflect anatomical and physiological characteristics in children (O'Flaherty 1995a), adults (O'Flaherty 1993) and Cynomolgus

monkeys (*Macaca fasicularis*) (O'Flaherty et al. 1998). Model parameters were modified to correspond with available information on species- and age-specific anatomy and physiological processes described above. In general, the model has been shown to reproduce blood lead observations in children and adults well, except in instances where lead is ingested at very high concentrations (O'Flaherty 1993, 1995a).

Target tissues. Output from the O'Flaherty Model is an estimate of age-specific blood lead concentrations. The O'Flaherty Model has also been used to predict lead concentrations in bone and other tissue compartments (O'Flaherty 1995a), in order to evaluate correspondence between predicted tissue concentrations and observed concentrations in different populations of children and adults.

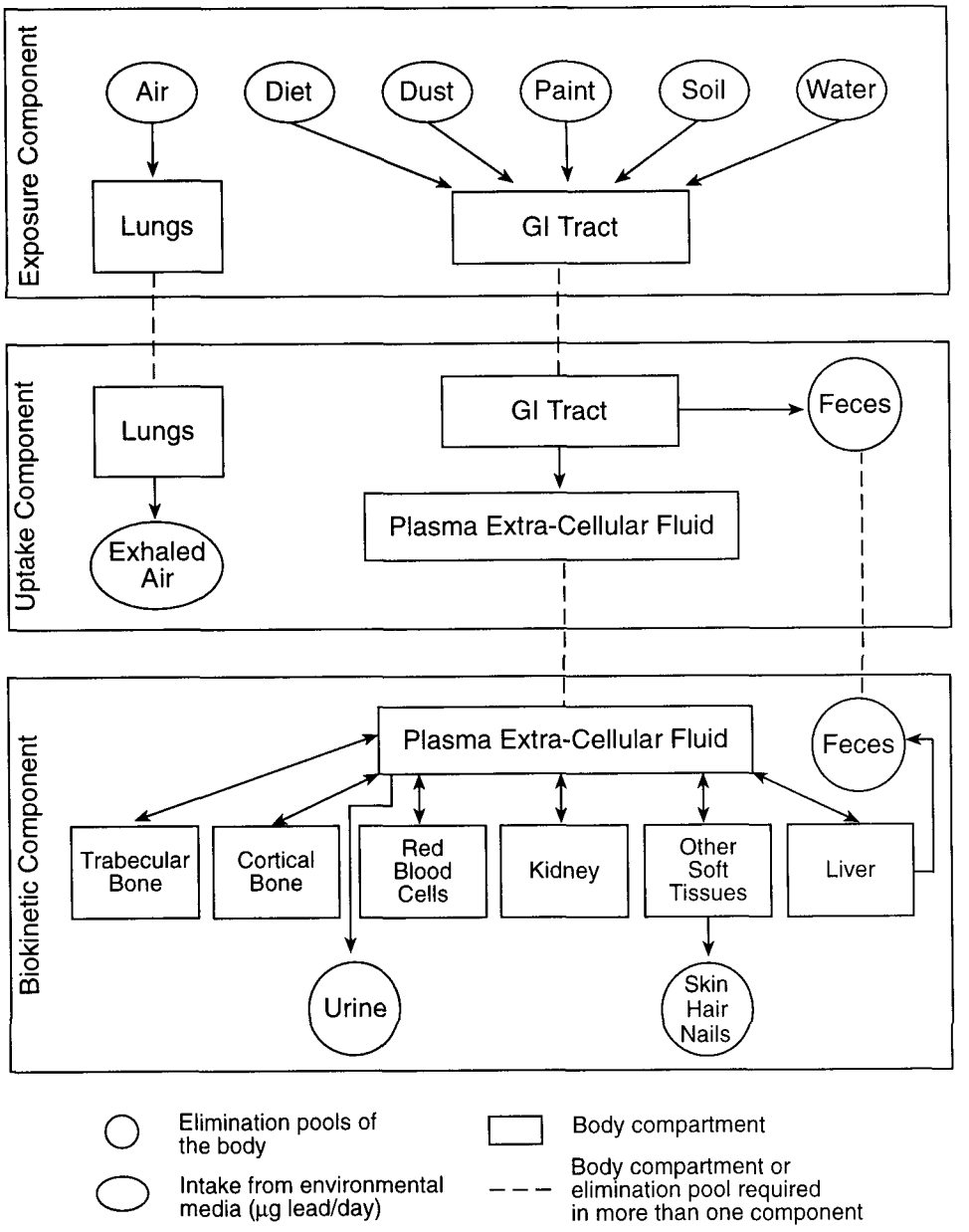
Species extrapolation. Data on both animals and humans (children and adults) describing the absorption, distribution, metabolism, and excretion of lead provide the biological basis of the biokinetic model and parameter values used in the O'Flaherty Model. The model is calibrated to predict compartmental lead masses for human children and adults. The model for humans was derived from a model for rats (O'Flaherty 1991a), and O'Flaherty suggests that certain parameter values describing bone physiology and metabolism are independent of species. For example, volume fractions of cortical bone and trabecular bone appear to be similar across species (i.e., 80% cortical, 20% trabecular) (Gong et al. 1964). In addition, surface-to-volume ratios (cm^2/cm^3) and blood flows to cortical and trabecular bone are proportional to bone formation rates. However, while the potential for bone resorption and accretion of new bone is present in all species, the magnitude and age dependence of these processes are variable with species (O'Flaherty 1995a). The mathematical structure of the O'Flaherty Model for humans is designed to accept parameter values that reflect the physiology and metabolism of different species (O'Flaherty 1993).

Interroute extrapolation. The values for pharmacokinetic variables in the O'Flaherty Model are independent of the route of exposure. However, the model does incorporate media-specific estimates of absorption from the gastrointestinal tract. Different exposure scenarios have been evaluated with the O'Flaherty Model for children and adults (O'Flaherty 1993, 1995a).

The IEUBK Model.

The Integrated Exposure Uptake and BioKinetic (IEUBK) Model for Lead in Children is a classical multicompartmental pharmacokinetic model linked to an exposure and probabilistic model of PbB distributions in populations of children ages 0–7 years (EPA 1994a, 1994b; White et al. 1998). Figure 2-8

Figure 2-8. Structure of the IEUBK Model for Lead in Children



Source: Derived from EPA 1994a, 1994b

shows a conceptualized representation of the IEUBK Model. The model has four distinct components: (1) exposure component, in which average daily intake of lead (μg/day) is determined from exposure to lead in air, diet, dust, lead-based paint, soil, and water; the model accepts exposure data on an annual basis, but allows one entry to characterize a cumulative average exposure for each environmental medium (EPA 1994c); (2) uptake component, which converts media-specific lead intake rates produced by the exposure component into media-specific uptake rates (μg/day) for the blood plasma; (3) biokinetic component, which simulates the transfer of absorbed lead between blood and other body tissues, or elimination of lead from the body via urine, feces, skin, hair, and nails; and (4) probability distribution component, which applies a geometric standard deviation to estimate the lognormal distribution of PbB concentrations in the exposed population (EPA 1994a, 1994b).

Description of the model. The biokinetic component of the IEUBK Model includes a central compartment, six peripheral body compartments, and three elimination pools, as illustrated in Figure 2-8. The body compartments include the plasma and extra cellular fluid pool, the kidney, the liver, trabecular bone, cortical bone, and other soft tissue pools (EPA 1994a). The model estimates weights and volumes for the body and body compartments, as well as the maternal PbB concentration, in order to determine the compartmental lead masses at birth. These quantities are then combined with the total lead uptake rate for each month to determine lead masses in each of the body compartments (EPA 1994b). Nonlinear relationships between uptake and PbB concentrations are estimated by simulating capacity-limited binding of lead to red blood cells. The total lead uptake is estimated as the sum of two components, one passive (represented by a first order, linear, relationship), the second active (represented by a saturable, Michaelis-Menten type relationship). These two terms are intended to represent two different mechanisms of lead absorption, an approach that is in accord with limited available data in humans and animals and also, by analogy, with what is known about calcium uptake from the gastrointestinal tract (see Sections 2.3.2 and 2.4.1).

Unidirectional, first-order transfer coefficients (referred to as residence times) determine the rate at which lead enters, leaves, and remains in each compartment during a monthly iteration (EPA 1994b). Monthly residence times are calculated based on age-specific body and organ weights using allometric scaling factors, as given in Table 2-7. The lead in the plasma portion of the central plasma/extra cellular fluid (ECF) compartment is combined with the lead in the red blood cells to determine the blood lead concentration (EPA 1994b).

Table 2-7. Residence Times in the Biokinetic Module of the IEUBK Model

Compartments of lead transfer	Equations for calculating age-specific transfer rates[a]
Plasma/RBC	0.172 / 30
Plasma/kidney	[13.6 * (Body/3.7)alscale] / 30
Plasma/liver	[1.20 * (Body/3.7)alscale] / 30
Plasma/other tissues	[10.9 * (Body/3.7)alscale] / 30
Plasma/urine	[0.075 * (Body/3.7)alscale] / 30
Plasma/cortical bone	[9.0 * (Body/70)alscale] / 30
Plasma/trabecular bone	[7.34 * (Body/70)alscale] / 30
RBC/plasma	2.16 / 30
Kidney/plasma	[60 * (Kidney/0.03)alscale] / 30
Liver/plasma	[120 * (Liver/0.17)alscale] / 30
Liver/feces	[60 * (Liver/0.17)alscale] / 30
Cortical bone/plasma	[30800 * (Body/4.0)alscale] / 30
Trabecular bone/plasma	[437 * (Trabecular/1.0)alscale] / 30
Other tissues/plasma	[426 * (Body/3.15)alscale] / 30
Other tissues/excreta	[60 * (Other/0.2)alscale] / 30

[a] Variables for body, tissues are inputted in units of kilograms. "Alscale" refers to the allometric scaling factor, and is assigned a default value of 0.333.

Source: Derived from EPA 1994a, 1994b

Inputs to the IEUBK model are point estimates that are intended to yield age-specific estimates of the geometric mean blood lead concentration among an exposed population (EPA 1994a, 1994b). The distribution of metals in tissues of relatively homogeneous human populations closely follows a lognormal distribution (EPA 1986a). Therefore, in order to estimate a plausible distribution of PbB concentrations for the exposed population, a geometric standard deviation (GSD PbB) is applied to the age-specific geometric mean blood lead estimate. The GSD PbB reflects variability associated with repeat sampling, and inter-individual and biological variability, as determined from community blood lead studies of children's residential settings (EPA 1994c).

Risk assessment. The IEUBK Model was developed to predict the probability of elevated blood lead concentrations in children. The model addresses three components of human health risk assessment: (1) the multimedia nature of exposures to lead; (2) lead pharmacokinetics; and (3) significant variability in exposure and risk (EPA 1994c). Thus, the IEUBK Model can be used to predict the probability that children ages 6 months to 7 years exposed to lead in multiple environmental media will have Pb concentrations exceeding a health-based level of concern (e.g., 10 μg/dL). These risk estimates can be useful in assessing the possible consequences of alternative lead exposure scenarios following intervention, abatement, or other remedial actions. The current version of the IEUBK Model (version 0.99D) was not developed to assess lead risks for age groups older than 7 years.

Validation of the model. An evaluation of the IEUBK model has been conducted in which model predictions of blood lead concentrations in children were compared to observations from epidemiologic studies of hazardous waste sites (Hogan et al. 1998). Data characterizing residential lead exposures and blood lead concentrations in children living at four Superfund NPL sites were collected in a study designed by ATSDR and EPA. The residential exposure data were used as input to the IEUBK model and the resulting predicted blood lead concentration distributions were compared to the observed distributions in children living at the same residences. IEUBK model predictions agreed reasonably well with observations for children whose exposures were predominantly from their residence (e.g., who spent no more than 10 hours per week away from home). The predicted geometric mean blood lead concentrations were within 0.7 μg/dL of the observed geometric means at each site. The prediction of the percentage of children expected to have blood lead concentrations exceeding 10 μg/dL were within 4% of the observed percentage at each site. This evaluation provides support for the validity of the IEUBK model for estimating blood lead concentrations in children at sites where their residential exposures can be adequately characterized. In addition to the above empirical comparisons, the computer code used to implement the IEUBK model

(IEUBK versus 0.99d) has undergone an independent validation and verification and has been shown to accurately implement the conceptual IEUBK model (Zaragoza and Hogan 1998).

Target tissues. The output from the IEUBK Model is an estimate of age-specific blood lead concentrations. The current version of the IEUBK Model does not save as output the interim parameter values determined for lead in other tissues or tissue compartments.

Species extrapolation. Data in both animals and humans (children and adults) describing the absorption, distribution, metabolism, and excretion of lead provide the biological basis of the biokinetic model and parameter values used in the IEUBK Model. The model is calibrated to predict compartmental lead masses for human children ages 6 months to 7 years, and is not intended to be applied to other species or age groups.

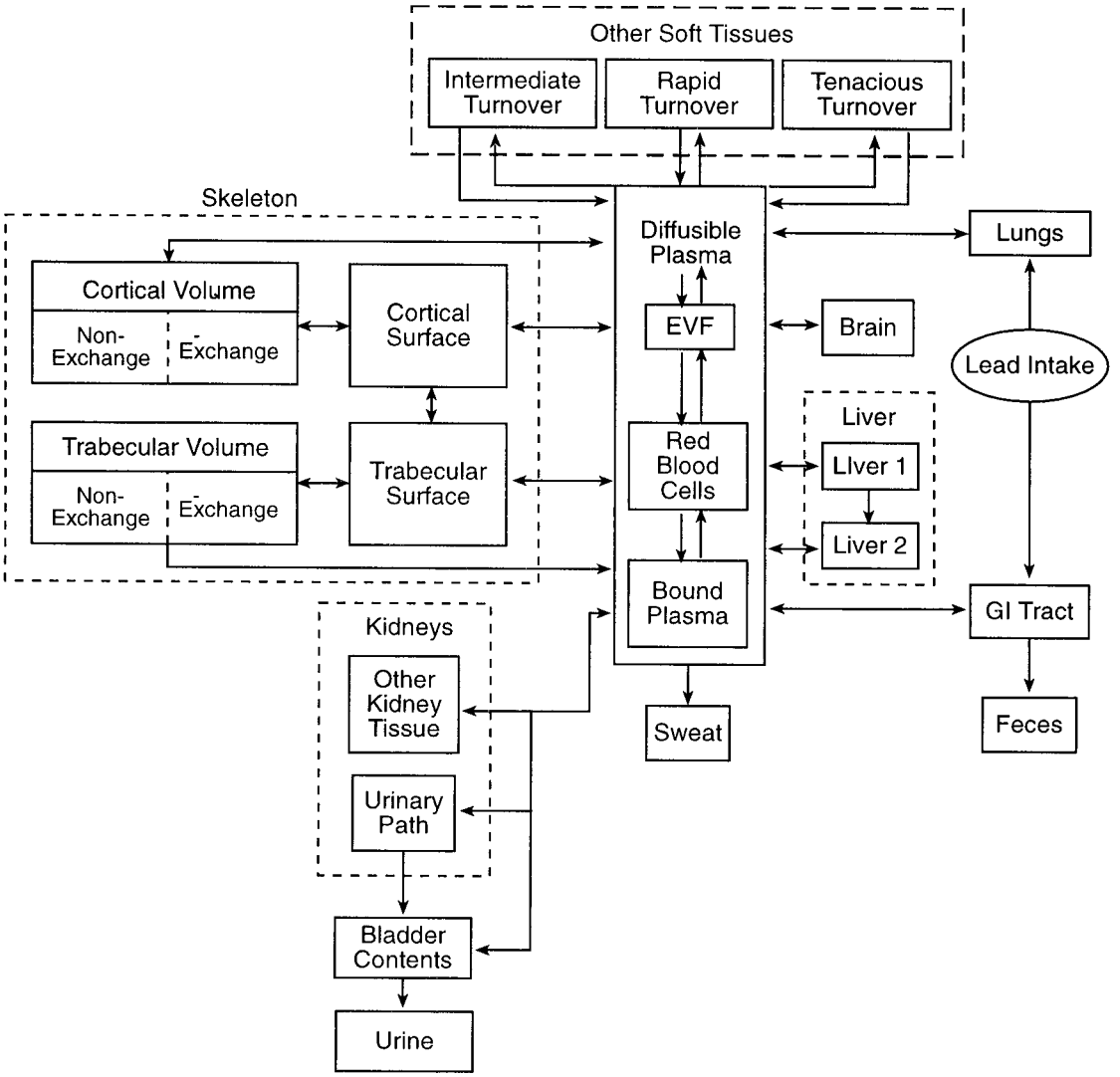
Interroute extrapolation. The IEUBK Model includes an exposure module that simulates age-specific lead exposures via inhalation, and ingestion of lead in diet, dust, lead-based paint, soil, and water. The total exposure from each route is defined as the total lead uptake (µg/day) over a 1-month period. Other routes of exposure may be simulated by the IEUBK Model pending available information from which to characterize both the exposure and media-specific absorption variables. Values for variables in the biokinetic component of the IEUBK Model are independent of the route of exposure.

The Leggett Model.

The Leggett Model is a classical multicompartmental pharmacokinetic model of lead uptake and disposition in children and adults (Leggett 1993). Figure 2-9 shows a conceptualized representation of the model, including the movement of lead from exposure media (i.e., intake via inhalation or ingestion) to the lungs and gastrointestinal tract, followed by the subsequent exchanges between diffusible blood plasma, soft tissues, bone compartments, and excretion from liver, kidneys, and sweat. As a classical compartmental model, tissue compartments, kinetic constants, and model parameters may not all have physiological correlates. A detailed exposure module is not linked to the Leggett Model; rather, lead exposure estimates are incorporated into the model as age-specific point estimates of average daily intake (µg/day) from inhalation and ingestion. A detailed description of the model and its potential application to risk assessment are provided below.

Description of the model. The Leggett Model includes a central compartment, 15 peripheral body compartments, and 3 elimination pools, as illustrated in Figure 2-9. Transport of lead between

Figure 2-9. Compartments and Pathways of Lead Exchange in the Leggett Model



Source: Derived from Leggett 1993

compartments is assumed to follow first-order kinetics provided the concentration in red blood cells stays below a nonlinear threshold concentration (assumed to be 60 µg/dL) (Leggett 1993). Nonlinear relationships between uptake and PbB concentrations are estimated by simulating capacity-limited binding of lead to red blood cells.

Unidirectional, first-order transfer rates (day^{-1}) between compartments were developed for 6 age groups, and intermediate age-specific values are obtained by linear interpolation. The range of age-specific transfer rate values are given in Table 2-8. The total transfer rate from diffusible plasma to all destinations combined is assumed to be 2,000 day^{-1}, based on isotope tracer studies in humans receiving lead via injection or inhalation. Values for transfer rates in various tissues and tissue compartments are based on measured deposition fractions, or instantaneous fractional outflows of lead between tissue compartments (Leggett 1993).

The Leggett Model was developed from a biokinetic model originally developed for the International Commission on Radiological Protection (ICRP) for calculating radiation doses from environmentally important radionuclides, including radioisotopes of lead (Leggett 1993). The Leggett Model simulates age-specific bone physiology using a model structure developed for application to the alkaline earth elements, but parameterized using data specific to lead where possible. Cortical and trabecular bone are viewed as consisting of exchangeable and nonexchangeable pools in order to model both rapid exchange of lead with plasma and slow loss by bone resorption. Assumptions in the bone module include: (1) bone lead is rapidly exchangeable if, and only if, it resides on bone surfaces; (2) bone volume is in exchange with bone surfaces and not plasma; and (3) all lead reaching bone volume is initially available for exchange (Leggett 1993).

The Leggett Model simulates lead biokinetics in liver with two compartments: the first simulates rapid uptake of lead from plasma and a relatively short removal half-life (days) for transfers to plasma and to the small intestine by biliary secretion; a second compartment simulates a more gradual transfer to plasma of approximately 10% of lead uptake in liver. Different transfer rates associated with each compartment are calibrated to reproduce patterns of uptake and retention of lead observed in humans, baboons, and beagles following intravenous injection, as well as blood-to-liver concentration ratios from data on chronically exposed humans. Similarly, the Leggett Model simulates lead biokinetics in three compartments of soft tissues, representing rapid, intermediate, and slow turnover rates (without specific physiologic correlates).

Table 2-8. Kinetic Constants and Model Parameters in the Leggett Model

Compartments of lead transfer	Range of age-specific transfer rates (day^{-1})
Diffusible plasma / tissue	
/ extravascular fluid	1,000
/ red blood cells	297–480
/ bound plasma ($x10^3$)	500–800
/ urinary bladder	19–30
/ urinary path	25–40
/ small intestine	7.4–12.0
/ trabecular bone surface	58–132
/ cortical bone surface	71–384
/ liver, rapid turnover rate	50–80
/ other kidney ($x10^3$)	350–400
/ other soft tissues, rapid turnover rate	103–178
/ other soft tissues, moderate turnover rate (x10)	100–178
/ other soft tissues, slow turnover rate (x102)	124–200
/ brain (x103)	188–763
/ sweat	4.3–7.0
Bone / tissue ($x10^3$)	
Cortical exch. volume / cortical nonexch. volume	4.6
Trabecular exch. volume / trabecular nonexch. volume	4.6
Cortical exch. volume / cortical surface	18.5
Trabecular exch. volume / trabecular surface	18.5
Cortical nonexch. volume / diffusible plasma	0.082–8.22
Trabecular nonexch. volume / diffusible plasma	0.049–8.22
Cortical surface / diffusible plasma	650
Trabecular surface/ diffusible plasma	650
Cortical surface/ cortical exch. volume	350
Trabecular surface/ trabecular exch. volume	350
Liver / tissue	
rapid turnover compartment / diffusible plasma	31.2
rapid turnover compartment / small intestine	31.2
rapid turnover compartment / slow turnover rate	6.9
slow turnover compartment / diffusible plasma	1.9–6.9
Other tissues ($xx10^3$)	
urinary path / urinary bladder	139
other kidney / diffusible plasma	1.9–6.9
other soft tissues, rapid turnover rate / diffusible plasma	2079
other soft tissues, moderate turnover rate / diffusible plasma	4.16
other soft tissues, moderate turnover rate / excreta	2.77
other soft tissues, slow turnover rate / diffusible plasma	0.38
brain / diffusible plasma	0.95

Source: Derived from Leggett 1993

The Leggett Model simulates the age-dependence of lead kinetics on such factors as bone turnover rates, partitioning between soft tissues and excreta, removal half-times in liver, kidneys, and red blood cells, and the deposition fraction in brain. The model structure represents a compromise between biological realism and practical considerations regarding the quantity and quality of information available to determine parameter values (Leggett 1993).

Risk assessment. The Leggett Model has several potential applications to risk assessment at hazardous waste sites. The model can be used to predict blood lead concentrations in both children and adults. The model allows the simulation of lifetime exposures, including assumptions of blood lead concentrations at birth (from which levels in other tissue in the first time step after birth would are calculated). Thus, exposures and absorption of lead prior to any given period of time during the lifetime can be simulated with the Leggett model. The model parameters may be calibrated to fit kinetic data from radiolabeled lead tracer studies that are ongoing. The model does not contain a detailed exposure module and, therefore, requires assumptions regarding total lead intake from multiple exposure media. In addition, it does not contain a probabilistic modeling component and, therefore, is not used to predict blood lead distributions in exposed populations.

Validation of the model. Output from the Leggett Model has been compared with data in children and adult subjects exposed to lead in order to calibrate model parameters. The model appears to predict blood lead concentrations in adults exposed to relatively low levels of lead; however, no information could be found describing efforts to compare predicted blood lead concentrations with observations in children.

Target tissues. The output from the Leggett Model is an estimate of age-specific PbB concentrations. The current version of the Leggett Model does not save as output the interim parameter values determined for lead in other tissues or tissue compartments.

Species extrapolation. Data on both animals and humans (children and adults) describing the absorption, distribution, metabolism, and excretion of lead provide the biological basis of the biokinetic model and parameter values used in the Leggett Model. The model is calibrated to predict compartmental lead masses only for humans, both children and adults.

Interroute extrapolation. The values for pharmacokinetic variables in the Leggett Model are independent of the route of exposure. Based on the description of the inputs to the model provided by

Leggett (1993), lead intake from different exposure routes is defined as a total lead intake from all routes of exposure.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption. Gastrointestinal absorption of lead occurs primarily in the duodenum (Mushak 1991). The exact mechanisms of absorption are unknown and may involve active transport and/or diffusion through intestinal epithelial cells (transcellular) or between cells (paracellular), and may involve ionized lead (Pb^{+2}) and/or inorganic or organic complexes of lead. Saturable mechanisms have been inferred from measurements of net flux kinetics of lead in the *in situ* perfused mouse intestine, the *in situ* ligated chicken intestine, and in *in vitro* isolated segments of rat intestine (Aungst and Fung 1981; Barton 1984; Flanagan et al. 1979; Mykkänen and Wasserman 1981). By analogy to other divalent cations, saturable transport mechanisms for Pb^{+2} may exist within the mucosal and serosal membranes and within the intestinal epithelial cell. For calcium, these are thought to represent membrane carriers (e.g., Ca^{2+}-Mg^{2+}-ATPase, Ca^{2+}/Na^{+} exchange) or facilitated diffusion pathways (e.g., Ca^{2+} channel) and intracellular binding proteins for Ca^{2+} (Bronner et al. 1986; Gross and Kumar 1990). Numerous observations of non-linear relationships between PbB concentration and lead intake in humans suggest the existence of a saturable absorption mechanism or some other capacity-limited process in the distribution of lead in humans (Pocock et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1984). In immature swine that received oral doses of lead in soil, lead dose-blood lead relationships were non-linear; however, dose-tissue lead relationships for bone, kidney, and liver were linear. The same pattern (nonlinearity for PbB and linearity for tissues) was observed in swine administered lead acetate intravenously (Casteel et al. 1997). These results raise the question of whether there is an effect of dose on absorption or on some other aspect of the biokinetics of lead.

Gastrointestinal absorption of lead is influenced by dietary and nutritional calcium and iron status. An inverse relationship has been observed between dietary calcium intake and PbB concentration (Mahaffey et al. 1986; Ziegler et al. 1978). Complexation with calcium (and phosphate) in the gastrointestinal tract and competition for a common transport protein have been proposed as possible mechanisms for this interaction (Barton et al. 1978a; Heard and Chamberlain 1982). Absorption of lead from the gastrointestinal tract is enhanced by dietary calcium depletion or administration of cholecalciferol. This "cholecalciferol-dependent" component of lead absorption appears to involve a stimulation of the serosal transfer of lead

from the epithelium, not stimulation of mucosal uptake of lead (Mykkänen and Wasserman 1981, 1982). This is similar to the effects of cholecalciferol on calcium absorption (Bronner et al. 1986; Fullmer and Rosen 1990). Iron deficiency is associated with increased PbB concentration in children (Mahaffey and Annest 1986; Marcus and Schwartz 1987). In rats, iron deficiency increases the gastrointestinal absorption of lead, possibly by enhancing binding of lead to iron binding proteins in the intestine (Morrison and Quatermann 1987). Iron ($FeCl_2$) added to the mucosal fluid of the everted rat duodenal sac decreases serosal transfer, but not mucosal uptake of lead (Barton 1984). Thus, interactions between iron and lead also appear to involve either intracellular transfer or basolateral transfer mechanisms. The above observations suggest that rate-limiting saturable mechanisms for lead absorption are associated with transfer of lead from cell to blood rather than with mucosal transfer. Similar mechanisms may contribute to lead-iron and lead-calcium absorption interactions in humans, and, possibly interactions between lead and other divalent cations such as cadmium, copper, magnesium and zinc.

The bioavailability of ingested soluble lead in adults has been found to vary from less than 10% when ingested with a meal to 60–80% when ingested after a fast (Blake and Mann 1983; Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1976, 1980). The general consensus is that food in the gastrointestinal tract decreases absorption of ingested lead, although the exact mechanisms by which this occurs are not entirely understood.

Inorganic lead in ambient air consists primarily of particulate aerosols which can be deposited in the respiratory tract when the aerosols are inhaled. Amounts and patterns of deposition of particulate aerosols in the respiratory tract are affected by the size of the inhaled particles, age-related factors that determine breathing patterns (e.g., nose breathing vs mouth breathing), airway geometry, and airstream velocity within the respiratory tract (EPA 1994a). In general, large particles (>2.5 μm) deposit in the nasopharyngeal tract where high airstream velocities and airway geometry facilitate inertial impaction (Chamberlain et al. 1978; Chan and Lippman 1980). In the tracheobronchial and alveolar regions, where airstream velocities are lower, processes such as sedimentation and interception become important for deposition of smaller particles (<2.4 μm). Breathing patterns, airflow velocity, and airway geometry change with age, giving rise to age-related differences in particle deposition (James 1978; Phalen et al. 1985). Deposition in the various regions of the respiratory tract in children may be higher or lower than in adults depending on particle size; for submicron particles, fractional deposition in 2-year-old children has been estimated to be 1.5 times greater than in adults (Xu and Yu 1986).

Absorption of deposited lead is influenced by particle size and solubility as well as the pattern of regional deposition within the respiratory tract. Larger particles (>2.5 μm) that are deposited in the ciliated airways (nasopharyngeal and tracheobronchial regions) can be transferred by mucociliary transport into the esophagus and swallowed. Particles deposited in the alveolar region can be absorbed after extracellular dissolution or ingestion by phagocytic cells. The relative contributions of these two pathways to lead absorption have not been quantified; however, data on cadmium suggests by analogy that their relative importance may depend on the chemical form of the metal as well as particulate size (Oberdörster 1992).

Inhaled tetraethyl and tetramethyl lead vapors behave as gases in the respiratory tract and, as a result, their pattern and extent of deposition and absorption differ from that of inhaled inorganic lead particles (EPA 1994a; Overton et al. 1987; Overton and Miller 1988). These differences result in a higher fractional absorption of inhaled tetraethyl and tetramethyl lead (Heard et al. 1979).

Distribution. Lead in blood partitions between plasma and red blood cells, with the larger fraction (90–99%) associated with red blood cells (Cake et al. 1996; DeSilva 1981; Everson and Patterson 1980; Manton and Cook 1984; Ong and Lee 1980a). Lead in plasma binds to albumin and γ-globulins (Ong and Lee 1980a). The fraction that is not bound to protein exists largely as complexes with low molecular weight sulfhydryl compounds; these may include cysteine, homocysteine, and cysteamine (Al-Modhefer et al. 1991). Approximately 75% was bound to protein when whole human blood was incubated with 50 μg/dL lead (as lead chloride); approximately 90% of the bound lead was associated with albumin (Ong and Lee 1980a). However, the fraction of lead in plasma bound to protein would be expected to vary with the plasma lead concentration.

Lead associated with red blood cells exists largely as complexes with hemoglobin, low molecular weight intracellular compounds, and unidentified membrane proteins (Bruenger et al. 1973; Ong and Lee 1980b, 1980c; Raghavan et al. 1980). A 10 kD inducible lead binding protein in human red blood cells has been reported, but not fully characterized (Lolin and O'Gorman 1988; Raghavan et al. 1980). Lead and calcium appear to share a common binding site on the red cell membrane (Ong and Lee 1980b). Binding to hemoglobin and other intracellular lead binding constituents of red blood cells is capacity limited and, as a result, the fraction of lead in whole blood that is associated with plasma increases as the whole PbB concentration increases (DeSilva 1981; Manton and Cook 1984). The capacity limitation has been postulated and modeled as a saturable binding site in the red cell (Leggett 1993; Marcus 1985a; O'Flaherty 1993).

As in red blood cells, lead in other soft tissues such as kidney, liver, and brain exists predominantly bound to protein. High affinity cytosolic lead binding proteins (PbBP) have been identified in rat kidney and brain (DuVal and Fowler 1989; Fowler 1989). The PbBP of rat is a cleavage product of $\alpha_{2\mu}$-globulin, a member of the protein superfamily known as retinol-binding proteins (Fowler and DuVal 1991). $\alpha_{2\mu}$-Globulin is synthesized in the liver under androgen control and has been implicated in the mechanism of male rat hyaline droplet nephropathy produced by certain hydrocarbons (EPA 1991c; Swenberg et al. 1989); however, there is no evidence that lead induces male-specific nephropathy or hyaline droplet nephropathy. The precise role for PbBP in the toxicokinetics and toxicity of lead has not been firmly established; however, it has been proposed that PbBP may serve as a cytosolic lead "receptor" that, when transported into the nucleus, binds to chromatin and modulates gene expression (Fowler and DuVal 1991; Mistry et al. 1985, 1986). Lead also binds to another prominent cytosolic metal binding protein, metallothionein. Binding of lead to either metallothionein or PbBP attenuates lead-induced inhibition of the enzyme ALAD; thus, these proteins may have a modulating effect on lead-induced inhibition of this and other cellular enzymes (Goering and Fowler 1984, 1985, 1987; Goering et al. 1986). A characteristic histologic finding in lead-induced nephropathy is the appearance of intranuclear inclusion bodies in renal proximal tubule cells (Goyer and Rhyne 1973; Vicente-Ortega et al. 1996). The intranuclear inclusion bodies contain lead complexed with acidic proteins which may include PbBP or similar proteins (Moore and Goyer 1974).

Storage. Approximately 95% of lead in adult tissues, and approximately 70% in children, resides in mineralized tissues such as bone and teeth (Barry 1975, 1981). A portion of lead in bone readily exchanges with the plasma lead pool and, as a result, bone lead is a reservoir for replenishment of lead eliminated from blood by excretion (Alessio 1988; Chettle et al. 1991; Hryhirczuk et al. 1985; Nilsson et al. 1991; Rabinowitz et al. 1976). Lead forms highly stable complexes with phosphate and can replace calcium in the calcium-phosphate salt, hydroxyapatite, which comprises the primary crystalline matrix of bone (Lloyd et al. 1975). As a result, lead deposits in bone during the normal mineralization process that occurs during bone growth and remodeling and is released to the blood during the process of bone resorption (O'Flaherty 1991b, 1993). The distribution of lead in bone reflects these mechanisms; lead tends to be more highly concentrated at bone surfaces where growth and remodeling are most active (Auferheide and Wittmets 1992). The association of lead uptake and release from bone with the normal physiological processes of bone formation and resorption renders lead biokinetics sensitive to these processes. Physiological states (e.g., pregnancy, menopause, advanced age) or disease states (e.g., osteoporosis, prolonged immobilization) that are associated with increased bone resorption will tend to promote the release of lead from bone which,

in turn, may contribute to an increase in the concentration of lead in blood (Bonithon-Kopp et al. 1986c; Markowitz and Weinburger 1990; Silbergeld et al. 1988; Thompson et al. 1985).

Metabolism. Metabolism of inorganic lead consists primarily of reversible ligand reactions, including the formation of complexes with amino acids and non-protein thiols, and binding to various proteins (DeSilva 1981; Everson and Patterson 1980; Goering and Fowler 1987; Goering et al. 1986; Ong and Lee 1980a, 1980b, 1980c; Raghavan and Gonick 1977).

Tetraethyl and tetramethyl lead under oxidative dealkylation metabolize to the highly neurotoxic metabolites, triethyl and trimethyl lead, respectively. In the liver, the reaction is catalyzed by a cytochrome P-450 dependent monoxygenase system (Kimmel et al. 1977). Complete oxidation of alkyl lead to inorganic lead also occurs (Bolanowska 1968).

Excretion. The precise mechanisms of excretion of lead into the urine have not been determined. Such studies have been hampered by the difficulties associated with measuring ultrafilterable lead in plasma and, thereby, in measuring the rate of glomerular filtration of lead. Measurement of the renal clearance of ultrafilterable lead in plasma indicates that, in dogs and humans, lead undergoes glomerular filtration and net tubular reabsorption (Araki et al. 1986, 1990; Victery et al. 1979). Net tubular secretion of lead has been demonstrated in dogs made alkalotic by infusions of bicarbonate (Victery et al. 1979). Renal clearance of blood lead increases with increasing blood lead concentrations above 25 µg/dL (Chamberlain 1983). The mechanism for this has not been elucidated and could involve a shift in the distribution of lead in blood towards a fraction having a higher glomerular filtration rate (e.g., lower molecular weight complex), a capacity-limited mechanism in the tubular reabsorption of lead, or the effects of lead-induced nephrotoxicity on lead reabsorption.

Lead undergoes biliary excretion in the dog, rat, and rabbit; biliary excretion is presumed to contribute to fecal excretion of lead in humans (EPA 1994b; Klaassen and Shoeman 1974; O'Flaherty 1993). The mechanism of biliary excretion has not been elucidated.

Tetraethyl lead is excreted in the urine as diethyl lead, ethyl lead and inorganic lead in both humans (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994) and rabbits (Aria and Yamamura 1990; Kozarzewska and Chmielnicka 1987).

Effect of Dose and Duration of Exposure on Toxicity. The principal adverse health effects of lead can be related to concentrations of lead in blood (see Section 2.2.1). Correlation and regression analyses of data on blood lead concentrations and various health effects define a spectrum of effects that become apparent in human populations having a range of PbB levels approaching 10–15 µg/dL. These include effects on heme metabolism, erythrocyte pyrimidine nucleotide metabolism, serum vitamin D levels, mental and physical development, and blood pressure. As PbB concentrations increase above the range of 10–15 µg/dL, more pronounced effects on all of the above end points occur. At levels exceeding 30 µg/dL, anemia, nephrotoxicity and more overt neurological impairment can occur. PbB concentration can be related to these diverse effects, presumably because it is related to plasma lead, which exchanges with lead in critical target tissues such as the brain, bone, erythroblasts, and kidney.

In using blood lead concentration as an internal dose metric to predict target tissue lead levels, it must be kept in mind that there are several potential sources of non-linearity in the relationship between PbB and target tissue lead: (1) absorption of lead from the gastrointestinal tract may be capacity limited (Aungst and Fung 1981; Barton 1984; Flanagan et al. 1979; Mykkänen and Wasserman 1981) and may contribute to a non-linear relationship between lead intake and PbB concentration that has been observed in human populations (Pocock et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1984); (2) red blood cells have a limited capacity to accumulate lead and, as a result, the relationship between plasma and PbB concentrations is non-linear (DeSilva 1981; Manton and Cook 1984), which may explain the observations that, in human populations, bone lead levels correlate more strongly with serum lead than with whole PbB levels (Cake et al. 1996), and that, in immature swine administered oral doses of lead in soil, the relationship between lead intake and PbB concentration is non-linear, while the relationship between lead intake and lead in bone, kidney, and liver is linear (Casteel et al. 1997); (3) elimination of lead from blood is much more rapid than from bone (Leggett 1993; Marcus 1985b; O'Flaherty 1993; Rabinowitz et al. 1976), and therefore, PbB concentrations will change more rapidly than bone lead levels when exposure changes, which would be expected to give rise to transient changes in the blood/bone lead ratio; and (4) renal clearance of blood lead increases with increasing PbB concentrations above 25 µg/dL (Chamberlain 1983), which would give rise to non-linearities in the relationship between lead intake and whole PbB concentration.

Route Dependent Toxicity. The toxicity of lead does not appear to be dependent on the route of exposure, but the time course may be affected.

2.4.2 Mechanisms of Toxicity

Target Organ Toxicity. This section focuses on mechanisms for sensitive health effects of major concern for lead—cardiovascular effects, hematological effects, and neurological effects, particularly in children. Bone is a major sink for lead, and there is some limited information regarding the effects of lead on bone and potential mechanisms of action. Renal effects occur at relatively high blood lead levels and evidence of renal carcinogenicity has been demonstrated only in animals; mechanisms for these effects will be discussed briefly.

Because lead affects virtually every organ or system in the body, it is not surprising that the proposed mechanisms of lead toxicity involve fundamental biochemical processes. These proposed mechanisms include lead's ability to inhibit or mimic the action of calcium and to interact with proteins (Bressler and Goldstein 1991; Fowler 1992; Goering 1993; Goldstein 1993; Goyer 1993). In its interaction with proteins, lead binds primarily with sulfhydryl, amine, phosphate and carboxyl groups, with sulfhydryl having the highest affinity. The stability of lead complexes increases with increasing numbers of binding sites, and with optimal spacing, such as with vicinal sulfhydryls. Lead's ability to mimic calcium in the activation of calmodulin (discussed below under cardiovascular and neurological effects) involves binding to carboxyl groups; lead's ability to mimic calcium in the activation of protein kinase C (discussed under cardiovascular, neurological and carcinogenic effects) probably involves binding to sulfhydryl groups. Hence, the calcium agonist and protein-binding mechanisms sometimes overlap (Goering 1993).

Cardiovascular Effects. Several mechanisms for lead's purported effects on blood pressure have been proposed, based on experimental findings. These include effects on several hormonal and neural regulatory systems, changes in vascular smooth muscle reactivity, cardiac muscle contractility, changes in cell membrane cation transport systems, and possible effects on vascular endothelial cells (Victery 1988). Limited evidence from studies of men exposed occupationally to lead suggested that the effect of lead on blood pressure may be mediated in part through the renin-angiotensin system, as evidenced by lead-related increases in plasma renin and angiotensin I levels (Campbell et al. 1985) and through the kallikrein-kinin system, as indicated by a correlation between renin and kallikrein (Boscolo et al. 1981). Evidence from patients with essential hypertension and renal impairment suggested that excessive lead absorption may be involved in the development of both conditions (Batuman et al. 1983). A review of the data on lead's hypertensive action in animals was presented in Section 2.2, and included effects on the renin-angiotensin system at low levels of lead exposure. These effects, however, have not been established as the cause of

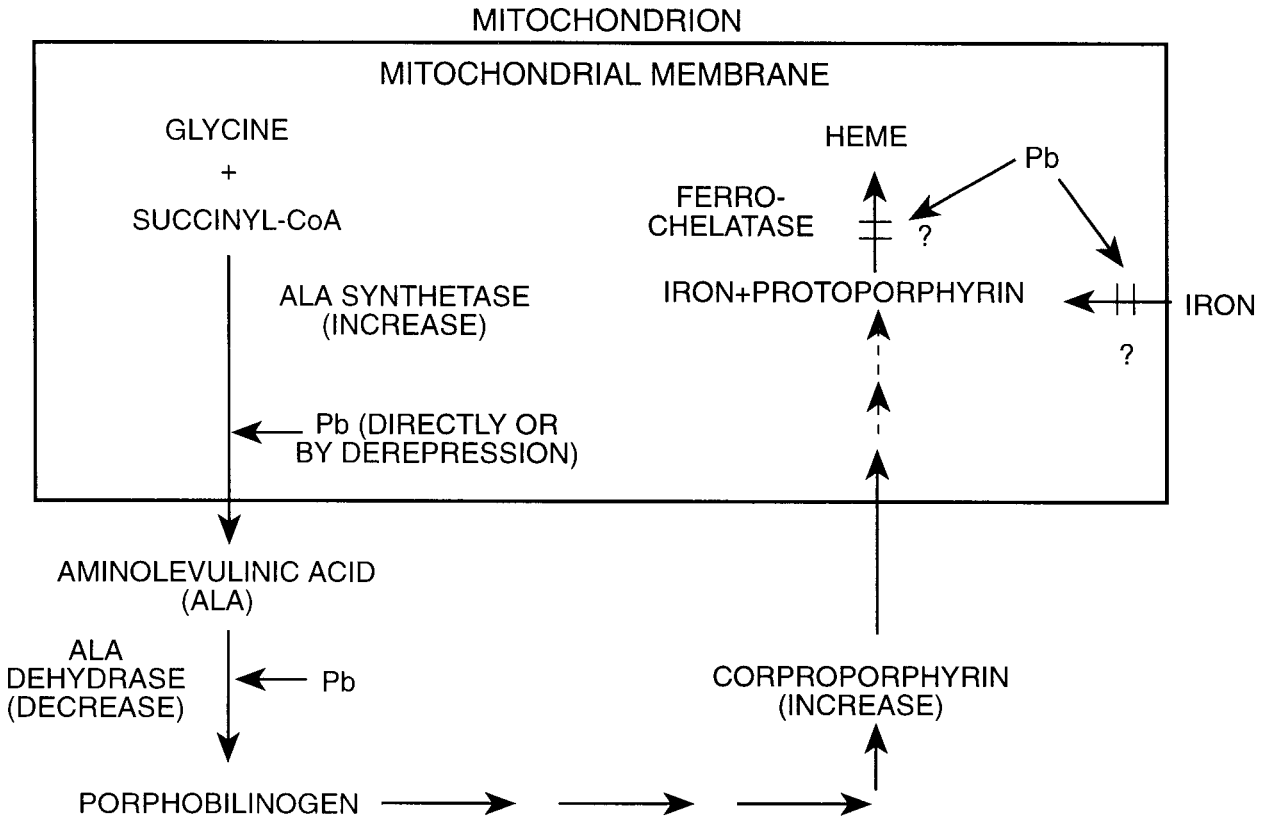
hypertension. The changes observed in both humans and animals are variable, and dependent on the exposure intensity and duration and on other stimuli of the renin-angiotensin system. Hypertension is more likely to be due to changes in vascular reactivity and level of sympathetic tone, both of which may be dependent on lead-related changes in intracellular calcium ion concentration. Although the effects of lead on intracellular calcium may also affect renin release from the juxtaglomerular cells of the kidney, there are a number of potential mechanisms by which lead could stimulate or inhibit calcium ion fluxes in these cells, such that the net direction of effect is uncertain (EPA 1986a, 1990g).

Lead causes increased intracellular concentrations of calcium in brain capillaries, neurons, osteoclasts, hepatocytes, and arteries. Increased intracellular calcium is the trigger for smooth muscle contraction; therefore, increased intracellular calcium stores may result in increased vascular smooth muscle tone. Furthermore, lead has been found to interfere with cellular calcium metabolism; it activates calmodulin in its role of activating c-AMP phosphodiesterase, the enzyme that converts cAMP into AMP. cAMP is involved in stimulating the calcium pump that removes calcium from the cytosol into the endoplasmic reticulum. This would be expected to reduce reactivity and tone, and a lead effect on increasing the conversion of cAMP into AMP would be expected to increase reactivity and tone (Schwartz 1988, 1991, 1992). Alternatively, it has been suggested that lead-induced hypertension may be partially mediated by activation of the protein kinase C branch of the calcium messenger system, which would, in turn, result in increased vascular reactivity (Chai and Webb 1988; Schwartz 1991, 1992). Both calmodulin and protein kinase C have a higher affinity for lead than for calcium (Bressler and Goldstein 1991; Goering 1993).

Results of a more recent series of investigations suggest that lead may cause hypertension in rats by increasing reactive oxygen species, which act as vasoconstrictors, and decreasing nitric oxide, a vasodilator released by the endothelium. The reactive oxygen species may be the hydroxyl radical, and did not appear to be the superoxide anion (Ding et al. 1998).

Hematological Effects. The effects of lead on the hematopoietic system have been well documented. These effects, which are seen in both humans and animals, include increased urinary porphyrins, coproporphyrins, ALA, EP, FEP, ZPP, and anemia. The process of heme biosynthesis is outlined in Figure 2-10. Lead interferes with heme biosynthesis by altering the activity of three enzymes: ALAS, ALAD, and ferrochelatase. Lead indirectly stimulates the mitochondrial enzyme ALAS, which catalyzes the condensation of glycine and succinyl-coenzyme A to form ALA. The activity of ALAS is the rate-limiting step in heme biosynthesis; increase of ALAS activity occurs through feedback derepression. Lead

Figure 2-10. Effects of Lead on Heme Biosynthesis



Source: Derived from EPA 1986a

inhibits the zinc-containing cytosolic enzyme ALAD, which catalyzes the condensation of two units of ALA to form porphobilinogen. This inhibition is noncompetitive, and occurs through the binding of lead to vicinal sulfhydryls at the active site of ALAD. Lead bridges the vicinal sulfhydryls, whereas Zn, which is normally found at the active site, binds to only one of these sulfhydryls. Inhibition of ALAD and feedback derepression of ALAS result in accumulation of ALA. Lead decreases in a non-competitively fashion the activity of the zinc-containing mitochondrial enzyme ferrochelatase, which catalyzes the insertion of iron (II) into the protoporphyrin ring to form heme. Inhibition of ferrochelatase (a mitochondrial enzyme) may occur through binding of lead to the vicinal sulfhydryl groups of the active site. Another possible mechanism is indirect, through impaired transport of iron in the mitochondrion, due to disruption of mitochondrial structure. Some other enzymes of the heme synthesis pathway contain single sulfhydryl groups at their active sites and are not as sensitive to inhibition by lead as are ALAD and ferrochelatase (EPA 1986a; Goering 1993).

Lead inhibition of ferrochelatase results in an accumulation of protoporphyrin IX, which is present in the circulating erythrocytes as ZPP, because of the placement of zinc, rather than iron, in the porphyrin moiety. ZPP is bound in the heme pockets of hemoglobin and remains there throughout the life of the erythrocyte. Assays used in studies of protoporphyrin accumulation measure ZPP or FEP, because ZPP is converted to FEP during extraction. Because accumulation of ZPP occurs only in erythrocytes formed during the presence of lead in erythropoietic tissue, this effect is detectable in circulating erythrocytes only after a lag time reflecting maturation of erythrocytes and does not reach steady state until the entire population of erythrocytes has turned over, in approximately 120 days (EPA 1986a).

A marked interference with heme synthesis results in a reduction of the hemoglobin concentration in blood. Decreased hemoglobin production, coupled with an increase in erythrocyte destruction, results in a hypochromic, normocytic anemia with associated reticulocytosis. Decreased hemoglobin and anemia have been observed in lead workers and in children with prolonged exposure at higher PbB levels than those noted as threshold levels for inhibition or stimulation of enzyme activities involved in heme synthesis (EPA 1986a).

The increase in erythrocyte destruction may be due in part to inhibition by lead of pyrimidine-5'-nucleo-tidase, which results in an accumulation of pyrimidine nucleotides (cytidine and uridine phosphates) in the erythrocyte or reticulocyte. This enzyme inhibition and nucleotide accumulation affect erythrocyte membrane stability and survival by alteration of cellular energetic (Angle et al. 1982; EPA 1986a).

Formation of the heme-containing cytochromes is inhibited in animals treated intraperitoneally or orally with lead compounds. An inverse dose-effect relationship between lead exposure and P-450 content of hepatic microsomes and also activity of microsomal mixed-function oxygenases has been observed (Goldberg et al. 1978). Increasing duration of exposure to lead was associated with decreasing microsomal P-450 content and decreasing microsomal heme content (Meredith and Moore 1979). In addition, delays in the synthesis of the respiratory chain hemoprotein cytochrome C have been noted during administration of lead to neonatal rats (Bull et al. 1979).

The impairment of heme synthesis by lead has a far-ranging impact not limited to the hematopoietic system. EPA (1986a) provided an overview of the known and potential consequences of the reduction of heme synthesis as shown in Figure 2-11. Well documented effects are indicated by solid arrows, and effects considered to be plausible further consequences of the impairment of heme synthesis are indicated by dashed arrows. Additional discussion is provided in the following sections on renal and neurological effects. More detailed information on the exposure levels or blood lead levels at which these impacts may be experienced was provided in Section 2.2 and the relevance to human health is discussed in Section 2.5.

Musculoskeletal Effects: Bone. Although a number of mechanisms have been proposed for lead toxicity to bone, little research has been performed in this area. Lead may affect bone indirectly through alteration of the circulating levels of hormones, particularly 1,25-dihydroxyvitamin D, that modulate calcium homeostasis and bone cell function (Pounds et al. 1991; Puzas et al. 1992). Lead decreases circulating levels of 1,25-dihydroxyvitamin D in children with chronic high lead exposure and poor nutrition (Section 2.2.1.2, Other Systemic Effects). In addition, lead may alter the responses of bone cells to these hormones, and disrupt many aspects of calcium homeostasis and signaling at the cellular level (Pounds et al. 1991), similar to the mechanisms discussed under neurological effects. Lead disrupted the modulation of intracellular calcium by 1,25-dihydroxyvitamin D in a biphasic manner in cultured osteoblast-like cells (Long and Rosen 1994). Another effect seen in this culture system was the inhibition by lead of 1,25-dihydroxyvitamin D3-stimulated synthesis of osteocalcin, a protein constituent of bone that may play a major role in normal mineralization of bone. Reduced plasma levels of osteocalcin have been reported in "moderately lead-poisoned" children (Pounds et al. 1991). Lead also inhibited secretion of osteonectin/SPARC, a component of bone matrix, and decreased the levels of osteonectin/SPARC mRNA from osteoblast-like cells in culture (Sauk et al. 1992). Lead inclusion bodies are commonly found in the cytoplasm and nuclei of osteoclasts, but not other bone cells, following *in vivo* lead exposure (Pounds et al. 1991). As discussed under the following section on renal effects and in Section 2.4.1, these inclusion

bodies may contain high-affinity binding proteins, and may sequester lead, but also may indicate a potential for modulation of gene expression. Another observation from *in vivo* studies was increased bone resorption activity, evident from increased osteoid coverage of trabecular surfaces and increased osteoclasts in the trabecular lacunae (Gruber et al. 1997).

Renal Effects. High-affinity cytosolic lead-binding proteins have been identified in the kidneys (and brain). These high-affinity zinc- and lead-binding proteins are thought to moderate the inhibition of ALAD by lead through chelating lead and donating zinc, and to translocate lead to the nucleus, where it may influence gene expression. In the rat kidney, the high-affinity lead-binding protein is an acidic carboxyl-rich protein, which has been found in intranuclear inclusion bodies and associated with nuclear chromatin. It has been further identified as the kidney-specific cleavage product of $\alpha_{2\mu}$-globulin, a protein specific to male rats. Similar lead-binding proteins have been demonstrated in human kidney, liver, and brain cytosol. In addition, lead can bind to metallothionein, but does not appear to be a significant inducer of the protein in comparison with the inducers cadmium and zinc. *In vivo*, only a small fraction of the lead in the kidney was bound to metallothionein, and lead did not displace cadmium or zinc. Metallothionein also may sequester lead (Fowler 1992; Goering 1993; Goyer 1993).

In some human studies where clinical chemistry measurements but no renal biopsies were performed, the only parameter of renal function shown to be affected was an increase in the levels of NAG in the urine. NAG is a lysosomal enzyme present in renal tubular cells that has been shown to be a sensitive indicator of early subclinical renal tubular disease. The mechanism by which lead affects the release of NAG from renal tubular cells is not known, but it is suggested that lead could attach to kidney cell membranes and alter membrane permeability (Chia et al. 1994).

Lead may affect renin release from the kidney by affecting calcium ion fluxes in the juxtaglomerular cells, as discussed previously under Cardiovascular Effects.

Lead has been shown to decrease circulating levels of the active form of vitamin D (1,25-dihydroxy-vitamin D) in children. The conversion of vitamin D to this active hormonal form takes place via hydroxy-lation to 25-hydroxyvitamin D in the liver, followed by 1-hydroxylation in the mitochondria of the renal tubule by a complex cytochrome P-450 (heme-containing) system (Mahaffey et al. 1982; Rosen and Chesney 1983). Comparisons of the serum 1,25-dihydroxyvitamin D levels in children with blood lead levels of $33 µg/dL with those in children with severe renal insufficiency (Rosen et al. 1980) and in

children with an inborn error of vitamin D metabolism in which the 1-hydroxylase system or component thereof is virtually absent (Rosen and Chesney 1983; Rosen et al. 1980) suggested that lead decreases the production of 1,25-dihydroxyvitamin D by renal 1-hydroxylase. This decrease may be mediated through the inhibition of heme synthesis.

Neurological Effects. Lead may substitute for calcium as a second messenger in neurons. The data from studies of nervous tissue *in vitro* following *in vivo* or *in vitro* lead exposure indicate that lead blocks the voltage-regulated calcium channels, inhibiting the influx of calcium and release of neurotransmitter that follows the depolarization of presynaptic nerve terminals, thus inhibiting synaptic transmission. Lead enters the cell by the same channels, where it acts as a calcium agonist to increase the spontaneous release of neurotransmitter, resulting in an increase in the frequency of miniature endplate potentials. These biphasic effects on neurotransmitter release were seen in the cholinergic and GABAergic systems. With regard to dopaminergic systems, lead inhibited depolarization-evoked neurotransmitter release and also inhibited dopamine uptake, and either did not affect spontaneous release (Bressler and Goldstein 1991; Goldstein 1993; Pages and Deloncle 1997) or decreased it (Kala and Jadhav 1995b). Lead has also been shown to decrease the activity of tyrosine hydroxylase in the brain, the rate-limiting enzyme in catecholamine biosynthesis (Jadhav and Ramesh 1997). In glutamatergic systems, lead inhibited depolarization-evoked glutamate release (Gilbert 1997). In addition, in the astroglia, lead inhibited high affinity glutamate uptake and glutamine synthetase activity, which catalyzes the formation of glutamine from glutamate. The glutamine synthesized by the astroglia is thought to be returned to the neurons for use in regenerating glutamate, which is a major excitatory neurotransmitter in the brain (Cory-Slechta 1995a; Tiffany-Castiglioni 1993; Tiffany-Castiglioni et al. 1996). The development of neural networks early in life involves pruning of excess synapses, and is influenced by the pattern of neural activity occurring in response to experiences of the infant. This process may be modulated by lead-induced increases in basal neurotransmitter release or persistence in the synaptic cleft and decreases in depolarization-induced neurotransmitter release. Whether or not there is an effect on the development of neural networks, adaptation to these changes in neurotransmitter release may alter the efficiency of synaptic transmission and, thereby, contribute to some of the neurobehavioral deficits in children at low-level lead exposure (Bressler and Goldstein 1991; Goldstein 1993; Pages and Deloncle 1997). Additional discussion of this possibility will be provided later in this section.

Additional studies in rats *in vivo* and in rat tissues or cells *in vitro* have focused on potential relationships between the effects of lead on neurotransmitter systems and neurobehavioral function. Lead exposure

decreased dopamine binding sites, suggesting excess dopamine availability. The decreased dopamine binding was localized in the nucleus accumbens (mesolimbic dopamine system) but not the dorsal striatum (nigrostriatal dopamine system). The nucleus accumbens has been shown to be critical to the mediation of fixed-interval schedule controlled behavior, which is altered by lead. Additional evidence of the involvement of dopaminergic system in fixed interval performance changes is that of a variety of agonists tested, only the dopamine agonists caused differential effects on fixed-interval performance of control and lead-exposed rats (Cory-Slechta 1997b; Cory-Slechta et al. 1996, 1997a; Pokora et al. 1996). A study in which dopamine was microinjected into the nucleus accumbens provided further evidence of the involvement of this neurotransmitter on fixed-interval performance (Cory-Slechta et al. 1998). The results also indicated possible similarites and differences in the behavioral mechanisms by which dopamine and lead induce alterations in fixed-interval performance, suggesting that additional mechanisms modulate the specific behavioral processes underlying fixed-interval increases produced by lead exposure (Cory-Slechta et al. 1998). Lead inhibition of the N-methyl-D-aspartate (NMDA) receptor complex activity, evidenced, for example, by decreases in MK-801 binding throughout the brain, appeared to play a role in learning deficits (Cory-Slechta 1995a; Cory-Slechta 1997; Cory-Slechta et al. 1997b, 1997c). MK-801 binding is a use-dependent binding that requires glutamate and glycine activation of the NMDA receptor complex; decreases in MK-801 binding suggest a hypoglutamatergic function. Some studies have suggested that lead inhibits NMDA receptor binding through the zinc allosteric site, which modulates receptor binding (Cory-Slechta 1995a; Guilarte 1997; Guilarte et al. 1995). The inhibitory effects of lead on the NMDA receptor were age-dependent, with greater effects occurring during early neuronal development (Guilarte 1997). An alternative explanation to the age-related differential susceptibility is that lead achieved a much greater concentration in the immature rat brain than in the adult brain. The relationship between cholinergic system dysfunction and lead-induced neurobehavioral impairments is not known, but evidence that lead decreases the depolarization-evoked release and increases the spontaneous release of acetylcholine (summarized previously), decreases choline acetyltransferase activity (which catalyzes acetylcholine synthesis), and increases the sensitivity of muscarinic cholinergic receptors, is suggestive (Cory-Slechta 1995a).

Lead may act as a calcium substitute in the activation of protein kinase C, which is important in cell growth and differentiation, including the differentiation of brain endothelial cells. The affinity of lead for protein kinase C is higher, however, than that of calcium. The blood-brain barrier consists of the endothelial cells of the brain microvessels, which are sealed together by continuous tight junctions, and the astroglia (astrocytes), which initiate and maintain the expression of this phenotype, extending foot processes that

almost completely sheathe the microvascular wall. In immature brain microvessels, most of the protein kinase C is in the cytosol, whereas in mature brain microvessels, this enzyme is membrane-bound. Activation of protein kinase C in other systems is known to result in a change in distribution from cytosol to membrane, and has been observed with exposure of immature brain microvessels to lead. An inhibition of microvascular formation has been observed with lead concentrations that are effective in activating protein kinase C. Thus, it appears that premature activation of protein kinase C by lead may impair brain microvascular formation and function, and at high levels of lead exposure, may account for gross defects in the blood-brain barrier that contribute to acute lead encephalopathy. The blood-brain barrier normally excludes plasma proteins and many organic molecules, and limits the passage of ions. With disruption of this barrier, molecules such as albumin freely enter the brain and ions and water follow. Because the brain lacks a well-developed lymphatic system, clearance of plasma constituents is slow, edema occurs, and intracranial pressure rises. At lower levels of exposure, subtle dysfunction of the blood-brain barrier may contribute to neurobehavioral deficits in children (Bressler and Goldstein 1991; Goldstein 1993). The particular vulnerability of the fetus and infant to the neurotoxicity of lead may be due in part to immaturity of the blood-brain barrier and to the lack of the high-affinity lead-binding protein in astroglia, which is discussed later in this section. Results of measurements of transendothelial electrical resistance across the blood-brain barrier from mice of various ages showed that lead potentiates cytokines-induced increase in ion permeability of the blood-brain barrier (Dyatlov et al. 1998). The effect was greater in younger animals which is consistent with age dependence of lead neurotoxicity.

In addition, the activation of protein kinase C is thought to contribute to long-term potentiation, which may function in memory storage. Lead has been reported to inhibit (Gilbert 1997) or to stimulate the activation of protein kinase C. Other processes involved in long-term potentiation that also are inhibited by lead are depolarization-induced neurotransmitter release, NMDA receptor-mediated activity, and cholinergic activity. Lead's effects on these processes and on protein kinase C would be expected to disrupt long-term potentiation, resulting in learning deficits (Gilbert 1997). Data from a recent study in rats showed that lead exposure during development influences protein kinase C distribution (membrane vs. cytoplasm) in fractions of the hippocampus (Chen et al. 1998), and the authors suggested that these changes may be involved in the subclinical neurotoxicity of chronic lead exposure in young children.

Lead also has been shown to substitute for calcium in the activation of calmodulin, but this requires higher levels of lead than does the activation of protein kinase C. Nevertheless, the affinity of lead for calmodulin is higher than that of calcium. Once activated, calmodulin regulates the activity of certain enzymes and

transporters. For example, it activates c-AMP phosphodiesterase to hydrolyze and terminate the action of cAMP, another second messenger (Bressler and Goldstein 1991; Goldstein 1993; Goering 1993).

Another mechanism by which lead may affect the nervous system is through its effect on neuronal cell adhesion molecules (NCAMs), membrane-bound cell-recognition molecules that regulates cell-cell interactions, including synapse formation. Chronic, low-level lead exposure impairs the desialylation of NCAMs during postnatal periods that coincide with synapse formation. This interference with sialylation pattern may perturb synapse selection, thus contributing to learning deficits. The exact mechanism of interference with desialylation has not been determined, but stimulation by lead of the enzyme that sialylates NCAMs has been reported (Regan 1993; Tiffany-Castiglioni 1993). Lead was found to increase the particulate form and decrease the soluble form of the amyloid β precursor protein (AβPP) in hippocampal cells *in vitro* (Davey and Breen 1998). The particulate form of AβPP plays a role as a mediator of cell-cell adhesion and cell interaction with components of the extracellular matrix and any changes in the partitioning of AβPP would be expected to produce major effects within the central nervous system, particularly during the period of neural development.

It has been also suggested that lead may perturb glucocorticoid-mediated events in the central nervous system hormonal target tissues (Tonner et al. 1997). Glucocorticoid receptors are widespread in neurons and glial cells and are known to modulate glial cell functions such as synthesis of myelin phosphatide precursors by glycerol phosphate dehydrogenase, amidation of the neurotransmitter glutamate, and detoxification of ammonia by glutamine synthetase. Tonner et al. (1997) found that addition of lead acetate to C6 glioma cells in *vitro* resulted in a significant reduction of the binding affinity of glucocorticoids for cytosolic receptors. Lead altered glucocorticoid signal transduction in other non-neural cell types *in vitro* as well (Heiman and Tonner 1995; Tonner and Heiman 1997).

As discussed previously under renal effects, high-affinity cytosolic lead-binding proteins have been identified in the brain (and kidneys) of rats. These high-affinity zinc- and lead-binding proteins are thought to moderate lead inhibition of ALAD through lead chelation and zinc donation, and to translocate lead to the nucleus, where it may influence gene expression. Similar lead-binding proteins have been demonstrated in human brain (and kidney and liver) cytosol. The rat brain lead-binding protein appears to be richly acidic, is not the same as that found in the kidney, and is developmentally regulated. Only traces of this protein were detectible in neonatal rats, increasing to adult levels within 2 weeks, with a concomitant increase in resistance to lead-induced encephalopathy. The development of this resistance is thought to be related to

the formation of lead-protein inclusion bodies in the astroglia, which sequester lead. Studies in astroglial cultures provide supporting evidence that astroglia develop the ability to sequester lead as they mature. In addition, lead can bind to metallothionein, which also is present in the astroglia (Fowler 1992; Goering 1993; Goyer 1990, 1993; Tiffany-Castiglioni 1993; Tiffany-Castiglioni et al. 1996).

The nervous system may be affected indirectly through lead's inhibition of heme synthesis (discussed previously in this section). For example, inhibition of heme synthesis may result in decreases in microsomal cytochrome P-450 (which metabolizes endogenous and exogenous chemicals), and mitochondrial cytochromes (which conduct cellular respiration) in the nervous tissue. In addition, tryptophan pyrrolase, a hepatic heme-requiring enzyme system, is inhibited via a reduction in the free hepatic heme pool. This inhibition results in elevated plasma tryptophan and elevated brain levels of tryptophan, serotonin (5-hydroxytryptamine), and 5-hydroxyindoleactic acid, which may increase aberrant neurotransmission in serotonergic pathways. Infusion of heme into lead-treated rats reduced the elevated levels of these compounds to normal levels; and intravenous administration of hematin, a heme-like molecule, to a lead-exposed worker diminished subjective symptoms of neurotoxicity and urinary ALA, providing some evidence of the potential clinical significance of decreased heme synthesis (EPA 1986a; Goering 1993).

ALA itself may be neurotoxic by interfering with neurotransmission by the inhibitory neurotransmitter GABA, which is similar in structure to ALA. Although ALA at very high levels may competitively inhibit GABA binding to the postsynaptic receptor *in vitro*, negative-feedback inhibition of GABA release via interaction of ALA with presynaptic GABA receptors is the more likely mechanism of action *in vivo* (EPA 1986a). In addition, it has been suggested that free radicals generated during the autoxidation of ALA and the promotion of oxyhemoglobin oxidation by ALA may contribute to the observed toxicity of lead. Lead itself may accelerate lipid peroxidation induced by ALA-generated oxygen radicals or by Fe^{2+} (Hermes-Lima et al. 1991; Monteiro et al. 1991).

Carcinogenesis. Suggested mechanisms for the renal carcinogenesis of lead in rodents include: (1) an alteration of genetic function by lead in association with the high-affinity lead-binding protein following translocation to the nucleus (see previous discussion on mechanism of renal effects); (2) tumor promotion by activation of protein kinase C, which, in addition to the functions noted above, phosphorylates growth factor receptors and oncogenes; and (3) stimulation of cellular proliferation or cystic hyperplasia (which may be secondary to other mechanisms) (Fowler 1992; Goyer 1992, 1993). Although the high-affinity

lead-binding protein is a cleavage product of $\alpha_{2\mu}$-globulin, it does not appear to act through the mechanism of male rat hyaline droplet nephropathy and associated tumorigenicity.

2.4.3 Animal-to-Human Extrapolations

Studies in rodents, dogs, and non-human primates have demonstrated all of the major types of health effects of lead that have been observed in humans, including cardiovascular, hematological, neurodevelopmental, and renal effects (EPA 1986a). These studies also provide support for the concept of blood lead concentration as a metric of internal dose for use in dose-response assessments in humans.

The effects of low-level lead exposure on cognitive development and function in humans are difficult to discern against the background of genetic, environmental, and socioeconomic factors that would be expected to affect these end points in children. Experimental studies in animals have been helpful for establishing the plausibility of the hypothesis that low-level exposures to lead can affect learning in mammals and for providing insights into possible mechanisms for these effects. Studies in rats and non-human primates have demonstrated deficits in learning associated with blood lead concentrations between 10 and 15 µg/dL, a range which is comparable to those reported in epidemiological studies which found learning deficits in children (Cory-Slechta 1995a).

The lead-induced nephropathy observed in humans and rodents shows a comparable early pathology (Goyer 1993). However, in rodents, proximal tubular cell injury induced by lead can progress to adenocarcinomas of the kidney (see Section 2.2.3.8). The observation of lead-induced kidney tumors in rats may not be relevant to humans. Conclusive evidence for lead-induced renal cancers (or any other type of cancer) in humans is lacking, even in populations in which chronic lead nephropathy is evident.

2.5 RELEVANCE TO PUBLIC HEALTH

People living near hazardous waste sites may be exposed to lead via ingestion of contaminated water or soils or by inhalation of lead particles in the air. For people not living in the vicinity of hazardous waste sites, the major route of exposure to lead is ingestion, particularly of lead-contaminated water, food, soil, lead-based paint chips, or dusts (the latter two are particularly relevant to children in lower-income urbanized populations). For occupationally exposed individuals, the predominant route of exposure is the inhalation of lead particles with oral ingestion also important in many cases.

Lead has been shown to affect virtually every organ and/or system in the body in both humans and animals (see Figure 2-11). The most sensitive target organs of lead appear to be the nervous system (particularly in children), the hematopoietic system, and the cardiovascular system. There is evidence in both humans and animals to suggest that the kidneys and the immune and reproductive systems are also adversely affected by lead. Lead has also been shown to be carcinogenic in animals. The adverse health effects noted in humans are generally supported by observations in laboratory animals. No MRLs have been developed for lead.

The lack of a clear threshold for health effects and the need to consider multi-media routes of exposure makes evaluating the risks from exposure to lead in the environment difficult. In addition, factors such as absorption potential of the lead compound of interest, and age and nutritional status of the population complicate the development of generic guidance. Despite these complexities, guidance is needed for the assessment of risk to humans from exposure to lead at NPL sites. Such guidance must be adaptable to site-specific information regarding exposure sources and demographic data; it must also provide default values where data may not be available in order to generate quantitative estimates of risk (DeRosa et al. 1991).

Numerous studies have attempted to correlate environmental lead levels with blood lead levels (Table 2-9). Slope factors have been calculated which attempt to predict increases in PbB (µg/dL) per unit lead concentration in environmental media (EPA 1986a, 1989g). The relationship between media concentration and PbB is curvilinear, such that the slopes decrease with increasing lead concentrations.

Air slope factors calculated from experimental and cross-sectional studies range from a 1- to at 2.7-µg/dL increase in PbB per µg/m^3 air lead concentration. A slope factor of 1.92±0.60 for children was calculated by Angle et al. (1984) from a study conducted between 1971 and 1977 in three areas of Omaha, Nebraska (Angle and McIntyre 1979). This study provides some of the most useful and relevant information because covariates (e.g., age, dust exposure, sex) were controlled. EPA analysis of two other reliable studies provide comparable slope factors for children of 2.46±0.58 (Roels et al. 1980) and 1.53±0.064 (Yankel et al. 1977). A study of 44 workers in five major operations in a U.S. high volume, lead acid battery plant calculated a slope factor of 1.14 (Hodgkins et al. 1992). This study, which also controlled for job category, seniority, age, ethnicity, sex, and smoking habit, covered a 30-month period in which workers received frequent measurements of lead in air and in blood. In both univariate and multivariate linear regressions, longitudinal analyses averaging air lead concentrations over the 30-month study period predicted PbB concentrations more accurately than cross-sectional analyses using only 6-month air lead averages.

Table 2-9. Summary of Blood Slope Factors from Various Environmental Media

Population	Slope	Comments	References
Air Slope Factors:	µg/dL per µg Pb/m^3		
Adults; N = 43	1.75±0.35	Experimental study; EPA analysis	Griffin et al. 1975
Adults; N=5	1.59–3.56	Experimental study; EPA analysis calculated	Rabinowitz et al. 1974, 1976, 1977
Adults; N=10	2.7	Experimental study; EPA analysis	Chamberlain et al. 1978
Children; 1–18 years of age; N=831; 1,074 blood samples	1.92±0.60	Omaha cross-sectional study; smelter	Angle et al. 1984
Children; N=148	2.46±0.58	Belgium cross-sectional study; smelter; EPA analysis	Roels et al. 1980
Children; N=880	1.53±0.064	Kellogg/Silver Valley cross-sectional study; EPA analysis; smelter	Yankel et al. 1977
Adult males; 5 groups, 30/group	2.57±0.04	Cross-sectional study; at air concentration of 1 µg/m^3	Azar et al. 1975
Adult males; 5 groups, 30/group	1.12	Reanalysis of Azar 1975 by Snee 1982; at air concentration of 1 µg/m^3	Azar et al. 1975
Adult males; 5 groups, 30/group	1–2.39	Analysis of Azar 1975 by EPA; at 1 µg/m^3	Azar et al. 1975
Adults; N=44	1.14	Occupational longitudinal study over 30 months; air concentration <30 µg/m^3	Hodgkins et al. 1992
Water Slope Factors:	µg/dL per µg Pb/L		
Infants N=131	0.25 at <15 µg Pb/L; 0.04 at >15 µg Pb/L	Scottish study of infants; EPA analysis	Lacey et al. 1985
School children N=495	0.16 at <15 µg Pb/L; 0.03 at >15 µg Pb/L	Scottish study; EPA analysis	Laxen et al. 1987

Table 2-9. Summary of Blood Slope Factors from Various Environmental Media (continued)

Population	Slope	Comments	References
Adult males N=7,735	0.06	24 British towns sampled; water lead levels <100 µg/L	Pocock et al. 1983
Adult Females N=114	0.03	Duplicate diet study; Ayr, Scotland; EPA analysis	Sherlock et al. 1982
Diet Slope Factors:	µg/dL per µg Pb ingested/day		
Infants and toddlers; N=29	0.24	Breast-fed and formula-fed; EPA analysis	Ryu et al. 1983; EPA 1990e
Adults; N=31	0.034--females	Duplicate diet study; Ayr, Scotland	Sherlock et al. 1982
Adults; N=15	0.014–0.017--males; 0.018–0.022--females	Experimental study; blood leads were not allowed to equilibrate	Stuik 1974
Adult males; N=15	0.027	Experimental study	Cools et al. 1976
Soil Slope Factors:	µg/dL per mg Pb/kg		
Mixed	0.002–0.016	Review of the literature	Reagan and Silbergeld 1989
Children; 1–18 years of age; N=831; 1,074 blood samples	0.0068±0.00097	Omaha study; urban/suburban	Angle et al. 1984
Children; 1–72 months of age; N=377; 926 blood leads	-0.00016–0.00223 (soil near house) 0.00073–0.0023 (soil at curb)	New Haven, CT; EPA analysis. The largest slopes were from the children under 1 year of age with SE=0.00091 (at house) and 0.0019 (at curb)	Stark et al. 1982
Children; N=880	0.0011 (avg. for all ages) 0.0025 (for 2–3 year olds)	Kellogg/Silver Valley cross-sectional study; smelter; EPA analysis	Yankel et al. 1977
U.S. males age 18–65 years old (NHANES III)	0.001–0.003	Slope derived from model anaylzed using Monte Carlo analysis to predict population distribution of blood lead from lead exposure	Stern 1996

Table 2-9. Summary of Blood Slope Factors from Various Environmental Media (continued)

Population	Slope	Comments	References
Dust Slope Factors:	µg/dL per mg Pb/kg		
Children; 1–18 years of age; N=831; 1074 blood samples	0.00718±0.00090	Omaha study; urban/suburban; housedust	Angle et al. 1984
Children; 1–6 years of age; N=32	0.008	Homes of lead workers; housedust	Baker et al. 1977
Children; 2 years of age; N=82	0.004	Area of high lead soil; housedust	Baltrop et al. 1974
Adults and children; N=80	0.0086–0.0096 (housedust); 0.0021–0.0067 (outside dust)	Smelter	Roberts et al. 1974
Children; N=377; 1–72 months of age; 926 blood lead levels	0.00402±0.0017 (0–1 year old); 0.00182±0.00066 (2–3 year old) 0.00022±0.00077 (4–7 year old)	New Haven, CT; EPA analysis	Stark et al. 1982

Source: adapted from Duggan and Inskip 1985; EPA 1986a, 1989g

Studies correlating lead concentration in water and blood report a diverse set of slope factors due to the wide range of water lead concentrations in the studies—50–2,000 µg/L (EPA 1986a). Over a wide range of water lead concentrations, the relationship to blood levels is curvilinear; however, at typical ambient water levels in the United States, the relationship appears to be linear. Pocock et al. (1984) provide data for adults at the lower range of water lead concentrations (<100 µg/L). Their slope factor estimates a PbB of 0.06 µg/dL per µg lead/L water. Lacey et al. (1985) provide data for infants. Regression analysis of their data gives 2 slope factors: 0.26 µg/dL blood per µg/L water at water lead levels below 15 µg/L and 0.04 µg/dL blood per µg/L water at water lead levels above 15 µg/L (EPA 1991a). Based on the results of an analysis of the relationship of environmental lead exposure to lead intake among a sample of 183 urban children, adjusted for exposure to lead-contaminated house dust, Lanphear et al. (1998a) estimated that an increase in water lead concentration from background levels to 0.015 mg/L, was associated with an increase of 13.7% in the percentage of children having a PbB concentration exceeding 10 µg/dL.

Slope factors for the blood lead contribution from diet in adults can be obtained from an experimental study (Cools et al. 1976) and a duplicate diet study (Sherlock et al. 1982). These slope factors range from 0.027 to 0.034 µg/dL blood per µg lead intake/day (EPA 1986a). The data from the duplicate diet infant study by Ryu et al. (1983) were reanalyzed to derive a slope factor of 0.24 µg/dL blood per µg/day lead intake (EPA 1990e).

Studies relating soil lead levels to blood lead levels are difficult to compare. The relationship depends on depth of the soil sampled, sampling method, cleanliness of the home, age of the children, and mouthing activities, among other factors. Slopes range between 0.0007 and 0.0068 µg/dL PbB increase per mg/kg soil lead. Angle et al. (1984) provide the most conservative slope estimates based on the Omaha childhood blood data. They compared their power function model against a linear model for the Omaha study and concluded that the linear model which predicted a slope of 0.0068, was "statistically equivalent" to the power model and provided more biologically credible PbB curves. They also determined similar slopes for dust—0.0072 µg/dL PbB increase per mg/kg house dust lead (Angle et al. 1984). An additional factor that impacts on the PbB levels from exposure to lead contaminated soil is the bioavailability of lead in the ingested soil and dust (for review see Chaney et al. [1989] and Mushak [1991]). In turn, bioavailability appears to be affected by a number of factors including solubility, particle size, and medium or matrix. Some forms of lead such as lead carbonates, lead sulfates, and lead oxides are more water soluble than lead sulfide. For any one chemical form of lead, the smaller the particle size, the easier it becomes solubilized. Furthermore, the concentration of lead in soil increases as particle size decreases and smaller particles are

more easily moved into the home to become lead-rich housedust and on to the hands of children who may ingest soil particles via mouthing behavior. Danse et al. (1995) examined blood lead data and environmental lead data of residents from 13 communities where mill tailings from prior activities were present. The majority of the samples (2,995 PbB measurements) were from children. The results were compared to 1,806 controls from nearby communities, national norms, and communities with active smelters. The authors found that PbB values in residents exposed to tailings were usually comparable to controls; however, at some smelter sites that generated fine soluble dusts, blood lead levels were found to be increased in populations residing downwind from smelters and in dusty areas. In a recent study of urban children, Lanphear et al. (1998a) estimated that increasing the concentration of soil lead from background to 400 µg/g produced an increase of 11.6% in the percentage of children estimated to have a PbB level exceeding 10 µg/dL, and increasing dust load loading from background to 200 µg/feet^2 was estimated to produce an increase of 23.3% in the percentage of children having a PbB concentration exceeding 10 µg/dL.

The information summarized above suggests that provision of health-based guidance requires an approach that uses site- and media-specific information. ATSDR has developed guidance with this approach which can be used by employing media-specific slope factors to integrate exposures from various pathways (Abadin et al. 1997a; see also Appendix D). For a given site, slope factors can be used with environmental data to predict media-specific contributions to blood lead. Summation of the individual media contributions will yield a total predicted PbB level. The uncertainties in predicting mean PbB can be estimated by using the standard errors associated with the slope values to generate a range of predicted PbB. Proposed default values can be used in lieu of missing environmental data.

By predicting PbB levels, a determination can be made about what health impacts may be occurring at a given site. This will assist health assessment personnel in deciding whether further action is needed. A site-specific evaluation must be made before reaching any conclusions (e.g., pica children, ground cover over contaminated soil, nutritional status and age of the population, etc.). Issues relevant to children are explicitly discussed in Sections 2.6, Children's Susceptibility, and 5.6, Exposures of Children.

Death. Death can be the end result in cases of severe lead encephalopathy in both adults and children. The National Academy of Sciences (NAS 1972) analyzed unpublished data obtained from the patient populations reported in Chisolm (1962, 1965) and Chisolm and Harrison (1956) and concluded that the range of blood lead levels associated with death from lead encephalopathy in children was approximately

125–750 µg/dL (mean, 327 µg/dL). A case report described a 70-year-old female nursing home resident who drank lead ceramic glaze (Roberge et al. 1994). During the next 10 days her mental status progressively deteriorated, and her abdomen became distended. On admission to the hospital her PbB level was 259 µg/dL. After several days of chelation therapy, her PbB decreased to 21 µg/dL. In spite of the reduction in PbB, the patient's lethargy and confusion persisted and she developed renal failure and associated anasarca, as well as brief apneic periods. She expired on the 16th day and the cause of death was listed as lead intoxication; an autopsy was not performed.

The results of mortality studies conducted on occupationally exposed workers are discrepant, and all the studies have design flaws that limit the validity of the conclusions that can be drawn from their results. One study found a statistically significant increase in mortality due to malignant neoplasms, chronic renal disease, and "ill-defined" causes in lead-exposed workers (Cooper 1988; Cooper et al. 1985). Another study found a statistically significant increase in mortality due to cardiovascular disease in lead-exposed workers (Fanning 1988), and another found a statistically significant increase in the incidence of deaths from cerebrovascular disease in lead-exposed newspaper printers (Michaels et al. 1991). Two additional studies found no statistically significant increase in mortality due to lead exposure (Gerhardsson et al. 1986b, 1995a). Slightly lower blood lead levels were recorded in the study by Gerhardsson et al. (1986b) than in the study by Cooper et al. (1985). A follow-up evaluation of the cohort studied by Gerhardsson et al. (1986b) provided evidence suggesting an increased mortality due to lung cancer among lead workers (Lundstrom et al. 1997). Suggestive evidence of excess death from cardiovascular disease among adults diagnosed with lead poisoning as children was presented by McDonald and Potter (1996). Weak evidence of an association between increase mortality due to renal cancer and long-term lead exposure was presented by Cocco et al. (1997).

High levels of lead have been suggested as a causative agent in Sudden Infant Death Syndrome (SIDS). Investigators have found that babies who died of SIDS had a greater number of the highest lead levels in dry blood (blood samples in which the water has been removed) as compared to control (alive or dead due to traumatic causes) babies (Drasch et al. 1988). These results suggest that there may be an association between high lead body burden and SIDS, but the mechanism behind this association cannot be determined at this time. Possibilities include an effect of lead on prenatal and/or postnatal neurological development.

Oral LD_{LO} values in a number of animal species are available for lead (see Table 2-3). Mortality data from longer-term studies in animals are often inconclusive. However, based on the information available in

humans, it is apparent that high body burdens of lead can result in death, which is most often secondary to lead-induced encephalopathy.

Systemic Effects

Respiratory Effects. There are no conclusive data available to indicate that lead adversely affects the respiratory system in humans. However, one inhalation study in animals indicates that continuous prolonged (28-day) exposure to lead nitrate particles may be irritating to the lungs, as evidenced by the pulmonary edema and hemorrhage seen in the lungs of the lead-exposed mice at necropsy (Hillam and Ozkan 1986). These effects were not seen in animals continuously exposed for 14 days, suggesting that the apparent adverse respiratory effects were dependent on the duration of exposure and are cumulative. However, the irritative properties of inhaled lead depend partially on the solubility and pH of the species. In this study, the animals were exposed to lead nitrate, which is acidic and, therefore, irritating. These results are not sufficient to determine whether prolonged inhalation exposure of humans to high levels of lead particles other than lead nitrate (such as may occur near hazardous waste sites) may result in pulmonary irritation.

Cardiovascular Effects. The evidence from occupational, clinical, and general population studies suggests that lead affects the cardiovascular system in humans, producing cardiac lesions and electrocardiographic abnormalities at high levels of exposure. However, the association between PbB and blood pressure is still a matter of controversy. The contribution of lead, compared with many other factors that affect blood pressure, appears to be relatively small, usually not accounting for more than 1–2% of the variation when compared with other significant factors (EPA 1986a). The evidence in humans, at this time, does not support a conclusive positive association between increased PbB levels and blood pressure.

The animal data demonstrate that lead increases blood pressure, despite confounding experimental design factors such as species tested, age of animals, route of administration, dose used (doses that are high enough to induce nephrotoxicity may produce hypertension as a secondary effect), method of measuring blood pressure, and use of anesthesia. In reviewing the database on the mechanism of lead's hypertensive action in animals, EPA (1986a) concluded that although lead, even at very low levels, produces effects on the renin-angiotensin system in animals, these changes are not established as the cause of hypertension. Rather, hypertension is more likely to be due to changes in vascular reactivity and level of sympathetic tone,

both of which may be dependent on lead-related changes in intracellular calcium ion concentration (EPA 1986a).

Interpretation of the blood lead-blood pressure data in epidemiological studies of the general population remains an area of controversy. Factors that contribute to the controversy include the methodology used to monitor blood lead and blood pressure, and statistical issues. The association between blood lead and blood pressure was the subject of a 1987 Symposium on Lead-Blood Pressure Relationships (Environmental Health Perspectives, Volume 78, June 1988) and of several population studies (Elwood et al. 1988; Grandjean et al. 1989; Neri et al. 1988; Pocock et al. 1988; Staessen et al. 1990, 1991). In addition, data from the NHANES II study were re-analyzed by Coate and Fowles (1989) and Gartside (1988). As summarized by Victery et al. (1988), both S. J. Pocock and J. Schwartz, considered the evidence from general population epidemiological studies and concluded that a doubling of PbB levels is associated with an increase of approximately 1–2 mm Hg in systolic blood pressure. Pocock concluded that the overall evidence from the human studies did not support a causal relationship between PbB and blood pressure. Schwartz concluded that, although a causal inference could not readily be drawn from the epidemiological data alone, such an inference was consistent with the animal data. Based on the data for both humans and animals, Schwartz concluded that a causal relationship is likely. Staessen et al. (1994a) reviewed 21 animal studies published since 1977 and concluded that most found a positive association between blood pressure and lead exposure. However, in the articles in which all the lead doses had been higher than 1 ppm, the association between blood pressure and exposure was found to be positive in 7, inconsistent in 3, absent in 4, and negative in one. Five out of 6 studies that employed doses not exceeding 1 ppm reported a small pressor effect, and one of these 5 failed to show a dose-response relationship when exposure was increased from 0.1 to 1 ppm. Staessen et al. (1994a) noted that publication bias may have inflated the number of positive studies appearing in the literature. They suggested that the significance to human health of lead doses between 0.1 pm and 1 ppm given to genetically heterogeneous rats, dogs, or pigeons still needs to be elucidated.

The results from more recent studies have not clarified the issue. In a study of the general population in Belgium in which 2 sets of data were collected at a 6-year interval, Staessen et al. (1996) found that blood pressure was not correlated with PbB or ZPP concentrations in men or women. The study further found that the risk of becoming hypertensive was not associated with PbB or ZPP concentrations measured at the first data collection. Results from the evaluation of participants in the Normative Aging Study showed that an increase in tibia bone lead of about 29 μg/g was associated with an increased odds ratio of hypertension of

1.5 (Hu et al. 1996a). However, the authors acknowledged that the procedures used to estimate long-term ethanol ingestion and smoking habits were rather crude. Hu et al. (1996a) further stated that given the cross-sectional nature of the investigation and the fact that tibia lead is an indicator of long-term absorption and stores in cortical bone, they could not specifically evaluate the temporality of the relationship, making premature any inference on causality.

Schwartz (1995) used meta-analysis to examine the evidence for an association between PbB concentrations and systolic blood pressure in males. The results of the analysis showed a highly significant and moderately consistent association—a decrease in PbB from 10 µg/dL to 5 µg/dL was associated with a decrease of 1.25 mm Hg (95% CI=0.87–1.63 mm Hg). Hertz-Picciotto and Croft (1993) reviewed all the major studies conducted since 1980 and concluded that an increase in blood pressure was associated with increases in blood lead in most, but not all, of the population-based studies. Regarding occupational cohorts, the reviewer's opinion was that the results are mixed, but that overall the studies suggested a small positive association between PbB and blood pressure. Staessen et al. (1994b) conducted a meta-analysis of 23 studies that included 33,141 subjects from either the general population (13 surveys) or from occupational groups (10 studies). Separate analyses (whenever possible) of data from men and women and white and black subjects showed that the association between blood pressure and PbB was similar in both genders and in each race. In all 23 studies combined, a doubling in the PbB concentration was associated with a 1 mm Hg rise in systolic pressure and with a 0.6 mm Hg increase in diastolic pressure. Staessen et al. (1994b) noted that the association with systolic pressure strongly relied on the inclusion of one study in which women had their blood pressure measured at the end of pregnancy (Rabinowitz et al. 1987). The association with diastolic blood pressure was, to a large extent, due to the results of the NHANES II survey (Harlan et al. 1985; Pirkle et al. 1985). IPCS (1995) also reviewed the literature and concluded that no causal relationship has been demonstrated between body burden of lead and blood pressure.

Limited data on occupationally exposed men indicate that the effect of lead on blood pressure may be mediated in part through the renin-angiotensin system, as evidenced by lead-related increases in plasma renin and angiotensin I levels (Campbell et al. 1985) and the kallikrein-kinin system, as indicated by a correlation between renin and kallikrein (Boscolo et al. 1981). Evidence from patients with essential hypertension and renal impairment suggests that excessive lead absorption may be involved in the development of both conditions (Batuman et al. 1983).

Gastrointestinal Effects. Colic, which is characterized by a combination of abdominal pain, constipation, cramps, nausea, vomiting, anorexia, and weight loss, is a consistent early symptom of lead poisoning in occupationally exposed cases or in individuals acutely exposed to high levels of lead. Colic is also seen in children with lead poisoning. Histopathological evidence of lead-induced gastrointestinal damage has not been reported. Adverse gastrointestinal effects have not been noted in animal studies, but it is difficult to study the symptoms of colic that are noted in humans in the laboratory situation.

Hematological Effects. Lead has long been known to have profound effects on heme synthesis. The impairment of heme synthesis has a far-ranging impact not limited to the hematopoietic system. EPA (1986a) summarized the known and potential consequences of the reduction of heme synthesis as shown in Figure 2-11. The mechanisms by which lead interferes with heme synthesis are discussed in Section 2.4.2.

Numerous studies of both occupationally-exposed subjects and the general population have tried to correlate PbB levels with changes in hematological parameters. Of all the parameters examined, ALAD activity appears to be the most sensitive indicator of lead exposure. For example, in studies of the general population, ALAD activity was inversely correlated with PbB levels over the entire range of 3–34 µg/dL. In contrast, the threshold for increase in urinary ALA in adults is a PbB concentration of approximately 40 µg/dL; for increases in blood EP or ZPP the threshold in adults is around 30 µg/dL; and the threshold for increased ZPP in children is about 15 µg/dL in children. Threshold PbB levels for decreased hemoglobin levels in adults and children have been estimated at 50 µg/dL and 40 µg/dL, respectively. Although the measurement of ALAD activity seems to be a very sensitive hematological marker of lead exposure, the inhibition of the enzyme is so extensive at PbB levels $30 µg/dL that the assay cannot distinguish between moderate and severe exposure.

Although the effects on some steps in the heme synthesis pathway occur at very low exposure levels, there is some controversy as to the toxicological significance of a depression in ALAD activity in the absence of a detectable effect on hemoglobin levels. EPA (1986a) and ATSDR (1988) are concerned about effects on the heme synthesis pathway, however, because of the emerging evidence of a constellation of effects (as seen in Figure 2-11), including inhibition of ALAD and pyrimidine-5'-nucleotidase activities, elevations in EP levels, reductions in serum 1,25-dihydroxyvitamin D levels, and also subtle neurobehavioral, electrophysiological, growth and blood pressure effects at low PbB levels (10–15 µg/dL and possibly lower). Of particular concern is the impact that this constellation of effects may cause in the developing organism, since exposure to lead may occur through the placenta and via maternal milk. In addition, young

children, particularly those growing in socioeconomically disadvantaged areas, have a greater potential for exposure and absorption, as reflected by their higher blood lead levels reported by recent population surveys (Brody et al. 1994; Pirkle et al. 1994).

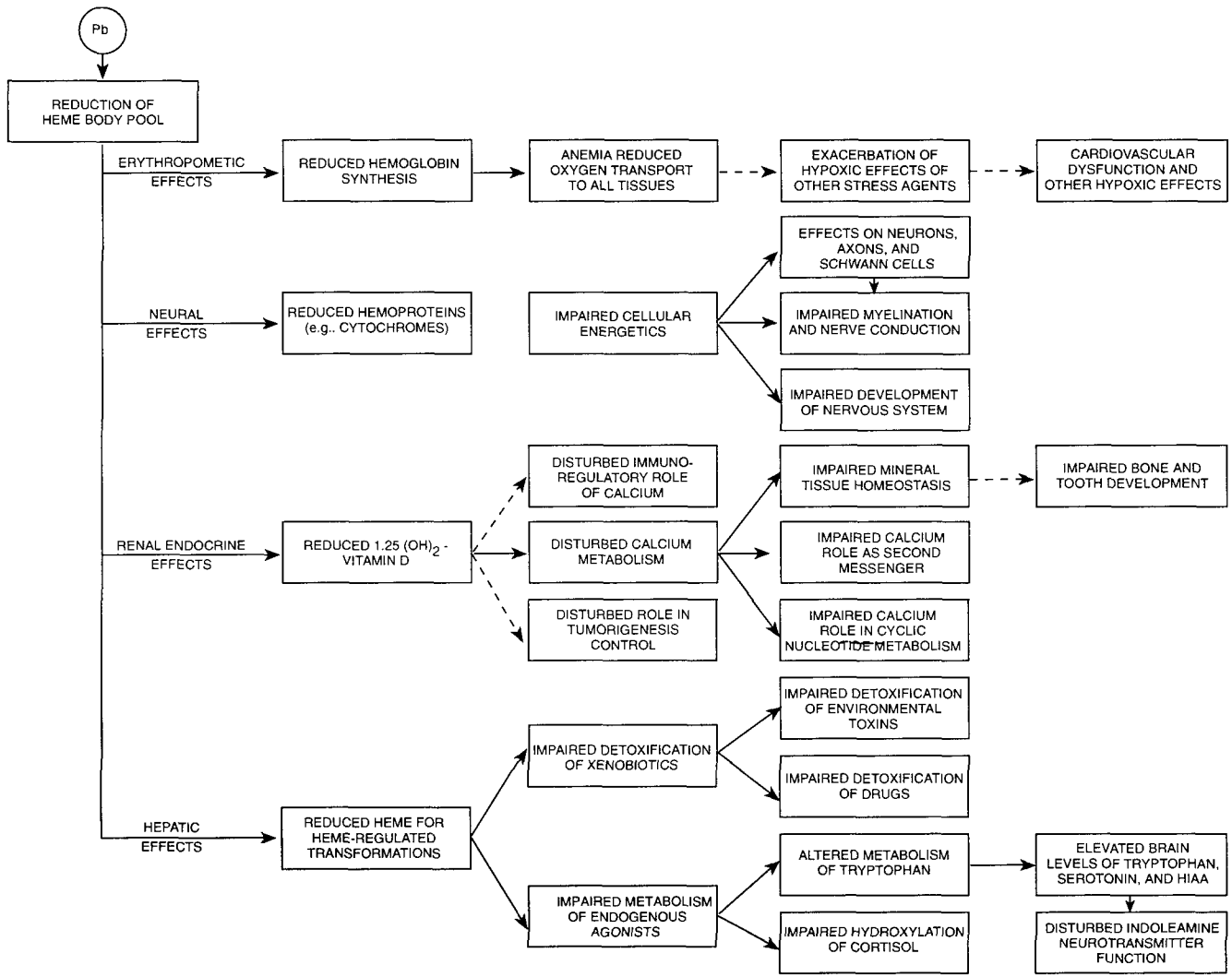
Musculoskeletal Effects. Individuals who have had high exposures to lead, either occupationally or by the consumption of alcohol from lead stills, have been reported to exhibit a bluish-tinged line in the gums (i.e., the "lead line"). In addition, case reports of high occupational exposure to lead have described the occurrence of muscle weakness, cramps, and joint pain.

Limited data from intermediate-duration experimental rat studies suggest that oral lead exposure may impair normal bone growth (Escribano et al. 1997; Gonzalez-Rialo et al. 1997; Hamilton and O'Flaherty 1994, 1995; Gruber et al. 1997). Epidemiological studies have found inverse relationships between lead exposure (reflected by PbB concentration) and growth of children (see Section 2.2.1.2, Other Systemic Effects). These observed relationships in humans have not been conclusively linked to either direct or indirect effects of lead on bone metabolism such as those suggested from the rat studies.

Hepatic Effects. Limited evidence exists to suggest that lead affects hepatic mixed function oxygenases by inhibiting the formation of the heme-containing protein, cytochrome P-450 (Alvares et al. 1975; Saenger et al. 1984). Abnormal liver function in individuals exposed to high levels of lead could not be conclusively linked to lead because prior medical histories were not known. Studies in animals provide limited evidence that lead may affect the liver. Reported in the literature include effects on hepatic glycogen and DNA content and the ability to incorporate amino acids into proteins (Barratt et al. 1989). This evidence is not conclusive because these end points are relatively non-specific, and no histopathological evaluation or organ function tests (i.e., serum enzymes) were performed. Based on the information available in humans and animals, it is difficult to conclude that lead adversely affects the liver.

Renal Effects. Exposure to lead that results in PbB ranging from approximately 60 to >100 µg/dL has been associated with nephropathy in some studies of lead-exposed workers (e.g., Chia et al. 1995a). The characteristics of early or acute lead-induced nephropathy in humans include nuclear inclusion bodies, mitochondrial changes, and cytomegaly of the proximal tubular epithelial cells; dysfunction of the proximal tubules (Fanconi's syndrome) manifested as aminoaciduria, glucosuria, and phosphaturia with hypophosphatemia; and increased sodium and decreased uric acid excretion. These effects appear to be reversible. Characteristics of chronic lead nephropathy include progressive interstitial fibrosis, dilation of

Figure 2-11. Multiorgan Impact of Reduction of Heme Body Pool by Lead



Source: Derived from EPA 1986a

tubules and atrophy or hyperplasia of the tubular epithelial cells, few or no nuclear inclusion bodies, reduction in glomerular filtration rate, and azotemia. These effects are irreversible. The acute form is reported in lead-intoxicated children, whose primary exposure is via the oral route, and sometimes in lead workers. The chronic form is reported mainly in lead workers, whose primary exposure is via inhalation. Animal studies provide evidence of nephropathy similar to that in humans, and particularly to the acute form.

In human studies where no renal biopsies have been performed to prove conclusively the occurrence of nephropathy, the results have not been consistent. This could partially be explained by the choice of the renal function parameter studied. The only parameter of renal function shown to be affected in some studies is an increase in the levels of N-acetyl-β-D-glucosaminidase (NAG). NAG is a lysosomal enzyme present in renal tubular cells that has been shown to be a sensitive indicator of early subclinical renal tubular disease. Increases in NAG in lead-exposed individuals have been seen at PbB levels of around #62 µg/dL, which suggests that lead may affect renal tubular function to a greater extent than glomerular function. The marker is not specific and is also increased by exposure to cadmium. IPCS (1995) reviewed the epidemiological data and concluded that renal function impairment was not associated with PbB levels below 62 µg/dL when measured by BUN and serum creatinine levels in workers exposed to lead. It should be mentioned, however, that Kim et al. (1996a) found an association between PbB and serum creatinine in a group of older men with PbB concentration lower than 62 µg/dL. IPCS (1995) stated that urinary NAG is a more sensitive indicator since altered levels were found at PbB levels <62 µg/dL. This is consistent with the results of a recent study that found a significant increase in urinary NAG in children with a mean PbB concentration of 34.2 µg/dL (Verberk et al. 1996). In that study, NAG activity increased 14% per 10 µg/dL PbB and was the only one out of 5 renal parameters evaluated that exhibited an association with PbB. Some investigators have suggested that the elevation of urinary NAG activity may be a response to a sharp increase in the renal lead burden rather than a response to the cumulative dose (Chia et al. 1994) and that a preferable early indicator of renal toxicity is an increase in urinary $\alpha_{1\mu}$-globulin, which correlated well with a time-integrated blood level index in lead exposed workers (Chia et al. 1995a, 1995b). The results from Verberk et al. (1996) suggest that tubular function may be a more sensitive target for lead toxicity in children than in adults, but the results need to be confirmed. A study of adults from the general population provided suggestive evidence of impaired renal function in subjects with PbB #70 µg/dL (Staessen et al. 1992).

Kidney function has been evaluated not only in relation to PbB levels, but also in relation to bone lead concentrations, which provide a better assessment of cumulative dose of lead to the kidneys than blood lead. In a study of lead-exposed workers whose mean tibia lead was three times that of controls (66 versus 21 µg/g bone mineral) bone lead showed a modest but positive statistical association with both baseline and peak creatinine clearance after a protein challenge (Roels et al. 1994). No association existed with PbB (mean 43 µg/dL), urinary lead, or blood ZPP.

Excessive lead exposure has also been implicated as a causative agent in kidney disease associated with gout and essential hypertension (Batuman et al. 1981, 1983). Gout patients with renal impairment, and hypertensive patients with renal impairment, had significantly higher lead stores (as determined by the 3-day EDTA lead mobilization test) than gout patients or hypertensive patients without renal impairment, respectively. Therefore, excessive lead absorption may be involved in the renal impairment seen in patients with gout or essential hypertension.

Several studies conducted in children known to have lead toxicity, indicate that nephropathy occurs in children only at PbB >80 µg/dL, and usually exceeding 120 µg/dL (NAS 1972).

The possible mechanism kidney-induced hypertension is discussed in Section 2.4.2, Mechanisms of Toxicity. Lead appears to affect vitamin D metabolism in renal tubule cells, such that circulating levels of the vitamin D hormone, 1,25-dihydroxyvitamin D, are reduced. This effect is discussed later in this section under Other Systemic Effects.

Endocrine Effects. Controversial data exist regarding thyroid function in workers occupationally exposed to lead. A weak but statistically significant negative correlation was found between duration of exposure to lead and thyroxin and free thyroxin levels in workers with PbB levels that were $56 µg/dL and had over 10 years of exposure (Tuppurainen et al. 1988). According to the author, this finding could be explained by a direct effect of lead on the thyroid gland; an effect on the hypothalamopituitary level; and an effect on the peripheral turnover of thyroid hormones. A different study found no indication of altered thyroid function in workers from a lead acid battery factory (Gennart et al. 1992a). However, in the latter study the PbB levels were generally lower than in the workers examined by Tuppurainen et al. (1988), which would indicate that thyroid changes are not good indicators of moderate lead exposure.

Adverse effects on the thyroid have not been observed in children, however. In a study of inner-city children, linear regression analysis revealed that there was no association between PbB levels and either thyroxin or free thyroxin (Siegel et al. 1989). Similar findings were reported by Huseman et al. (1992) in a group of 12 children from the Omaha Lead and Poison Prevention Program with PbB levels in the range of 41 to 72 µg/dL. Siegel et al. (1989) offered four possible explanations to account for this apparent lack of effect of lead on thyroid function in children. First, children may be less susceptible than adults to the toxic effects of lead on the thyroid gland. However, this is not consistent with the greater susceptibility of children to the other toxic effects of lead (e.g., neurotoxicity). Second, the lead-exposed workers had higher PbB levels than the children in this study (51.9 µg/dL versus 25 µg/dL). However, no effect on thyroxin was seen even in children with PbB $60 µg/dL. Third, the workers had a longer duration of exposure (average exposure of 5.8 years versus 2.8 years in the children). Finally, thyroxin levels may not be a sensitive enough indicator of thyroid function. In addition, the iodine content of the adult versus children's diet should be compared because iodine intake affects thyroid function.

Ocular Effects. Visual problems have been noted in some human studies. These are mostly anecdotal in nature and not well documented.

Long-term scotopic visual system deficits have been observed in laboratory animals following low-level exposure during early postnatal development. A series of experiments were conducted in rats to determine whether these effects are secondary to an effect on the central nervous system or are the result of a direct effect on the eye following low-level exposure during early postnatal development. The results demonstrated an adverse effect on the rods of the retina. This was evidenced by changes in single-flash electroretinograms, selective degeneration of rod (but not cone) photoreceptor cells, accumulation of glycogen particles in the retinas, decreased retinal sensitivity and rhodopsin content, and a decrease in rod outer segment length with a selective loss of 20% of the rod cells (Fox and Chu 1988; Fox and Farber 1988; Fox and Rubinstein 1989; Fox et al. 1997). These investigators also demonstrated that most of the effects occur within the first 30 days of life, although the changes remain throughout the first year. A possible mechanism of action for this selective adverse effect on the rods of the retina was proposed. This effect could be due to a lead-induced alteration in cyclic nucleotide metabolism resulting in a change in the activity of the sodium channels in the rods. To investigate this possibility, cyclic nucleotide content and the activity of the enzymes associated with their metabolism were measured. A significant increase in cGMP but not cAMP was found in the lead-treated rats. This increase in cGMP content was in turn found to be associated with decrease cGMP-PDE activity (Fox and Farber 1988). Using cGPM-PDE isolated from

frozen dark-adapted bovine rod outer segments, Fox and Srivastava (1995) showed that lead binds at the magnesium site of the enzyme, but with 4–6 log units higher affinity. Effects of lead on the retina were also reported in monkeys following lifetime exposure to lead (Kohler et al. 1997). In this study, the effects were observed at a time when PbB levels were near control levels following a 3-year maintenance in a lead-free diet.

Other Systemic Effects.

Effects on Vitamin D Metabolism. Lead appears to interfere with the conversion of vitamin D to its hormonal form, 1,25-dihydroxyvitamin D. In children with PbB levels of 33–55 µg/dL, 1,25-dihydroxy-vitamin D levels were reduced to levels comparable to those observed in children with severe renal insufficiency (Rosen et al. 1980). In lead-exposed children with blood lead levels of 33–120 µg/dL, 1,25-dihydroxyvitamin D levels were depressed to levels (#20 pg/mL) comparable to those found in vitamin D-dependent rickets, type I—an inborn error of vitamin D metabolism in which the 1-hydroxylase system or component thereof is virtually absent (Rosen and Chesney 1983; Rosen et al. 1980). These comparisons are consistent with an effect of lead on the production of 1,25-dihydroxyvitamin D by renal 1-hydroxylase. However, in children with low to moderate lead exposure (average lifetime PbB levels ranging from 4.8–23.6 µg/dL) and adequate dietary intake of calcium, phosphorus, and vitamin D, no effect was observed on vitamin D metabolism, calcium and phosphorus homeostasis, or bone mineral content (Koo et al. 1991). Based on these results, it appears that adverse effects on vitamin D metabolism may be manifested only at chronically high lead exposures in children deficient in calcium, phosphorus, and vitamin D. After reviewing the human data, IPCS (1995) also concluded that in the presence of adequate nutritional status, PbB levels below 20 µg/dL appear to have no demonstrable effect on circulating concentrations of 1,25-dihydroxyvitamin D.

It is possible that lead's interference with heme synthesis may underlie the effects on vitamin D metabolism. Evidence that lead affects heme synthesis in the kidney was presented in the section on hematological effects. In addition, apparent thresholds for the effects of lead on renal vitamin D metabolism and for erythrocyte protoporphyrin accumulation are similar.

Because the vitamin D-endocrine system is responsible in large part for the maintenance of extra- and intracellular calcium homeostasis, it is reasonable to conclude that the interference of lead with renal

1,25-dihydroxyvitamin D production will have an impact on fundamental processes throughout the body (EPA 1986a). The potential impact is presented in Figure 2-11.

Lead was found to decrease tissue levels of vitamin C in a study in rats (Vij et al. 1998). Since vitamin C is required for the synthesis of heme, the authors suggested that some hematological effects of lead (e.g., inhibition of ALAD) may be due at least partially to a lead-induced decrease in bioavailability or increased demand of vitamin C. Supplementation with vitamin C almost completely restored ALAD activity in blood and liver.

Effects on Growth. Some of the available evidence suggests a growth retardant effect of lead in children (Angle and Kuntzelman 1989; Frisancho and Ryan 1991; Huseman et al. 1992; Lyngbye et al. 1987; Schwartz et al. 1986; Shukla et al. 1989, 1991). These findings are supported by the results of independent prospective studies of prenatal effects on human development discussed in Section 2.2.1.6 on developmental toxicity and by numerous animal studies. However, several other studies have failed to identify a significant association between PbB level and growth in children (Greene and Ernhart 1991; Kim et al. 1995; Sachs and Moel 1989). The finding of a suppressed release of thyrotropin-stimulating hormone (TSH) in response to thyrotropin-releasing hormone (TRH) in two young lead-intoxicated children suggests pituitary involvement (Huseman et al. 1987). *In vitro* studies with rat pituitary cells showed that lead inhibited the TRH-stimulated release of TSH in a dose-related manner (Huseman et al. 1987), supporting the conclusions drawn from the human data. Alternatively, it is possible that nutritional deficits that retard growth also increase lead absorption.

Immunological Effects. The effects on the immune system of young rats at PbB levels of 29 µg/dL (Faith et al. 1979; Luster et al. 1978), of mice at PbB levels of 15–45 µg/dL (Hillam and Ozkan 1986), and of rabbits at PbB of 1–2 µg/dL (Zelikoff et al. 1993) raise the concern that low-level exposure of humans to lead may also have adverse effects on the immune system. The best available human data, while not fully adequate to address this issue, gave no indication of immune system effects in children with blood lead levels of $40 µg/dL (Reigart and Graher 1976) and very inconsistent responses of both the cell and humoral components of the immune system in lead workers with mean blood lead levels ranging from 19 to 80 µg/dL (Alomran and Shleamoon 1988; Ewers et al. 1982; Fischbein et al. 1993; Pinkerton et al. 1998; Sata et al. 1998; Ündeger et al. 1996). The inconsistent results may reflect differences in measures of exposure (i.e., current PbB versus cumulative indices of exposure) and/or methodological differences in the

evaluation of specific immunological endpoints. Overall, there has been no evidence of marked immunotoxic effects of lead at the exposure levels studied.

Neurological Effects. The data on neurobehavioral toxicity of exposure to lead suggest that children are more sensitive, as indicated by responses at lower PbB levels, than are adult humans, and that animals are affected at roughly the same PbB levels as are humans.

In humans, encephalopathy can occur at PbB levels as low as 100–120 µg/dL in some adults (Kehoe 1961a, 1961b, 1961c; Smith et al. 1938) and at PbB levels as low as 80–100 µg/dL in some children (EPA 1986a; NAS 1972). This condition can result in death or in permanent cognitive impairment, particularly in children. Furthermore, children with high PbB levels (>80–100 µg/dL) and symptoms of lead poisoning, but no symptoms of acute encephalopathy, also have an increased incidence of lasting neurological and behavioral impairment (EPA 1986a).

Adults may have overt neurological signs and symptoms and impairment on neurobehavioral tests at blood lead levels as low as 40–60 µg/dL (Baker et al. 1979, 1983; Campara et al. 1984; Haenninen et al. 1979; Maizlish et al. 1995; Williamson and Teo 1986; Zimmerman-Tanselia et al. 1983). These blood lead levels are comparable to those at which other symptoms of lead poisoning, such as gastrointestinal symptoms, occur. Common limitations of studies examining neurobehavioral effects of lead in adults include inadequate estimation of cumulative exposure and inadequate control for age and intellectual ability before exposure. The importance of evaluating several measures of exposure (present, past, and cumulative) is illustrated, for example, by Lindgren et al. (1996), who found no association between current, and relatively low (27.5 µg/dL) PbB levels and neuropsychological variables in lead workers. The lack of association at these PbB levels was not inconsistent with what others had found, but a significant association became apparent when performance was measured against a cumulative dose estimate. Ehle and McKee (1990) reviewed several studies published between 1978 and 1986 and concluded that "the issue of psychological and neuropsychological effects of low-level lead in adults remains to be resolved in the studies reviewed. The methodologies were so varied and the cultures in which the studies were conducted so diverse that it is impossible to generalize across findings." Similar conclusions were drawn by Balbus-Kornfeld et al. (1995) after evaluation of 21 studies, mostly cross-sectional studies. Two recent studies presented evidence of an association between decreased neurobehavioral performance and PbB in aging subjects with mean PbB concentrations around 5 µg/dL (Muldoon et al. 1996; Payton et al. 1998).

The overall results from evaluations of peripheral nerve function, specifically conduction velocity, suggest that an inverse relationship exists between blood lead and speed of conduction. The role of lead was apparent in a study by Araki et al. (1980) who found significant improvement in motor nerve conduction velocity in workers following reduction of PbB by chelation therapy. The inconsistencies among studies may reflect differences in the nerves evaluated, methodologies, characterization of lead exposure, and control for confounding. Davis and Svendsgaard (1990) conducted a meta-analysis of 32 studies and found that the median motor nerve shows more reliable effects of lead than other nerves. The LOAEL for decreased nerve conduction velocity observed in adults appeared to be a PbB concentration of 30 µg/dL (Seppalainen et al. 1983). It is possible that decreased peripheral conduction velocity may have affected performance on some of the behavioral tests such as reaction time, grip strength, and eye-hand coordination.

In children with no symptoms of lead intoxication, the results have been inconsistent, but the overall evidence suggests a negative association between lead exposure and cognitive development in children. Neurobehavioral impairment, including IQ deficits of approximately 5 points, has been associated with mean PbB levels of approximately 50–70 µg/dL (de la Burde and Choate 1972; Rummo 1974; Rummo et al. 1979). IQ deficits of approximately 4 points have been associated with PbB levels of 30–50 µg/dL (estimated from dentin lead values and other data by the EPA [1986a]) (Needleman et al. 1979). The highly significant inverse linear relationship between IQ and PbB levels over the range of 6 to 46 µg/dL found by Hawk et al. (1986) and Schroeder and Hawk (1987) in black children of low socioeconomic status indicates that IQ decrements may occur without an evident threshold down to very low PbB levels. A study of children of higher and less uniform socioeconomic status in Edinburgh, Scotland, also reported a significant inverse dose-effect relationship between PbB level and cognitive ability, with no threshold evident from the mean PbB of 22.1 µg/dL in the highest lead group down to the mean PbB level of 5.6 µg/dL in the lowest lead group (Fulton et al. 1987). Hence, the lack of threshold in the inverse relationship between PbB level and cognitive function pertains not only to a particular socioeconomic status, but to the general population of children. The data of Fulton et al. (1987) provide evidence of IQ deficits in children with lead exposure at PbB levels <25 µg/dL (ATSDR 1988).

Several prospective studies have reported an inverse relationship between indices of lead exposure and persistent neurobehavioral deficits in children (see also Section 2.2.1.6, Developmental Toxicity). The most recent assessments are summarized below. In the Kosovo cohort (Yugoslavia) PbB, measured every 6 months from birth to age 4, was significantly associated with a decrease in GCI at each age point

(Wasserman et al. 1994). The 4-year GCI scores declined by an estimated 4 points, while PbB, measured between 24 and 48 months, increased from 10 to 25 µg/dL. A subsequent evaluation at age 7 found that a change in lifetime PbB from 10 µg/dL to 30 µg/dL was associated with an estimated decrease of approximately 4 IQ points (Wassermann et al. 1997). In the Port Pirie cohort (Australia), children's scores on neurobehavioral tests were significantly and inversely correlated with log PbB levels at 6, 24, and 36 months, and with the integrated average for birth to 4 years (McMichael et al. 1988). The estimated decrease in GCI score was approximately 7.2 points for an increase in integrated average PbB from 10 to 30 µg/dL. At 7 years of age, the IQ was reduced by 4.4–5.3 points for an increase in PbB level of 10 to 30 µg/dL (Baghurst et al. 1992). Also at this age, a deficits in visual motor performance were significantly associated with increases in lifetime average PbB, suggesting that this parameter may be a more sensitive index than IQ (Baghurst et al. 1995). There was also an inverse relationship between tooth lead concentration and intellectual development when the children were tested in their eighth year (McMichael et al. 1994). Neurobehavioral deficits persisted in this cohort at the age of 11–13 years (Tong et al. 1996). Evaluation of the Boston cohort showed similar results. At 5 years of age, deficits in GCI scores correlated significantly with PbB levels at 24 months of age (mean 7 µg/dL), but not with prenatal PbB levels (Bellinger et al. 1991). Reevaluation at age 10 revealed that the decline in Full Scale IQ corresponded to 5.8 points per 10 µg/dL increase in 24-month PbB (Bellinger et al. 1992). In this cohort, tooth lead concentration at age 8 was significantly associated with total problem behavior scores in school (Bellinger et al. 1994); the association, however, was considered modest (<1% of the variance). Evaluation of the Cincinnati cohort when the children were approximately 6.5 years old showed that almost every index of postnatal exposure was associated with Wechsler Performance IQ, including PbB at 66 and 72 months of age (Dietrich et al. 1993a). The analysis also showed that average lifetime PbB concentrations in excess of 20 µg/dL were associated with deficits in Performance IQ on the order of about 7 points compared with children with mean PbB concentrations #10 µg/dL. In addition, at the age of 6 years, children from this cohort having an average mean lifetime PbB of approximately $9 µg/dL appeared to have a deficit on both the Bilateral Coordination subset and Fine Motor Composite relative to children in the lowest PbB quartile (Dietrich et al. 1993b).

Several studies have reported no association between neurobehavioral impairment and low levels of lead exposure. Cooney et al. (1989a) reported that PbB levels of approximately 10 µg/dL had little or no effect on neurobehavioral development at age 4. Harvey et al. (1988) concluded that the effects of lead (mean PbB, 13 µg/dL) were small and generally not significant. Likewise, Ernhart et al. (1988), Lansdown et al. (1986), and Pocock et al. (1989) found no effect of lead on intelligence.

The seemingly inconsistent nature of the database on lead-induced neurobehavioral effects in children has been the subject of many reviews (i.e., Bellinger 1995; Gatsonis and Needleman 1992; Mushak 1993; Needleman and Gatsonis 1990; Pocock et al. 1994; Schwartz 1994; Winneke et al. 1990, 1996; IPCS 1995). According to Bellinger (1995), the "lack of consistency in findings could be due to differences among study cohorts in exposure/toxicokinetic factors (e.g., dose, timing), differences in the environmental characteristics (e.g., co-exposures, co-morbidity, developmental supports, assessment setting), or differences in the distribution of genetic characteristics that affect lead metabolism." Gatsonis and Needleman (1992) identified a different set of statistical and methodological issues that have contributed to the inconsistencies: (1) selection of adequate markers of exposure or internal dose, (2) measuring outcome with instruments of adequate sensitivity, (3) identifying, measuring and controlling for factors which might confound the lead effect, (4) recruiting and testing a sample large enough to provide adequate statistical power to detect a small effect, (5) designing a study which avoids biases in sample selection and (6) assessing the effect of measurement error. Despite the problems encountered, the overall conclusion is that there appears to be a modest association between indices of lead burden, usually PbB, and global indices of development or neuropsychological functioning, usually IQ. Support for this is provided by the results of several meta-analyses and other analyses of cross-sectional and/or prospective studies (Needleman and Gatsonis 1990; Pocock et al. 1994; Schwartz 1994; IPCS 1995). These analyses, briefly summarized below, concluded that a doubling of PbB from 10 to 20 μg/dL is associated with an average IQ loss of 1–3 points.

Needleman and Gatsonis (1990) conducted a meta-analysis of 12 studies 7 of which used blood lead as measure of exposure and 5 used tooth lead. Covariates examined by the studies were socioeconomic status (SES); parental factors (i.e., parent health score); parent IQ; parental rearing measures; perinatal factors (i.e.,birth weight, length of hospital stay after birth); physical factors (i.e., age, weight, medical history), and gender. The t-value of the regression coefficient for lead was negative in all but one study, and ranged from -0.36 to 0.48 in the PbB group and from -3 to -.03 in the tooth lead group. Their analysis also showed that no single study appeared to be responsible for the significance of the final finding.

Pocock et al. (1994) analyzed 5 prospective studies, 14 cross-sectional studies of blood lead, and 7 cross-sectional studies of tooth lead separately and all together. Only studies published since 1979 were included in the analysis. Analyses of the prospective studies showed no association of cord blood lead or antenatal maternal blood lead with subsequent IQ. PbB at around age 2 had a small and significant inverse association with IQ which was greater than that for mean PbB over the preschool years; the estimated mean

change was -1.85 IQ points for a change in PbB from 10 to 20 µg/dL. For the cross-sectional studies of PbB, the combined estimate for mean change in IQ for a change in PbB from 10 to 20 µg/dL was -2.53 IQ points. For the cross-sectional studies of tooth lead, the mean change in IQ for a change in tooth lead from 5 to 10 µg/g was -1.03 IQ points. Comparison of the association with and without adjustment for covariates showed that, with few exceptions, adjusting reduced the association by less than 1.5 points. Analysis of the 26 studies simultaneously indicated that a doubling of PbB from 10 to 20 µg/dL or of tooth lead from 5 to 10 µg/g is associated with a mean deficit in Full Scale IQ of around 1–2 IQ points. A threshold below which there is negligible influence of lead could not be determined.

The analysis carried out by Schwartz (1994) included a total of eight studies, three longitudinal and five cross-sectional, relating blood lead to Full Scale IQ in school age children. To evaluate potential confounding, the baseline meta-analysis was followed by sensitivity analyses in order to contrast results across studies that differ on key factors that are potential confounders. The analyses showed an estimated decrease of 2.57 IQ points for an increase in PbB from 10 to 20 µg/dL. Analyses that excluded individual studies showed that no single study appeared to dominate the results. For longitudinal studies, the loss was 2.96 IQ points and for cross-sectional, 2.69 IQ points. For studies in disadvantaged populations, the estimated IQ loss was 1.85 IQ points versus 2.89 IQ points in nondisadvantaged populations. Also of interest in Schwartz's analysis was the fact that a trend towards a higher slope at lower blood lead levels was seen. Direct analysis of the Boston prospective study (Bellinger et al. 1992), which had the lowest mean PbB concentration (6.5 µg/dL) showed no evidence of a threshold for the effects of lead on IQ.

The European Multicenter Study (Winneke et al. 1990) combined eight individual cross-sectional studies from eight European countries which shared a common protocol with inherent quality assurance elements. A total of 1,879 children, age 6–11 years, were studied. PbB concentration was used as a measure of exposure and the range was 5–60 µg/dL. The overall statistical analysis was done using a uniform predetermined regression model with age, gender, occupational status of the father, and maternal education as confounders or covariates. The results of the analyses showed an inverse association between PbB and IQ of only borderline significance ($p<0.1$), and a decrease of 3 IQ points was estimated for a PbB increase from 5 to 20 µg/dL. Much higher and significant associations were found for tests of visual-motor integration and in serial choice reaction performance. Yet, the outcome variance explained by lead never exceeded 0.8% of the total variance. No obvious threshold could be located on the dose-effect curves.

A Task Group on Environmental Health Criteria for Inorganic Lead conducted separate meta-analyses on four prospective studies and four cross-sectional studies (IPCS 1995). The European Multicenter Study was one of the cross-sectional studies included in the analyses. The outcome measured was Full Scale IQ at age 6–10 years old, and the measure of exposure was concentration of lead in blood. In the analyses of prospective studies, when cumulative exposure rather than lead at a specific time was used as measure of exposure, the association between changes in PbB and changes in IQ did not reach statistical significance ($p>0.05$). However, weighing studies according to the inverse of their variance produced a weighed mean decrease in Full Scale IQ of 2 points for a 10 µg/dL increase in PbB level. When blood lead levels at specific times were considered, the inverse association varied from significant and very strong to less strong and of borderline significance, depending on the specific time chosen. Analyses of cross-sectional studies showed a significant inverse association between increase in blood lead an decrease in IQ in only 2 out 10 studies, however, there was no evidence of statistical heterogeneity. The meta-analysis estimated that Full Scale IQ was reduced by 2.15 IQ points for an increase on PbB from 10 to 20 µg/dL. IPCS (1995) also confirmed that the positive association between lead measures and indicators of social disadvantage. When social and other confounding factors are controlled, the effect in most cases was to reduce the strength of the association between lead measures and IQ without, however, changing the direction.

It should be noted that the effects of blood lead on IQ and other neurobehavioral scores are very small compared with the effects of other factors such as parent's IQ or vocabulary (Fulton et al. 1987; Pocock et al. 1987; Winneke et al. 1985a). Lead neurotoxicity, however, may have major implications for public health when exposure is considered in terms of large populations and its preventable nature (Davis and Svendsgaard 1987; Grant and Davis 1989).

Hearing thresholds in children may be affected adversely by lead exposure at low blood lead levels (Robinson et al. 1985; Schwartz and Otto 1987, 1991). Robinson et al. (1985) reported that hearing thresholds increased linearly with maximum historical PbB levels of 6.2–56.0 µg/dL. In the analyses by Schwartz and Otto (1987, 1991), the probability of lead levels studied (NHANES II and HHANES data, respectively), from <4 to >50 µg/dL, with no apparent threshold. There is also some evidence suggesting that lead exposure may cause postural disequilibrium in children (Bhattacharya et al. 1993). The children evaluated in that study had a geometric mean PbB for the first 5 years of life of 11.9 µg/dL, the range was 5.1 to 28.2 µg/dL.

Evidence of electrophysiological changes (altered slow-wave voltage during conditioning, changes in evoked potential measures and peripheral nerve conduction velocities) has been observed in children at low PbB levels (15–30 µg/dL and possibly lower) (EPA 1986a; Holdstein et al. 1986; Landrigan et al. 1976; Otto et al. 1981, 1982, 1985; Robinson et al. 1987; Rothenberg et al. 1994; Winneke et al. 1984). Results from recent studies have also suggested that lead may affect visual evoked potentials in children who had a geometric PbB concentration of 4.3 µg/dL (range, 1.4-17.4 µg/dL) (Altmann et al. 1998; Winneke et al. 1994).

Delays in reflex development have been reported in rats during early postnatal life at PbB levels $59 µg/dL (Kishi et al. 1983), and alterations in visual evoked responses and decreased visual acuity in young rats occurred at mean PbB levels of 65 µg/dL (Cooper et al. 1980; Fox et al. 1977, 1982; Impelman et al. 1982; Winneke 1980). Decreased visual acuity persisted through 90 days of age even though exposure was terminated at 21 days of age.

Neurobehavioral effects, measured in various discrimination reversal and operant learning tests, were observed in lead exposed rats. PbB levels in rats as low as 15–20 µg/dL were associated with slower learning and higher rates of inappropriate responses (Cory-Slechta et al. 1985; Jadhav and Areola 1997). Neurobehavioral alterations were also reported in young rats that had been exposed to lead via maternal milk, but that at the time of testing had PbB levels below the detection limit (Cory-Slechta et al. 1992). Similar experiments in monkeys support the findings in rats, with even lower PbB levels associated with adverse effects, levels that were comparable to those at which subtle effects are seen in human children. Monkeys given a soluble lead compound at 0.05 mg lead/kg/day orally from birth until neurobehavioral testing at 3–4, 6–7, and 9–10 years of age had peak and steady-state PbB levels of 15.4 and 10.9 µg/dL and performed significantly less well in learning discrimination reversal and delayed alternation tasks than did controls (Gilbert and Rice 1987; Rice 1985a, 1985b). In addition, monkeys orally exposed to lead for the first year with average blood lead levels of 32 µg/dL had neurobehavioral effects that persisted from termination of exposure at 1 year through 49–55 months of age, at which time PbB levels had decreased to 5 µg/dL, virtually the same as control values (Bushnell and Bowman 1979b, 1979c). Lilienthal and Winneke (1996) reported long lasting altered brain stem auditory evoked potentials in monkeys 18 months after termination of chronic lead exposure, at which time PbB concentration had returned to nearly normal values. Persistent neurobehavioral alterations (open field behavior) were reported also by Ferguson and Bowman (1990) in monkeys tested 3 years after cessation of exposure; however, no such effects were observed when the monkeys were tested at 7 years of age (Ferguson et al. 1996).

The overall evidence from studies in animals supports the observations of lead neurobehavioral effects in humans. As pointed out by Cory-Slechta (1995), studies in animals "have provided a direct measurement of the behavioral process per se, and have done so in the absence of the covariates (e.g., socioeconomic status, parental IQ) known to affect IQ scores in human studies." It is also worth noting that animal studies, in which the experimental design is carefully controlled, have shown that the timing of exposure is crucial, that different neurobehavioral outcomes are affected differently (different thresholds), and that some behavioral alterations last longer than others.

Reproductive Effects. There is sufficient qualitative evidence to support the conclusion that at high occupational exposure levels lead has significant adverse effects on human reproduction, including increased incidences of spontaneous abortion, miscarriages, and stillbirths. The mechanisms responsible for these effects are unknown at this time, but many factors may contribute to these results. These factors include indirect effects of lead on maternal nutrition or hormonal status before and during pregnancy to more direct gametogenic effects that could affect parental fertility in either sex. The available data do not permit any estimate of effect levels in women, although two studies found no effect on the rate of spontaneous abortions at PbB levels of 10 μg/dL. Regarding male reproductive function, evidence is accumulating from the more recent studies (Alexander et al. 1996; Gennart et al. 1992b; Lerda 1992; Lin et al. 1996) that adverse effects such as lowered sperm counts, and increases in the numbers of abnormal sperm may be associated with PbB concentrations below the currently accepted worker protection criteria of 40 μg/dL. Studies that did not find decreased fertility among lead-exposed male workers are not necessarily in contradiction with those that did find such an effect. As discussed for example by Bonde and Kolstad (1997) in their study of Danish workers, reduced fecundity does not necessarily translate into reduced fertility in populations such as the Danish one where most couples plan the size of their family and have easy access to contraception. Impairment of fecundity may go on unnoticed because couples continue to try until they become pregnant.

Studies in animals have, in general, been supportive of the reproductive findings of studies in humans. Studies in male monkeys exposed for lifetime and using exposure protocols to evaluate different developmental ages have reported structural alterations in the testis at PbB levels relevant to the human population (Foster et al. 1996, 1998). Moreover, exposure only during infancy resulted in noticeable alterations at the age of 10 years (Foster et al. 1998). Studies in a rat "lifetime" model showed that continuous lead exposure produces a developmental delay in sexual maturity (Ronis et al. 1998b, 1998c) by suppressing the normal sex steroid surges observed at birth and during puberty.

Developmental Effects. Evidence from human studies on congenital anomalies as an end point (Ernhart et al. 1985, 1986; McMichael et al. 1986; Needleman et al. 1984) indicate no association between prenatal exposure to low levels of lead and the occurrence of major congenital anomalies. This conclusion is further supported by developmental toxicity studies conducted in rats and mice; these studies provide no evidence that lead compounds (acetate or nitrate) are teratogenic when exposure is by natural routes (i.e., inhalation, oral, dermal). Intravenous or intraperitoneal injection of lead compounds (acetate, chloride, or nitrate) into pregnant rats, mice, or hamsters, however, has produced malformations in several studies reviewed by EPA (1986a).

The effects of low levels of lead on birth weight and gestational age are controversial. The earlier evidence for such effects was not reproduced in more studies by Factor-Litvak et al. (1991) and Greene and Ernhart (1991). A significant inverse association between prenatal maternal blood lead levels and birth weight was reported in the Cincinnati study (Bornschein et al. 1989; Dietrich et al. 1986, 1987a). An earlier study showed that the percentage of small-for-gestational-age infants increased with increasing cord blood lead, although the trend was not quite statistically significant (Bellinger et al. 1984). Significant direct associations between maternal and cord PbB levels and birth weight were reported by McMichael et al. (1986). On the other hand, no association has been observed between maternal or cord PbB levels and birth weight in several other studies (Ernhart et al. 1985, 1986; Factor-Litvak et al. 1991; Greene and Ernhart 1991; Moore et al. 1982; Needleman et al. 1984).

Evidence from some of the above studies also indicates that gestational age may be reduced as prenatal lead exposure increases, even at blood lead levels below 15 µg/dL (EPA 1986a). Significant negative correlations between maternal or cord PbB levels and gestational age were reported by Dietrich et al. (1986, 1987a), McMichael et al. (1986), and Moore et al. (1982). Based on parameter estimates of Dietrich et al. (1986), the reduction in gestational age was 0.6 week per natural log unit of PbB increase (EPA 1986a). Based on risk estimates of McMichael et al. (1986), the risk of preterm delivery increases by at least fourfold as either cord PbB or maternal PbB level at delivery increases from #8 to >14 µg/dL. However, other investigators did not find a significant relationship between maternal or cord PbB level and gestational age (Bellinger et al. 1984; Factor-Litvak et al. 1991; Needleman et al. 1984).

As mentioned in the section on Neurological Effects, studies that examined the neurodevelopmental effects of low level lead exposure in children have not been totally consistent. Part of the difference can be attributed to different experimental designs (Bellinger 1995). Several indices of exposure have been used

including prenatal (maternal) PbB, neonatal (cord lead) blood lead, postnatal PbB at various ages, and dentin lead. In addition, studies used different neurobehavioral tests. In spite of this, it appears that some neurodevelopmental deficits observed around 2 years of age and thereafter are much better correlated with postnatal indices of lead exposure than with prenatal or cord PbB levels. In some studies, neurodevelopmental impairment (at age 5) has been correlated at 24 months of age with mean PbB levels as low as 7 μg/dL (Bellinger et al. 1991). In general, the degree of neurodevelopmental impairment is considered modest. However, although a 2–8-point decline in Mental Developmental Index (MDI) score for an individual child may not be clinically significant, a 4-point downward shift in a normal distribution of MDI scores of a population of children would result in 50% more children scoring below 80, a consequence of great concern to public health (Davis and Svendsgaard 1987; Grant and Davis 1989). Furthermore, even small decrements in performance, when they occur at a critical or important time such as the early years of school when children learn the most fundamental skills, can have detrimental effects for long periods thereafter. Additional evidence of an association between relatively low PbB levels and neurobehavioral effects in children is reported in Section 2.2.1.4.

Some studies demonstrating neurobehavioral and developmental effects discussed in this section on developmental toxicity as well as in the previous section on neurobehavioral toxicity have been criticized for methodological flaws, including handling of cofactors (EPA 1986a; Ernhart 1988). ATSDR (1988) and EPA (1986a) have taken such criticisms into account, and have concluded that the findings associating relatively low blood lead levels with neurobehavioral and developmental effects in children are nonetheless cause for concern. It should be noted that some of the studies that demonstrated no such association, have also been criticized for methodological flaws and bias towards Type II (false negative) errors (Needleman 1987b; Needleman and Bellinger 1987). Although no single study associating low blood lead levels with reduced cognitive performance in children is definitive, the results of several meta-analyses of both prospective and cross-sectional studies suggest a small inverse association between measures of lead exposure and neurodevelopmental indices (IPCS 1995; Needleman and Gatsonis 1990; Pocock et al. 1994; Schwartz 1994).

In summary, on the basis of IQ measurements, which provide a better degree of comparability between the studies than various sensorimotor paradigms, it appears that a highly significant IQ decrement of 1–3 points is associated with a change of PbB from 10 to 20 μg/dL. This relationship is supported by prospective and cross-sectional studies (see IPCS 1995; Needleman and Gatsonis 1990; Pocock et al. 1994; Schwartz 1994 for individual studies included in the meta-analyses).

Children appear to be much more sensitive to lead-related neurobehavioral alterations than adults. Neurobehavioral dysfunction has not been demonstrated in lead-exposed workers at PbB concentrations below 40 µg/dL, whereas cognitive and sensorimotor deficits have been shown in children to be associated with PbB concentrations as low as 10 to 15 µg/dL. To put these findings in perspective, a 1–3 point IQ decrement corresponds to 1/5 or less of a standard deviation of the typical IQ distribution. While this qualifies as a small population-effect, the normal variability of individual susceptibility means that there may be a larger IQ deficit in particularly vulnerable individuals.

Animal studies support he human evidence of neurobehavioral toxicity from prenatal exposure to low levels of lead. In an extensive review of the literature, Davis et al. (1990) discussed similarities between human effects and those in animals. The authors concluded that qualitatively ". . . the greatest similarities between human and animal effects involve cognitive and relatively complex behavioral processes such as learning." They further reported that quantitative relationships for PbB levels across species that cause developmental neurobehavioral effects are 10–15 µg/dL in children, <15 µg/dL in primates, and <20 µg/dL in rodents.

In contrast to the animal studies for prenatal exposure, animal studies for postnatal exposure report effects at blood lead levels similar to those associated with effects in humans.

Genotoxic Effects. Evaluation of the genotoxicity of lead in humans has focused on evaluations of lymphocytes from occupationally or environmentally exposed persons (Table 2-10) and *in vitro* studies of structural chromosomal aberrations and sister chromatid exchange in cultures of lymphocytes taken from healthy individuals (Table 2-11). Results of studies with human lymphocyte cultures exposed *in vitro* to lead acetate were nearly equally divided between positive (Beek and Obe 1974; Niebuhr and Wulf 1984) and negative (Beek and Obe 1975; Deknudt and Deminatti 1978; Gasiorek and Bauchinger 1981; Schmid et al. 1972).

Maternal and fetal chromosomal aberrations were observed in mice following prenatal exposure to subembryotoxic doses of lead nitrate (Nayak et al. 1989a). Pregnant Swiss Webster mice were given intravenous doses of lead nitrate at levels of 12.5, 25, 50, and 75 mg/kg body weight on the 9th day of gestation. On day 18, the animals were killed, and maternal bone marrow cells and fetal liver cells were examined for chromosomal aberrations. Low levels of constitutive changes mostly in the form of deletions were seen at all doses administered in both maternal and fetal cells indicating that prenatal exposure to lead may induce genotoxic changes in the fetus.

Table 2-10. Genotoxicity of Lead *In Vivo*

Species (test system)	End point	Results	Reference
Drosophila melanogaster	Chromosome loss or nondisjunction	–	Ramel and Magnusson 1979
Mouse bone marrow, rat bone marrow, mouse leukocyte, monkey lymphocyte, rabbit	Structural chromosomal aberrations or gaps, micronucleus formation; unscheduled DNA synthesis, sister chromatid exchange	±	Bruce and Heddle 1979; Deknudt and Gerber 1979
		+	Deknudt et al. 1977
		+	Jacquet and Tachon 1981
		–	Jacquet et al. 1977
		–	Muro and Goyer 1969
		+	Tachi et al. 1985
		–	Willems et al. 1982
		+	Jagetia and Aruna 1998
Human, occupational	Chromosomal aberration	+	Al-Hakkak et al. 1986
		–	Bauchinger et al. 1977
		+	Forni et al. 1976
		–	Mäki-Paakkanen et al. 1981
		+	Nordenson et al. 1978
		±	O'Riordan and Evans 1974
		+	Schwanitz et al. 1970, 1975
		+	Huang et al. 1988b
		–	Schmid et al. 1972
Human, occupational exposure	Sister chromatid exchange	–	Grandjean et al. 1983
		–	Mäki-Paakkanen et al. 1981
Human, environmentally exposed children		–	Dalpra et al. 1983
		–	Leal-Garza et al. 1986
		–	Huang et al. 1988b
Human	Effects on cell division	+	Bulsma and DeFrance 1976
		+	Forni et al. 1976
		+	Sarto et al. 1978
		+	Schwanitz et al. 1970

– = negative result; + = positive result; —/+ = inconclusive result; DNA = deoxyribonucleic acid

Table 2-11. Genotoxicity of Lead *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Salmonella typhimurium (reverse mutation); *Escherichia coli* (forward mutation, DNA modification); *Saccharomyces cerevisia* (reverse mutation); *Bacillus subtilis* (rec assay)	Gene mutation or DNA modification	–	–	Bruce and Heddle 1979; Dunkel et al. 1984; Fukunaga et al. 1982; Kharab and Singh 1985; Nestmann et al. 1979; Nishioka 1975; Rosenkranz and Poirier 1979; Simmon 1979b
S. cerevisiae	Gene conversion or mitotic recombination	–	–	Fukunaga et al. 1982; Kharab and Singh 1985; Nestmann et al. 1979; Simmon 1979a
E. coli RNA polymerase or Avian myetoblastosis DNA polymerase	RNA or DNA synthesis	NA	+	Hoffman and Niyogi 1977; Sirover and Loeb 1976
Chinese hamster ovary cells; Syrian hamster embryo cells	Chromosomal aberration, DNA repair, mitotic disturbance	NA	+	Bauchinger and Schmid 1972; Costa et al. 1982; Robison et al. 1984; Zelikoff et al. 1988; Ariza et al. 1998
Human lymphocyte cultures	Structural chromosomal aberration	NA	+	Beek and Obe 1974
			–	Deknudt and Deminatti 1978
			–	Gasiorek and Bauchinger 1981; Schmid et al. 1972
Human lymphocyte cultures	Sister chromatid exchange	NA	–	Beek and Obe 1975
			+	Niebuhr and Wulf 1984

— = negative result; + = positive result; DNA = deoxyribonucleic acid; NA = not applicable; RNA = ribonucleic acid

A single intracardiac dose of 40 µg/g body weight lead acetate induced a 25-fold increase in mitosis of mouse liver cells 5 hours after injection (Choie and Richter 1978). Results were mixed for various manifestations of genotoxicity or cell cycle disruptions in several experiments with lead acetate in mammals (Bruce and Heddle 1979; Deknudt and Gerber 1979; Deknudt et al. 1977; Jacquet and Tachon 1981; Jacquet et al. 1977; Muro and Goyer 1969; Tachi et al. 1985; Willems et al. 1982).

Acute intraperitoneal exposure to 25 mg lead/kg as acetate resulted in no increase in the number of micronuclei in bone marrow polychromatic erythrocytes in mice examined 6 hours after dosing (Jacquet et al. 1977). In contrast, a significant increase in the frequency of micronuclei was observed in bone marrow from mice treated intraperitoneally with single doses of 0.4 to 50 mg lead/kg as lead nitrate; increases were observed 12 to 36 hours after dosing (Jagetia and Aruna 1998). The response was not dose-related. With few exceptions, the frequency of micronuclei was significantly higher in male mice than in females at all doses and at all post-treatment periods. Lead acetate administered intraperitoneally to Sprague-Dawley rats caused an increase in the percentage of aberrant bone marrow cells in female, but not male rats. The aberrations were primarily chromatid gaps, although there was no dose dependency across the four dose points used (Tachi et al. 1985).

Several genotoxic end points were assayed in male rabbits after subcutaneous injection of doses of 0, 0.25, and 0.50 mg lead acetate/kg body weight 3 times a week for 14 weeks. No treatment-related effects were seen in sperm count, morphologic abnormalities of sperm, histopathology of the testes, or on the number of sister chromatid exchanges in lymphocytes or the relative number of micronuclei in bone marrow erythrocytes (Willems et al. 1982). Tests for gene mutations, DNA modification, and recombinations in various microorganisms (See Table 2-11) using lead acetate (Bruce and Heddle 1979; Dunkel et al. 1984; Nishioka 1975; Rosenkranz and Poirier 1979; Simmon 1979a, 1979b; Simmon et al. 1979), lead nitrate (Kharab and Singh 1985), and lead chloride (Fukunaga et al. 1982; Nishioka 1975) were consistently negative with or without metabolic activation. Lead chloride was shown to be mutagenic in *Salmonella typhimurium* strain TA102 without S9 activation; it was nonmutagenic in three other strains with and without activation (Wong 1988). A positive response was observed by Nestmann et al. (1979) for lead chromate, but further testing clarified that the positive response was associated with the chromate rather than the lead moiety. Lead chloride has been shown to inhibit both RNA (Hoffman and Niyogi 1977) and DNA (Sirover and Loeb 1976) synthesis.

In mammalian test systems *in vitro* (Syrian or Chinese hamster cells), lead acetate gave conflicting results for structural chromosomal aberrations (Bauchinger and Schmid 1972; Robison et al. 1984). Lead acetate increased the frequency of DNA repair (Robison et al. 1984), and the frequency of achromatic lesions and gaps (Bauchinger and Schmid 1972); both lead acetate (Bauchinger and Schmid 1972) and lead sulfate (Costa et al. 1982) interfered with normal mitotic division. Both lead sulfide and lead nitrate were mutagenic at the hypoxanthine guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster V79 cells (Zelikoff et al. 1988). Because these investigators failed to demonstrate either sister chromatid exchange induction or DNA single-strand breaks following treatment with either lead compound, they propose an indirect mechanism of genotoxicity probably involving DNA repair enzymes. A series of experiments with lead acetate alone and lead acetate in conjunction with ultraviolet radiation indicate that the mechanism of genotoxicity of lead ions may indeed be an indirect one (Hartwig et al. 1990). Lead acetate alone did not induce DNA-strand breaks in HeLa cells or mutations at the HPRT locus, nor did it increase sister chromatid exchange frequency in V79 Chinese hamster cells. However, for all end points tested, lead ions interfered with the processing of UV-induced DNA damage, thus increasing the frequency of the end points measured. These authors suggested the possibility of interference with repair enzymes such as polymerase or ligase, or else interaction with calcium-regulated processes. An interaction with calcium-regulated processes, such as those modified by calmodulin, would be consistent with other observed interactions with calcium levels (Deknudt et al. 1977). Lead is also known to form complexes with amine and carboxyl groups of proteins, which in turn can lead to enzyme inactivation (Bota et al. 1982). A recent study using Chinese hamster ovary cells suggested that the mutagenicity of lead may be due to lead-induced formation of reactive oxygen intermediates such as hydrogen peroxide (Ariza et al. 1998).

Cancer. The information available on the carcinogenicity of lead in occupationally exposed humans is limited in its usefulness because the lead compound(s), the route(s) of exposure, and the levels of exposure were not always reported. Furthermore, concurrent exposure to other chemical (including arsenic, particularly in lead smelters) and confounding variables, such as smoking, were often not evaluated. Therefore, the data currently available do not support an assessment of the potential carcinogenic risk of lead in humans.

Fu and Boffetta (1995) conducted a meta-analysis of case-control and cohort epidemiology studies focusing on overall cancer, stomach cancer, lung cancer, kidney cancer, and bladder cancer. They found a significant excess risk of overall cancer, lung cancer, and bladder cancer. The corresponding relative risk ratios (RR)

and 95% CI were 1.11 (1.05–1.17), 1.29 (1.10–1.50), and 1.41 (1.16–1.71). The RR for kidney cancer was also high, but did not achieve statistical significance. When meta-analysis was restricted to studies that were conducted in battery or smelter industries where exposure to lead was heavy, slightly higher RRs for cancers of the stomach (1.50) and lung (1.42) were found. A serious limitation of this analysis is that no corrections for confounders could be made because there were no data available in most reports. Some of these confounders included cumulative exposure to lead, smoking and dietary habits, and exposure to other chemicals.

According to EPA (IRIS 1999), the available human epidemiological studies lack quantitative exposure data for lead and for possible confounding exposures (e.g., arsenic, smoking). Cancer excesses in the lung and stomach of lead-exposed workers that are reported are relatively small, dose-response relationships are not demonstrated neither is there consistency in the site of cancers reported. EPA (IRIS 1999) concluded that the human data are inadequate to refute or demonstrate the potential carcinogenicity of lead exposure.

The available data on the carcinogenicity of lead following ingestion by laboratory animals indicate that lead is carcinogenic, and that the most common tumors to develop are renal tumors (Azar et al. 1973; Koller et al. 1985; Van Esch and Kroes 1969). Administration of lead compounds by the parenteral route produced similar results. Lead subacetate was positive at high dosages in the strain A mouse lung adenoma bioassay (Poirier et al. 1984; Stoner et al. 1976), but the positive response was blocked by simultaneous administration of calcium or magnesium acetate (Poirier et al. 1984). Subcutaneous administration of lead phosphate to rats was associated with high incidence of renal tumors (Balo et al. 1965; Zollinger 1953). Lead acetate was positive in Syrian hamster embryo cell transformation tests (Dunkel et al. 1981; Pienta et al. 1977), in MLV-infected rat embryo cell transformation test (Dunkel et al. 1981), and in enhanced simian adenovirus (SA-7) transformation of Syrian hamster embryo cells (Casto et al. 1979). Lead oxide also enhanced SA-7 transformation of Syrian hamster embryo cells (Casto et al. 1979).

The extremely high cumulative doses of lead used in these studies are difficult to extrapolate to low-level exposure in humans, and thus do not provide a sufficient basis for quantitative risk assessment (see discussion below). In addition, it is possible that the high doses required to induce renal tumors may have produced a carcinogenic effect that resulted from nonspecific tissue damage and was independent of any direct effect of lead. Furthermore, the relevance of chemically-induced male rat kidney tumors to potential carcinogenicity in humans has been questioned (EPA 1991c). IPCS (1995) reviewed the literature on cancer and lead and concluded that “renal tumors can occur in rats and mice administered high doses of

lead. However, the evidence for the carcinogenicity of lead and inorganic lead compounds in humans is inadequate."

Nonetheless, EPA (1988b) concludes that the animal data are sufficient to demonstrate that lead and (inorganic lead) compounds, particularly soluble lead salts, are carcinogenic to animals. Although dose-response data are available from animal studies, EPA (1988b) recommends that a numerical estimate of cancer potency or risk based on such data should not be used because of the uncertainties involved in such an extrapolation, some of which may be unique to lead. Current knowledge of the pharmacokinetics of lead indicates that an estimate derived by standard methods would not adequately delineate the potential risk (IRIS 1999). EPA (IRIS 1999) has assigned lead and (inorganic) lead compounds a classification of B2, probable human carcinogen.

The International Agency for Research on Cancer (IARC 1987) concluded that the evidence for carcinogenicity of lead and inorganic lead compounds was inadequate in humans and sufficient in animals. IARC (1987) classified lead and inorganic lead compounds in IARC Group 2B, possible human carcinogen. The Department of Health and Human Services (DHHS) has determined that lead acetate and phosphate may reasonably be anticipated to be carcinogens based on sufficient evidence from animal studies, but inadequate evidence from human studies (NTP 1994).

The association of colorectal cancer with exposure to tetraethyl lead manufacturing is currently being investigated (Fayerweather et al. 1997).

2.6 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 5.6, Exposures of Children.

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

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

Health effects that have been associated with lead exposures during infancy or childhood include, anemia (Schwartz et al. 1990) (and related disorders of heme synthesis), neurological impairment (e.g.,

encephalopathy), renal alterations, and colic (Chisolm 1962, 1965; Chisolm and Harrison 1956), and impaired metabolism of vitamin D (Mahaffey et al. 1982; Rosen and Chesney 1983). Death from encephalopathy may occur with PbB levels $125 µg/dL. In addition to the above effects, the following health effects have been associated with lead exposures either *in utero*, during infancy or during childhood: delays or impairment of neurological development, neurobehavioral deficits including IQ deficits, growth retardation, low birth weight, and low gestational age (Bellinger et al. 1987a; Dietrich et al. 1987a, 1987b; McMichael et al. 1986; et al. 1989a). These effects, which are discussed in Section 2.2.1, are consistent with findings in animals exposed to lead. Effects of lead observed at relatively high exposures such as anemia, colic and encephalopathy, also occur in adults. There is no evidence that exposure to lead causes structural birth defects in humans or in animals. Exposure to lead during childhood may result in neurobehavioral effects that persist into adulthood (e.g., Stokes et al. 1998).

Children are more susceptible to lead toxicity than adults. This higher susceptibility derives from numerous factors. Children exhibit more severe toxicity at lower exposures than adults, as indicated by lower PbB concentrations and time-integrated PbB concentrations that are associated with toxicity in children (See Sections 2.2.1.4 and 2.2.1.6 for more detailed discussion). This suggests that children are more vulnerable to absorbed lead than adults. The mechanism for this increased vulnerability is not understood. Children also absorb a larger fraction of ingested lead than do adults; thus, children will experience a higher internal lead dose per unit of body mass than adults at similar exposure concentrations (Alexander et al. 1974; Blake et al. 1983; James et al. 1985; Rabinowitz et al. 1980 Ziegler et al. 1978). Absorption of lead appears to be higher in children who have low dietary iron or calcium intakes; thus, dietary insufficiencies, which are not uncommon in lower socioeconomic children, may contribute to their lead absorption (Mahaffey and Annest 1986; Mahaffey et al. 1986; Marcus and Schwartz 1987; Ziegler et al. 1978) (see Section 2.3.1.2 for more detailed discussion of lead absorption in children). Insufficient dietary zinc, also not uncommon in children, may contribute to their increased susceptibility to lead, since lead impairs the activity of zinc-requiring enzymes in the heme biosynthesis pathway (see Section 2.4.2). Infants are born with a lead body burden that reflects the burden of the mother (Abdulla et al. 1997b; Goyer 1990; Graziano et al. 1990; Schuhmacher et al. 1996). During gestation, lead from the maternal skeleton is transferred across the placenta to the fetus (Gulson et al. 1997). Additional lead exposure may occur during breast feeding (Keller and Doherty 1980a; Palminger Hallén et al. 1995, 1996a, 1996b) (see Section 2.3.3 for more detailed discussion). This means that lead stored in the mother's body from exposure prior to conception can result in exposure to the fetus or nursing neonate. Behavioral patterns of children can result in higher rates of ingestion of soil and dust, both of which are often important environmental depots for lead (Barnes 1990;

Binder et al. 1986; Calabrese et al. 1989, 1997; Clausing et al. 1987). Examples of activities that tend to promote soil and dust ingestion preferentially in children include playing and crawling on the ground and floor, hand-to-mouth activity, mouthing of objects, and indiscriminate eating of food items dropped or found on the ground or floor (see Section 5.6 for more detailed discussion). Some children engage in pica, or the ingestion of non-food items (e.g., soil). This behavior can lead to excess exposure if a child consumes soil contaminated with lead.

The toxicokinetics of lead in children appears to be similar to that in adults, with the exception of the higher absorption of ingested lead in children. Most of the lead body burden in both children and adults is in bone; a slightly large fraction of the body burden in adults resides in bone (Barry 1975). The difference may reflect the larger amount of trabecular bone and bone turnover during growth; trabecular bone has a shorter retention halftime for lead than does cortical bone (See Section 2.3.3 for details). Limited information suggests that organic lead compounds undergo enzymatic (cytochrome P-450) biotransformation and that inorganic lead is complexed (non-enzymatically) with proteins and non-protein ligands. However, the information available is insufficient to determine whether the metabolism of lead in children is similar to adults. Several models of lead pharmacokinetics in children have been developed (EPA 1994a, 1994b; Leggett 1993; O'Flaherty 1993, 1995a); these are described in Section 2.3.5.

The important biomarkers of exposure that have been explored in children include PbB concentration (CDC 1991), bone lead levels (as measured from non-invasive with XRF measurements of phalanx, patella, tibia or ulna), and lead levels in deciduous teeth (Hu et al. 1998). Lead in blood has a much shorter retention half-time than lead in bone (days compared to years); therefore, PbB concentration provides a marker for more recent exposure, while lead in bone appears to reflect longer-term cumulative exposures (Borjesson et al. 1997; Nilsson et al. 1991; Schutz et al. 1987). Lead in tooth enamel is thought to reflect exposures *in utero* and during early infancy, during which development of tooth enamel and coronal dentine is completed. Lead appears to accumulate in dentin after formation of the dentin is complete; therefore, lead in dentin is thought to reflect exposures that occur up to the time the tooth is shed (Gulson 1994, 1996; Rabinowitz 1995; Rabinowitz et al. 1993). A more detailed discussion of the above biomarkers of exposure, as well as other less important biomarkers, is presented in Section 2.7.1. The most sensitive biomarkers of effects of lead in children relate to the effects of lead on heme metabolism, they include δ-amino levulinic acid dehydratase (ALAD) activity, erythrocyte protoporphyrin (EP), free erythrocyte protoporphyrin (FEP), and zinc protoporphyrin (ZPP); however, these are not specific for lead (Bernard and Becker 1988; CDC 1991; Hernberg et al. 1970). EP has been used as a screening test. However, it is not

sensitive below a PbB of about 25 µg/dL. These and other biomarkers of effects of lead are discussed in Section 2.7.2.

Methods for preventing or decreasing the absorption of lead following acute exposures to potentially toxic levels of lead include, removal of the child from the exposure source, removal of lead-containing dirt and dust from the skin and, if the lead has been ingested, standard treatments to induce vomiting. Ensuring a diet that is nutritionally adequate in calcium and iron may decrease the absorbed dose of lead associated with a given exposure level, because lead absorption appears to be higher in children who have low levels of iron or calcium in their diets (Mahaffey and Annest 1986; Mahaffey et al. 1986; Marcus and Schwartz 1987; Ziegler et al. 1978). Diets that are nutritionally adequate in zinc also may be helpful for reducing the risks of lead toxicity because zinc may protect against lead-induced inhibition of zinc-dependent enzymes, such as ALAD (Chisolm 1981; Johnson and Tenuta 1979; Markowitz and Rosen 1981). Methods for reducing the toxicity of absorbed lead include the injection or oral administration of chelating or complexing agents (e.g., EDTA, penicillamine, DMSA) (CDC 1991). These agents form complexes with lead that are more rapidly excreted and, thereby, decrease the body burden of lead. These methods for reducing the toxic effects of lead are described in greater detail in Section 2.10.

2.7 BIOMARKERS OF EXPOSURE AND EFFECT

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

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

nutrients such as copper, zinc, and selenium). Biomarkers of exposure to lead are discussed in Section 2.7.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are often not substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by lead are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.9, Populations That Are Unusually Susceptible.

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Lead

2.7.1.1 Lead in Soft Tissues

Biomarkers of exposure for inorganic and organic forms of lead are usually the measurement of total lead levels in tissues or fluids. Total lead measurements of biological media includes all metabolites and endogenous lead sources as well as any original lead-containing exposure agent. Tetraalkyl lead compounds may also be measured in the breath.

Measurement of PbB concentration is the most widely used biomarker of lead exposure. A PbB level greater than 10 µg/dL indicates that excessive lead exposure may be occurring (CDC 1991). The half-life of lead in human blood is 28–36 days (Griffin et al. 1975b; Rabinowitz et al. 1976); thus, levels in blood reflect relatively recent exposure (Graziano 1994; Lyngbye et al. 1990b). Nevertheless, because lead cycles between the blood and bone, a single blood lead determination cannot distinguish between low-level intermediate or chronic exposure and high-level acute exposure. Both types of exposure could result in the

same blood level because of recycling from bone. Therefore, PbB levels cannot serve as exact measures of lead exposure or the total body lead burden because of the intervening processes of transfer, mobilization, and storage among the different body compartments. Furthermore, the relationship between blood lead and lead exposure and uptake for both inhalation and gastrointestinal exposure is nonlinear, such that the increase in PbB concentration is less at high exposure levels than at low exposure levels (EPA 1986a; Manton and Cook 1984). This behavior may be attributed to changes in tissue lead kinetics, reduced lead absorption, or increased excretion, such that blood lead may be an imperfect measure of tissue lead burdens and of changes in tissue levels in relation to changes in external exposure (EPA 1986a). In addition, there are nonlinear relationships between different metabolic and toxic effects on one hand, and PbB on the other; this is most likely due to saturation of the erythrocytes. Despite the limitations of PbB levels in indexing tissue burden and exposure changes (Skerfving et al. 1993), this parameter still remains the one readily accessible measure that can demonstrate in a relative way the relationship of various effects to increases in exposure. The biological exposure index (BEI) for lead in blood of exposed workers is 30 µg/dL (ACGIH 1996). This PbB level represents the threshold for effects seen in at least some adults; therefore, because of individual variations in sensitivity, many people may not experience the stated effect until much higher PbB levels are reached and conversely, effects can be seen below the stated blood levels. Furthermore, instability of PbB levels have been reported to occur in infants in which the average increase in blood lead from birth to 2 years of age was 5 µg/dL while levels for older children were found to be more stable (Rabinowitz et al. 1984). The influence of age, sex, and smoking may also be potential confounders for the interpretation of PbB measurements (Rabinowitz et al. 1976; Somashekaraiah et al. 1990; Watanabe et al. 1987).

The low concentrations of lead in plasma, relative to red blood cells, has made it extremely difficult to accurately measure plasma lead concentrations in humans, particularly at low PbB concentrations (i.e., less than 20 µg/dL). However, more recent measurements have been achieved with inductively coupled mass spectrometry (ICP-MS), which has a higher analytical sensitivity than earlier atomic absorption spectrometry methods. Using this analytical technique, recent studies have shown that plasma lead concentrations may correlate more strongly with bone lead levels than do PbB concentrations (Cake et al. 1996; Hernandez-Avila et al. 1998). The above studies were conducted in adults, similar studies of children have not been reported.

Urinary lead levels have also been used to measure current exposure (Robinson 1974) but they are of questionable value as biomarkers of exposure because of the relatively low and fluctuating lead levels that

are excreted in the urine (ACGIH 1986; Ibels and Pollock 1986; Jensen 1984). In contrast, the determination of urinary lead following a single injection of the chelating agent, calcium disodium EDTA, which mobilizes extracellular lead and produces increased urinary excretion of lead, is presumed to be indicative of an elevated body burden of lead (Cory-Slechta et al. 1987; Ibels and Pollock 1986; Janin et al. 1985). Children whose PbB levels are $45 µg/dL should not receive a provocative chelation test; they should be immediately referred for appropriate chelation therapy (CDC 1991). Furthermore, work by Cory-Slechta et al. (1987) indicates that diagnostic calcium disodium EDTA chelation may increase the levels of lead in the liver and brain, raising serious concern about continued use of calcium disodium EDTA as a diagnostic tool in children. Other disadvantages of this test are the unknown physiological source of the lead mobilized into urine, and the requirement of parenteral drug administration and nursing care. However, there is some experimental evidence that supports the use of the EDTA chelation test to assess bone lead at least in adults who are not currently exposed to excessive lead burdens (Wedeen 1992). Urinary diethyl lead has been proposed as a qualitative marker of exposure to tetraethyl lead (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

Another indicator of current exposure to lead is hair, which offers the advantage of being a noninvasive stable medium. Hair has been used as an indicator for intermediate exposure (2 months) in children (Wilhelm et al. 1989). However, artificial hair treatment (i.e., dyeing, bleaching, permanents) can invalidate metal analysis of hair (Wilhelm et al. 1989), and external surface contamination make it difficult to differentiate between externally and internally deposited lead (EPA 1986a). Drasch et al. (1997) found lead hair levels to be a poor predictor of PbB concentrations in a group of unexposed subjects with relatively low PbB levels (<12 µg/dL). For example, they estimated that with a statistical probability of 95%, hair with a concentration of 770 ng lead/g may be associated with PbB levels from <0.9 to 12.8 µg/dL. Nevertheless, levels of lead in hair were positively correlated with children's classroom attention deficit behavior in a study (Tuthill 1996) (see Section 2.2.1). Lead in hair was correlated with liver and kidney lead in a study of deceased smelter workers (Gerhardsson et al. 1995b). Nail lead has also been utilized as a marker (Gerhardsson et al. 1995b).

Another method for studying not only lead exposure, but also the source of exposure, is the measurement of stable lead isotopes. Lead has four stable nonradioactive isotopes ^{204}Pb, ^{206}Pb, ^{207}Pb, and ^{208}Pb; the last three are continually being produced by radioactive decay. By measuring the ratio ^{206}Pb/^{207}Pb, which varies greatly according to the geological age of the lead deposit, one can identify the source of the lead in any matrix providing that there is a predominant source. For example, Graziano et al. (1996) observed that the

$^{206}Pb/^{207}Pb$ ratios for subjects from New York City were 1.195 or higher, subjects from Brisbane (Australia) had ratios ranging from 1.095 to 1.145, and Scottish subjects from Glasgow had ratios between 1.105 and 1.115. By using the isotope dilution method, Graziano et al. (1996) estimated in six volunteers that, on the average, 70% of lead ingested from drinking wine stored in a lead-crystal decanter was absorbed, indicating high bioavailability. This method has also been used to determine the source of lead exposure by measuring $^{206}Pb/^{204}Pb$ ratios in teeth, blood, and home environments (Gulson and Wilson 1994; Gulson et al. 1996).

Physiological changes that are associated with lead exposure may be used as biomarkers of exposure. Generally, blood lead levels are determined concurrently with these physiological biomarkers. Interference with heme synthesis following lead exposure can lead to a reduction of hemoglobin concentration in blood (Bernard and Becker 1988) and an increase in urinary coproporphyrin (EPA 1986a). Measurement of specific enzymes or intermediates in the heme synthesis pathway can suggest that lead exposure has occurred. ALAD activity measured in erythrocytes may be associated with recent exposure to lead because, as with PbB levels, there is not a large time lag between exposure and decreased activity of this enzyme in workers occupationally exposed to lead for the first time (Tola et al. 1973). A negative correlation between ALAD activity and PbB levels of 5–95 µg/dL was observed by Hernberg et al. (1970). ALAD was found to be a more sensitive biomarker than urinary ALA and ZPP at PbB concentrations between 21 and 30 µg/dL (Schuhmacher et al. 1997). Consistent with this, PbB, but not ALAD, could be used to discriminate between controls (PbB, 11.3 µg/dL) and workers (PbB, 15.7 µg/dL) exposed to lead for <2 hours/day (Schuhmacher et al. 1997). A limitation of ALAD activity measurement, as a biomarker of exposure, is that the inhibition of the enzyme is so extensive at PbB levels $30 µg/dL that the assay cannot distinguish between moderate and severe exposure (Graziano 1994). A marked increase in urinary excretion of ALA, the intermediate that accumulates from decreased ALAD, can be detected when PbB levels exceed 35 µg/dL in adults and 25–75 µg/dL in children (NAS 1972; Roels and Lauwerys 1987; Schuhmacher et al. 1997); thus, ALA in urine is not considered as sensitive a measure of current lead exposure as ALAD activity (Hernberg et al. 1970).

ALA in plasma was as good a discriminator of lead exposure as ALAD activity in workers at PbB levels between 10 and 40 µg/dL and continued to discriminate up to PbB levels approaching 100 µg/dL (Sakai and Morita 1996). The same group of investigators recently showed that the activity of adenine dinucleotide synthetase (NADS) in erythrocytes is a better predictor of PbB levels >40 µg/dL than ALAD (Morita et al.

1997). The decrease in NADS activity between PbB concentration of 5 and 80 µg/dL was linear with a correlation coefficient of -0.87.

Inhibition of ferrochelatase in the heme pathway causes accumulation of protoporphyrin in erythrocytes (CDC 1985). Most protoporphyrin in erythrocytes (about 90%) exists as zinc protoporphyrin (ZnPP). This fraction is preferentially measured by hematofluorometers. Extraction methods measure all the protoporphyrin present, but strip the zinc from the ZnPP during the extraction process. For this reason, extraction results are sometimes referred to as [zinc] free erythrocyte protoporphyrin (FEP). Although the chemical forms measured by the two methods differ slightly, on a weight basis they are roughly equivalent; thus, results reported as EP, ZnPP, or FEP all reflect essentially the same analyte. The concentration of EP rises above background at blood lead levels of 25–30 µg/dL (CDC 1985); there is a positive correlation between PbB levels and EP (CDC 1985; Hernberg et al. 1970; Tola et al. 1973). Determination of EP in blood is an indicator of past exposure since elevated EP reflects average PbB levels for the past 4 months (ACGIH 1986; Janin et al. 1985). Therefore, EP is better for population investigations than for routine occupational exposure (Haeger-Aronsen et al. 1971). However, other diseases or conditions such as porphyria, liver cirrhosis, iron deficiency, age, and alcoholism may also produce similar effects on heme synthesis (Somashekaraiah et al. 1990). In addition, EP is not sensitive enough to identify children with PbB levels below 25 µg/dL (CDC 1991). Therefore, PbB concentration is a better biomarker of exposure.

Reduction in the serum 1,25-dihydroxyvitamin D concentration has been reported as an indicator of increased lead absorption or lead levels in the blood (Rosen et al. 1980). Lead inhibits the formation of this active metabolite of vitamin D, which occurs in bone mineral metabolism (EPA 1986a; Landrigan 1989). Children with PbB concentrations of 12–120 µg/dL lead showed decreased serum 1,25-dihydroxyvitamin D concentrations comparable to those found in patients with hypoparathyroidism, uremia, and metabolic bone disease (Mahaffey et al. 1982; Rosen et al. 1980). This biomarker is clearly not specific for lead exposure and several diseases can influence this measurement.

In summary, several indices in blood and body tissues are available to serve as biomarkers for lead exposure. Blood lead levels are the easiest and most widely used index of lead exposure. Currently, PbB measurement is the screening test of choice to identify children with elevated PbB levels below about 25 µg/dL (CDC 1991). Venous sampling of blood is preferable to finger prick sampling, which has a considerable risk of surface lead contamination from the finger if proper finger cleaning is not carried out. In children, PbB levels between 10 and 14 µg/dL should trigger community-wide childhood lead poisoning

prevention activities (CDC 1991). Since the half-life of lead in blood is 28–36 days, PbB levels generally reflect relatively recent exposure. However, because of continuous mobilization and recycling of lead from soft tissue and bone, blood lead levels cannot be used to distinguish between low-level intermediate or chronic exposure and high-level acute exposure. Recently, the CDC issued new guidance on screening children for lead poisoning that recommends a systematic approach to the development of appropriate lead screening in states and communities (CDC 1997c). The objective of the new guidelines is maximum screening of high-risk children and reduced screening of low-risk children, as contrasted with previous guidelines (CDC 1991), which recommended universal screening. A PbB level of 50 µg/dL has been determined to be an approximate threshold for the expression of lead toxicity in exposed workers.

Urinary lead is generally not a useful biomarker to estimate general population (i.e., low-level) exposure to lead. However, elevated urinary lead-chelate complexes resulting from the EDTA mobilization test provide a good means to assess increased lead body burden. Lead in hair and nails are useful confirmatory markers and their significances are not understood. Lead in both hair and nails showed good correlation with liver and kidney lead at autopsy in one study (Gerhardsson et al. 1995b).

ALAD in blood is a sensitive indicator of recent exposure to lead. Urinary ALA becomes elevated at PbB levels $50 µg/dL, and is not as sensitive an indicator as ALAD. EP becomes elevated at PbB levels of 25–30 µg/dL and is a good indicator of past exposure to lead. It should be noted, however, that ALAD, ALA, and EP are not specific biomarkers for lead.

With any of these biomarkers of exposure, it is not possible to predict how long they remain elevated after exposure has ceased. Refer to Section 2.3 for additional information on potential biomarkers of lead exposure.

2.7.1.2 Lead in Bones and Teeth

The development of noninvasive X-ray fluorescence (XRF) techniques for measuring lead concentrations in bone has enabled the exploration of bone lead as a biomarker of lead exposure in children and in adults (Batuman et al. 1989; Hu et al. 1989, 1990, 1991, 1995; Rosen et al. 1993; Wedeen 1988, 1990, 1992). Lead in bone is considered as a biomarker of cumulative exposure to lead because lead accumulates in bone over the lifetime and most of the lead body burden resides in bone. Lead is not distributed uniformly in bone. Lead will accumulate in those regions of bone undergoing the most active calcification at the time of

exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in cortical and trabecular bone. This would suggest that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Auferheide and Wittmets 1992). Patella, calcaneus and sternum XRF measurements primarily reflect lead in trabecular bone, whereas XRF measurements of mid-tibia, phalanx, or ulna reflect primarily lead in cortical bone. Lead levels in cortical bone may be a better indicator of long-term cumulative exposure than lead in trabecular bone, possibly because lead in trabecular bone may exchange more actively with lead in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of lead in cortical bone, compared to trabecular bone (Borjesson et al. 1997; Nilsson et al. 1991; Schutz et al. 1987). Evidence that cortical bone lead measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone lead measurements have been compared to concentrations of lead in blood. Lead levels in trabecular bone (in adults) correlate more highly with contemporary PbB concentrations than do levels of lead in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical bone lead measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary blood lead measurements (Borjesson et al. 1997; Roels et al. 1994). Bone lead levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone lead may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

Relationships between bone lead levels and health outcomes have been studied in several cross-sectional epidemiology studies, however, not as extensively as have other biomarkers of exposure such as PbB concentration (Hu 1998a, 1998b). These studies suggest that bone lead levels may be better predictors of certain health outcomes in adults than are contemporary PbB concentrations; these include declines in hematocrit and blood hemoglobin, hypertension and decreased birthweight (Gonzalez-Cossio et al. 1997; Hu et al. 1994, 1996b).

Tooth lead has been considered a potential biomarker for measuring long-term exposure to lead (e.g., years) because lead that accumulates in tooth dentin and enamel appears to be retained until the tooth is shed or extracted (Rabinowitz et al. 1989; Steenhout and Pourtois 1987). Formation of enamel and coronal dentin of deciduous teeth is complete prior to the time children begin to crawl, however, lead in shed deciduous teeth is not uniformly distributed. Differences in lead levels and stable isotope signatures of the enamel and

dentin suggest that lead uptake occurs differentially in enamel and dentin after eruption of the tooth (Gulson and Wilson 1994, 1996). Lead in enamel is thought to reflect primarily lead exposure that occurs *in utero* and early infancy, prior to tooth eruption. Dentin appears to continue to accumulate lead after eruption of the tooth, therefore, dentin lead is thought to reflect exposure that occurs up to the time the teeth are shed or extracted (Gulson 1994, 1996; Rabinowitz 1995; Rabinowitz et al. 1993). Accumulation of lead in dentin of permanent teeth may continue for the life of the tooth (Steenhout 1982; Steenhout and Pourtois 1981). Because it is in direct contact with the external environment, enamel lead levels may be more influenced than dentin lead by external lead levels and tooth wear (Purchase and Ferguson 1986).

An analysis of eight cross-sectional and/or prospective studies which reported tooth lead and PbB levels of the same children found considerable consistency among the studies (Rabinowitz 1995). The mean tooth lead levels ranged from under 3 to over 12 µg/g. In a study of 63 subjects, dentin lead was found to be predictive of concentrations of lead in the tibia, patella, and mean bone lead 13 years after tooth lead assessment in half of them (Kim et al. 1996b). The authors estimated that a 10 µg/g increase in dentin lead levels in childhood was predictive of a 1 µg/g increase in tibia lead levels, a 5 µg/g in patella lead levels and a 3 µg/g increase in mean bone lead among the young adults.

2.7.2 Biomarkers Used to Characterize Effects Caused by Lead

One of the most sensitive effects of lead exposure is the inhibition of the heme biosynthesis pathway, which is necessary for the production of red blood cells. Hematologic tests such as hemoglobin concentration may suggest toxicity, but this is very nonspecific (Bernard and Becker 1988). Measurements of FEP and ZPP, the form of EP in red blood cells, reflect essentially the same compound and can both be used as biomarkers of effect (CDC 1985). An elevated EP level is one of the earliest and most reliable indicators of impairment of heme biosynthesis and reflects average lead levels at the site of erythropoiesis over the previous 4 months (Janin et al. 1985). Lead toxicity is generally considered to be present when a PbB of $10 µg/dL is associated with an EP level of $35 µg/dL (CDC 1991; Somashekaraiah et al. 1990). This effect is detectable in circulating erythrocytes only after a lag time reflecting maturation in which the entire population of red blood cells has turned over (i.e., 120 days) (EPA 1986a; Moore and Goldberg 1985). Likewise, elevated erythrocyte protoporphyrin can reflect iron deficiency, sickle cell anemia, and hyperbilirubinemia (jaundice). Therefore, reliance on EP levels alone for initial screening could result in an appreciable number of false positive cases (CDC 1985; Mahaffey and Annest 1986; Marcus and Schwartz 1987). On the other hand, some have estimated that relying only on ZPP screening to predict future lead

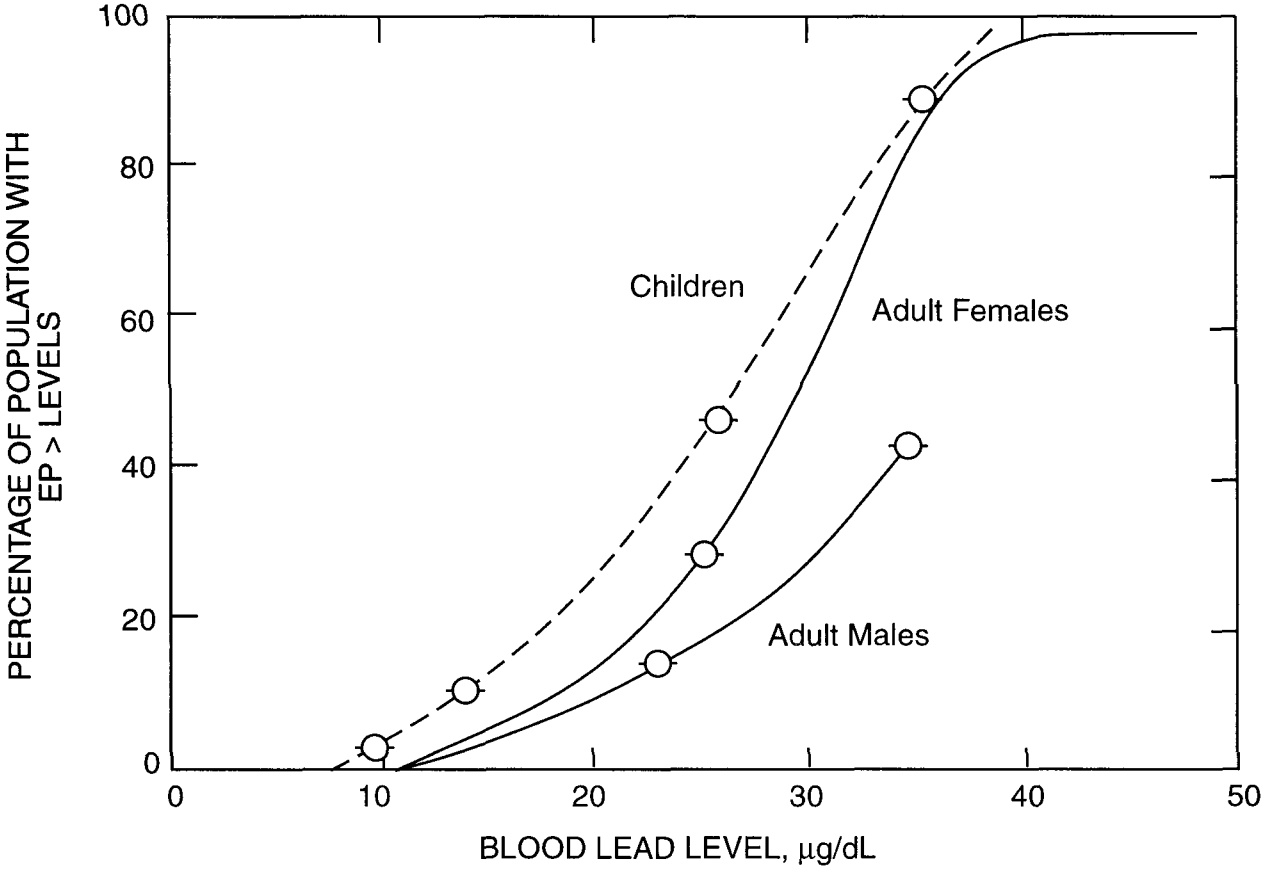
toxicity would miss about 3 cases with toxic blood lead concentrations in every 200 workers at risk (Froom et al. 1998). A limitation of measuring porphyrin accumulation is that porphyrin is labile because of photochemical decomposition; thus, assay samples must be protected from light. A dose-response curve for EP as a function of blood lead level is depicted in Figure 2-12.

ALAD, an enzyme occurring early in the heme pathway, is also considered a sensitive indicator of lead effect (Hernberg et al. 1970; Morris et al. 1988; Somashekaraiah et al. 1990; Tola et al. 1973). Because there is no well-defined blood lead threshold at which inhibition of ALAD does not occur, it allows measurement of the effect on the general population at environmental lead levels and does not require high exposure levels as with occupational workers (Hernberg et al. 1970). However, ALAD activity may also be decreased with other diseases or conditions such as porphyria, liver cirrhosis, and alcoholism (Somashekaraiah et al. 1990).

Another potential biomarker for hematologic effects of lead is the observation of basophilic stippling and premature erythrocyte hemolysis (Paglia et al. 1975, 1977). Lead can impair the activity of pyrimidine 5'-nucleotidase, resulting in a corresponding increase in pyrimidine nucleotides in red blood cells, which leads to a deficiency in maturing erythroid elements and thus, decreased red blood cells. However, this effect is nonspecific; it is encountered with benzene and arsenic poisoning (Smith et al. 1938) and in a genetically-induced enzyme-deficiency syndrome (Paglia et al. 1975, 1977). Furthermore, since basophilic stippling is not universally found in chronic lead poisoning, it is relatively insensitive to lesser degrees of lead toxicity (CDC 1985).

A multisite study of populations living near four NPL sites was conducted to assess the relationship between exposure (PbB and area of residence) and biomarkers of four organ systems: immune function disorders, kidney dysfunction, liver dysfunction, and hematopoietic dysfunction (ATSDR 1995). The geometric mean PbB concentration in those living in the target areas was 4.26 µg/dL (n=1,645) compared with 3.45 µg/dL for a group living in comparison areas (n=493). In children <6 years old, the corresponding means were 5.37 versus 3.96 µg/dL. In subjects 15 years old or older, the target and comparison values were 3.06 µg/dL and 3.63 µg/dL, respectively. Ninety percent of target and 93% of comparison area participants had PbB levels <10 µg/dL. Lead in soil and in water was found to be higher in comparison areas than in the target areas, but lead in house dust and in interior paint was higher in the target areas. PbB correlated with lead in soil and dust, but not with lead in paint and water. Multivariate regression analyses showed that of all the biomarkers analyzed, PbB was significantly associated with and

Figure 2-12. Dose-Response Curve for Erythrocyte Protoporphyrin (EP) as a Function of Blood Level in Subpopulations



Source: Derived from Roels et al. 1976

predictive of hematocrit in adults 15 years of age or older and with increased mean serum IgA in children 6–71 months of age. The biological significance of these associations is unclear since both hematocrit and IgA levels were well within normal ranges and were hardly different than levels in subjects from the comparison areas.

One of the most sensitive systems affected by lead exposure is the nervous system. Encephalopathy is characterized by symptoms such as coma, seizures, ataxia, apathy, bizarre behavior, and incoordination (CDC 1985). Children are more sensitive to neurological changes. In children, encephalopathy has been associated with PbB levels as low as 70 µg/dL (CDC 1985). The most sensitive peripheral index of neurotoxicity of lead is reported to be slowed conduction in small motor fibers of the ulnar nerve in workers with 30–40 µg/dL lead in blood (Landrigan 1989). Other potential biomarkers of lead suggested for neurotoxicity in workers are neurological and behavioral tests, as well as cognitive and visual sensory function tests (Williamson and Teo 1986). However, these tests are not specific to elevated lead exposure.

The kidneys are affected by high-level, chronic exposure to lead (Landrigan 1989). Increases in BUN or serum creatinine are clinical manifestations of kidney damage (Landrigan 1989), but they do not reflect early loss of renal function and are nonspecific (Bernard and Becker 1988). Intranuclear inclusion bodies in the lining cells of the proximal tubules are reported to be the most characteristic feature of early nephropathy (Bernard and Becker 1988). These lead inclusion bodies disappear with appropriate chelation and shed into the urine. Thus, EDTA lead mobilization test may be the best test for diagnosing persons at risk of chronic lead nephropathy. Results from some occupational studies suggested that elevation of urinary NAG might be an early marker of nephrotoxicity (Ong et al. 1987; Verschoor et al. 1987). However, there is evidence suggesting that the increase in NAG activity may be a response to a sharp increase in the renal lead burden rather than to the cumulative dose (Chia et al. 1994). A study compared the relationship of several exposure indices and various early markers of tubular and glomerular dysfunction in 128 occupationally exposed subjects (Chia et al. 1995b). The markers examined were urinary and serum $\beta_{2\mu}$-globulin, urinary $\alpha_{1\mu}$-globulin, urinary retinol binding protein (RNP-U), and urinary albumin. The result showed that a time-integrated PbB level index (µg lead/[dL x years of exposure]) rather than current PbB level (mean 32.6 µg/dL) was the most important exposure variable in describing the variability in urinary $\alpha_{1\mu}$-globulin, $\beta_{2\mu}$-globulin, and RNP. Moreover, urinary $\alpha_{1\mu}$-globulin was the only marker that was significantly higher in the exposed workers, showing a good dose-response and dose-effect relationship with the time-integrated PbB level. Chia et al. (1995b) suggested that the relatively high sensitivity of the

urinary $\alpha_{1\mu}$-globulin marker may be due to its higher molecular weight, and hence the lower efficiency in its tubular reabsorption.

2.8 INTERACTIONS WITH OTHER CHEMICALS

The toxicokinetic and toxicological behavior of lead can be affected by interactions with essential elements and nutrients (for a review see Mushak and Crocetti 1996). In humans, the interactive behavior of lead and various nutritional factors is particularly significant for children, since this age group is not only sensitive to the effects of lead, but also experiences the greatest changes in relative nutrient status. Nutritional deficiencies are especially pronounced in children of lower socioeconomic status; however, children of all socioeconomic strata can be affected.

Available data from a number of reports document the association of lead absorption with suboptimal nutritional status. In infants and children 1–6 years of age, lead retention (as measured by PbB content) was inversely correlated with calcium intake, expressed either as a percentage of total or on a weight basis (Johnson and Tenuta 1979; Mahaffey et al. 1986; Sorrell et al. 1977; Ziegler et al. 1978). Dietary intakes of calcium and vitamin D were significantly ($p<0.001$) lower in children with PbB levels >60 µg/dL (Johnson and Tenuta 1979). The gastrointestinal uptake of ^{203}Pb was monitored in eight adult subjects as a function of dietary calcium and phosphorus intakes (Heard and Chamberlain 1982). The label absorption rate was 63% without supplementation of these minerals in fasting subjects, compared with 10% in subjects supplemented with 200 mg calcium plus 140 mg phosphorus, the amounts present in an average meal. Calcium and phosphorus alone reduced lead uptake by a factor of 1.3 and 1.2, respectively; both together yielded a reduction factor of 6. Copper, iron, and zinc have also been postulated to affect lead absorption (Klauder and Peterini 1975).

Children with elevated PbB (12–120 µg/dL) were found to have significantly lower serum concentrations of the vitamin D metabolite 1,25-dihydroxyvitamin D compared with age-matched controls ($p<0.001$), and showed a negative correlation of serum 1,25-dihydroxyvitamin D with lead over the range of blood lead levels measured (Mahaffey et al. 1982; Rosen et al. 1980).

Zinc is in the active site of ALAD and can play a protective role in lead intoxication by reversing the enzyme-inhibiting effects of lead. Children with high PbB levels (50–67 µg/dL) were reported to consume less zinc than children with lower PbB (12–29 µg/dL) (Johnson and Tenuta 1979). In a group of

13 children, Markowitz and Rosen (1981) reported that the mean serum zinc levels in children with plumbism were significantly below the values seen in normal children; chelation therapy reduced the mean level even further. An inverse relationship between ALA in urine and the amount of chelatable or systemically active zinc was reported in 66 children challenged with EDTA and having PbB levels ranging from 45–60 µg/dL (Chisolm 1981). Zinc sulfate administration to a lead-intoxicated man following calcium disodium EDTA therapy restored the erythrocyte ALAD activity that was inhibited by lead (Thomasino et al. 1977).

Forty-three children with elevated PbB (>30 µg/dL) and EP (>35 µg/dL) had an increased prevalence of iron deficiency (Yip et al. 1981). An inverse relationship between chelatable iron and chelatable body lead levels as indexed by urinary ALA levels has been demonstrated in 66 children with elevated blood lead (Chisolm 1981). Another study reported that the lead absorption rate was 2 to 3 times greater in iron-deficient adults compared to subjects who were iron replete (Watson et al. 1980). Daily nutritional intake of dietary fiber, iron, and thiamine were negatively correlated with blood lead levels in male workers occupationally exposed to lead in a steel factory (Ito et al. 1987). Results from the NHANES II national survey showed that in children low iron status increases the lead hematotoxic dose response curves (Marcus and Schwartz 1987) and that iron deficiency plus elevated blood lead levels produce a greater degree of hematotoxicity compared with either factor alone (Mahaffey and Annest 1986). A study of 299 children from 9 months to 5 years old from an urban area found a significant negative association between PbB and dietary iron intake (Hammad et al. 1996). Graziano et al. (1990) studied a population of pregnant women in Kosovo, Yugoslavia. They found that serum ferritin concentrations were associated with lower PbB levels, suggesting that dietary iron may inhibit lead absorption.

Results from a recent study showed a marginally significant association of Parkinson's disease with more than 20 years of occupational exposure to lead (Gorell et al. 1997); when the analysis included more than 20 years of combined exposure to lead and iron, the association greatly increased, with the odds ratios exceeding that for exposure to one of the metals alone.

An *in vitro* study demonstrated that cadmium and zinc have an antagonistic effect on the inhibitory effects of lead on human ALAD activity (Davis and Avram 1978). Cadmium was 40–100 times more potent than zinc in activating ALAD. Furthermore, the combined effects of cadmium and lead in tissue resulted in an additively increased risk of mortality related to cardiac failure in humans with significant relation to age in 80% of the cases (Voors et al. 1982).

The relationship between nutritional factors, other than those mentioned above, and PbB levels of preschool children was examined by Lucas et al. (1996). The objective of the study was to determine whether total caloric intake, dietary fat, dietary protein, and carbohydrates are associated with PbB while simultaneously controlling for other nutrient and environmental exposures. The cohort comprised 296 children aged 9–72 months, predominantly black (82%), from an urban area. The mean PbB concentration was 11.4 µg/dL (range, 1–55 µg/dL). After adjusting for confounders, the study found significant positive associations for total caloric intake and dietary fat with PbB. Lucas et al. (1996) speculated that bile secreted into the gastrointestinal to aid in the digestion and absorption of fat may increase lead absorption, as shown in rats (Cikrt and Tichy 1975). The influence of total caloric intake may just reflect increased intake of lead through contaminated food.

Reports of lead-nutrient interactions in experimental animals have generally described such relationships in terms of a single nutrient, using relative absorption or tissue retention in the animal to index the effect. Most of the data are concerned with the impact of dietary levels of calcium, iron, phosphorus, and vitamin D. These interaction studies are summarized in Table 2-12.

Lead has also been found to interact with a number of other metals in the bodies of animals with resultant synergistic, additive, or antagonistic effects.

Animals on low-calcium diets exhibit increased susceptibility to lead as a consequence of increased lead retention associated with decreased renal excretion of lead (Barton et al. 1978a; Goyer 1986). For example, rat systolic blood pressures during the third trimester of gestation were significantly higher in rats exposed to lead and fed a low calcium diet than in rats exposed to lead alone (Bogden et al. 1995). A low-calcium diet has been shown to promote genetic damage by lead (Deknudt and Gerber 1979). Lead administered to mice in combination with a low-calcium diet produced an excess of chromosomal aberrations compared with low-calcium controls fed no lead or with mice administered lead on a normal-calcium diet. In addition, a significantly increased frequency of severe chromosomal abnormalities (dicentrics, rings, translocations, and exchanges) was found in monkeys given lead in conjunction with a low-calcium diet compared with a group given as much lead but on a normal diet (Deknudt et al. 1977). Calcium and magnesium prevented an increase in lung adenoma formation in mice administered lead subacetate (Poirier et al. 1984). It has been postulated that calcium and lead compete for similar binding sites on intestinal mucosal proteins, which are important in the absorptive process (Barton et al. 1978a). A high calcium diet was also shown to influence the toxicity of lead. Dam and pup hemoglobin

Table 2-12. Effects of Nutritional Factors on Lead Uptake in Animals

Factor	Species	Index of effect	Interactive effect	References
Calcium	Rat	Lead in tissues and severity of effect at low levels of dietary calcium	Low dietary calcium (0.1%) increase lead absorption and severity of effects	Six and Goyer 1970; Mahaffey et al. 1973
Calcium	Rat	Lead retention	Retention increased in calcium deficiency	Barton et al. 1978a
Calcium	Rat	Lead in tissues at high levels of dietary calcium during pregnancy	Reduced release of lead from bone	Bogden et al. 1995
Calcium	Pig	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Hsu et al. 1975
Calcium	Horse	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Willoughby et al. 1972
Calcium	Lamb	Lead in tissues at low levels of dietary calcium	Increased absorption of lead with low dietary calcium	Morrison et al. 1977
Iron	Rat	Tissue levels and relative toxicity of lead	Iron deficiency increases lead absorption and toxicity	Six and Goyer 1972
Iron	Rat	Lead absorption in everted duodenal sac preparation	Reduction in intubated iron increases lead absorption; increased levels decrease lead uptake	Barton et al. 1978b
Iron	Rat	*In utero* or milk transfer of lead in pregnant or lactating rats	Iron deficiency increases both *in utero* and milk transfer of lead to sucklings	Cerklewski 1980
Iron	Mouse	Lead retention	Iron deficiency has no effect on lead retention	Hamilton 1978
Protein	Rat	Body lead retention	Low dietary protein either reduces or does not affect retention in various tissues	Quarterman et al. 1978
Protein	Rat	Tissue levels of lead	Casein diet increases lead uptake compared to soybean meal	Anders et al. 1982
Protein	Rat	Lead uptake by tissues	Both low and high protein in diet increases lead absorption	Barltrop and Khoo 1975
Milk components	Rat	Lead absorption	Lactose-hydrolyzed milk does not increase lead absorption, but ordinary milk does	Bell and Spickett 1981
Milk components	Rat	Lead absorption	Lactose in diet enhances lead absorption compared to glucose	Bushnell and DeLuca 1981
Zinc	Rat	Lead absorption	Low zinc in diets increases lead absorption	Cerklewski and Forbes 1976
Zinc	Rat	Lead transfer *in utero* and in milk during lactation	Low-zinc diet of mother increases lead transfer *in utero* and in maternal milk	Cerklewski 1979
Zinc	Rat	Tissue retention	Low zinc diet enhances brain lead levels	Bushnell and Levin 1983

Table 2-12. Effects of Nutritional Factors on Lead Uptake in Animals (continued)

Factor	Species	Index of effect	Interactive effect	References
Copper	Rat	Lead absorption	Low copper in diet increases lead absorption	Klauder and Peterini 1975
Phosphorus	Rat	Lead uptake in tissues	Reduced phosphorus increases ^{203}Pb uptake 2.7-fold	Barltrop and Khoo 1975
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances lead retention; no effect on lead resorption in bone	Quarterman and Morrison 1975
Phosphorus	Rat	Lead retention	Low dietary phosphorus enhances both lead retention and lead deposition in bone	Barton and Conrad 1981
Vitamin D	Rat	Lead absorption using everted sac techniques	Increasing vitamin D increases intubated lead absorption	Smith et al. 1978
Vitamin D	Rat	Lead absorption using everted sac techniques	Both low and excess levels of vitamin D increase lead uptake by affecting motility	Barton et al. 1980
Thiamin	Mouse	Whole body lead retention	Increased retention with increased thiamin concentration	Kim et al. 1992
Lipid	Rat	Lead absorption	Increases in lipid (corn oil) content up to 40% enhance lead absorption	Barltrop and Khoo 1975

^{203}Pb = Lead 203

concentrations and hematocrits were reduced in rats exposed perinatally to lead and a high calcium diet relative to rats treated with lead and a normal calcium diet (Bogden et al. 1995). Also, body weight and length of day-old pups were decreased in the group fed the high calcium diet. These results were consistent with a reduced iron absorption caused by the increased dietary calcium.

It has also been demonstrated in animals that lead blocks the intestinal responses to vitamin D and its metabolites (Smith et al. 1981). Dietary concentrations of lead in combination with a low phosphorus or a low calcium diet administered to rats suppressed plasma levels of the vitamin D metabolite, 1,25-dihydroxy-cholecaliferol, while dietary intakes rich in calcium and phosphorus protected against this effect (Smith et al. 1981). Thus, animals fed a diet high in calcium or phosphorus appear to be less susceptible to the effects of lead, because of hindered tissue accumulation of lead.

Cadmium also affects the toxicity of lead. A synergistic effect of these metals was found on prostatic cytology and testicular damage in male rats following intraperitoneal injection (Fahim and Khare 1980). Rats fed lead and cadmium or zinc had a marked reduction of reticulocytosis compared with rats fed lead alone (Thawley et al. 1977). Mice exposed simultaneously to lead and cadmium for 10 weeks had higher mortality rates than mice exposed to either metal alone (Exon et al. 1979). In addition, interactions between cadmium and lead have been reported at the behavioral effects level (Nation et al. 1990).

Several interactions of lead and iron have been documented in animals. Low dietary iron tends to increase the susceptibility to lead intoxication because of enhanced gastrointestinal absorption, suggesting a common absorption pathway for these two elements (Six and Goyer 1972). There is a synergistic action between lead intoxication and iron deficiency on impairment of hematopoiesis, specifically on hemoglobin level and red blood cell size (Hashmi et al. 1989a; Waxman and Rabinowitz 1966). In addition, iron and lead appear to be antagonistic with respect to ALAD activity; iron deficiency enhances blood ALAD activity while lead exposure suppresses ALAD activity (Hashmi et al. 1989a). Iron appeared to reduce the effects of orally or subcutaneously administered lead on blood enzyme and liver catalase activity (Bota et al. 1982). Treatment of pregnant hamsters with iron- or calcium-deficient diets in conjunction with orally administered lead resulted in embryonic or fetal mortality and abnormalities (runting, edema) in the litters, while treatment with complete diets and lead did not (Carpenter 1982). Inadequate levels of iron in association with increased body burdens of lead enhanced biochemical changes associated with lead intoxication (Waxman and Rabinowitz 1966). Ferrous iron was reported to protect against the inhibition of hemoglobin synthesis and cell metabolism by lead; it has been speculated that iron competes with lead uptake by the cell

(Waxman and Rabinowitz 1966). In addition, the incorporation of iron into heme in the mouse embryonic liver was greatly decreased in lead-treated mice, resulting in retarded embryo growth due to impaired heme synthesis (Gerber and Maes 1978). Another study demonstrated that both the decrease in plasma iron and the increased total iron binding capacity observed in iron deficient rats, or in rats exposed to lead, were more marked in animals exposed simultaneously to lead and fed an iron deficient diet (Hashmi et al. 1989b). The same study showed that plasma ceruloplasmin, a copper binding protein, was significantly reduced by iron deficiency or lead exposure, and a synergistic effect was seen in rats exposed to lead and fed an iron deficient diet.

Dietary copper also appears to be antagonistic to the adverse effects of lead on the hematopoietic system, growth depression, and tissue hypertrophy (Klauder and Peterini 1975). The reduction in uptake of lead and decrease of lead-induced ALAD inhibition upon administration of copper may be achieved through a competition between the two metals for binding to proteins (Underwood 1977).

Zinc can have a protective effect against lead toxicity. Zinc added in the diet has been found to protect horses grazing on lead-contaminated pastures from clinical signs of lead toxicity (Goyer 1986). Zinc almost entirely eliminated the inhibition of ALAD by lead in rabbits (Haeger-Aronsen et al. 1976) and was shown to protect rats against the effects of orally administered lead (Brewer et al. 1985; Cerklewski and Forbes 1976), even during gestation and lactation (Cerklewski 1979) and intraperitoneally administered lead (Satija and Vij 1995). A protective effect of zinc against lead toxicity in the chick embryo has also been shown (Srivastava and Tandon 1984). In addition, lead exposure and zinc deficiency exerted additive effects on decreased body weights of rats (Bushnell and Levin 1983). The protective action of zinc on lead toxicity is thought to be mediated by an inhibition of gastrointestinal absorption via an intestinal metallothionein mechanism, which binds lead (Brewer et al. 1985; Cerklewski and Forbes 1976). Also, excess zinc protects zinc-containing enzymes like ALAS, ferrochelatase, and ALAD. *In vivo*, aqueous solution containing zinc administered to rats significantly reduced the genotoxic effects induced by lead (Kowalska-Wochna et al. 1988). It was postulated that zinc's protective action may be related to its functioning in DNA and RNA polymerases and consequent enhancement of cell repair processes.

Evidence suggests that lead exacerbates the toxic effects of mercury. In the rat, the administration of lead nitrate increased kidney and liver glutathione content and resulted in increased mercury deposition in the kidney, along with increased lethality in rats (Congiu et al. 1979).

Chandra et al. (1981) studied the effects of simultaneous daily exposure to lead and manganese in rats. Manganese was administered via drinking water and lead was administered intraperitoneally for 14 days. Simultaneous dosing with lead and manganese reduced motor activity, impaired learning, and increased aggressive behavior to a much greater degree than did lead alone. Also, while lead alone increases the content of norepinephrine in the brain, the manganese-lead combination produced a decrease in norepinephrine. Furthermore, manganese significantly increased the accumulation of lead in the brain compared to administration of lead alone. In a subsequent study, Chandra et al. (1983) reported that simultaneous administration of lead and manganese to rats during gestation and lactation induced a significant and greater decrease in body weight and brain weight in the offspring than lead alone. The metal combination also decreased the content of DNA and RNA in the brain to a greater extent than did lead alone. As seen in their earlier report, treatment with the metal combination resulted in a much greater accumulation of lead in the brain of 21-day-old pups than that observed after only lead. These results suggest that manganese in some way facilitates the absorption of lead, but the mechanism by which this may happen is unknown.

In summary, lead appears to interact with all elements that can form divalent cations.

The interaction of lead and ethanol has been studied by Flora and Tandon (1987), who suggested that rats exposed to lead and ethanol are more susceptible to the neurological and hepatotoxic effects of lead. In this study, the simultaneous exposure of rats to lead and ethanol resulted in a significantly higher concentration of lead in blood, brain, and liver tissues compared with rats treated with lead alone. Lead given with ethanol resulted in more pronounced inhibition of the activities of hepatic glutamic oxaloacetic transaminase (GOT, AST) and glutamic pyruvic transaminase (GPT, ALT) than did treatment with lead by itself. In addition, exposure to lead plus ethanol resulted in a greater depression of dopamine and 5-hydroxytryptamine levels in the rat brain than did lead treatment alone. A subsequent study conducted by the same investigators, found that rats co-exposed to lead and ethanol (20% in drinking water) experienced more marked inhibition of blood ALAD activity, elevation of blood ZPP, urinary elimination of lead and ALA, and increased blood, liver, kidney, and brain lead levels than rats exposed to lead alone (Dhawan et al. 1989).

Another study investigated the interactive effects of lead and alcohol during pregnancy on fetal development and offspring learning (Zajac and Abel 1990). No differences were found in maternal weight gain, percent resorptions, litter size, or fetal weight in rats treated simultaneously with lead and alcohol,

compared with alcohol-treated rats; however, these parameters were significantly different for lead-plus-alcohol-dosed rats compared with lead-treated rats. In addition, no potentiation of activity, passive avoidance, or active avoidance learning was observed compared to animals treated with alcohol or lead alone. The authors concluded that neither lead nor alcohol attenuate or potentiate each other's effects on reproduction or learning behavior.

Gelman et al. (1978) found that the interaction between lead and phenylhydrazine produced an additive effect in the acute hemolytic phase of anemia and a probable synergistic effect during the compensatory phase of anemia in rabbits. The mechanism postulated for anemic interaction appears to be primarily related to depressed bone marrow production of erythrocytes rather than to increased hemolysis.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population exhibits different or enhanced response to lead than do most persons exposed to the same level of lead in the environment. Reasons include genetic make-up, developmental stage, health and nutritional status, and chemical exposure history. These parameters result in decreased function of the detoxification and excretory processes (mainly hepatic and renal) or the pre-existing compromised function of target organs. For these reasons we expect the elderly with declining organ function and the youngest of the population with immature and developing organs generally to be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.7, Populations With Potentially High Exposure.

Certain subgroups of the population may be more susceptible to the toxic effects of lead exposure. These include crawling and house-bound children (<6 years old), pregnant women (and the fetus), the elderly, smokers, alcoholics, and people with genetic diseases affecting heme synthesis, nutritional deficiencies, and neurological or kidney dysfunction. This is not an exhaustive list and reflects only current data available, further research may identify additional susceptible subgroups.

Children. Children are at the greatest risk for experiencing lead-induced health effects, particularly in the urbanized, low-income segments of this pediatric population. Young children (<5 years old) have been documented to absorb lead via the gastrointestinal tract more efficiently (50% relative absorption) than adults (15% relative absorption) (Chamberlain et al. 1978). The use of leaded seams in cans used for canned food is not nearly as prevalent as it once was, so this is no longer as important a source of dietary exposure to lead. Behavior such as thumb sucking and pica result in an elevated transfer of lead-

contaminated dust and dirt to the gastrointestinal tract (Schroeder and Hawk 1987). Also, children frequently have a greater prevalence of nutrient deficiency (Yip et al. 1981; Ziegler et al. 1978). For example, the diets of young children are commonly deficient in zinc, a condition that exacerbates some of the toxic effects of lead. Children have also been documented to have lower blood thresholds for the hematological and neurological effects induced by lead exposure. In addition, the resultant encephalopathy, central nervous system deficits, and neurologic sequelae tend to be much more severe in children than adults (Bellinger et al. 1988; Bradley et al. 1956; Wang et al. 1989). Breast-fed infants of lead-exposed mothers are also a susceptible group since lead is also secreted in the breast milk (Dabeka et al. 1988).

Susceptibility to lead toxicity is influenced by dietary levels of calcium, iron, phosphorus, vitamins A and D, dietary protein, and alcohol (Calabrese 1978). Low dietary ingestion of calcium or iron increased the predisposition to lead toxicity in animals (Barton et al. 1978a; Carpenter 1982; Hashmi et al. 1989a; Six and Goyer 1972; Waxman and Rabinowitz 1966). Iron deficiency combined with lead exposure acts synergistically to impair heme synthesis and cell metabolism (Waxman and Rabinowitz 1966). Nutritional surveys indicate that children of low-income groups consume less than recommended dietary allowances of calcium and iron. Dietary deficiencies of these two minerals have been shown to potentiate the toxicity of lead (Johnson and Tenuta 1979; Yip et al. 1981; Ziegler et al. 1978). Thus, nutrient deficiencies in conjunction with a developmental predisposition to absorb lead makes this subset of children at a substantially elevated risk. More information on children's susceptibility to lead is presented in Section 2.6.

Embryo/Fetus. The embryo/fetus are at increased risk because of transplacental transfer of maternal lead (Bellinger et al. 1987a; Moore et al. 1982). Thompson et al. (1985) reported the case of a woman whose PbB level increased to 74 µg/dL over the course of pregnancy resulting in the baby's PbB level of 55 µg/dL and showing clinical signs of intoxication. No evidence of increased exposure to external lead source during this period was apparent, but it was found that the mother had excessive exposure to lead 30 years prior to the pregnancy. Lead has been demonstrated in animal studies to increase the incidence of fetal resorptions (McClain and Becker 1972) and to induce adverse neurobehavioral effects in offspring exposed *in utero* (Draski et al. 1989).

Women. Studies of women suggest that conditions of pregnancy, lactation, and osteoporosis may intensify bone demineralization, thus mobilizing bone lead into the blood resulting in increased body burdens of lead (Silbergeld et al. 1988). For example, women show an increased rate of bone lead loss with

age relative to men (Drasch et al. 1987). Women with postmenopausal osteoporosis may be at an increased risk since lead inhibits activation of vitamin D, uptake of calcium, and several aspects of bone cell function to aggravate the course of osteoporosis. Using data collected from 2,981 women in the NHANES II study, a significant increase in PbB levels was observed after menopause (Silbergeld et al. 1988). However, the actual prevalence of osteoporosis was not reported in this study, so it is not possible to conclude that increased mobilization of lead from bone in postmenopausal women is directly related to an increased incidence of osteoporosis based on these data. Furthermore, in a study of 3,098 55–66 year-old women, it was found that PbB levels were not elevated to toxic levels as a result of lead mobilization from bone during conditions of bone demineralization, such as osteoporosis (Ewers et al. 1990). The highest PbB levels measured in this study ranged from 15 to 30 µg/dL. Long-term effects of lead exposure were also reported by Hu (1991) who found that pregnant women who had experienced childhood plumbism had a higher rate of spontaneous abortion or stillbirth than matched controls, and their offspring were more likely to experience learning disabilities.

Elders. The aged population may be at an increased risk for toxic effects of lead as suggested by two recent studies that found an association between decreased neurobehavioral performance and PbB in aging subjects with PbB around 5 µg/dL (Muldoon et al. 1996; Payton et al. 1998). In addition to the mobilization of bone lead and increased lead body burden due to osteoporosis, animal data suggest that aged animals may be more susceptible to the effects of lead than adult or young animals (Cory-Slechta 1990b). For example, increases in ZPP and urinary ALA were observed in aged rats sooner than in young or adult rats with comparable PbB levels. Also, aged rats exposed to lead had a higher mortality rate than nonexposed aged rats. Aged rats also had higher brain lead levels than did young or adult rats.

People with Inheritable Genetic Diseases. The toxic effects of lead exposure become exacerbated in individuals with inherited genetic diseases, such as thalassemia, which is characterized by an abnormality in the rate of hemoglobin synthesis (Calabrese 1978). Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are also unusually susceptible and may exhibit hemolytic anemia following lead exposure (Calabrese 1978). In a study of 148 subjects, Cocco et al. (1991) found that chronic lead poisoning tended to decrease total cholesterol and LDL in both G6PD-deficient and G6PD-nondeficient populations, but positive slopes were seen for cholesterol esters in G6PD deficient subjects and for HDL in G6DP normal subjects. Another study from the same group found that mortality from all causes and cancer mortality were lower among lead smelter workers with the glucose-6-phosphate dehydrogenase deficient phenotype compared to coworkers with the wild phenotype; the study comprised 867 workers with the wild

phenotype and 213 with the deficient phenotype (Cocco et al. 1996). Because of the relatively small number of subjects with the deficient phenotype, the study may have lacked statistical power to examine deaths among this group. It has also been postulated that children with sickle cell disease have an increased risk of developing neuropathy with exposure to lead (Erenberg et al. 1974). People with metabolic disorders associated with the synthesis of porphyrins (important intermediates in the synthesis of hemoglobin, cytochromes, and vitamin B_{12}), collectively known as porphyrias, are especially susceptible to lead exposure since lead inhibits two critical enzymes, ALAD and ferrochelatase, concerned with heme synthesis in erythrocytes (Hubermont et al. 1976; Silbergeld et al. 1982). The presence of genetic disorders that induce excessive ALA synthetase activity in addition to lead exposure produce higher than normal levels of ALA, resulting in excessive ALA excretion, accumulation, and lack of negative feedback on the ALA synthetase activity from heme (Calabrese 1978).

Human ALAD is a polymorphic enzyme with two common alleles, $ALAD^1$ and $ALAD^2$ (Petrucci et al. 1982). This results in an enzyme system with three distinct isozyme phenotypes, designated ALAD 1-1, ALAD 1-2, and ALAD 2-2. Several white populations express the alleles $ALAD^1$ and $ALAD^2$ with gene frequencies of 0.9 and 0.1, respectively (Astrin et al. 1987; Battistuzzi et al. 1981; Benkmann et al. 1983; Petrucci et al. 1982). The existence of this common polymorphism in a gene whose product was implicated in the pathogenesis of lead toxicity suggested that differential susceptibility to lead may be genetically determined. Wetmur (1994) summarized the results of an analysis of ALAD isozyme types in blood and blood lead from two populations. One group consisted of 202 lead workers in a factory in Germany. The other group was composed of 1,278 children subjected to low-level environmental lead exposure in New York City. The results showed that in the 40–60 percentile group for PbB in each phenotype group, PbB levels in individuals with the $ALAD^2$ allele (phenotypes ALAD 1-2 and ALAD 2-2) were approximately 10 µg/dL higher than in similarly exposed individuals homozygous for the $ALAD^1$ allele (phenotype ALAD 1-1). These results strongly suggested that a relationship exists between the $ALAD^2$ allele and the accumulation of lead in blood. It was hypothesized that the increased susceptibility of those with the $ALAD^2$ allele is due to the $ALAD^2$ subunit binding lead more tightly than the $ALAD^1$ subunit (Astrin et al. 1987).

Smith et al. (1995) examined the association between ALAD polymorphism and lead concentration in blood and bone in a group of 122 subjects with relatively modest overall lead exposure. Mean PbB in $ALAD^2$ carriers was 7.78 µg/dL compared with 7.73 for $ALAD^1$ µg/dL allele indicating that the $ALAD^2$ phenotype was not a significant determinant of blood lead concentrations among individuals exposed at relatively low

levels. When the age-adjusted difference patellar-minus-tibial lead was compared between $ALAD^2$ and $ALAD^1$ subjects it was found that the latter showed a greater difference (3.4 vs 8.6 µg Pb/g bone mineral), and this suggested that ALAD status may modify the way in which lead partitions between these two storage sites. According to Smith et al. (1995), this differential partitioning could provide a sensitive indicator of genotype-related differences in the overall pharmacokinetics of lead. Schwartz et al. (1997) found that lead battery manufacturing workers with the ALAD 1-2 phenotype excreted on average 24 µg less lead after oral administration of the chelating agent DMSA than did workers with the ALAD 1-1 phenotype. Schwartz et al. (1997) stated that if urinary excretion of lead after DMSA is a surrogate for bioavailable lead stores, their findings implicated that subjects with ALAD 1-2 had lower bioavailable lead stores. According to the authors, this provided evidence that ALAD genotype modifies the toxicokinetics of lead by, for example, differential binding of current lead stores or by differences in long term retention and disposition of lead.

Alcoholics and Smokers. Alcoholics, and people who consume excess amounts of alcohol, may be at increased risk of hematological, neurological, and hepatotoxic effects. In animal studies, lead and alcohol synergistically inhibited blood ALAD activity and hepatic glutamic oxaloacetic transaminase (GOT, AST) and glutamic pyruvic transaminase (GPT, ALT) activity, depressed dopamine and 5-hydroxytryptamine levels in rat brain, increased lead burdens in tissue organs, and elevated blood ZPP (Dhawan et al. 1989; Flora and Tandon 1987). Smokers are also at elevated risks of lead intoxication since cigarette smoke contains lead and other heavy metals such as cadmium and mercury (Calabrese 1978), which have been shown to be synergistic in experimental animals (Congiu et al. 1979; Exon et al. 1979; Fahim and Khare 1980).

People with Neurologic Dysfunction or Kidney Disease. This population is unusually susceptible to lead exposure. The neurologic and renal systems are the primary target organs of lead intoxication, which may become overburdened at much lower threshold concentrations to elicit manifestations of lead intoxication (Benetou-Marantidou et al. 1988; Chisolm 1962, 1968; Lilis et al. 1968; Pollock and Ibels 1986).

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to lead. However, because some of the treatments discussed may be experimental and unproven,

this section should not be used as a guide for treatment of exposures to lead. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.10.1 Reducing Peak Absorption Following Exposure

Individuals potentially exposed to lead can prevent inhalation exposure to particles by wearing the appropriate respirator. The mechanism and rate of lead absorption from the gastrointestinal tract is not completely understood, but it is believed that absorption occurs in the small intestine by both active and passive transport following solubilization of lead salts by gastric acid (see Section 2.4.1). Lead is poorly absorbed from the gastrointestinal tract; however, toxic effects can result from the relatively small amount of lead that is absorbed. It has been estimated that approximately 10% of an administered dose is absorbed by adults and 4–50% of ingested lead is absorbed by children (Chamberlain et al. 1978). Lead absorption from the gut appears to be blocked by calcium, iron, and zinc. Although no treatment modalities to reduce lead absorption have yet been developed that make use of these observations; it is recommended that a child's diet contain ample amounts of iron and calcium to reduce the likelihood of increased absorption of lead (CDC 1991). General recommendations to reduce absorption following acute exposure to lead, include removing the individual from the source of exposure and decontaminating exposed areas of the body. Contaminated skin is washed with soap and water, and eyes exposed to lead are thoroughly flushed with water or saline (Stutz and Janusz 1988). Once lead is ingested, it is suggested that syrup of ipecac be administered to induce emesis. Administration of activated charcoal following emesis has not been proven to reduce absorption of any lead remaining in the gastrointestinal system, but is frequently recommended (Stutz and Janusz 1988). Gastric lavage has been used to remove ingested lead compounds. Whole gut lavage with an osmotically neutral (polyethylene glycol electrolyte solution [GO-Lytely®, Co-lyte®]) has successfully removed ingested lead-containing pottery glazes according to anecdotal case reports. However, this procedure is not universally accepted. Patients who ingest lead foreign objects should be observed for the possible, although rare, development of signs or symptoms of lead poisoning until the ingested object has been proven to have passed through the gut. Surgical excision has been recommended when lead bullets or shrapnel are lodged near joint capsules (reaction with synovial fluid leads to systemic uptake of lead in some cases). The blood lead level can be monitored and used as an indication for surgical removal of the projectile.

2.10.2 Reducing Body Burden

Lead is initially distributed throughout the body and then redistributed to soft tissues and bone. In human adults and children, approximately 94% and 73% of the total body burden of lead is found in bones, respectively. Lead may be stored in bone for long periods of time, but may be mobilized, thus achieving a steady state of intercompartmental distribution (see Section 2.3.2).

All of the currently available methods to obviate the toxic effects of lead are based on their ability to reduce the body burden of lead by chelation. All of the chelating agents bind inorganic lead, enhance its excretion, and facilitate the transfer of lead from soft tissues to the circulation where it can be excreted. Since the success of chelation therapy depends on excretion of chelated lead via the kidney, caution should be used when treating a patient with renal failure. The standard chelating agents currently in use are dimercaprol (British Anti-Lewisite, or BAL) and $CaNa_2$-EDTA (or EDTA). Both of these agents are administered parenterally. Penicillamine has been used as an oral chelating agent. It increases urinary excretion of lead by an unknown mechanism but is not as effective as EDTA and is not yet approved for use by the FDA for lead poisoning (Ellenhorn and Barceloux 1988; Goldfrank et al. 1994). The preferred chelating agent and the treatment regimen depend on the nature of the intoxication (i.e., the symptomology present and the extent of lead exposure as determined by blood lead level). BAL chelates both intracellular and extracellular stores. BAL-lead chelates are excreted primarily in the bile, with some excretion in the urine. Thus, in individuals with kidney impairment, BAL is the chelating agent of choice. EDTA mobilizes lead from bone and soft tissue stores, and thus may aggravate acute toxic symptoms by increasing PbB if not given in conjunction with BAL. Therefore, for adults that are symptomatic or have PbB levels >70 µg/dL and for children (symptomatic or asymptomatic) with PbB levels >70 µg/dL, therapy with BAL followed by EDTA is used (CDC 1991; Ellenhorn and Barceloux 1988; Goldfrank et al. 1994). For asymptomatic children with PbB levels of 45–69 µg/dL, a course of EDTA chelation therapy is used (CDC 1991; Ellenhorn and Barceloux 1988; Goldfrank et al. 1994). 2,3-Dimercaptosuccinic acid (DSMA; Succimer®) is an orally administered chelating agent approved by the FDA for treating children with PbB levels >45 µg/dL, for which indication it is the treatment of choice. Although not yet FDA labeled for this indication, DSMA is also being used to treat lead poisoning in adults. The effectiveness of chelation therapy for treating children with PbB levels ranging from 25 to 44 µg/dL is still being debated (Angle 1993; Graziano 1994), and treatment of children in this range varies. At a minimum, it is recommended that exposure to lead be minimized, sufficient calcium and iron intake be ensured, and regular blood lead level testing be conducted in children who fall into this range (CDC 1991). Children with PbB levels of

20–24 µg/dL are generally not chelated. Management of these children includes reducing sources of lead exposure, ensuring proper nutritional status, and routine blood lead testing (CDC 1991).

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

One of the mechanisms underlying the diffuse effects of lead is thought to be the result of its ability to combine with ligand groups (predominantly sulfhydryl groups) on proteins, thereby affecting many enzyme systems and cellular processes throughout the body (e.g., the enzymes involved in heme synthesis, see Sections 2.2.1.2, 2.4, and 2.5). Therefore, interfering with the binding of lead to these macromolecules would reduce the toxicity of lead. For example, the efficacy of treatment with a sulfhydryl donor for lead to bind to, such as acetylcysteine, could be investigated. The chelating agents discussed in Section 2.10.2 bind to lead and, therefore, prevent its binding to proteins. All chelating agents have more or less significant potential adverse effects, and some are contraindicated or must be used with extreme caution in some situations or in some patients (e.g., patients with renal impairment). It is advisable to consult with a medical toxicologist or other physician familiar with those medications before commencing treatment. CDC (1991) summarized information on the pharmacology of chelating agents. For example, some clinicians recommend that for patients with glucose-6-phosphate dehydrogenase, BAL be used only in life-threatening situations, since the drug may induce hemolysis. Also, medicinal iron should never be administered during BAL therapy because the combination of iron and BAL has been implicated in serious reactions. BAL should not be used for children allergic to peanuts or peanuts products. Na_2-EDTA should never be used for treating children with lead poisoning because it will induce tetany and possibly fatal hypocalcemia; only $CaNa_2$-EDTA can be used for treating children with lead poisoning. D-penicillamine should not be administered to patients with known penicillin allergy. Succimer is chemically similar to BAL but it is more water soluble, has a high therapeutic index, and is absorbed from the gastrointestinal tract. Toxicity due to succimer appears to be minimal, but clinical experience with succimer is limited.

In cases of lead encephalopathy with cerebral edema, edema can be treated with mannitol, corticosteroids, and hypothermia. Convulsions can be treated with diazepam, phenytoin, and/or phenobarbital (Garrettson 1990).

2.11 ADEQUACY OF THE DATABASE

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

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

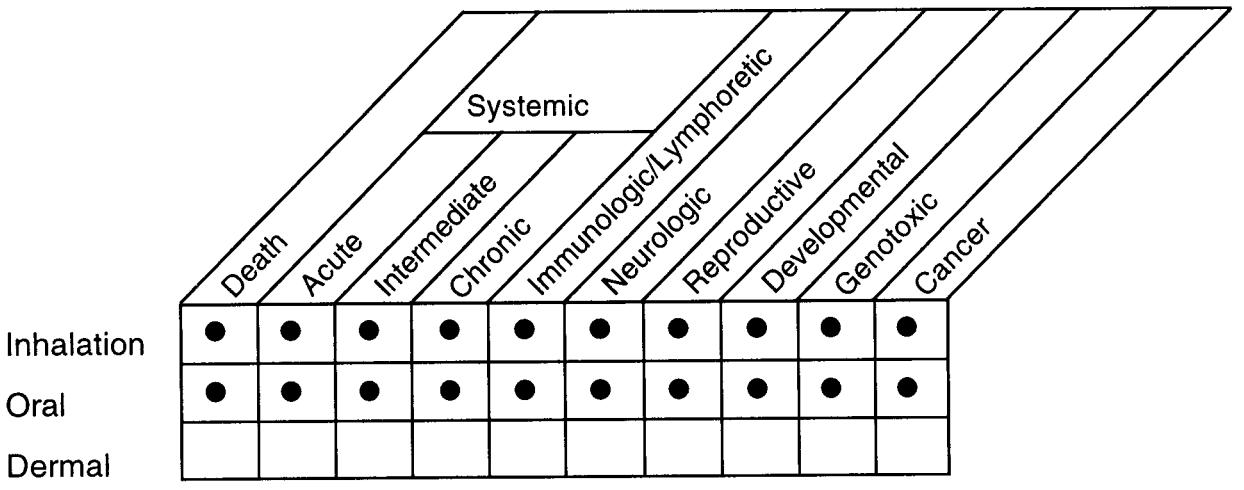
2.11.1 Existing Information on Health Effects of Lead

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to lead are summarized in Figure 2-13. The purpose of this figure is to illustrate the existing information concerning the health effects of lead. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need." A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

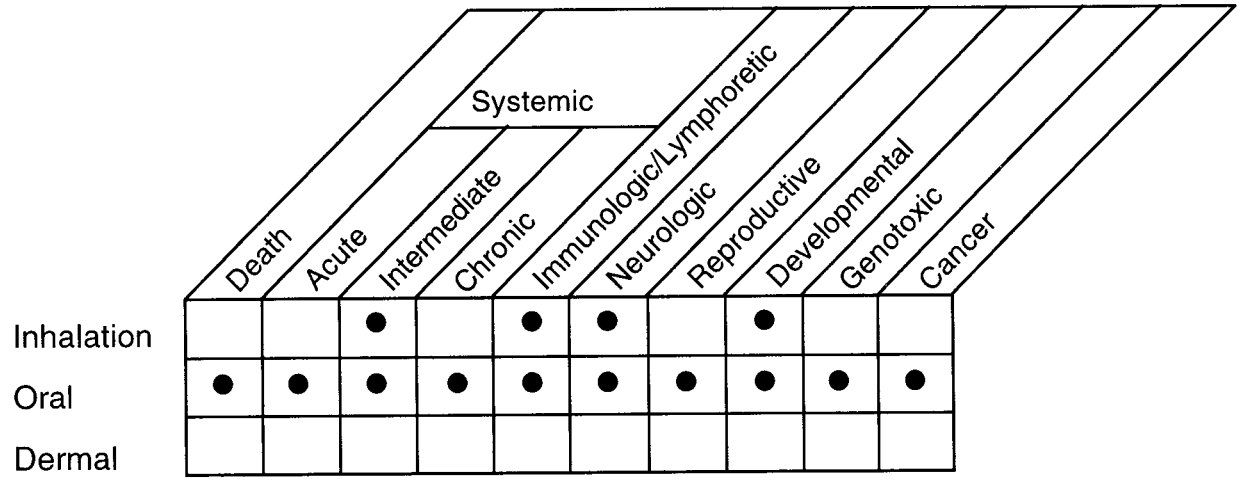
2.11.2 Identification of Data Needs

Acute-Duration Exposure. There are few data available for acute exposures in humans. This may be a function of the time required for the expression of effects (decreased heme synthesis, neurobehavioral changes, increased blood pressure, and interference with vitamin D metabolism) and the usual modes of exposure in humans, which are repeated ingestion of lead-containing dirt or lead-based paint chips in

Figure 2-13. Existing Information on Health Effects of Lead



Human



Animal

● Existing Studies

children and continuous occupational inhalation exposures for adults. Both of these modes of exposure occur simultaneously with exposure to other metals so that the effect of lead may be modulated by the presence of other metals. More data need to be generated in studies that include multi-elemental analyses. One case report reviewed described a patient that presented with headache, fatigue, nausea, abdominal cramps, and arthralgias with a PbB level of 90 µg/dL following a 12-hour exposure to lead from sand-blasting old lead-based paint, indicating that lead toxicity can occur in humans after acute-duration exposures (Schneitzer et al. 1990). A 70-year-old woman who was a nursing home resident died of lead intoxication 16 days after drinking lead ceramic glaze (Roberge et al. 1994). On admission to the hospital her PbB level was 259 µg/dL, but decreased to 21 µg/dL after chelation therapy. In spite of this, the patient's lethargy and confusion persisted and she developed renal failure and associated anasarca, as well as a brief apneic period before dying. Some data exist that show death occurred in children who had severe lead-induced encephalopathy (Chisolm 1962; Chisolm and Harrison 1956). The duration of exposure associated with this effect is not clear; it may have been a few weeks or more and, in some cases, may have been acute. There are data that show human ingestion of lead acetate producing a decrease in erythrocyte ALAD within 3 days (Stuik 1974). There are no data available on acute inhalation exposures in animals.

A 7-day oral study in rats fed lead acetate (Smith et al. 1981) reported a depression of 1,25-dihydroxy-vitamin D plasma levels providing support for the evidence seen in humans that vitamin D metabolism may be a target for lead toxicity. Additional data relating environmental measurements of exposure, blood lead levels, and toxic effects from acute inhalation and oral exposures would be useful for assessment of the public health concern with acute exposure to lead. Further data that provided dose-response information would be useful for determining if there is a threshold for lead toxicity in animals and, if so, the thresholds for lead toxicity for both oral and inhalation exposures. There are no pharmacokinetic data that specifically address whether or not the route of exposure alters the health effects caused by lead, but the available information indicates that the toxic effects of lead are the same regardless of route of exposure. Dermal exposures are not considered to be significant in humans because the dermal absorption rate of lead is so low for inorganic compounds. Significant dermal absorption occurs for organolead compounds, but because the potential exposure levels are very low, additional studies do not seem warranted at this time.

Intermediate-Duration Exposure. Intermediate and chronic exposures in humans should be considered together, because the length of exposure is not usually known. The database for lead is unusual in that it contains a great deal of data concerning dose-effect relationships in humans. However, the dose data for humans are usually expressed in terms of blood lead levels rather than as environmental exposure

levels. Dose-effect data in terms of environmental levels (mg/kg/day or mg/m^3) by a single route of exposure are not generally available for humans.

The dose-effect relationship between blood lead and ALAD has been reported to extend through the lowest blood lead levels detectable (Chisolm et al. 1985; Hernberg and Nikkanen 1970; Lauwerys et al. 1978; Roels and Lauwerys 1987; Sakai and Morita 1996; Secchi et al. 1974). Inhibition of enzyme activity results in reduced heme synthesis, which affects not only the oxygen-carrying potential of erythrocytes but also decreases formation of cytochrome P-450. This effect can influence many metabolic energy-transfer processes. Formation of heme-containing cytochromes is also inhibited in animals treated intraperitoneally or orally with lead compounds (Azar et al. 1973; Goldberg et al. 1978; Krasovskii et al. 1979; Overmann 1977; Walsh and Ryden 1984). Additional data from 90-day animal studies would be useful for correlating environmental exposure measurements with both blood lead levels and health effects. Further data that provided dose-response information would be useful for determining if there is a threshold for lead toxicity for both oral and inhalation exposures. There are no pharmacokinetic data that specifically address whether or not the route of exposure alters the health effects caused by lead, but the available information indicates that the toxic effects of lead are the same regardless of route of exposure. Dermal exposures are not considered to be significant in humans because the dermal absorption rate of inorganic lead is so low. Significant dermal absorption occurs for organolead compounds, but because the potential exposure levels are very low, additional studies do not seem warranted at this time.

Chronic-Duration Exposure and Cancer. As stated in the preceding section, intermediate and chronic exposures in humans should be considered together, because the length of exposure is usually not known. Effects on heme synthesis and erythropoiesis (Adebonojo 1974; Alessio et al. 1976; Awad et al. 1986; Baker et al. 1979; Betts et al. 1973; Chisolm et al. 1985; Grandjean 1979; Hernberg and Nikkanen 1970; Lauwerys et al. 1974, 1978; Lilis et al. 1978; Meredith et al. 1978; Pollock and Ibels 1986; Roels and Lauwerys 1987; Roels et al. 1975, 1976, 1979; Rosen et al. 1974; Schwartz et al. 1990; Secchi et al. 1974; Selander and Cramer 1970; Solliway et al. 1996), neurobehavioral toxicity (Arnvig et al. 1980; Awad et al. 1986; Baker et al. 1979; Baloh et al. 1979; Campara et al. 1984; de la Burde and Choate 1972, 1975; Ernhart et al. 1981; Glickman et al. 1984; Haenninen et al. 1979; Hogstedt et al. 1983; Holness and Nethercott 1988; Khera et al. 1980b; Kotok 1972; Kotok et al. 1977; Lindgren et al. 1996; Maizlish et al. 1995; Mantere et al. 1982; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Parkinson et al. 1986; Pasternak et al. 1989; Pollock and Ibels 1986; Rummo et al. 1979; Schneitzer et al. 1990; Stollery et al. 1989, 1991; Zimmerman-Tanselia et al. 1983), cardiovascular toxicity (de Kort et al. 1987; Kirkby and

Gyntelberg 1985; Kline 1960; Kosmider and Petelenz 1962; Pocock et al. 1984, 1985, 1988; Pollock and Ibels 1986; Marino et al. 1989; Silver and Rodriguez-Torres 1968; Weiss et al. 1986, 1988), renal toxicity (Batuman et al. 1981, 1983; Biagini et al. 1977; Chisolm 1962; Cramer et al. 1974; Kim et al. 1996a; Lilis et al. 1968; Maranelli and Apostoli 1987; Ong et al. 1987; Pollock and Ibels 1986; Pueschel et al. 1972; Staessen et al. 1992; Verschoor et al. 1987; Wedeen et al. 1979), and vitamin D metabolism (Mahaffey et al. 1982; Rosen et al. 1980) have been noted. Additional data providing dose-response information would be useful for determining if there is a threshold for lead toxicity for both oral and inhalation exposures. There are no pharmacokinetic data that specifically address whether or not the route of exposure alters the health effects caused by lead, but the available information indicates that the toxic effects of lead are the same regardless of route of exposure, but the time course differs. Dermal exposures are not considered to be significant in humans because the dermal absorption rate of lead is so low. This is not so for organolead compounds (Stauber et al. 1994).

No acute, intermediate, or chronic MRLs have been derived for any route of exposure because of the lack of a clear threshold for the most sensitive effects in humans. However, ATSDR has developed a framework to provide health guidance at lead sites (see appendix D).

Several epidemiological studies of occupationally exposed persons have examined the potential carcinogenicity of lead (Anttila et al. 1995, 1996; Cocco et al. 1997; Cooper 1976; Cooper and Gaffey 1975; Fayerweather et al. 1991; Kang et al. 1980; Lundstrom et al. 1997; Selevan et al. 1985; Steenland et al. 1992). These studies all exhibit some methodological limitations, which include no identification of the actual lead compounds, no specification of the route of exposure, no adjustment for concomitant exposure to other chemicals, and no adjustment for other confounders such as cigarette smoking. Increased incidences of total malignant neoplasms were reported in some studies; statistical significance was reached in some categories, but not others. Three studies reported a non-significant increase in renal cancer, which is supportive of animal studies that associate lead exposure with kidney cancer (Cocco et al. 1997; Selevan et al. 1985; Steenland et al. 1992). Two additional case reports of renal cancer in occupationally exposed men also provide anecdotal support for this effect (Baker et al. 1980; Lilis 1981). These case reports are the only occupational cancer reports to include blood lead levels. There are no data regarding the carcinogenicity of lead in humans exposed solely by the oral route. The association of exposure to tetraethyl lead with colon/rectal cancer was published in 1997 (Fayerweather et al. 1997) and needs to be confirmed.

Several animal studies associate oral exposure to several lead compounds with renal tumors in various species (Azar et al. 1973; Koller et al. 1985; Van Esch and Kroes 1969). Most studies used one or two doses; good dose-effect data are not available. One 2-year study in rats used six doses as well as a control group (Azar et al. 1973). This study measured both exposure levels and blood levels, and correlated these with increased tumor incidence, as well as reduced heme synthesis. There are no animal data on the carcinogenicity of lead by inhalation exposure. Additional long-term studies of other species are needed to evaluate the potential carcinogenic effects of lead in humans. Information on inhalation exposures would be particularly useful because most long-term human exposures are thought to be occupational and primarily by inhalation. There are recognized species differences in the pharmacokinetics of lead that may have a bearing on the carcinogenic potential for this compound across species (see "Comparative Toxicokinetics").

Genotoxicity. Data are available on the genotoxicity of lead both from *in vitro* and *in vivo* studies. Human lymphocytes have been examined from both occupationally or environmentally exposed persons and from healthy controls as well (Beek and Obe 1974; Deknudt and Deminatti 1978; Gasiorek and Bauchinger 1981; Niebuhr and Wulf 1984; Schmid et al. 1972). The results of these studies are mixed. The positive data indicate that lead is a clastogen. The results of *in vivo* tests are also contradictory, but there is some evidence that lead has an effect on chromosomes. Increased sister chromatid exchange occurred in some lead-exposed workers (Huang et al. 1988b), but not in others (Maki-Paakkanen et al. 1981). A positive correlation between increased frequency of sister chromatid exchange and duration of occupational exposure independent of blood level (Grandjean et al. 1983), or between chromosomal aberrations and blood levels (Huang et al. 1988b) has been reported. In mammalian test systems *in vitro*, there are conflicting results for lead acetate-induced structural chromosomal aberrations (Bauchinger and Schmid 1972; Robison et al. 1984).

Tests for gene mutations, DNA modifications, and recombinations in various microorganisms using lead acetate, lead nitrate, and lead chloride gave equivocal results (Bruce and Heddle 1979; Dunkel et al. 1984; Fukunaga et al. 1982; Hoffman and Niyogi 1977; Kharab and Singh 1985; Nestmann et al. 1979; Nishioka 1975; Rosenkranz and Poirier 1979; Simmon 1979a, 1979b; Sirover and Loeb 1976). As summarized by Winder and Bonin (1993), some reasons for the equivocal results may be related to solubility differences among the lead compounds in biological fluids, chemical interferences, nonspecificity of the assays used, the delivery of toxic doses to specific genetic processes, or the mediation of genotoxicity through indirect mechanisms. There are some data to indicate that the status of calcium availability may be important in the

expression of lead-induced clastogenicity in both *in vitro* and *in vivo* tests (Deknudt et al. 1977; Hartwig et al. 1990). Studies in monkeys indicated that calcium deficiency may enhance the genotoxicity of lead as it does for other manifestations of lead toxicity (Deknudt et al. 1977). In a study in mice, males were found to be more susceptible to the clastogenic effects of lead than females (Jagetia and Aruna 1998). Additional studies are needed to clarify the clastogenic potential of lead and its compounds and to assess the possible implications for carcinogenic potential. Specific aberrations, if identified, would offer insight into a mechanism for carcinogenesis.

Reproductive Toxicity. Human data on reproductive toxicity come from observations in occupational cohorts (Alexander et al. 1996; Assennato et al. 1987; Baghurst et al. 1987; Bonde and Kolstad 1997; Braunstein et al. 1978; Chowdhury et al. 1986; Cullen et al. 1984; Gennart et al. 1992b; Hu et al. 1991; Lancranjan et al. 1975; Lerda 1992; Lin et al. 1996; McMichael et al. 1986; Murphy et al. 1990; Ng et al. 1991; Nordstrom et al. 1979; Rodamilans et al. 1988; Sallmen et al. 1995; Wibberley et al. 1977; Wildt et al. 1983). Although no dose-effect data were presented, occupational exposure to inorganic lead has been associated with a higher likelihood of spontaneous abortion (Baghurst et al. 1987; Hu et al. 1991; McMichael et al. 1986; Nordstrom et al. 1979; Wibberley et al. 1977). Studies of increased frequency of spontaneous abortion in women living close to a lead smelter or working in highly contaminated areas of the smelter were confounded by the presence of other toxic agents and by the lack of matching for socioeconomic status. There are data that indicate that reproductive effects occur in men exposed to lead manifested as asthenospermia, hypospermia, teratospermia, and reduced fertility and that these effects are related to blood lead levels (Alexander et al. 1996; Assennato et al. 1987; Braunstein et al. 1978; Chowdhury et al. 1986; Cullen et al. 1984; Lancranjan et al. 1975; Lerda 1992; Lin et al. 1996; Rodamilans et al. 1988; Wildt et al. 1983).

Animal studies support the evidence of lead-induced reproductive toxicity in humans. Rats dosed with oral lead acetate show irregular estrous cycles in females and testicular damage in males (Hilderbrand et al. 1973). Recent lifetime exposure studies in male monkeys, using exposure protocols to evaluate different developmental ages, have reported structural alterations in the testis at PbB levels relevant to the human population (Foster et al. 1996, 1998). Studies in rats have suggested that continuous lead exposure delays sexual maturation by suppressing normal sex steroid surges at birth and during puberty (Ronis et al. 1998b, 1998c). There are no data on the reproductive toxicity of inhaled lead in animals.

There are enough data to provide qualitative evidence in support of the association with high levels of lead and reproductive effects in humans and animals. However, the data cannot be used to estimate effect levels in women and can be used only with caution to describe effects on sperm or testes from specific blood levels of lead. Additional dose-effect data on inhalation exposures (the most common occupational exposure in adults) in humans are needed to determine the potential for reproductive effects. Ninety-day inhalation animal studies that quantify lead-induced reproductive toxicity are needed to confirm the qualitative data in humans.

Developmental Toxicity. Three human studies that described congenital malformations as an end point allow no definitive conclusion to be drawn regarding an association between prenatal lead exposure and the occurrence of congenital anomalies (Ernhart et al. 1985, 1986; McMichael et al. 1986; Needleman et al. 1984). The limitations of these studies include possible bias introduced by use of hospital records and a restricted range of maternal and cord blood lead levels. The sizes of the groups studied were not sufficient for the detection of differences in low frequencies of anomalies.

The data are mixed regarding reduced birth weight and prenatal lead exposure in humans. Studies evaluating exposure to low levels of lead and its influence upon birth weight and gestational age are more controversial. The earlier evidence for such effects has not been reproduced in the studies by Factor-Litvak et al. (1991) and Greene and Ernhart (1991). A significant inverse association between prenatal maternal blood lead levels and birth weight was reported in the Cincinnati study (Bornschein et al. 1989; Dietrich et al. 1986, 1987a). An earlier study showed that the percentage of small-for-gestational-age infants increased with increasing cord blood lead, although the trend was not quite statistically significant (Bellinger et al. 1984). Significant direct associations between maternal and cord PbB levels and birth weight were reported by McMichael et al. (1986). On the other hand, no association has been observed between maternal or cord blood levels and birth weight in several other studies (Ernhart et al. 1985, 1986; Factor-Litvak et al. 1991; Greene and Ernhart 1991; Moore et al. 1982; Needleman et al. 1984).

Evidence from some of the above studies also indicates that gestational age may be reduced as prenatal lead exposure increases, even at PbB levels below 15 µg/dL (EPA 1986a). Significant negative correlations between maternal or cord blood lead levels and gestational age were reported by Dietrich et al. (1986, 1987a, 1987b), McMichael et al. (1986); and Moore et al. (1982). Based on parameter estimates of Dietrich et al. (1986), the reduction in gestational age was 0.6 week per natural log unit of blood lead increase (EPA 1986a). Based on risk estimates of McMichael et al. (1986), the risk of preterm delivery increases by at

least fourfold as either cord blood or maternal PbB level at delivery increases from #8 to >14 µg/dL. However, other investigators did not find a significant relationship between maternal or cord PbB level and gestational age (Bellinger et al. 1984; Factor-Litvak et al. 1991; Needleman et al. 1984). These studies also indicate that adverse neurobehavioral affects can occur because of prenatal lead exposure (see the discussion on "Neurotoxicity" below). The intellectual development of children exposed prenatally to lead has been followed in several prospective studies. Some of these include the Yugoslavia cohort (Wasserman et al. 1994, 1997, 1998), the Port Pirie cohort (Baghurst et al. 1992, 1995; McMichael et al. 1994; Tong et al. 1996), the Boston cohort (Bellinger et al. 1989a, 1989b, 1992, 1994) and the Cincinnati cohort (Dietrich et al. 1989, 1991, 1992, 1993a, 1993b). These studies found that a typical doubling of PbB from 10 to 20 µg/dL is associated with an average IQ loss of 1–3 IQ points. The continued evaluation of these groups is expected to provide information as to the persistency of some of the neurodevelopmental effects. The research should focus on neurobehavioral outcome measures while controlling for socio-hereditary factors. Additional studies on the mobilization of lead from bone during gestation and lactation would provide valuable information on the potential toxic consequences on both the mother and the neonate. Also, further research on the relationship between paternal lead exposure and fetal/infant development should be considered. As most adult exposures associated with hazardous waste sites are via the inhalation or oral routes, studies examining these routes of exposure would be particularly useful.

Inhalation and oral teratogenicity studies in rats and mice provide no evidence that lead acetate or lead nitrate are teratogenic after oral or inhalation exposure (Draski et al. 1989; Grant et al. 1980; Kimmel et al. 1980; Miller et al. 1982; Prigge and Greve 1977; Rabe et al. 1985). Intravenous and intraperitoneal injections of lead acetate, chloride, or nitrate into pregnant rats, mice, or hamsters have produced malformations in several studies (Gale 1978; McClain and Becker 1972; Snowden 1973). Based on these results, it would appear that parenteral administration of lead leads to greater target tissue doses than oral or inhalation exposure. Additional data on dose-effect relationships for these exposure routes would be useful because these data, along with pharmacokinetic data, could be used to assess the apparent difference in blood lead effects between injected lead compounds and more conventional route of exposure (i.e., inhalation or oral).

Immunotoxicity. The data in humans are limited to a few studies of immune function in lead workers and a study of firearm instructors. In both type of studies, inhalation is assumed to be the primary route of exposure. One study reported significant suppression of IgA levels (Ewers et al. 1982). Another study

indicated that serum immunoglobulin levels were not significantly altered (Alomran and Shleamoon 1988). Another large study examined several parameters of immune function (serum immunoglobulins, PHA response, and natural killer cell activity) and found no differences in exposed workers and controls (Kimber et al. 1986b). The study of firearm instructors found functional impairment of cell-mediated immunity in subjects with PbB levels >25 µg/dL (Fischbein et al. 1993). A recent study that evaluated a comprehensive panel of immunologic parameters among lead workers found minor differences in some specific parameters between exposed and nonexposed controls, but there was no evidence of marked immunotoxic effects of lead (Pinkerton et al. 1998). The information available in children show no difference in several measures of immune response between children with PbB $40 µg/dL and children without elevated PbB (Reigart and Graher 1976).

The best human data available on immune response involve small numbers of subjects and lack of adequate controls. Additional studies on immune function parameters in both children and adults are needed to verify or refute the lack of immunotoxicity seen in humans to date. These studies should include a well defined set of immunologic assays in order to facilitate comparisons between studies.

One inhalation study in animals showed no effect on phagocytosis of bacteria in mice exposed to lead (Hillam and Ozkan 1986). No PbB data were available. An inhalation study in rabbits showed that *in vitro* lung macrophage function can be altered by exposure to lead even though blood lead levels remained at control levels (Zelikoff et al. 1993). An intermediate-duration study in mice indicated that several components of the immune system were depressed following both inhalation and oral exposure, and that the immunosuppressive effect is most pronounced when the antigen is introduced by the same route as the pollutant (Hillam and Ozkan 1986). Dose-effect data for immune system effects at low blood levels and external lead exposure levels are available from rat studies (Faith et al. 1979; Kimber et al. 1986a; Luster et al. 1978). Prenatal and postnatal exposure of rats to lead acetate at 25 ppm in drinking water resulted in marked depression of antibody responses to sheep red blood cells, decreased serum IgG, decreased lymphocyte responsiveness to mitogens, impaired delayed hypersensitivity reactions, and decreased thymus weights as compared with controls (Faith et al. 1979; Luster et al. 1978). One study in mice suggests that lead-induced immunosuppression may be greater following inhalation exposure; inhalation exposures can be significant for human adults. The available rat data are both quantitative and broad in scope. These positive data are suggestive of an effect on the immune system that may or may not be species specific. Additional data are needed from 90-day inhalation studies in species other than rats to provide good dose-effect information on a variety of immune system parameters.

Neurotoxicity. There is a very large database on the neurotoxic effects of lead. The most severe neurobehavioral effect of lead toxicity in adults is lead encephalopathy (Kehoe 1961a; Kumar et al. 1987; Smith et al. 1978). Early symptoms, which may develop within weeks of initial exposure, include dullness, irritability, poor attention span, headache, muscular tremor, loss of memory, and hallucinations. These symptoms worsen, sometimes abruptly, to delirium, convulsions, paralysis, coma, and death. Other nervous system effects seen in adults at lower exposure levels include extensor muscle weakness, loss of appetite, paresthesias in lower limbs, weakness of upper limbs, poor performance on cognitive and visual-motor coordination tasks, and impaired verbal reasoning ability (Arnvig et al. 1980; Awad et al. 1986; Baker et al. 1979; Baloh et al. 1979; Campara et al. 1984; Glickman et al. 1984; Haenninen et al. 1979; Hogstedt et al. 1983; Holness and Nethercott 1988; Khera et al. 1980b; Lindgren et al. 1996; Maizlish et al. 1995; Mantere et al. 1982; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Parkinson et al. 1986; Pasternak et al. 1989; Pollock and Ibels 1986; Schneitzer et al. 1990; Stollery et al. 1989, 1991; Stollery 1996; Zimmerman-Tanselia et al. 1983). Taken together, the results of these studies on adults (primarily occupational and therefore predominantly inhalation exposures) indicate that the PbB levels at which neurological signs occur in adults are in the range of 40–60 µg/dL and that neurological effects occur at roughly the same blood lead levels as other symptoms of lead poisoning, such as gastrointestinal complaints.

In children, most exposures are oral, but the neurotoxic effects are similar to those seen in adults (Bradley and Baumgartner 1958; Bradley et al. 1956; Chisolm 1962, 1965; Chisolm and Harrison 1956; de la Burde and Choate 1972, 1975; Ernhart et al. 1981; Gant 1938; Kotok 1972; Kotok et al. 1977; Rummo et al. 1979; Smith et al. 1983). There are data available that indicate children with symptomatic lead poisoning without encephalopathy have an increased incidence of lasting neurological and behavioral impairments. While no adverse neurological effects have been clearly documented at low blood lead levels, an inverse relationship between lead burden and IQ is well documented and some studies indicate that PbB levels as low as 7 µg/dL may also decrease IQ (Bellinger and Needleman 1983; Bergomi et al. 1989; Fulton et al. 1987; Hansen et al. 1989; Hawk et al. 1986; Needleman et al. 1979, 1985, 1990; Schroeder and Hawk 1987; Schroeder et al. 1985) and meta-analyses of the epidemiological data have provided no evidence of a threshold (IPCS 1995; Needleman and Gatsonis 1990, Pocock et al. 1994; Schwartz 1994). These data suggest that children are more sensitive to lead-induced neurotoxicity than adults, as indicated by responses at lower PbB. Pharmacokinetic data indicate that young children are more susceptible to the effects of lead because of the greater absorption and retention rates in children, a greater prevalence of nutrient deficiency, which can affect gastrointestinal absorption, differences in the efficiency of lead sequestration in bone, and incomplete

development of the blood-brain barrier (Barry 1975; Chamberlain et al. 1978). Virtually all neurotoxic effects are reported as related to blood lead level. More information on the relationship of health effects to environmental exposure levels would be useful for quantifying the potential risk to environmentally exposed human populations. Additional data on the relationships between blood lead levels and environmental levels are needed to quantify these risks. Additional information is needed on the pharmacokinetic differences between human adults and children to improve risk estimates for the more susceptible groups. Further information on the effects of lead during advanced age and/or its relationship to aging processes to determine the extent to which aging populations are vulnerable to lead and the extent to which lead may contribute to age-related dysfunction, particularly the neurological disturbances and neurodegeneration is needed. Two recent studies provided preliminary evidence of an association between PbB and impaired neurobehavioral performance in aging populations with relatively low blood lead levels (Muldoon et al. 1996; Payton et al. 1998). Tests designed to directly compare behavioral data from humans and animals would provide valuable information that could be used to study in animals the underlying biological mechanisms responsible for well defined behavioral changes.

There are no animal inhalation studies but many oral ones that describe adverse neurological effects (Bushnell and Bowman 1979a, 1979b; Bushnell and Levin 1983; Cory-Slechta et al. 1983, 1985; Ferguson and Bowman 1990; Gilbert and Rice 1987; Hopper et al. 1986; Krasovskii et al. 1979; Levin et al. 1988; Massaro and Massaro 1987; Overmann 1977; Rice 1985a). It appears that animals are affected at roughly the same blood lead levels as humans. Measured neurotoxic effects in animals include significantly delayed motor function and reflexes, decreased performance on learning tasks, and impaired spatial discrimination. Additional animal studies are needed to investigate the neurotoxic effects of subchronic inhalation exposures to establish external dose-effect relationships.

Epidemiological and Human Dosimetry Studies. There are dozens of epidemiological studies in both adults and children that investigate the health effects of lead. However, epidemiological studies on environmental chemicals are faced with the task of identifying relevant confounders and dealing with them effectively in order to arrive at valid conclusions within the risk assessment process. The general population is exposed to lead in ambient air, in many foods, in drinking water, and in dust. Segments of the general population at highest risk from lead exposure are preschool-age children (especially those in lower-income, inner city housing where there is old lead-based paint), pregnant women and their fetuses, and white males between 40 and 59 years of age. Within these groups, strong relationships have been established between lead exposure (as measured by PbB levels) and adverse health effects. Because the effects generally appear

to be small in magnitude, the usefulness of small sample size studies is questionable, except to clarify physiologic mechanisms. It is possible to measure lead in blood, bone, teeth, sweat, nails, and hair, and there is a substantial body of data relating health effects to PbB levels. The most obvious weakness in most epidemiological studies is the difficulty in quantifying environmental measures of exposure. Information correlating levels of lead in the environment and blood lead levels in children is available (i.e., Lanphear et al. 1998a, 1998b; Mielke et al. 1989, 1997a). This kind of information is useful for evaluating potential health effects not only for populations located near hazardous waste sites but also for those living in urban sites where exposure potential is known to be much higher that in suburban and rural areas.

Biomarkers of Exposure and Effect. Inorganic lead can be measured in blood, serum, urine, sweat, cerebrospinal fluid, tissues, bone, teeth, and hair (Aguilera de Benzo et al. 1989; Blakley and Archer 1982; Blakley et al. 1982; Christoffersson et al. 1986; Delves and Campbell 1988; Ellen and Van Loon 1990; Exon et al. 1979; Hewitt 1988; Hoppin et al. 1995; Hu et al. 1995; Jason and Kellogg 1981; Manton and Cook 1984; NIOSH 1977a, 1977d, 1977e, 1977f, 1977g; Que Hee and Boyle 1988; Que Hee et al. 1985a; Rabinowitz et al. 1989; Steenhout and Pourtois 1981; Tabuchi et al. 1989; Tomokuni and Ichiba 1988; Thatcher et al. 1982; Wielopolski et al. 1986; Wilhelm et al. 1989). These measures of lead in body fluids are sensitive and reliable for indicating that background exposures have occurred, as well as higher exposures at which health effects have been observed to occur. Only PbB levels have been found to be correlated with exposure concentrations. However, PbB levels are not an exact measure of exposure to lead either because of the transfer, mobilization, and storage among different compartments in the body, and because PbB does not reflect the entire lead body burden. Because lead cycles between blood and bone, a single blood lead determination cannot distinguish between exposure to a given level for an extended period of time and a previous exposure to a high level that would result in the same PbB level due to recycling from bone. Lead levels in tissues, bones, and teeth are generally reliable indicators of lead exposure but are only sensitive at relatively high exposure concentrations. The need exists for the development of a biomarker that would accurately reflect the total body burden from both acute- and chronic-duration at both low and high level exposures. X-ray fluorescence of bone has emerged as a promising approach to development of noninvasive assessment of the lead burden in bone. For tetraethyl lead exposure, urinary diethyl lead has been found to be a qualitative biomarker (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

There is no clinical disease state that is pathognomonic for lead exposure. The neurotoxic effects and hematopoietic effects of lead are well recognized. The primary biomarkers of effect for lead are EP, ALAD, basophilic stippling and premature erythrocyte hemolysis, and presence of intranuclear lead inclusion bodies in the kidneys. Of these, activity of ALAD is a sensitive indicator of lead exposure (Hernberg et al. 1970; Morris et al. 1988; Somashekaraiah et al. 1990; Tola et al. 1973), but the assay can not distinguish between moderate and severe exposure (Graziano 1994). Sensitive, reliable, well-established methods exist to monitor for these biomarkers; however, they are not specific for lead exposure. Therefore, there is a need to develop more specific biomarkers of effect for lead. Recent data suggest that the concentration of $\alpha_{1\mu}$-globulin in urine may be a early marker of nephrotoxicity, although this is still nonspecific (Chia et al. 1995b).

Absorption, Distribution, Metabolism, and Excretion. Studies of absorption of inhaled lead in adult humans indicate that following deposition of between 30 and 50% of inhaled airborne lead in the respiratory tract, lead is almost completely absorbed (EPA 1986a; Morrow et al. 1980). About 70% of inhaled lead is absorbed within 10 hours. There are no data on the deposition and absorption of inhaled lead in children. However, models of age-related changes in airway geometry and physiology predict that, particle deposition in the various regions of the respiratory tract in children may be higher or lower than in adults depending on particle size; for submicron particles, fractional deposition in 2-year-old children has been estimated to be 1.5 times greater than in adults (Xu and Yu 1986).

Oral intake of lead in humans can result from consuming lead-containing food, drinking water and beverages, from ingesting lead-containing dusts, and from swallowing lead deposited in the upper respiratory tract after inhalation exposure. Children can ingest lead-containing dusts, lead-based paint, and other non-food materials through their normal mouthing activity and pica (abnormal ingestion of non-food items). Fractional absorption of ingested lead appears to vary in magnitude with age, being as much as 5 to 10 times greater in infants and young children than in adults (Alexander et al. 1974; Chamberlain et al. 1978; James et al. 1985; Ziegler et al. 1978). However, there are no data on the absorption of lead in older children and adolescents; thus, it is uncertain whether lead absorption in this population is more similar to that of adults or to that of infants and young children. Ingested soil lead is less readily absorbed than ingested water soluble lead acetate (Casteel et al. 1997; EPA 1996a, 1996b, 1996c; Freeman et al. 1996). This difference may reflect a lower solubility of soil lead because of its chemical or physical form; for example, there is an inverse relationship between lead particle size and gastrointestinal absorption (Barltrop and Meek 1979). There is one published study that assessed the bioavailability of lead in adults who

ingested hazardous waste site soil (Maddaloni et al. 1998). Additional studies of this type would provide an improved basis for estimating lead uptake in people who are exposed to lead in soil and soil-derived dusts. A variety of other factors are known to influence the absorption of ingested lead, including the chemical form of the ingested lead, the presence of food in the gastrointestinal tract, diet, and nutritional status with respect to calcium, vitamin D, and iron (Mushak 1991); however, for the most part, the mechanisms by which these interactions occur are not fully understood. This reflects, in part, a lack of understanding of the mechanisms by which lead is absorbed in the gastrointestinal tract. A better understanding of absorption mechanisms is critical to developing physiologically based models that accurately simulate relationships between lead exposure and lead in blood and other target and biomarker tissues.

Limited information is available regarding absorption after dermal exposure of inorganic lead compounds in humans. In contrast, alkyl lead compounds have been shown to be rapidly and extensively absorbed through the skin of rabbits and rats (Kehoe and Thamann 1931; Laug and Kunze 1948). Recent studies provide evidence for rapid dermal absorption of inorganic lead in adults, however, these studies have not quantified the fraction of applied dose that was absorbed (Stauber et al. 1994). The quantitative significance of the dermal absorption pathway as a contributor to lead body burden remains an uncertainty. In children who may experience extensive dermal contact with lead in soil, sand, or surface water and suspended sediment (e.g., beach or shoreline exposure scenario), even a low percent absorption across the skin may represent a significant internal dose. Therefore, additional studies designed to quantify dermal absorption of inorganic lead compounds from both aqueous media and from soil, in particular, studies that enable measurements to be extrapolated to children, are important for estimating internal doses that children might receive in relatively common exposure scenarios.

Comparative Toxicokinetics. Inhaled lead is absorbed extensively and rapidly by experimental animals as well as humans. Absorption of 98% within 7 days in adult rats breathing ^{203}Pb-labeled engine exhaust aerosols has been measured (Morgan and Holmes 1978). Similar results were obtained in studies with other species (Boudene et al. 1977; Griffin et al. 1975b). The extent of gastrointestinal absorption of lead in adult experimental animals (1–15%) is similar to that measured for adult humans (Aungst et al. 1981; Garber and Wei 1974). Similarly, gastrointestinal absorption of lead in experimental animals (rats, monkeys) is also age dependent (Forbes and Reina 1972; Kostial et al. 1978). In experimental animals, the relative contribution of the urinary and fecal routes to overall lead excretion is both dose and species dependent (see discussion on "Absorption, Distribution, Metabolism, and Excretion" above). Species

differences also exist in the rate and extent of total lead excretion. Rats, mice, dogs, and monkeys have been shown to excrete lead at different rates (Boudene et al. 1977; Castellino and Aloj 1964; Keller and Doherty 1980a; Kostial and Momcilovic 1974; Kozlowski and Wojcik 1987; Lloyd et al. 1975; Momcilovic and Kostial 1974; Morgan et al. 1977; Pounds et al. 1978). These studies represent oral, parenteral, and injection exposures; therefore, the apparent species differences may be confounded by exposure route differences. Additional data from directly comparable studies would be useful for clarifying this issue.

The metabolism of alkyl lead compounds appears to begin with dealkylation mediated by cytochrome P-450 in the rat, mouse, and rabbit. This step creates triethyl and trimethyl metabolites from tetraethyl and tetramethyl lead. Further biotransformation of these metabolites is highly species specific (Bolanowska 1968; EPA 1986a; Kehoe and Thamann 1931).

Rats are not known to convert triethyl lead to the diethyl form (Bolanowska 1968), but rabbits excrete large amounts of diethyl lead following exposure to alkyl lead (Klaassen and Shoeman 1974). Final conversion to inorganic lead may take place, although trialkyl lead compounds are usually stable in biological tissues.

Methods for Reducing Toxic Effects. The extent of lead absorption in the gastrointestinal tract depends on numerous factors including nutritional factors and the presence or absence of other metals which interact with lead. Thus, further studies that could identify additional factors that affect lead absorption would be valuable. These factors may be nutritional factors or specific pathologic conditions. Chelators have been used in the management of lead poisoning, particularly in children. However, further research should address questions such as what blood lead levels warrant chelation therapy and whether chelation therapy may redistribute lead from bone to other tissues. Moreover, the effectiveness of chelation therapy in reducing neuropsychologic impairment in children with clinically inapparent lead poisoning is unknown. Clinical studies of oral chelation should not only monitor PbB concentrations, but also the possibility of ongoing lead exposure, the child's age, sources of lead exposure, length of exposure, and general health status. Lead inhibits heme synthesis by inhibiting the enzyme ALAD, and this results in a diffuse effect that involves many organs. Even if ALAD inhibition could be prevented, because of the ability of lead to inhibit and/or substitute for calcium in many cellular processes (such as neurotransmitter exocytosis) it appears that the question of how to interfere with the mechanism of toxic action of lead will not be easily solved.

Children's Susceptibility. Many of the known health effects that have been associated with low level lead exposure have been detected in children who experienced lead exposures both *in utero* and postnatally. Considerable uncertainty remains about the relative contribution of *in utero* and postnatal exposures to the development of health outcomes that are expressed later in childhood. This information is important for distinguishing those health outcomes that might be mitigated during the post-natal period from those that must be mitigated by limiting *in utero* exposure. Considerable uncertainty also remains about the long-term consequences of the lead-related neurobehavioral deficits detected in infants and children with respect to manifestation of chronic neurobehavioral problems in adolescence and adulthood.

The interaction between exposure intensity and duration of exposure in the development of neurobehavioral deficits is not understood, in part because of a lack of biomarkers of long-term lead exposure. The strongest evidence for health effects of low level lead exposures on neurodevelopmental deficits is based on relationships between measured health outcomes and PbB concentrations. Although these studies suggest that a significant amount of the variability in the health outcomes (e.g., neurobehavioral deficits) can be attributed to variability in PbB concentrations, a substantial amount of variability in the outcomes usually cannot be assigned to PbB, even after many known potential confounders have been considered (i.e., Needleman and Gatsonis 1990; Pocock et al. 1994; Schwartz 1994; Winneke 1996).

Efforts to explore alternative biomarkers of exposure that provide a better reflection of long-term cumulative exposure may be of value for exploring the above issues. Two potential biomarkers of long-term exposure are bone lead measurements and plasma lead measurements (Cake et al. 1996; Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Recent advances in XRF techniques have made it possible to estimate lead levels in bone. Such measurements hold promise as biomarkers of long-term cumulative exposure during childhood. However, standard techniques for measuring bone lead have not yet been developed. Moreover, there continues to be uncertainty about how to interpret bone lead measurements in terms of lead exposure, their relationship to PbB concentrations, and their relationships to the various health effects that have been associated with lead exposure in children. Thus, while dose-response relationships based on PbB concentrations are becoming understood, much less is known about bone lead-response relationships. This information is important for gaining a better understanding of the relationship between cumulative exposures and toxicity. The development of inductively coupled mass spectrometry (ICP-MS) (see Chapter 6) has provided adequate analytical sensitivity to measure plasma lead concentrations with greater confidence than in the past. Recent studies using this technique have shown that plasma lead concentrations in adults correlate more strongly with bone

lead levels than do blood lead concentrations (Cake et al. 1996; Hernandez-Avila et al. 1998). Since most of the body lead burden resides in bone, measurements of plasma lead concentration may turn out to be a better predictor of lead body burden than are measurements of PbB concentration. This observation has not been explored in children, and few studies have attempted to explore relationships between plasma lead concentration and health outcomes in children.

Studies in animals have provided abundant support for the plausibility of the neurodevelopmental effects of lead that have been associated with lead exposure in children, and researchers have begun to identify potential mechanisms (i.e., Cory-Slechta 1995a). However, mechanistic connections between behavioral deficits, or changes observed in animals, and those that have been associated with lead exposure in children have not been completely elucidated. Understanding of such connections would be valuable for developing better and more relevant animal models of lead toxicity.

Studies of the effects of lead on bone metabolism indicate that, in addition to being a reservoir for the lead body burden, bone may also be a toxicological target (Hamilton and O'Flaherty 1994, 1995). Studies in rats have shown effects of lead on bone mineralization and bone growth. The effects observed in rats may be relevant to our understanding of the mechanisms for the growth deficits that have been associated with low-level *in utero* and childhood lead exposures. Additional studies of the effects of lead on bone metabolism in humans and in animal models would improve our understanding of the toxicological significance of lead in bone.

Further research on the relationship between paternal lead exposure and fetal/infant development should be conducted. Additional information on relationships between nutritional deficits and vulnerability of the fetus and child to lead would be valuable.

Absorption of ingested lead is higher in infants and young children than in adults; however, available data on lead absorption during the ages between childhood and adulthood are very limited (Alexander et al. 1974; Ziegler et al. 1978). The higher absorption of lead in childhood contributes to the greater susceptibility of children to lead; therefore, it is important to know at what age the higher absorption status of the child changes to the lower absorption status observed in adults. Limited data suggest that this conversion may occur early in adolescence. This information is particularly important for accurately simulating biokinetics of lead in older children and adolescents. Additional information on interactions

between nutritional deficiencies and lead absorption and other aspects of lead biokinetics would be valuable.

Recent studies provide evidence for rapid dermal absorption of inorganic lead in adults; however, these studies have not quantified the fraction of applied dose that was absorbed (Stauber et al. 1994). The quantitative significance of the dermal absorption pathway as a contributor to lead body burden remains an uncertainty. In children who experience extensive dermal contact with lead in soil, sand, or surface water and suspended sediment (e.g., beach or shoreline exposure scenario), even a low percent absorption across the skin may represent a significant internal dose. Therefore, additional studies designed to quantify dermal absorption of inorganic lead compounds from both aqueous media and soil, in particular, studies that enable measurements to be extrapolated to children, are important for estimating internal doses that children might receive in relatively common exposure scenarios.

The kinetics of bone formation and remodeling are important factors in the overall biokinetics of lead. Most of the body burden of lead resides in bone; a portion of the maternal bone lead stores is transferred to the fetus during gestation and incorporated into fetal bone during the development of the fetal skeleton. Thus, changes in maternal bone metabolism (e.g., formation and remodeling) is likely to have a significant impact on *in utero* exposure of the fetus. However, very little is known about the kinetics of the mobilization of maternal bone lead, or its incorporation into the fetal skeleton. This information is critical for developing models that accurately simulate *in utero* exposures and maternal lead biokinetics during pregnancy and for understanding how changes in maternal bone metabolism might affect the susceptibility of the fetus to lead toxicity. Bone formation undergoes rapid changes during infancy, childhood, and adolescence. These changes may give rise to periods of greater or lower susceptibility to environmental lead; however, little is known about the potential consequences of these changes on the biokinetics of lead in children.

Child health data needs relating to exposure are discussed in Section 5.8.1, Data Needs: Exposures of Children.

2.11.3 Ongoing Studies

Ongoing studies regarding the health effects of lead were reported in the Federal Research in Progress File (FEDRIP 1998) database. Table 2-13 presents a summary of these studies.

Table 2-13. Ongoing Studies on Lead

Investigator	Affiliation	Research description	Sponsor
Albuquerque EX	University of Maryland, Baltimore, MD	Understand the mechanisms by which lead (Pb2+) exerts neurotoxic effects in the central nervous system particularly in the developing brain	National Institute of Environmental Health Sciences
Angle CR	Univ of Nebraska Medical Center, Omaha, NE	Endogenous and exogenous sources of blood lead from pregnancy through 2 years of age	National Institute of Environmental Health Sciences
Audesirk GJ	University of Colorado, Denver, CO	The mechanisms of developmental neurotoxicity (rat)	National Institute of Environmental Health Sciences
Beitzel PM	NCI, NIH, Division of Cancer Treatment	Develop bifunctional ligands which have a high affinity for Pb(II) and Bi(III); systematic exploration of incorporating thiol donor groups into chelating agents	NCI, NIH
Bellinger DC	Children's Hospital, Boston, MA	Environmental lead and children's psychologic function	National Institute of Child Health and Human Development
Benjamin SA	Colorado State University, Fort Collins, CO	Drinking water and various submixtures of the full seven-chemical mixture as a promoter in the carcinogenic process (arsenic, benzene, chloroform, chromium, lead, trichloroethylene, and phenol) (rats)	National Institute of Environmental Health Sciences
Bergman SM	University of Alabama, Birmingham, AL	Evaluate the influence of body stores of lead and chronic low dose exposure to lead from the environment	Nat Inst of Diabetes And Digestive And Kidney Diseases
Berkowitz G	Mount Sinai School of Medicine, New York, NY	The mobilization of lead during pregnancy and lactation (humans)	National Institute of Environmental Health Sciences
Berkowitz G	Mount Sinai School of Medicine, New York, NY	The mobilization of lead from bone during menopause and associated neuropsychological dysfunction	National Institute of Environmental Health Sciences
Bhattacharya A	University of Cincinnati, Cincinnati, OH	Understand developmental benefits of chelation therapy and other measures to reduce lead in the range of exposures	National Institute of Environmental Health Sciences
Billings RE	Colorado State University, Fort Collins, CO	Interactions among metals and organics in the induction of stress response proteins (rat)	National Institute of Environmental Health Sciences

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Bogden JD	UMDNJ-New Jersey Medical School, Newark, NJ	Investigate relationships during pregnancy among five factors: blood pressure, temporal changes in blood lead, dietary calcium intake, current lead ingestion, and bone lead mobilization (rats)	National Heart, Lung, and Blood Institute
Bornschein R	University of Cincinnati, Cincinnati, OH	The long-range adverse neurological effects of lead exposure, from birth through the early school years	National Institute of Environmental Health Sciences
Bowen WH	University of Rochester, Rochester, NY	The influence of prenatal lead exposure on susceptibility to dental caries and on salivary gland development and function (rat)	National Institute of Dental Research
Bressler JP	Kennedy/Krieger Research Institute, Baltimore, MD	Toxicokinetic model to predict risk factors for lead toxicity	National Institute of Environmental Health Sciences
Bressler JP	Kennedy Research Institute, Baltimore, MD	Mechanism for lead toxicity and children	National Institute of Environmental Health Sciences
Brockel BJ	University of Rochester School of Medical/Dental, Rochester, NY	Attentional basis of Pb-associated cognitive changes (rats)	National Institute of Environmental Health Sciences
Burchiel SW	Univ of New Mexico, Albuquerque, NM	Examine the effects of various environmental agents on human peripheral blood leukocytes (hPbl) following in vitro exposures; to develop biomarkers for immunotoxicity using flow cytometry	National Center For Research Resources
Campbell JR	Rochester General Hospital, Rochester, NY	Derive preliminary data regarding the association between lead exposure and caries in children	National Institute of Environmental Health Sciences
Clements WH	Colorado State University, Fort Collins, CO	Influence of previous heavy metals exposure on responses to subsequent stress (macroinvertebrate populations)	National Institute of Environmental Health Sciences
Cory-Slechta DA	University of Rochester, Rochester, NY	Behavioral toxicity of lead; role of the NMDA receptor	National Institute of Environmental Health Sciences
Cory-Slechta DA	University of Rochester, Rochester, NY	Pb levels that can be linked to deleterious behavioral effects	National Institute of Environmental Health Sciences

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Cory-Slechta DA	University of Rochester, Rochester, NY	Determine the functional significance of Pb-induced meso systems changes; determine the extent of Pb as a risk factor; assess chemical and behavioral therapeutic strategies for meso system alterations	National Institute of Environmental Health Sciences
Dietrich KN	University of Cincinnati, Cincinnati, OH	Impact of lead exposure on neuropsychological functioning and social adjustment in adolescence	National Institute of Environmental Health Sciences
Donaldson WE	North Carolina State University, Raleigh, NC	Effects of lead (Pb) on immune function, and how those effects could be altered by nutrition	U. S. Department of Agriculture, Cooperative State Res
Dowd TL	Montefiore Medical Center, New York, NY	Understand the mechanism of Pb2+ toxicity at the molecular level, in bone, by comparing precise structural and functional data of ca2+ - and Pb2+ - osteocalcin	National Institute of Environmental Health Sciences
Ercal N	University of Missouri, Rolla, MO	The adjunctive use of NAC to enhance the effectiveness of chelation-oriented therapies in lead poisoning	National Institute of Environmental Health Sciences
Ericson JE	University of California, Irvine, CA	Establish a biomarker of ambient lead (Pb) exposure during prenatal and postnatal development (rats)	National Institute of Child Health And Human Development
Evans HL	New York University Medical Center, New York, NY	Behavioral and biochemical markers of human lead exposures (human, rat)	National Institute of Environmental Health Sciences
Fiedler NL	University of Medicine & Dentistry of NJ, Newark, NJ	Compare the neurobehavioral performance of 60 construction workers exposed to lead and/or solvents	National Institute for Occupational Safety and Health
Fox DA	University of Houston, Houston, TX	Cellular mechanisms of rod-mediated visual deficits resulting from developmental lead exposure (rat)	National Institute of Environmental Health Sciences
Gandley RE	MaGee-Womens Research Institute, Pittsburgh, PA	The effects of low-level lead acetate exposure on cardiovascular and renal adaptations to pregnancy (rats)	National Institute of Environmental Health Sciences
Geller AM	Health Effects Research Laboratory, Research, Triangle Park, NC	The mechanisms, location, and severity of the effects of lead exposure on the mammalian retina	National Institute of Environmental Health Sciences
Gill F	Children's Hospital of Philadelphia, Philadelphia, PA	To evaluate the effect of lead chelation in conjunction with consumption of multivitamins and minerals on developmental status (humans)	National Center for Research Resources

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Gillett JW	Cornell University, Ithaca, NY	Biological responses associated with exposure, biodegradation and chemodynamics of lead	National Institute of Environmental Health Sciences
Gray LC	University of Texas Health Science Center, Houston, TX	The effects of lead and carbon disulfide on the measurement of cognitive and sensory function (chick model)	National Institute of Environmental Health Sciences
Graziano JH	Columbia University Health Sciences, New York, NY	Precisely determine the bioavailability of Pb in soils representative of the U.S., which contain negligible amounts	National Center For Research Resources
Graziano JH	Columbia University Health Sciences, New York, NY	Neurotoxicity and treatment of lead exposure	National Institute of Environmental Health Sciences
Graziano JH	Columbia University Health Sciences, New York, NY	Aim to elucidate the pathophysiologic mechanism(s) whereby Pb exposure induces anemia	National Institute of Environmental Health Sciences
Guilarte TR	Johns Hopkins University, Baltimore, MD	Study the mechanism(s) underlying the relationship between lead exposure during development and neurological and behavioral dysfunction (rat)	National Institute of Environmental Health Sciences
Hall DB	Michigan State University, Chicago, IL	After describing the properties of the young spiral ganglion cells within the mammalian auditory system then investigate the neurotoxic effects of lead on the sodium current	National Institute on Deafness & Other Communication Disorders
Hammock BD	University of California Davis, Davis, CA	Develop assays to assess human exposure and effect; to probe the mechanistic basis of toxicity	National Institute of Environmental Health Sciences
Hammond PB	University of Cincinnati, Cincinnati, OH	Mechanisms underlying lead-induced depression of growth (rat)	National Institute of Environmental Health Sciences
Hanbauer I	NHLBI, NIH	To understand the neurotoxic effect of lead (Pb)	National Heart, Lung, And Blood Institute
Harry GJ	National Institute of Environmental Health Sciences	The effects of environmental lead on the level of specific nervous system genes and cell types	National Institute of Environmental Health Sciences
Hassett JJ	University of Illinois, Urbana, IL	Continued studies on bioavailability of lead (Pb) in soil (rats)	U. S. Department of Agriculture, Cooperative State Res

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Hess DL	Oregon Reg Primate Research Center, Beaverton, OR	Effects of lead on testicular function in rabbits correlating blood levels with physiologically significant effects	National Center For Research Resources
Hicks DG	University of Rochester, Rochester, NY	Th e effects of lead on cartilage metabolism and skeletal growth (chicken, rat)	National Institute of Environmental Health Sciences
Hooser SB	Purdue University, West Lafayette, IN	Feed additives and tissue concentrations of heavy metals and/or alterations in toxicity	U. S. Department of Agriculture
Howard H	Brigham & Women's Hospital, Boston, MA	Examine the relationship between lead exposure and hypertension, renal dysfunction and cognitive deficits in middle-aged adults	National Center for Research Resources
Hu H	Harvard School of Public Health, Boston, MA	Lead exposure and reproduction among married women and men	National Institute of Environmental Health Sciences
Hu H	Harvard School of Public Health, Boston, MA	Contribution of body lead stores in the development of adverse cognitive effects that accompany aging	National Institute of Environmental Health Sciences
Hu H	Department of Environmental Health, Boston, MA	Measure in vivo bone lead level in a new longitudinal study of lead exposure and reproduction among married women and men	National Institute of Environmental Health Sciences
Hughes JM	Tulane University, New Orleans, LA	Determinants of lead exposure; hypertension and pediatric respiratory diseases in relation to lead exposure	National Institute of Environmental Health Sciences
Iranmanesh A	Department of Veterans Affairs Medical Center, Salem, VA	Effects of lead, iron, and gold overload on the gonadal, thyroid, and adrenal function	Department of Veterans Affairs Research and Development
Kamel F	National Institute of Environmental Health Sciences	The development of neurodegenerative disease after exposure to environmental neurotoxins	National Institute of Environmental Health Sciences
Karol MH	University of Pittsburgh, Pittsburgh, PA	The mechanism(s) underlying sensitization responses (humans)	National Institute of Environmental Health Sciences
Kavanaugh TJ	University of Washington, Seattle, WA	Glutathione regulation as a biomarker of exposure to toxicants and of susceptibility to such exposures	National Institute of Environmental Health Sciences
Kelsey K	Harvard School of Public Health, Boston, MA	Identify and validate biomarkers of lead poisoning	National Institute of Environmental Health Sciences

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Keogh JP	University of Maryland at Baltimore, Baltimore, MD	Validation of new biomarkers as predictors of long term health effects after lead intoxication	National Institute of Environmental Health Sciences
Kerper LE	University of Rochester, Rochester, NY	Intracellular lead-calcium interactions (bovine brain endothelial cells)	National Institute of Environmental Health Sciences
Klein RF	Department of Veterans Affairs, Medical Center, Portland, OR	Chronic lead exposure impairs osteoblast function in vivo; gain insight into the consequences of lead intoxication on the skeleton	Department of Veterans Affairs, Research and Development
Kohler PF	Tulane University School of Medicine, New Orleans, LA	To determine lead poisoning process; to evaluate the use of the oral chelator of lead, Succimer, in the diagnosis and treatment of lead poisoning in adults	National Center for Research Resourcesl
Korrish S	Harvard School of Public Health, Boston, MA	Associations of in utero environmental exposures with newborn and infant health outcomes	National Institute of Environmental Health Sciences
Kosnett M	University of California, San Francisco, CA	Determine the mechanism for lead-associated increases in blood pressure	National Center for Research Resources
Landrigan PJ	Mount Sinai School of Medicine of CUNY, New York, NY	Lead and organochlorines in New York City: study the current urban sources, environmental distribution and toxic effects on human health of lead and persistent chlorinated hydrocarbons--in particular PCBs and DDT	National Institute of Environmental Health Sciences
Lanphear BP	University of Rochester, Rochester, NY	Confirm that lead exposure appears to disrupt cognitive functions known to involve mesofrontal dopaminergic systems	National Institute of Environmental Health Sciences
Lasley SM	University of Illinois, Peoria, IL	Pb-induced alterations of the glutamate-mediated regulation of intracellular Ca+2 concentrations and synaptic plasticity in hippocampal neurons (rats)	National Institute of Environmental Health Sciences
Laughlin NK	Harlow Primate Laboratory, Madison, WI	Effect of succimer therapy on lead-induced neurobehavioral and organ system toxicity (rhesus monkey)	National Institute of Environmental Health Sciences

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Laughlin NK	University of Wisconsin, Madison, WI	Validate the efficacy of chelation agents such as succimer (dimercaptosuccinic acid, DMSA) not only to reduce body lead stores in young children but also to alleviate neurobehavioral and target organ toxicity (Rhesus monkey)	National Institute of Environmental Health Sciences
Laughlin NK	University of Wisconsin, Madison, WI	Rhesus monkey and determine if the presence of lead stored in bones affects the mobilization of Ca from bone	National Center For Research Resources
Laughlin NK	University of Wisconsin, Madison, WI	Evaluate blood and soft tissue in adult and geriatric monkeys previously exposed to lead; to compare these biomarkers with behavioral endpoints	National Center For Research Resources
Laughlin NK	University of Wisconsin, Madison, WI	Examine auditory system function and attention in the rhesus monkey as a model of childhood lead exposure	National Center For Research Resources
Laughlin NK	University of Wisconsin, Madison, WI	Determine the efficacy of succimer chelation in alleviating lead toxicity in rhesus monkeys; evaluate the redistribution of lead from endogenous sources in response to chelation	National Center For Research Resources
Law J	Microbiology Path & Parasito, Raleigh, NC	Continued development of the isolated skin flap model for study of the transport and biotransformation processes of toxic substances and drugs through the skin	U. S. Department of Agriculture, Cooperative State Research
Lawrence DA	NYS Dept of Health, Albany, NY	Identify the mechanisms by which Pb and Hg are immunomodulatory and assist evaluation of their health hazard and the molecular basis for the risks in exposure	National Institute of Environmental Health Sciences
Lee BN	Department of Veterans Affairs, Medical Center, Sepulveda, CA	Test effect of lead on blood pressure (Bp) in three different strains of rats with different genetic susceptibility to the development of hypertension	Department of Veterans Affairs, Research and Development
Legare ME	Texas A&M University, College Station, TX	Molecular changes in astroglia and endothelial cells in culture following exposure to low levels of Pb (rat)	National Institute of Environmental Health Sciences
Lever SZ	The Johns Hopkins University, Baltimore, MD	Identify the complexes formed in vivo with lead upon administration of meso-DMSA	National Institute of Environmental Health Sciences

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Liebelt E	Yale University, New Haven, CT	Efficacy of three forms of inpatient chelation that are being utilized in the treatment of children with elevated blood lead levels	National Center For Research Resources
Liebelt E	Yale University, New Haven, CT	Investigate whether children with lead poisoning have lower erythropoietin production compared to children without lead poisoning; determine if there is a threshold for diminished erythropoietin production in children with lead poisoning	National Center For Research Resources
Markowitz ME	Montefiore Medical Center, New York, NY	Examine the interaction between elevated lead and low iron levels on the response to clinical intervention in young children between 18 and 30 months of age	National Institute of Child Health And Human Development
Markowitz ME	Montefiore Medical Center, New York, NY	Define the role of Ca supplementation as a treatment for children with mild to moderate Pb poisoning	National Institute of Environmental Health Sciences
Mc Cabe MJ Jr.	Metropolitan Center for Higher Technology, Detroit, MI	Mechanisms and consequences of Pb modulation of cell-mediated and humoral immunity (*in vitro* culture system; mice *in vivo*)	National Institute of Environmental Health Sciences
Mc Michael AJ	University of Adelaide, Adelaide, Australia	Investigate the relative contribution to the infant in utero of mother's current environmental lead compared with mobilization of lead from maternal stores, especially bone lead	National Institute of Environmental Health Sciences
Milder FL	Applied Biomedical Corp., Danvers, MA	Use x-ray fluorescence in a transmission geometry to measure the total body-burden of lead, in vivo, noninvasively	HHS
Moline J	Mt Sinai School of Medicine, New York, NY	Effects of mobilization of skeletal lead during pregnancy	National Center for Research Resources
Monson RR	Harvard School of Public Health, Boston, MA	Assessment of human health risks from toxic substances in the environment	National Institute of Environmental Health Sciences
Muldoon SB	University of Florida, Gainesville, FL	Association of menopausal bone loss with blood lead levels in women	National Institute of Environmental Health Sciences
Narahashi T	Northwestern University Medical School, Chicago, IL	The effects of therapeutic drugs and toxins on neuronal ion channels	National Institute of Neurological Disorders and Stroke

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Nation JR	Texas A&M University Health Science Center, College Station, TX	Heavy metals and cocaine interactions: possible link between xenobiotic contamination and the response to a prominently abused psychoactive drug	National Institute on Drug Abuse
Neary JT	Department of Veterans Affairs, Medical Center, Miami, FL	Effects of lead on nerve growth factor-induced neurite outgrowth and branching due to an interaction of lead with signal transduction mechanisms important for neuronal differentiation	Department of Veterans Affairs, Research and Development
Needleman HL	University of Pittsburgh at Pittsburgh, Pittsburgh, PA	Lead exposure is related to delinquent behavior; understand one of the causal factors of delinquent and aggressive behavior, and plan effective preventive strategies	National Institute of Environmental Health Sciences
Nelson LM	Stanford University, Stanford, CA	Investigate the role of environmental toxicants and genetic susceptibility factors in the etiology of ALS	National Institute of Environmental Health Sciences
Osterloh JD	San Francisco General Hospital, San Francisco, CA	Alterations in storage of environmental Pb burdens in bone	National Institute of Environmental Health Sciences
Paglia DE	Univ of California School of Medicine, Los Angeles, CA	The use of nucleotidase isozymes as sensitive and reliable indices of low lead overburden in humans	National Institute of Environmental Health Sciences
Pattillo RA	Morehouse School of Medicine, Atlanta, GA	Neurobehavioral effects of low-level exposure in human newborns	ATSDR
Pepper L	Boston University, Boston, MA	Determine why high blood levels of lead continue to occur in bridge construction workers despite government regulations and industry recommendations	National Institute for Occupational Safety and Health
Pollitt E	Univ of California, Administration, Davis, CA	The effects of lead and iron interaction on behavioral development; the effects of iron treatment on iron status, blood lead level, and behavioral development in children with elevated lead levels and iron deficiency	U. S. Department of Agriculture, Competitive Research
Poretz RD	Rutgers University Biochemistry & Microbiology, New Brunswick, NJ	To define a possible genetic factor which may cause certain individuals to be hypersusceptible to lead-incuded neurobehavioral abnormality	U. S. Department of Agriculture, Cooperative State Res

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Poretz RD	Rutgers The State Univ, New Brunswick, NJ	Lead-induced neurotoxicity; define a genetic factor which may cause certain individuals to be hypersusceptible to lead-induced neurobehavioral abnormalities	National Institute of Environmental Health Sciences
Pounds JG	Wayne State University Detroit, MI	Lead toxicity is mediated via perturbation of the signal transduction processes; further our understanding of the skeleton as a target of lead toxicity, skeletal metabolism of lead, and the physiological factors which mobilize skeletal lead	National Institute of Environmental Health Sciences
Proctor SP	Boston University Medical Center, Boston, MA	Epidemiologic study of neurobehavioral effects due to neurotoxicant exposure	National Institute for Occupational Safety and Health
Puzas JE	University of Rochester, Rochester, NY	An in vitro cell model resembles the remodeling process of osteoclastic bone resorption followed by osteoblastic bone formation; investigate the influence of lead on the communication between these cells; determine if lead in the medium (i.e. extracellular fluid) or in the matrix (i.e. in the bone) has different effects on osteoclasts and osteoblasts	National Institute of Environmental Health Sciences
Rajanna B	Alcorn State University, Lorman, MS	Developmental exposure to Pb or Mm affect signal transduction process, possibly related to the modulation of nitric oxide as well as alterations in receptor-mediated phosphoinositide hydrolysis and protein kinase C (rats)	National Institute of General Medical Sciences
Raymond KN	University of California, Berkeley, CA	Develop new chelating agents for lead decorporation	National Institute of Environmental Health Sciences
Renner SW	Department of Veterans Affairs, Medical Center, West Los Angeles, CA	Assess the value and feasibility of using nucleotidase isozymes as sensitive and reliable indices of low lead overburden in humans	Department of Veterans Affairs, Research and Development
Renner SW	Department of Veterans Affairs, Medical Center, West Los Angeles, CA	Establish the validity of using two specific erythrocyte enzyme measurements as sensitive indicators of very low body burdens of lead and other heavy metals	Department of Veterans Affairs, Research and Development
Rogan WJ	National Institute of Environmental Health Sciences	Use of succimer in the prevention of developmental delay, slowed growth, and behavior disorders in toddlers	National Institute of Environmental Health Sciences

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Ronis MJ	University of Arkansas, Little Rock, AR	The molecular mechanisms underlying the lead-induced developmental impairment of the endocrine systems of reproduction and growth (rats)	National Institute of Environmental Health Sciences
Rosen HAN	Beth Israel Hospital Boston, MA	The relationship between lead intoxication or increased lead levels and bone mineral content in humans	National Center for Research Resources
Rosen JF	Montefiore Medical Center, Bronx, NY	Treatment outcomes in moderately lead toxic children (human)	National Institute of Environmental Health Sciences
Rossman TG	New York University Medical Center, New York, NY	The main goal of this project is to delineate cellular mechanisms of lead resistance (rat)	National Institute of Environmental Health Sciences
Rothenberg SJ	Charles R. Drew University of Medicine & Science, Los Angeles, CA	The role of prepregnancy maternal bone lead and prenatal maternal blood lead upon alterations in infant saccadic and smooth pursuit eye movements	National Institute of General Medical Sciences
Rothenberg SJ	Charles R. Drew University of Medicine and Science, Los Angeles, CA	Correlation between blood lead levels and blood pressure during pregnancy	ATDSR
Rude CS	University of Vermont, Burlington, VT	Determine the prevalence of lead poisoning among children less than six years of age; determine the predictive ability of a prescreening lead questionnaire	National Center for Research Resources
Schell LM	State University of New York at Albany, Albany, NY	To identify the maternal characteristics which determine fetal exposure to lead and to identify the effects of pre- and postnatal lead exposure on early human development	National Institute of Environmental Health Sciences
Scholl TO	Univ of Medical/Dental NJ-School of Osteopathic Medicine, Stratford, NJ	This prospective study will allow the investigators to examine lead mobilization from bone turnover in still-growing, adolescent and mature mothers	National Institute of Environmental Health Sciences
Schonfeld D	Yale University, New Haven, CT	The efficacy of various forms of inpatient chelation in the treatment of children with elevated blood lead levels are being studied	National Center for Research Resources
Schramm W	Bioquant Inc., Ann Arbor, MI	The potential use of saliva as a biological medium for the screening of elevated lead levels in humans	HHS

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Schwartz BS	John Hopkins University School of Hygiene & Public Health, Baltimore, MD	Study of the relations among BLLS, DMSA-chelatable lead, bone lead, and health effects (heme synthesis, renal early biologic effects and function, blood pressure, and CNS and PNS function) in lead workers in South Korea	National Institute of Environmental Health Sciences
Schwarz D	Joseph Stokes Jr *Research Institute* Children's Hospital Philadelphia, PA	Effects of Chelation With Succimer on *Growth and Development of Children* with Low Levels of Blood Lead	National Center For *Research Resources*
Sens DA	West Virginia University, North Morgantown, WV	Validation of cultured human proximal tubule cells as a model for the study of human metal-induced nephropathies	National Institute of Environmental Health Sciences
Shuster TA	California State University, Long Beach, CA	The roles of nucleotides and divalent cations in normal and degenerating rod outer segments (rd mouse)	National Institute of General Medical Sciences
Sinclair JA	Dartmouth College, Hanover, NH	The effects of heavy metals on the synthesis and degradation of heme and hemoproteins in the P450 superfamily (cell culture; rat, chick and rabbit)	National Institute of Environmental Health Sciences
Sokol RZ	Health Research Association, Inc., Los Angeles, CA	Pb exposure in utero may induce an inherited change in DNA methylation patterns in Pb exposed pups, the mechanism by which Pb exposure during the critical time of sexual differentiation induces reproductive axis abnormalities in adulthood	National Institute of Environmental Health Sciences
Soliman KFA	Florida A&M University, Tallahassee, FL	The effects of lead exposure on hypothalamus, pituitary and adrenal gland function (rats)	National Institute of General Medical Sciences
Smith D	University of California, Santa Cruz, CA	Factors contributing to increased lead exposures in postmenopausal females, and the effects of lead on the aged skeleton	National Institute of Environmental Health Sciences
Stewart WF	Johns Hopkins University, Baltimore, MD	Change in cognitive function in current and former lead exposed workers	National Institute on Aging
Strupp BJ	Cornell University, Ithaca, NY	The efficacy of dimercaptosuccinic acid (DMSA) in alleviating Pb-induced cognitive dysfunction	National Institute of Environmental Health Sciences
Suszkiw JB	University of Cincinnati, Cincinnati, OH	The mechanism and functional consequences of lead's effects on cholinergic cells (rats)	National Institute of Environmental Health Sciences

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Terrian DM	East Carolina University, Greenville, NC	How low levels of lead exposure may promote the use-independent release of glutamate, a physiologically inappropriate activity that can be expected to have a devastating effect on the establishment of synaptic connections early in development	National Institute of Environmental Health Sciences
Thomas PM	University of Texas Austin, Austin, TX	That lead and Aroclor 1254 alter GTH secretion by disrupting different components of the 5-HT-GNRH-GTH stimulatory neuroendocrine pathway controlling reproduction	National Institute of Environmental Health Sciences
Tiffany-Castiglinoi E	Texas A&M University, College Station, TX	The intracellular mechanisms of lead toxicity	U. S. Department of Agriculture
Tiffany-Castiglioni E	Texas A&M University, College Station, TX	Molecular-and cellular uptake and tolerance to Pb and associated behavioral deficits (rat)	National Institute of Environmental Health Sciences
Todd AC	Mt. Sinai School of Medicine, New York, NY	Relationship between relatively low-level environmental exposure to lead in adults and chronic neurotoxicity	National Institute of Environmental Health Sciences
Waalkes MP	National Cancer Institute, NIH, Division of Cancer Etiology	The mechanism of action of metals in human and rodent carcinogenesis (mouse, rat)	NCI, NIH
Wedeen RP	Veterans Administration Medical Center, East Orange, NJ	*In vivo* tibial XRF measurement of bone lead	Veterans Administration
Wedeen RP	Department of Veterans Affairs Medical Center, East Orange, NJ	Renal-hypertensive and cardiovascular effects of environmental lead, zinc, and cadmium exposure	Department of Veterans Affairs Research and Development
Wetmur JG	Mount Sinai School of Medicine, New York, NY	Biochemical basis for the differential genetic susceptibility of individuals to lead exposure (transgenic mice, humans)	National Institute of Environmental Health Sciences
Williams JC	Memphis State University, Memphis, TN	Develop and improve quantitative methods for the determination of both metal and nonmetal elements in biological samples	National Institute of General Medical Sciences

Table 2-13. Ongoing Studies on Lead (continued)

Investigator	Affiliation	Research description	Sponsor
Wolff MS	Mount Sinai School of Medicine of CUNY, New York, NY	Analytical support for comprehensive assessment of lead exposures; body burden measures will include blood lead, plasma lead, ZPP, bone lead, representing multiple compartments for deposition of lead and widely variable rates of elimination; measurement of total lead in soil extracts to validate quantitative measures	National Institute of Environmental Health Sciences
Woolley DE	University of California, Davis, CA	To determine immediate and long-term effects of exposure to environmental toxicants, especially insecticides and heavy metals (rat)	U. S. Department of Agriculture
Worobey J	Rutgers University Nutritional Sciences, New Brunswick, NJ	Measure the cognitive status of lead burdened children via developmental assessments before and after an intervention and examine the influence of lead-nutrient interactions on development via an analysis of dietary *status before and after the intervention*	U. S. Department of Agriculture, Cooperative State Res
Xu X	Harvard School of Public Health, Boston, MA	The effects of lead exposure on endocrine dysfunction and adverse reproductive outcomes in China	National Institute of Environmental Health Sciences
Zawia NH	Meharry Medical College, Nashville, Tn	Understanding the mechanism of lead neurotoxicity with models and experiments	National Institute of Environmental Health Sciences
Zheng W	Columbia University, New York, NY	The effects of DMSA on blood lead concentrations and urinary Pb excretion	National Institute of Environmental Health Sciences
Zidenberg-Cherr S	University of California, Davis, CA	The relationship between nutritional status and lead toxicity in children	U. S. Department of Agriculture
Not specified	University of Cincinnati and Gradient Corporation	Develop a sophisticated, flexible model to be used in a site- and application-specific way to predict impact of lead in various media on general population blood lead levels	ILZRO
Not specified	Imperial College of Science, Technology and Medicine	Lead and male reproductive function, evaluate impact of changes in indicators of semen quality and reproductive hormones as function of occupational lead exposure	ILZRO

Source: FEDRIP 1998

ALAD = delta-aminolevulinic acid dehydratase; DMSA = dimercaptosuccinic acid; NMDA = N-methyl- D-aspartate; PCBs = polychlorinated biphenyls; XRF = X-ray fluorescence

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

The chemical identities of lead and several of its compounds are given in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical properties of lead and several of its compounds are listed in Table 3-2. Lead readily tarnishes in the atmosphere but is one of the most stable fabricated metals because of its corrosive resistance to air, water, and soil (Howe 1981). A waste that contains lead or lead compounds may (or may not) be characterized a hazardous waste following testing by the Toxicity Characteristic Leaching Procedure (TCLP) as prescribed by the Resource Conservation and Recovery Act (RCRA) regulations.

Divalent lead can interfere with the action of other divalent cations, such as Ca^{+2}, in biological systems.

Under the authority of the RCRA, a solid waste would be defined as hazardous if it exhibits any of the four (ignitability, corrosivity, reactivity, and toxicity) characteristics used to identify hazardous wastes.

A solid waste containing lead or lead compounds may be defined as a hazardous waste if it exhibits the characteristic of toxicity. The waste is said to exhibit the toxicity characteristic if the lead concentration in the extract obtained by subjecting a sample of the waste to the TCLP exceeds 5.0 mg/L. Tetraethyl and tetraethyl lead are combustible. If they are in sufficient quantity in a waste, tetraethyl lead may show an ignitability characteristic. More details on the regulatory requirements are presented in Chapter 7.

Table 3-1. Chemical Identity of Lead and Compounds

Characteristic	Lead[a]	Lead acetate[a]	Lead azide[b]	Lead bromide[c]
Synonym(s)	*Lead metal; plumbum;* olow (Polish); pigment metal	*Lead(2+) acetic acid;* plumbous acetate	*Initiating explosive (lead* azide, dextrinated type only)	*Lead (II) bromide* [d]
Registered trade name(s)	CI77575	Salt of Saturn; sugar of lead; Unichem PBA	No data	No data
Chemical formula[b]	Pb	$PbC_4H_6O_4$	PbN_6	$PbBr_2$
Chemical structure	Pb	$[CH_3COO]^-Pb^{2+}$ $[CH_3COO]^-$	$N_3^-Pb^{2+}N_3^-$	$Br^-Pb^{2+}Br^-$
Identification numbers:				
CAS registry	7439-92-1	301-04-2	13424-46-9	10031-22-8
NIOSH RTECS	OF7525000	AI5250000	OF8650000	No data
EPA Hazardous Waste	D008	U144, D008	No data	No data
OHM/TADS	7216776	7217255	No data	No data
DOT/UN/NA/IMO Shipping	NA	UN 1616, IMO 6.1	UN 0129	No data
HSDB	231	1404	No data	No data
NCI	No data	No data	No data	No data

Table 3-1. Chemical Identity of Lead and Compounds (continued)

Characteristic	Lead chloride[a]	Lead chromate[a]	Lead fluoroborate[a]	Lead iodide[a]
Synonym(s)	Lead(2+) chloride; lead (II) chloride; plumbous chloride	Chromic acid (H_2CrO_4) lead(2+) salt; lead chromate (VI); phoenicochroite; and others	Borate(1-), tetrafluoro, lead(2+); lead borofluoride; lead boron fluoride; lead tetrafluoroborate	Lead diiodide; lead(II) iodide; plumbous iodide
Registered trade name(s)	No data	Canary Chrome Yellow 40-2250; Cologne Yellow; King's Yellow	No data	No data
Chemical formula[b]	$PbCl_2$	$PbCrO_4$	$Pb(BF_4)_2$	I_2Pb
Chemical structure	$Cl^-Pb^{2+}Cl^-$	$Pb^{2+}[CrO_4]^{2-}$	$[BF_4]^-Pb^{2+}[BF_4]^-$	$I^-Pb^{2+}I^-$
Identification numbers:				
CAS registry	7758-95-4	7758-97-6	13814-96-5	10101-63-0
NIOSH RTECS	OF9450000[b]	GB2975000	ED2700000	OG1515000
EPA Hazardous Waste	No data	D007, D008	D008	D008
OHM/TADS	7217256	No data	7217378	No data
DOT/UN/NA/IMO Shipping	NA 2291	No data	NA 2291; 1MO 6.1	NA 2811
HSDB	6309	1650	1991	636
NCI	No data	No data	No data	No data

Table 3-1. Chemical Identity of Lead and Compounds (continued)

Characteristic	Lead molybdenum chromate[b]	Lead nitrate[a]	Lead oxide[a]	Lead phosphate[a]
Synonym(s)	Chromic acid, lead and molybdenum salt; lead chromate, sulphate and molybdate; molybdenum-lead chromate; molybdenum orange	Lead dinitrate; nitric acid lead(2+) salt; lead (II) nitrate; plumbous nitrate	Lead(2+) oxide; lead monoxide; litharge; massicot	Lead(2+) phosphate; Phosphoric acid lead(2+) salt;
Registered trade name(s)	C.I. Pigment Red 104	No data	CI 77577; CI Pigment Yellow 46	Perlex Paste 500; Perlex Paste 600A; CI 77622
Chemical formula	$25PbCrO_4 \cdot 4PbMoO_4 \cdot PbSO_4$[e]	PbN_2O_{64}	PbO	$Pb_3(PO_4)_2$
Chemical structure	No data	$[NO_3]^-Pb^{2+}[NO_3]^-$	Pb=O	$[PO_4]^{3-}$ $Pb^{2+}Pb^{2+}Pb^{2+}[PO_4]^{3-}$
Identification numbers:				
CAS registry	12709-98-7	10099-74-8	1317-36-8	7446-27-7
NIOSH RTECS	OG1625000	OG2100000	OG1750000	No data
EPA Hazardous Waste	No data	D008	D008	D008, U145
OHM/TADS	No data	7217257	No data	No data
DOT/UN/NA/IMCO Shipping	No data	UN 1469, IMO 5.1	No data	No data
HSDB	No data	637	638	2637
NCI	No data	No data	No data	No data

Table 3-1. Chemical Identity of Lead and Compounds (continued)

Characteristic	Lead styphnate[b]	Lead sulfate[a]	Lead sulfide[a]	Tetraethyl lead[a]
Synonym(s)	Initiating explosive lead styphnate; lead trinitroresorcinate; styphnate of lead	Sulfuric acid lead(2+) salt; lead (II) sulfate	Lead monosulfide; lead(2+) sulfide; Lead (II) sulfide; plumbous sulfide; natural galena	Lead tetraethide; TEL; tetraethyllead; tetraethylplumbane
Registered trade name(s)	No data	CI 77630; Fast White; Lead Bottoms; Mulhouse White	No data	No data
Chemical formula	$C_6H(NO_2)_3(O_2Pb)$ [c]	$PbSO_4$	PbS	$C_8H_{20}Pb$
Chemical structure	No data	$Pb^{2+}[SO_4]^{2-}$	$Pb^{2+}S^{2-}$	$(CH_3CH_2)_4Pb$
Identification numbers:				
CAS registry	63918-97-8	7446-14-2	1314-87-0	78-00-2
NIOSH RTECS	OG6425000	OG4375000 [b]	OG4550000	TP4550000
EPA Hazardous Waste	No data	No data	D008	P110; D008
OHM/TADS	No data	No data	7800071	7216922
DOT/UN/NA/IMCO Shipping	UN 0130	UN 1794; NA 1794; IMO 8.0	NA 2291; IMO 6.1	NA 1649; IMO 6.1
HSDB	No data	6308	639	841
NCI	No data	No data	No data	C54988

[a]HSDB 1996
[b]RTECS 1996
[c]Lewis 1993
[d]Lenga 1988
[e]USPATFULL 1997

CAS = Chemical Abstracts Services; DOT/UN/NA/IMO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System; RTECS = Registry of Toxic Effects of Chemical Substances

Table 3-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead[a]	Lead acetate[a]	Lead azide[b]	Lead bromide[b]
Molecular weight	207.20	325.28	291.25	367.04
Color	Bluish-gray	White	White	White
Physical state	Solid	Solid	Needles or powder	Crystalline powder
Melting point	327.4 °C	280 °C	No data	373 °C
Boiling point	1,740 °C	Decomposes above 200 °C	Explodes at 350 °C	916 °C[c]
Density	11.34 g/cm^3 at 20 °C	3.25 g/cm^3 at 20 °C	No data	6.66 g/cm^3 [d]
Odor	None	Slightly acetic	No data	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	Insoluble	2,210,000 mg/L at 50 °C	230 mg/L at 18 °C	8,441 mg/L at 20 °C[c]
Nitric acid	Soluble	No data	No data	No data
Hot conc. sulfuric acid	Soluble	No data	No data	No data
Organic solvent(s)	Insoluble	Soluble in glycerol, very slight in alcohol	Acetic acid[c]	Insoluble in alcohol
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1.77 mm Hg at 1,000 °C 10 mm Hg at 1,162 °C 100 mm Hg at 1,421 °C 400 mm Hg at 1,630 °C	No data	No data	1 mmHg at 513 °C 100 mm Hg at 745 °C[c]
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	Not flammable	No data
Conversion factors:				
Air	None[e]	None[e]	None[e]	None[e]
Water	1 ppm(w/v) = 1 mg/L = 1 1 µg/mL	1 ppm(w/v) = 1 mg/L = 1 µg/mL	1 ppm(w/v) = 1 mg/L = 1 µg/mL	1 ppm(w/v) = 1 mg/L = 1 µg/mL
Solid	1 ppm(w/w) = 1 mg/kg = 1 1 µg/g	1 ppm(w/w) = 1 mg/kg = 1 µg/g	1 ppm(w/w) = 1 mg/kg = 1 µg/g	1 ppm(w/w) = 1 mg/kg = 1 µg/g
Explosive limits	No data	Lead acetate-lead bromate double salt is explosive	No data	No data
Valence state	0, +2, +4[f]	+2	+2	+2

Table 3-2. Physical and Chemical Properties of Lead and Compounds (continued)

Property	Lead chloride[a]	Lead chromate[a]	Lead fluoroborate[b]	Lead iodide[a]
Molecular weight	278.11	323.22	380.81	461.01
Color	White	(Orange-)yellow	Colorless	Bright or golden yellow
Physical state	Solid	Solid	Crystalline powder	Hexagonal crystals; powder
Melting point	501 °C	844 °C	No data	402 °C
Boiling point	950 °C	Decomposes[c]	No data	954 °C[c]
Density	5.85 g/cm^3 at 20 °C[d]	6.12 g/cm^3 at 15 °C	1.75 g/cm^3 at 20 °C[d]	6.16 g/cm^3 at 20 °C
Odor	No data	Faint odor (solution)	Odorless	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	9,900 mg/L at 20 °C[c]	0.2 mg/L	No data	630 mg/L at 20 °C
Nitric acid	No data	Soluble in dilute acid	No data	No data
Hot concentrated sulfuric acid	No data	No data	No data	No data
Organic solvent(s)	Insoluble in alcohol[c]	Insoluble in acetic acid	Decomposes in alcohol[c]	Insoluble in alcohol[b]
Partition coefficients				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	1 mmHg at 547 °C	No data	No data	1 mmHg at 479 °C
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	Flammable with combustible organic or other oxidizable materials	Not ignited readily	Not flammable
Conversion factors:				
Air	None[e]	None[e]	None[e]	None[e]
Water	1 ppm(w/v) = 1 mg/L = 1µg/mL	1 ppm(w/v) = 1 mg/L = 1 µg/mL	No data	No data
Solid	1 ppm(w/w) = 1 mg/kg = 1µg/g	1 ppm(w/w) = 1 mg/kg = 1 µg/g	No data	No data
Explosive limits	No data	No data	No data	No data
Valence state	+2	+2	+2	+2

Table 3-2. Physical and Chemical Properties of Lead and Compounds (continued)

Property	Lead molybdenum chromate[a]	Lead nitrate[a]	Lead oxide[a]	Lead phosphate[a]
Molecular weight	9,852 (comples)[g]	331.23	223.21	811.54
Color	Red[h]	Colorless or white	Reddish-yellow; yellow (above 489 °C)	White
Physical state	No data	Solid	Solid	Solid
Melting point	No data	Decomposes at 470 °C	886 °C (Litharge); no data (Massicot)	1,014°C
Boiling point	No data	No data	Decomposes at 1,472 °C	No data
Density	No data	4.53 g/cm^3 at 20 °C	9.3 g/cm^3 (Litharge); 8.0 g/cm^3 (Massicot)[d]	6.9–7.3 g/cm^3 [d]
Odor	No data	Odorless	No data	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	No data	376,500 mg/L at 0 °C (Litharge: 23 mg/L at 23 °C (Massicot)	10 mg/L at 20 °C	0.14 mg/L at 20 °C[c]
Nitric acid	No data	Insoluble	Soluble (Litharge)	Soluble
Hot conc. sulfuric acid	No data	No data	No data	No data
Organic solvent(s)	No data	1 g in 2,500 mL absolute alcohol; 1 g in 75 mL absolute alcohol	Soluble in alkali chlorides; soluble in alkali (Massicot); insoluble in alcohol	Soluble in fixed alkali hydroxides; insoluble in alcohol
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
Vapor pressure	No data	No data	1 mmHg at 943 °C[c]	No data
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	Fire risk with organics	Not readily ignited	No data
Conversion factors:				
Air	No data	None[e]	None[e]	None[e]
Water	No data	1 ppm(w/v) = 1 mg/L = 1 µg/mL	1 ppm(w/v) = 1 mg/L = 1µg/mL	1 ppm(w/v) = 1 mg/L = 1µg/mL
Solid	No data	1 ppm(w/w) = 1 mg/kg = 1 µg/g	1 ppm(w/w) = 1 mg/kg = 1µg/g	1 ppm(w/w) = 1 mg/kg = 1µg/g
Explosive limits	No data	Explosive with easily oxidizable substances, and lead nitrate-lead hypophosphite double salt	2–3 drops 90% peroxyformic acid causes violent explosion	No data
Valence state	No data	+2	+2	+2

Table 3-2. Physical and Chemical Properties of Lead and Compounds (continued)

Property	Lead styphnate[i]	Lead sulfate[a]	Lead sulfide[a]	Tetraethyl lead[a]
Molecular weight	450.28[g]	303.26	239.26	323.45
Color	Orange-yellow	White	Black, blue, or silvery	Colorless (unless dyed)
Physical state	Crystals	Solid	Cubic or metallic crystals; powder	Oily liquid
Melting point	No data	1,170 °C	1,114 °C	-130 °C
Boiling point	No data	No data	1,281 °C (with sublimation)	200 °C; 227.7 °C (with decomposition)
Density	No data	6.2 g/cm^3 [d]	7.5 g/cm^3	1.653 g/cm^3 at 20 °C
Odor	No data	No data	Musty, pleasant, sweet	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water	Insoluble	42.5 mg/L at 25 °C[c]	0.86 mg/L at 13 °C	0.29 mg/L at 25 °C
Nitric acid	No data	More than in water	Soluble	No data
Hot conc. sulfuric acid	No data	Slightly soluble[d]	Soluble (in acid)	No data
Organic solvent(s)	No data	Insoluble in alcohol	Nitric acid, hot diluted hydrochloric acid[b]; insoluble in alcohol[c]	Benzene, ethanol, diethyl ether, gasoline petroleum ether
Partition coefficients:				
Log K_{ow}	No data	No data	No data	No data
Log K_{oc}	No data	No data	No data	No data
	No data	No data	1 mmHg at 852 °C[c]	0.2 mm Hg at 20 °C
Henry's law constant	No data	No data	No data	No data
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	93 °C (closed cup); 85 °C (open cup)
Flammability limits	Detonates at 260 °C	Not flammable	Noncombustible	1.8%
Conversion factors:				
Air	No data	None[e]	None[e]	No data
Water	No data	1 ppm(w/v) = 1 mg/L = 1 µg/mL	1 ppm(w/v) = 1 mg/L = 1µg/mL	No data
Solid	No data	1 ppm(w/w) = 1 mg/kg = 1 µg/g	1 ppm(w/w) = 1 mg/kg = 1µg/g	No data
Explosive limits	No data	No data	No data	Potentially, above 80 °C
Valence state	No data	+2	+2	No data

[a]HSDB 1996;[b]Merck 1989; [c]Lide 1996; [d]Temperature not specified; [e]Since these compounds exist in the particulate state, their concentrations are expressed as µg/m^3 only; [f]Howe 1981; [g]Molecular weight calculated from atomic weights; [h]USPATFULL 1997; [i]Lewis 1993

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

The lead industry consists of mine production, where lead ore (which occurs naturally mainly in the form of galena, lead sulfide) is crushed ground, conditioned, and concentrated (most commonly by flotation); primary metal production, where lead ore concentrate is treated through sintering, smelting, drossing, and refining to 99.99% purity; and secondary metal production, where scrap lead, primarily in the form of spent lead-acid batteries, product wastes, refinery drosses, and residues, is recycled (IARC 1980; Larrabee 1998; Woodbury 1985a). Mine production (ores and concentrates) is the feedstock used for primary production, and scrap metal is the feedstock used for secondary production. Almost all lead-producing mines in the United States are underground operations. Lead obtained as a by-product from open-pit copper mines is the only source of aboveground lead. Battery scrap is converted to impure lead or lead alloys by pyrometallurgical processes employing blast, electric arc, reverberatory, and/or rotary furnaces (Howe 1981; Larrabee 1998).

In 1996, the U.S. domestic lead industry was comprised of 17 mines located primarily in Alaska, Colorado, Idaho, Missouri, and Montana; two primary smelter-refineries in Missouri; a primary smelter in Montana; and 25 secondary (recycling) producers operating 31 plants. Of the lead recycled in 1996, 99% was produced by 10 companies operating 17 plants in Alabama, California, Florida, Georgia, Indiana, Louisiana, Minnesota, Missouri, New York, Pennsylvania, Tennessee, and Texas. Lead is also sold by the Defense National Stockpile Center (DNSC) as a result of legislation passed in 1992 authorizing the disposal of the entire 545,000 metric tons in the stockpile over several years. The law, however, requires the task to be completed without undue disruption of commercial lead markets (Larrabee 1997; Smith 1998).

In 1996, mines in Missouri and Alaska accounted for 93% of total U.S. lead mine production. Domestic lead mine production decreased in 1992 and 1993 as a result of low lead, gold, and silver metal prices, but increased the following three years when several mines either expanded or reopened due to increased metal prices. Domestic lead mine production reached 436,000 metric tons in 1996 and an estimated 450,000 metric tons in 1997, which was still less than the 484,000 metric tons produced in 1990 (Larrabee 1997; Smith 1998).

Domestic lead metal production rose at an annual rate of 1.3% between 1990 and 1996, going from 1.33 million metric tons to a record high of 1.43 million metric tons. Primary lead production declined at an annual average rate of 3.2% during this time period, dropping from 404,000 metric tons in 1990 to 326,000 metric tons in 1996. This decline was a result of cutbacks in production in 1991 and 1992 in response to low lead prices and of the closure of the primary lead refinery in Nebraska in 1996 (Larrabee 1997; Smith 1998). Primary lead production increased to 343,000 metric tons in 1997 (Smith 1998). Secondary lead production, however, rose at an average annual rate of 3.2%, climbing from 922,000 metric tons in 1990 to 1.1 million metric tons in 1996 and 1997 as the closure of 5 small secondary refineries was more than offset by the opening of a new secondary refinery and an increase of capacity at a number of other secondary facilities. As a result, secondary lead's share of total lead metal production rose from 69.5% in 1990 to 77.1% in 1996. In addition, between 1993 and 1996, the amount of lead in DNSC's inventory declined from 545,000 metric tons to 388,500 metric tons, and the disposal of about 54,000 metric tons has been authorized for each of fiscal years 1997 and 1998 by the respective Annual Materials Plans (Larrabee 1997; Smith 1998).

Table 4-1 lists the number of facilities in each state that have lead on site, the intended use, and the range of maximum amounts of lead that are stored on site. There are currently 1,476 facilities that produce or process lead or that have lead in some form on site in the United States. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TRI96 1998). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list. Table 4-2 shows the U.S. production volumes for lead during the years 1990 through 1997.

4.2 IMPORT/EXPORT

Imports of lead metal, which accounted for 17.5% of U.S. domestic consumption in 1996, rose from 90,900 metric tons in 1990 to 268,000 metric tons in 1996 and dropped slightly to an estimated 265,000 metric tons in 1997. In 1997, almost all imports came from Canada, Mexico, and Peru. Imports of lead waste and scrap, primarily from scrap lead-acid batteries, increased from 8,500 metric tons in 1990 to 14,800 metric tons in 1996, while the lead content of scrap lead-acid battery imports decreased from 6,800 metric tons in 1990 to an estimated 4,600 metric tons in 1996. Lead is also imported in the form of lead-acid batteries and other lead-containing products (Smith 1998; Larrabee 1998).

Table 4-1. Facilities That Manufacture or Process Lead

STATE [a]	NUMBER OF FACILITIES	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS [b]	ACTIVITIES AND USES [c]
AL	38	100 - 99,999,999	1 ,2 ,4 ,5 ,8 ,9 ,10 ,13
AR	28	0 - 9,999,999	1 ,4 ,5 ,8 ,9 ,12 ,13
AZ	15	1,000 - 1E12	1 ,2 ,3 ,4 ,5 ,6 ,8 ,9 ,10 ,12 ,13
CA	77	100 - 49,999,999	1 ,2 ,3 ,4 ,5 ,6 ,7 ,8 ,9 ,11 ,12 ,13
CO	8	1,000 - 999,999	2 ,3 ,7 ,9 ,12 ,13
CT	28	0 - 49,999,999	1 ,2 ,3 ,4 ,7 ,8 ,9 ,10 ,11 ,12
DE	4	1,000 - 9,999,999	12 ,13
FL	12	1,000 - 9,999,999	1 ,4 ,7 ,8 ,9 ,11 ,12
GA	40	100 - 9,999,999	1 ,2 ,3 ,5 ,8 ,9 ,10 ,12 ,13
IA	15	100 - 49,999,999	1 ,2 ,3 ,4 ,5 ,6 ,9 ,10
ID	3	10,000 - 999,999	9
IL	100	0 - 49,999,999	1 ,2 ,3 ,4 ,8 ,9 ,10 ,12 ,13
IN	93	100 - 49,999,999	1 ,2 ,3 ,4 ,5 ,7 ,8 ,9 ,10 ,12 ,13
KS	25	0 - 9,999,999	1 ,2 ,3 ,8 ,9 ,12 ,13
KY	35	100 - 9,999,999	1 ,2 ,3,4 ,5 ,7 ,9 ,10 ,11
LA	14	0 - 49,999,999	1 ,3, 5 ,7 ,9 ,11 ,12
MA	35	1,000 - 9,999,999	8 ,9 ,12
MD	7	1,000 - 999,999	9 ,12 ,13
ME	1	1,000 - 9,999	2 ,3 ,9
MI	59	0 - 999,999	2 ,3 ,4 ,5 ,8 ,9 ,10 ,11 ,12 ,13
MN	18	1,000 - 9,999,999	1 ,4 ,9 ,13
MO	41	0 - 499,999,999	1 ,3 ,4 ,5 ,7 ,8 ,9 ,10 ,11 ,12
MS	32	1,000 - 9,999,999	2 ,3 ,8 ,9 ,12 ,13
MT	2	10,000 - 499,999,999	1 ,2 ,3 ,4 ,7
NC	35	0 - 49,999,999	1 ,5 ,8 ,9 ,10 ,12 ,13
ND	1	100,000 - 999,999	11
NE	16	100 - 99,999,999	2 ,5 ,8 ,9 ,12
NH	11	100 - 99,999	9
NJ	46	100 - 9,999,999	1 ,2 ,3 ,4 ,7 ,8 ,9 ,12 ,13
NM	3	10,000 - 999,999	13
NV	3	10,000 - 999,999	2 ,3 ,4 ,9 ,10
NY	58	0 - 49,999,999	1 ,2 ,3 ,4 ,5 ,8 ,9 ,10 ,11 ,12 ,13
OH	154	0 - 49,999,999	1 ,2 ,3 ,4 ,5 ,6 ,7 ,8 ,9 ,10 ,11 ,12 ,13
OK	16	100 - 49,999,999	1 ,5 ,9 ,10 ,11 ,12
OR	9	1,000 - 9,999,999	9 ,11
PA	94	100 - 49,999,999	1 ,2 ,3 ,5 ,7 ,8 ,9 ,10 ,12 ,13
PR	4	100 - 99,999	2 ,3 ,9 ,12
RI	15	100 - 999,999	2 ,3 ,4 ,8 ,9 ,13
SC	30	0 - 9,999,999	1 ,5 ,6 ,7 ,8 ,9 ,10 ,12 ,13
SD	2	1,000 - 9,999	9
TN	47	100 - 49,999,999	1 ,2 ,3 ,4 ,5 ,7 ,9 ,10 ,11 ,12 ,13
TX	92	0 - 9,999,999	1 ,2 ,3 ,4 ,5 ,6 ,8 ,9 ,10 ,11 ,12 ,13
UT	13	1,000 - 9,999,999	1 ,3 ,4 ,5 ,8 ,9 ,11 ,12 ,13
VA	24	0 - 999,999	1 ,2 ,3 ,5 ,6 ,8 ,9 ,12 ,13
VT	5	1,000 - 999,999	9 ,12
WA	13	100 - 9,999,999	1 ,2 ,3 ,4 ,6 ,8 ,9 ,10 ,12
WI	44	0 - 999,999	1, 2 ,3 ,4 ,5 ,7 ,8 ,9 ,10 ,12 ,13
WV	9	1,000 - 999,999	1 ,2 ,3 ,5 ,8 ,9 ,12
WY	2	1,000 - 99,999	1 ,4 ,10

Source: TRI96 1998

[a] Post office state abbreviations used

[b] Range represents maximum amounts on site reported by facilities in each state

[c] Activities/Uses:

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

Table 4-2. U.S. Lead Production January 1990 through 1997

	Production volumes in metric tons							
Type of lead	1990	1991	1992	1993	1994	1995	1996	1997
Mined (recovered): domestic ores, recoverable lead content	484,000	466,000	397,000	355,000	363,000	386,000	426,000	448,000
Primary (refined): domestic/foreign ores and base bullion	404,000	345,900	304,800	334,900	351,400	374,000	326,000	343,000
Secondary (refined): lead content	922,000	885,000	916,000	893,000	931,000	1,020,000	1,070,000	1,110,000

Source: DOI/USGS 1997a; Smith 1995, 1998

Exports of lead metal increased from 55,500 metric tons in 1990 to 94,400 metric tons in 1991, then fell to 44,000 metric tons in 1996 and 37,400 metric tons in 1997. In 1997, the U.S. exported lead metal primarily to South Korea, Canada, United Kingdom, Malaysia, Belgium, and Taiwan. Lead waste and scrap exports, which amounted to 71,900 metric tons in 1990, rose to 104,300 metric tons in 1995, dropped to 85,300 metric tons in 1996, and rose to 88,400 metric tons in 1997. The lead content of exported scrap lead-acid batteries went from 4,800 metric tons in 1990 to 1,400 metric tons in 1995. No later export tonnage figures for scrap lead-acid batteries are available for 1996 because the data were collected by dollar value only. Most exports are in the form of lead-acid batteries or products containing either lead-acid batteries or other applications of lead (Larrabee 1998; Smith 1998).

4.3 USE

Lead may be used in the form of metal, either pure or alloyed with other metals, or as chemical compounds. The commercial importance of lead is based on its ease of casting, high density, low melting point, low strength, ease of fabrication, acid resistance, electrochemical reaction with sulfuric acid, and chemical stability in air, water, and soil (Howe 1981; Shea 1996). At least half of all lead consumed worldwide goes into producing lead-acid batteries used in automotive and various industrial applications. Certain dispersive or readily bio-available uses, such as lead in gasoline, as a solder in piping for drinking water and food cans, and in house paints, have been or are being phased out due to environmental and health concerns (Larrabee 1998).

Prior to the EPA beginning to regulate the lead content in gasoline during the early 1970s, approximately 250,000 tons of organic lead (e.g., tetraethyl lead) were added to gasoline on an annual basis in the United States (Giddings 1973). These lead-based “anti-knock” additives increased the octane rating of the gasoline and as a result increased engine efficiency (Giddings 1973). In 1971, the average lead content for a gallon of gasoline purchased in the United States was 2.2 grams per gallon (Giddings 1973). After determining that lead additives would impair the performance of emission control systems installed on motor vehicles, and that lead particle emission from motor vehicles presented a significant health risk to urban populations, in 1973 EPA initiated a phase-down program designed to minimize the amount of lead in gasoline over time. By 1988, the phase-down program had reduced the total lead usage in gasoline to less than 1% of the amount of lead used in the peak year of 1970 (EPA 1996f). In 1990, a Congressional amendment to the Clean Air Act (CAA) banned the use of gasoline containing lead or lead additives as fuel in motor vehicles. On February 2, 1996, the EPA incorporated the statutory ban in a direct final rule which defined unleaded

gasoline as gasoline containing trace amounts of lead up to 0.05 gram per gallon (EPA 1996f). The definition still allowed trace amounts of lead but expressly prohibited the use of any lead additive in the production of unleaded gasoline. The term "lead additive" was defined to include pure lead as well as lead compounds (EPA 1996f). Although the regulatory action of Congress banned the use of leaded gasoline as fuel in motor vehicles, it did not restrict other potential uses of gasoline containing lead or lead additives (EPA 1996f). Gasoline produced with lead additives continues to be made and marketed for use as fuels in aircraft, race cars, and non-road engines such as farm equipment engines and marine engines, to the extent allowed by law (EPA 1996f), but tetraethyl lead has not been produced in the United States since March 1991, and all gasoline sold for motor vehicle use since January 1, 1996, has been unleaded (EPA 1997).

In 1996, lead was consumed by 186 facilities in the United States. The most significant use of lead metal is for lead-acid storage batteries used in automotive and industrial applications (Larrabee 1998). Other current commercial uses of lead metal include producing ammunition in the form of shot and bullets; bearing metals for machinery, electrical and electronic equipment, motor vehicles and other transportation equipment; brass and bronze billets and ingots; cable coverings in the power and communication industries; pipes, traps, and other extruded products for building construction, storage tanks, process vessels. Lead-based metal products also include sheet lead for building construction, storage tanks, process vessels, and medical radiations shielding; solder for building construction, motor vehicles, equipment, metal cans and shipping containers, and electronic components and accessories; storage batteries, including storage battery grids and posts. Lead oxides are used in paint, glass, and ceramic products (Smith 1998).

Reported consumption of lead increased at an average annual rate of 3.3% between 1990 and 1996. Consumption patterns have long been shifting to a market dominated by one major end use: the lead-acid battery. Increasing lead-acid battery demand has more than made up for all end-uses that have either significantly declined or been legislated out of existence for environmental and health reasons. The lead-acid battery share of total domestic lead consumption increased from 79.7% in 1990 to 87.6% in 1996 and grew at an average annual rate of 5.2% over the period. At the same time, non-battery uses of lead declined at an average annual rate of 4.5%. Except for a sharp increase in 1995, lead used in ammunition (the largest non-battery end-use) remained fairly constant during this period. Other uses, such as cable covering, caulking, and solder, have declined significantly while tetraethyl lead additives for gasoline, which once accounted for 20% of domestic consumption, has been phased out except for the exceptions noted above (Larrabee 1998; Smith 1998).

The lead-acid battery is the driving force behind the lead industry both globally and domestically. This sector consists of two main markets: starting, lighting, and ignition (SLI) batteries, which presently account for 83% of the market; and industrial batteries, which currently account for 17% of the market. SLI batteries are used in passenger cars and light trucks, heavy commercial vehicles, motorcycles, special tractors, marine equipment, aircraft, and military vehicles. Between 1990 and 1996, SLI battery production increased at an average annual rate of 4.3%, rising from 79.6 million units to 100 million units. An estimated 1.1 million metric tons of lead was consumed in SLI batteries (Battery Council International 1998; Larrabee 1998; Smith 1998).

The industrial battery market is divided into two sectors: motive power and stationary power. Motive power includes batteries for industrial trucks, mining vehicles, and railroad cars and presently accounts for 39% of the industrial battery market. Stationary power includes batteries for telecommunications, uninterruptable power supply (UPS) units, and control and switchgear equipment and presently accounts for the remaining 61% of the industrial battery market. The industrial battery market jumped 19% in 1995 and registered an average annual growth rate of 11.2% between 1990 and 1996, with the strongest rise in the stationary sector, which grew at an average annual rate of 20.5% during this period. The rapid rise in the stationary power sector was due to strong demand for communications and UPS batteries. The pace of market activity for these batteries is expected to accelerate further due to de-regulation of the telecommunications industry (Battery Council International 1998; Larrabee 1998).

The domestic use pattern for lead in 1990 was as follows: lead-acid storage batteries, used for motor vehicles, motive power, and emergency back-up power, accounted for 80% of total lead consumption; ammunition, bearing metals, brass and bronze, cable covering, extruded products, sheet lead, and solder, represented 12.4%; the remaining 7.6% was used for ceramics, type metal, ballast or weights, tubes or containers, oxides, and gasoline additives (USDOC 1992).

The substitution of plastics could continue to reduce the use of lead in building construction, electrical cable covering, and cans and containers. In addition to plastics, aluminum, tin, and iron continue to compete with lead in other uses such as packaging and coatings (DOI/USGS 1997b). In the United States, tin has replaced lead as solder used in new or replacement potable water systems (DOI/USGS 1997b). Despite these market losses, new uses have been or are being developed that hopefully do not present the environmental and health problems associated with some of the old uses of lead. The following list shows some recent and possible new critical uses of lead:

- Lead's advantages in providing protection against radiation exposure have facilitated advances in computers and televisions (which emit gamma rays and X-rays while in operation), medical procedures such as magnetic imaging for diagnostics and many kinds of radiation therapy, and nuclear technology used in a variety of commercial and military applications.

- Lead alloy solder is critical to the transistors, relays, and other components in the printed circuit boards used in all computers and advanced electronic equipment.

- Piezoelectric ceramics, which depend on lead compounds, are used to produce transducers and sensors which make possible ultrasound technologies used in wide-ranging medical and commercial applications, guidance and sensing systems used in defense and commerce, and in addition, new "smart materials" research projects.

- High-purity lead oxide is used to make precision glasses needed for lasers, low-dose X-ray machines, fiber optic probes, medical camera systems, and low-light military equipment such as night vision scopes and goggles.

- A new cogeneration technology is now being developed outside the United States operates by recirculating molten lead throughout a sealed system. This concept could result in highly efficient energy generation and reduced depletion of fossil reserves.

- Lead-based, high-temperature superconductors are being studied in several research projects. Their superior performance characteristics are expected to facilitate development of new hyper-fast computers, as well as more sensitive medical diagnostic equipment, more efficient energy delivery systems, and new forms of high-speed surface transportation.

- Lead continues to be used in pigments. For example, lead chromate and lead oxide are used in paints, and lead acetate is used in hair dyes.

4.4 DISPOSAL

Although certain uses of lead preclude recycling (e.g., use as a gasoline additive), lead has a higher recycling rate than any other metal (Larrabee 1998). An estimated 90-95% of the lead consumed in the United States is considered to be recyclable. In the United States, 77.1% of the lead requirements were satisfied by recycled lead products (mostly lead-acid batteries) in 1996. This compares to 69.5% in 1990 and 55.2% in 1980 (Larrabee 1997, 1998).

Disposal of wastes containing lead or lead compounds is controlled by a number of federal regulations (see Chapter 7). Lead is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1988). Lead-containing waste products include storage batteries, ammunition waste, ordnance, sheet lead, solder, pipes, traps, and other metal products; solid waste and tailings from

lead mining; items covered with lead-based paint; and solid wastes created by mineral ore processing, iron and steel production, copper and zinc smelting, and the production and use of various lead-containing products (DOI 1987a; EPA 1982a).

Presently, 37 states have enacted legislation to encourage recycling of lead-acid batteries. These states have adopted laws that prohibit disposal of lead-acid batteries in municipal solid waste streams and require all levels of the collection chain to accept spent lead-acid batteries. Four other states ban only the land-filling and incineration of lead-acid batteries. Battery recycling rates are determined by comparing the amount of lead recycled from batteries with the quantity available for recycling in a given year. Recycling facilities can usually provide data on the amount of lead produced from scrapped batteries; however, the amount of lead available for recycling is largely influenced by the battery's useful life span. Therefore, to determine the amount of lead available from batteries for a given year requires historical data on battery production and average lead content, as well as import and export data on new batteries, vehicles containing batteries, scrap lead and scrapped batteries (Larrabee 1998). The 1995 annual study released by the Battery Council International reported an average annual lead-acid battery recycling rate of 94.9% between 1990 and 1995 (Battery Council International 1998).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Lead is dispersed throughout the environment primarily as the result of anthropogenic activities. Environmental fate processes may transform one lead compound to another; however, lead is not degraded and is still available for human exposure, even though the compounds containing it vary enormously.

The general population is exposed to lead in ambient air, in many foods, in drinking water, in soil, and in dust. Segments of the general population at highest risk of health effects from lead exposure are preschool-age children and pregnant women and their fetuses. Within these groups, relationships have been established between lead exposure and adverse health effects. Other segments of the general population at high risk include white males between 40 and 59 years of age and individuals living near sites where lead was produced or disposed.

Human exposure to lead above baseline levels is common. Baseline refers to the naturally-occurring level of lead in soil or dust that is not due to the influence of humans. Some of the more important lead exposures occur as a result of living in urban environments, particularly in areas near stationary emission sources (e.g., smelters); consumption of produce from family gardens; renovation of homes containing lead-based paint; pica (an abnormal eating habit in children); contact with interior lead paint dust; occupational exposure; secondary occupational exposure (e.g., families of workers using lead); smoking; and wine consumption. Higher than normal exposures may also occur to residents living in close proximity to National Priorities List (NPL) sites that contain elevated levels of lead. The highest and most prolonged lead exposures are found among workers in the lead smelting, refining, and manufacturing industries.

The primary source of lead in the environment has historically been anthropogenic emissions to the atmosphere. In 1984, combustion of leaded gasoline was responsible for approximately 90% of all anthropogenic lead emissions. EPA phased out the use of lead alkyls in gasoline, however, and by 1990, auto emissions accounted for only 33% of the annual lead emissions (EPA 1996h). Use of lead additives in motor fuels was totally banned after December 31, 1995 (EPA 1996f). The ban went into effect on February 2, 1996. Atmospheric deposition is the largest source of lead found in soils. Lead is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be

important sinks for lead. Lead particles are removed from the atmosphere primarily by wet and dry deposition. The average residence time in the atmosphere is 10 days. Over this time, long-distance transport, up to thousands of kilometers, may take place. Lead is extremely persistent in both water and soil. The speciation of lead in these media varies widely depending upon such factors as temperature, pH, and the presence of humic materials. Lead is largely associated with suspended solids and sediments in aquatic systems, and it occurs in relatively immobile forms in soil.

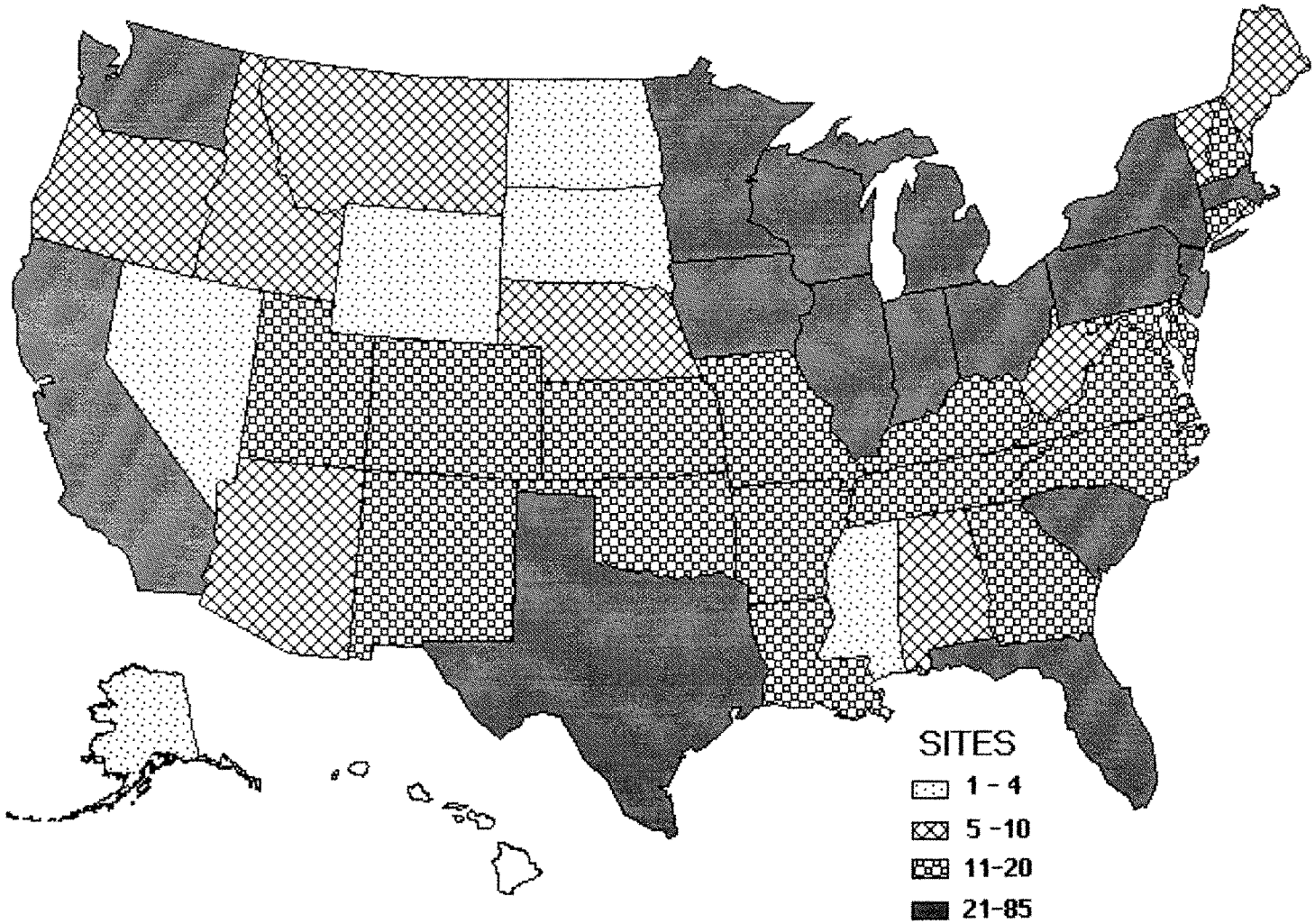
Lead has been identified in at least 1,026 of the 1,467 current or former EPA National Priorities List (NPL) hazardous wastes sites (HazDat 1998). However, the number of sites evaluated for lead is not known. The frequency of these sites within the United States can be seen in Figure 5-1. Of these sites, 1,017 are located in the United States, 1 is located in Guam (not shown), 1 is located in the Virgin Islands (not shown), and 7 are located in the Commonwealth of Puerto Rico (not shown).

5.2 RELEASES TO THE ENVIRONMENT

Lead is a naturally occurring element that has been found in the earth's crust, mostly as the sulfide galena, and in all compartments of the biosphere in various chemical forms. Although both natural and anthropogenic processes are responsible for the distribution of lead throughout the environment, anthropogenic releases of lead are predominant. Lead is regulated by several federal statutes and is a priority water pollutant and a hazardous air pollutant (see Chapter 7). Although combustion of leaded gasoline was once the primary source of anthropogenic atmospheric releases of lead, industrial releases to soil from nonferrous smelters, battery plants, chemical plants, and disturbance of older structures containing lead-based paints are now major contributors to total lead releases.

According to the Toxics Release Inventory, in 1996, a total of 16,938,957 pounds (7,683,382 kg) of lead was released to the environment from 1,494 large processing facilities (TRI96 1998). Table 5-1 lists amounts released from these facilities. In addition, an estimated 47,886 pounds (21,721 kg) were released by manufacturing and processing facilities to publicly owned treatment works (POTWs), and an estimated 350,783,734 pounds (159,112,825 kg) were transferred offsite (TRI96 1998). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Figure 5-1. Frequency of NPL Sites with Lead Contamination



Derived from HazDat 1998

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Lead

		Total of reported amounts released in pounds per year [a]						
STATE [b]	NUMBER OF FACILITIES	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
AL	36	65,811	2,946	162,682	0	290	1,396,876	1,628,605
AR	28	20,992	151	31,608	0	339	3,164,254	3,217,344
AZ	15	50,091	0	3,161,245	0	103	7,483,002	10,694,441
CA	77	12,975	1,449	19,534	0	506	22,124,851	22,159,315
CO	8	3,307	1	21,400	0	262	956,475	981,445
CT	28	1,272	126	2,961	0	21	602,596	606,976
DE	4	3,176	3	0	0	859	5,180,089	5,184,127
FL	10	7,170	29	0	0	259	7,135,984	7,143,442
GA	38	24,366	933	78,755	0	230	16,693,844	16,798,128
IA	14	14,725	463	75,505	0	307	11,441,116	11,532,116
ID	3	140	0	0	0	73	325,555	325,768
IL	99	215,426	2,165	825,038	0	3,494	13,220,136	14,266,259
IN	92	42,695	6,331	252,632	0	3,038	43,425,409	43,730,105
KS	25	9,242	129	334	26	210	36,021,657	36,031,598
KY	35	18,572	486	34,010	0	1,581	8,519,181	8,573,830
LA	14	12,509	858	141,507	0	354	12,306,959	12,462,187
MA	34	26,288	265	0	0	257	494,906	521,716
MD	7	277	3,221	1,600	0	93	141,564	146,755
ME	1	4	0	0	0	0	4,476	4,480
MI	58	30,696	588	140,721	0	2,835	2,186,206	2,361,046
MN	18	20,125	10	0	0	847	4,217,763	4,238,745
MO	41	578,521	1,011	4,209,789	0	2,567	18,807,358	23,599,246
MS	31	8,073	1,216	66,631	0	551	602,724	679,195
MT	2	43,547	1,053	3,696,200	0	5	211,193	3,951,998
NC	35	9,058	1,265	7,456	0	628	6,175,024	6,193,431
ND	1	370	0	8	0	0	407	785
NE	16	27,710	2,111	3,766	0	649	4,624,654	4,658,890
NH	11	3,483	10	255	0	42	503,346	507,136
NJ	45	18,895	2,707	103,342	0	2,605	13,231,577	13,359,126
NM	3	12,973	0	137,044	0	120	15,300	165,437
NV	3	1,025	0	0	0	1	433,931	434,957
NY	57	29,860	1,085	3,902	0	1,651	4,543,097	4,579,595
OH	151	83,375	5,632	338,116	0	9,881	20,121,578	20,558,582

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process Lead (continued)

		Total of reported amounts released in pounds per year [a]						
STATE [b]	NUMBER OF FACILITIES	AIR [c]	WATER	LAND	UNDERGROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
OK	16	2,476	109	204	408	108	1,529,271	1,532,576
OR	8	1,149	30	0	0	62	5,171,205	5,172,446
PA	95	131,991	6,604	81,490	0	2,920	19,412,751	19,635,756
PR	4	2,735	1	1	0	32	135,582	138,351
RI	14	923	62	0	0	43	291,972	293,000
SC	30	25,388	950	45,352	0	1,691	8,622,651	8,696,032
SD	2	10	5	0	0	10	34,400	34,425
TN	46	20,123	1,883	5,589	0	3,801	2,666,922	2,698,318
TX	89	101,176	4,464	580,600	360	2,145	34,812,211	35,500,956
UT	13	20,277	641	873,943	0	292	1,364,131	2,259,284
VA	24	5,046	459	43,229	0	348	719,947	769,029
VT	5	38	5	346	0	250	976,762	977,401
WA	13	5,320	250	590	0	49	620,089	626,298
WI	44	9,952	290	0	0	1,406	7,786,748	7,798,396
WV	9	5,560	10,657	0	0	71	246,004	262,292
WY	2	5	0	0	0	0	80,000	80,005

Source: TRI96 1998

[a] Data in TRI are maximum amounts released by each facility

[b] Post office state abbreviations used

[c] The sum of fugitive and stack releases are included in releases to air by a given facility

[d] The sum of all releases of the chemical to air, land, and water, and underground injection wells; and transfers off-site by a given facility

POTW = publicly owned treatment works

Lead has been identified in a variety of environmental media (air, surface water, groundwater, leachate, soil, sediment, fish and game animals) collected at 1,026 of the 1,467 current and former NPL hazardous waste sites (HazDat 1998). Lead is the most frequently found metal at hazardous waste sites (Reed et al. 1995).

5.2.1 Air

According to the Toxics Release Inventory, in 1994, the estimated releases of lead of 1,728,918 pounds (784,224 kg) to air from 1,454 large processing facilities accounted for about 10.2% of the total environmental releases of lead (TRI96 1998). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

Lead has been identified in air samples collected at 65 of the 1,026 NPL hazardous waste sites where it was detected in some environmental medium (HazDat 1998).

Of particular importance are emissions of lead to the atmosphere, which is the initial recipient for much of the lead released to the environment. Estimated atmospheric emissions of lead from anthropogenic point and nonpoint sources in the United States during 1989 (6 years before the total ban on lead in gasoline) were estimated to be 6,304 short tons (EPA 1996h). Stationary sources of lead, although found throughout the nation, tend to be concentrated near smelters, nonferrous foundries, and industrial operations dealing with lead-containing products. Lead may also be released in aerosol form from waste incinerators (Biswas et al. 1992). Natural emissions of lead to the atmosphere from volcanoes and windblown dust are believed to be of minor importance (EPA 1986a).

As indicated in Table 5-2, by 1988, transportation (i.e., automotive) emissions were no longer the largest source of lead emitted to the atmosphere. When such emissions were prevalent, more than 90% (mass basis) of automotive lead emissions from leaded gasoline were in the form of inorganic particulate matter (e.g., lead bromochloride [PbBrCl]) and <10% (mass basis) were in the form of organolead vapors (e.g., lead alkyls). In 1984 the average lead content of gasoline was 0.44 g lead/gallon (EPA 1986a); however, as of January 1986, the allowable lead content of leaded gasoline dropped to 0.1 g lead/gallon

Table 5-2. National Lead Emission Estimates, 1979–1989

Source category	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
Transporation	94.6	59.4	46.9	46.9	40.8	34.7	15.5	3.5	3.0	2.6	2.2
Fuel combustion	4.9	3.9	2.8	1.7	0.6	0.5	0.5	0.5	0.5	0.5	0.5
Industrial processes	5.2	3.6	3.0	2.7	2.4	2.3	2.3	1.9	1.9	2.0	2.3
Solid waste	4.0	3.7	3.7	3.1	2.6	2.6	2.8	2.7	2.6	2.5	2.3
Total[a]	108.7	70.6	56.4	54.4	46.4	40.1	21.1	8.6	8.0	7.6	7.2

[a]The sums of sub-categories may not equal total because of rounding.

Source: Derived from EPA 1990c, 1991b

(EPA 1985g), and as of February 2, 1996, a ban on addition of lead compounds to gasoline went into effect. Between January and June of 1990, the actual average lead concentration in leaded gasoline was 0.085 g lead/gallon, indicating consumption of approximately 230,000 kg of lead for the production of 2.74 billion gallons of leaded gasoline. During the same 6-month period, 49 billion gallons of unleaded gasoline were produced in the United States (EPA 1990b). In the early 1980s EPA allowed up to 0.05 g lead per gallon of unleaded gasoline (EPA 1982b). An analysis of unleaded gasolines conducted in the winter of 1991–1992 indicated that regular grade unleaded gasoline contained, on average, less than 0.0003 g lead/gallon (MVMA 1992). On February 2, 1996, addition of lead to any grade of gasoline intended for on-road transportation was banned in the United States.

Reduction trends for air emissions of lead have continued from the late 1970s through the 1980s for both point sources (from 2.9 $\mu g/m^3$ in 1979 to 0.4 $\mu g/m^3$ in 1988) and urban sites (from 0.8 $\mu g/m^3$ in 1979 to 0.1 $\mu g/m^3$ in 1988) (EPA 1990a). The large decrease for point sources resulted from the use of emission controls for industrial processes as well as automotive controls; the decrease for urban sites was primarily the result of the decreased use of leaded gasoline. In June 1990, unleaded gasoline comprised 94% of all gasoline produced compared with 91% in July 1989 (EPA 1990b).

Releases from lead-based paints are frequently confined to the area in the immediate vicinity of painted surfaces, and deterioration or removal of the paint can result in high localized concentrations of lead in indoor air (from sanding and sandblasting) and on exposed surfaces.

The largest volume of organolead vapors released to the atmosphere results from industrial processes; prior to its phaseout and ban, leaded gasoline containing tetraethyl lead as an anti-knock additive was also a major contributor. Tetraalkyl lead vapors are photoreactive, and their presence in local atmospheres is transitory. Halogenated lead compounds are formed during combustion by reaction of the tetraalkyl lead compounds with halogenated lead scavenger compounds. These halogenated lead compounds ultimately give rise to lead oxides and carbonates in the environment (EPA 1985b). Tetraalkyl lead compounds once contributed 5–10% of the total particulate lead present in the atmosphere. Organolead vapors were most likely to occur in occupational settings (e.g., gasoline transport and handling operations, gas stations, and parking garages) and high-traffic areas (Nielsen 1984).

5.2.2 Water

Of the known aquatic releases of lead, the largest ones are from the steel and iron industries and lead production and processing operations (EPA 1982a). Urban runoff and atmospheric deposition are significant indirect sources of lead found in the aquatic environment. Lead reaching surface waters is sorbed to suspended solids and sediments (EPA 1982a).

Although aquatic releases from industrial facilities are expected to be small, lead may be present in significant levels in drinking water. In areas receiving acid rain (e.g., northeastern United States) the acidity of drinking water may increase; this increases the corrosivity of the water, which may, in turn, result in the leaching of lead from water systems, particularly from older systems during the first flush of water through the pipes (McDonald 1985). In addition, the grounding of household electrical systems to the plumbing can increase corrosion rates and the subsequent leaching of lead from the lead solder used for copper pipes. Areas where the pH of the water is less than 8.0 may have higher drinking water lead levels as well (Lee et al. 1989).

According to the Toxics Release Inventory, in 1996, the estimated releases of lead of 62,654 pounds (28,418 kg) to water from 1,454 large processing facilities accounted for about 0.4% of total environmental releases (TRI96 1998). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

Lead has been identified in groundwater samples collected at 781 of the 1,026 NPL hazardous waste sites, in leachate samples collected at 146 of the 1,026 NPL hazardous waste sites, and in surface water samples collected at 458 of the 1,026 NPL hazardous waste sites where it was detected in some environmental medium (HazDat 1998).

5.2.3 Soil

Solid wastes that contain lead are produced primarily as a result of domestic ore production and ammunition use. Other sources include solder, weights and ballasts, bearing metals, and iron and steel production. These sources of lead-contaminated waste are concentrated primarily in landfills.

According to the Toxics Release Inventory, in 1996, the estimated releases of lead of 15,147,385 pounds (6,870,738 kg) to land from 1,454 large processing facilities accounted for about 89.4% of total environmental releases (TRI96 1998). An additional 794 pounds (360 kg), constituting less than 0.005% of the total environmental releases, were released via underground injection (TRI96 1998). Also, some of the estimated 370,905,354 pounds (168,239,838 kg) of lead transferred off-site may be ultimately disposed of on land. It should be noted that TRI-reported releases to land include, but are not limited to, releases to soil. Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

Lead has been identified in soil samples collected at 675 of the 1,026 NPL hazardous waste sites, in sediment samples collected at 456 of the 1,026 NPL hazardous waste sites, and in soil-gas samples collected at 2 of the 1,026 NPL hazardous waste sites where it was detected in some environmental medium (HazDat 1998).

5.2.4 Paint

Flaking paint, paint chips, and weathered powdered paint, which are most commonly associated with deteriorated housing stock in urban areas, are major sources of lead exposure for young children residing in these houses, particularly for children with pica (the compulsive, habitual consumption of nonfood items) (Bornschein et al. 1986; EPA 1986a). Lead concentrations of 1–5 mg/cm^2 have been found in chips of lead-based paint (Billick and Gray 1978), suggesting that consumption of a single chip of paint would provide greater short-term exposure than any other source of lead (EPA 1986a). An estimated 40–50% of currently occupied housing in the United States may contain lead-based paint on exposed surfaces (Chisolm 1986).

In the late 1980s, the U.S. Department of Housing and Urban Development (HUD) conducted a national survey of lead-based paint in housing. The EPA subsequently sponsored a comprehensive technical report on the HUD-sponsored survey to provide estimates of the extent of lead-based paint in housing. In the EPA report, a home is considered to have lead-based paint if the measured lead concentration on any painted surface is 1.0 mg/cm^2 or greater. The EPA report estimates that 64 million (±7 million) homes, or 83% (±9%) of privately-owned housing units built before 1980, have lead-based paint somewhere in the building. Approximately 12 million (±5 million) of these homes are occupied by families with children under the age of 7 years. Approximately 49 million (±7 million) privately owned homes have lead-based

paint in their interiors. By contrast, approximately 86% (±8%) of all pre-1980 public housing family units have lead-based paint somewhere in the building (EPA 1995c).

Damaged lead-based paint is associated with excessive dust lead levels. Approximately 14 million homes (19% of pre-1980 housing) have more that 5 square feet of damaged lead-based paint, and nearly half (47%) of those homes have excessive dust lead levels (EPA 1995c).

In the Cincinnati prospective lead study of public and private low- and moderate-income housing, the lead concentration ranges were: painted interior walls, 0.1–35 mg/cm^2; interior home surface dust, 0.04–39 mg/m^2 and 72–16,200 µg/g; interior home dustfall, 0.0040–60 mg/m^2/30 days; exterior dust scrapings, 20–108,000 µg/g; and dust on children's hands, 1–191 µg. The lead levels in older private deteriorating or dilapidated housing were higher than the levels in newer public and rehabilitated housing (Clark et al. 1985).

Releases from lead-based paints are frequently confined to the area in the immediate vicinity of painted surfaces, and deterioration or removal of the paint can result in high localized concentrations of lead in indoor air (from sanding and sandblasting) and on exposed surfaces. Disturbance of older structures containing lead-based paints is now a significant contributor to total lead releases.

The authors of a report of findings from the Third National Health and Nutrition Examination Survey (NHANES III), conducted in 1988 to 1991, comment that of the multiple sources of exposure, lead-based paint is the principal high-dose source of lead. Exposure occurs not only through the direct ingestion of flaking and chalking paint but also through the inhalation of dust and soil contaminated with paint (Brody et al. 1994). According to a study by the New York State Department of Health, renovation and remodeling activities that disturb lead-based paints in homes can produce significant amounts of lead dust, which can be inhaled or ingested (CDC 1997d).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

In the atmosphere, non-organic compounds of lead exist primarily in the particulate form. Upon release to the atmosphere, lead particles are dispersed and ultimately removed from the atmosphere by wet or dry deposition. Approximately 40–70% of the deposition of lead is by wet fallout; 20–60% of particulate lead once emitted from automobiles is deposited near the source. An important factor in determining the atmospheric transport of lead is particle size distribution. Large particles, particularly those with aerodynamic diameters of >2 μm, settle out of the atmosphere fairly rapidly and are deposited relatively close to emission sources (e.g., 25 m from the roadway for those size particles emitted in motor vehicle exhaust in the past); smaller particles may be transported thousands of kilometers. The dry deposition velocity for lead particles with aerodynamic diameters of 0.06–2.0 μm was estimated to range between 0.2 and 0.5 cm/second in a coniferous forest in Sweden, with an overall particle-size weighted dry deposition velocity of 0.41 cm/second (Lannefors et al. 1983). However, the use of an average net deposition velocity of 0.6 cm/second and an average atmospheric residence time of 10 days has been recommended by the National Academy of Sciences (NAS 1980). The amount of lead scavenged from the atmosphere by wet deposition varies widely; wet deposition can account for 40–70% of lead deposition depending on such factors as geographic location and amount of emissions in the area (Nielsen 1984). An annual scavenging ratio (concentration in precipitation, mg/L, to concentration in air, μg/m^3) of 0.18×10^{-6} has been calculated for lead, making it the lowest value among seven trace metals studied (iron, aluminum, manganese, copper, zinc, cadmium); this indicates that lead (which initially exists as fine particles in the atmosphere) is removed from the atmosphere by wet deposition relatively inefficiently. Wet deposition is more important than dry deposition for removing lead from the atmosphere; the ratio of wet to dry deposition was calculated to be 1.63, 1.99, and 2.50 for sites in southern, central, and northern Ontario, Canada, respectively (Chan et al. 1986). Lead particles from automobile emissions are quite small (<0.1 μm in diameter) but can grow in size by coagulation (Chamberlain et al. 1979). Lead has been found in sediment cores of lakes in Ontario and Quebec, Canada, that were remote from any point sources of lead releases, indicating that long-range atmospheric transport was occurring (Evans and Rigler 1985).

The amount of lead that remains in solution in surface waters depends upon the pH of the water and the dissolved salt content. Equilibrium calculations show that at pH >5.4, the total solubility of lead is approximately 30 μg/L in hard water and approximately 500 μg/L in soft water. Sulfate ions, if present in

soft water, limit the lead concentration in solution through the formation of lead sulfate. Above pH 5.4, the lead carbonates, $PbCO_3$ and $Pb_2(OH)_2CO_3$, limit the concentration. The carbonate concentration is in turn dependent upon the partial pressure of carbon dioxide, pH, and temperature (EPA 1986a). In most surface waters and groundwaters, the concentration of dissolved lead is low because the lead will form compounds with anions in the water such as hydroxides, carbonates, sulfates, and phosphates that have low water solubilities and will precipitate out of the water column (Mundell et al. 1989).

A significant fraction of lead carried by river water is expected to be in an undissolved form, which can consist of colloidal particles or larger undissolved particles of lead carbonate, lead oxide, lead hydroxide, or other lead compounds incorporated in other components of surface particulate matters from runoff. Lead may occur either as sorbed ions or surface coatings on sediment mineral particles, or it may be carried as a part of suspended living or nonliving organic matter in water. The ratio of lead in suspended solids to lead in dissolved form has been found to vary from 4:1 in rural streams to 27:1 in urban streams (Getz et al. 1977).

The fate of lead in soil is affected by the specific or exchange adsorption at mineral interfaces, the precipitation of sparingly soluble solid forms of the compound, and the formation of relatively stable organic-metal complexes or chelates with soil organic matter. These processes are dependent on such factors as soil pH, soil type, particle size, organic matter content of soil, the presence of inorganic colloids and iron oxides, cation exchange capacity (CEC), and the amount of lead in soil (NSF 1977; Reddy et al. 1995; Royer et al. 1992). Soil samples were extracted from the Powder River Basin in Wyoming to determine the relative distribution and chemical forms of lead and other metals in acidic environments (Reddy et al. 1995). As pH increased, the dissolved concentration of lead increased and then decreased. At near neutral pH, dissolved organic carbon-lead complexes were the predominant species in the soil water extracts. At low pH, the lead ionic form (Pb^{2+}) and ion pairs (e.g., $PbSO_4^0$) were predominant. It was also concluded that the availability and mobility of lead will increase in low pH environments due to the chemical form in which the metal is present in the soil solutions. The accumulation of lead in most soils is primarily a function of the rate of deposition from the atmosphere. Most lead is retained strongly in soil, and very little is transported into surface water or groundwater (EPA 1986a; NSF 1977). Clays, silts, iron and manganese oxides, and soil organic matter can bind metals electrostatically (cation exchange) as well as chemically (specific adsorption) (Reed et al. 1995). Lead is strongly sorbed to organic matter in soil, and although not subject to leaching, it may enter surface waters as a result of erosion of lead-containing soil particulates. Lead bromochloride, the primary form of lead emitted from motor vehicles which once burned

leaded gasoline in the presence of organohalogen scavenger compounds, may be converted to the less soluble lead sulfate either by reactions in the atmosphere or by reactions at the soil surface. It has been determined that lead oxides, carbonates, oxycarbonates, sulfates, and oxysulfates become the most prominent constituents of aged automobile exhaust particles (i.e., those collected at locations more remote from traffic sources) (Ter Haar and Bayard 1971). Lead may also be immobilized by ion exchange with hydrous oxides or clays or by chelation with humic or fulvic acids in the soil (Olson and Skogerboe 1975). In soils with pH of $5 and with at least 5% organic matter content, atmospheric lead is retained in the upper 2–5 cm of undisturbed soil. Inorganic lead may be bound into crystalline matrices of rocks and remain essentially immobile; it can also be entrapped in the immobile water surrounding soil macro- and micropores (Reed et al. 1995). Lead complexes and precipitates in soil and their transformation depend on the soil type. In soil with a high organic matter content and a pH of 6–8, lead may form insoluble organic lead complexes; if the soil has less organic matter at the same pH, hydrous lead oxide complexes may form or lead may precipitate out with carbonate or phosphate ions. At a pH of 4–6, the organic lead complexes become soluble and leach out or may be taken up by plants (EPA 1986a). Entrainment or suspension of soil particles in moving air is another route of lead transport (EPA 1982f). This process may be important in contributing to the atmospheric burden of lead around some lead smelting facilities and NPL sites that contain elevated levels of lead in soil.

The downward movement of elemental lead and inorganic lead compounds from soil to groundwater by leaching is very slow under most natural conditions except for highly acidic situations (NSF 1977). The conditions that induce leaching are the presence of lead in soil at concentrations that either approach or exceed the cation exchange capacity (CEC) of the soil, the presence of materials in soil that are capable of forming soluble chelates with lead, and a decrease in the pH of the leaching solution (for example, acid rain) (NSF 1977). Partial favorable conditions for leaching may be present in some soils near lead smelting and NPL sites. Leaching of soluble lead from contaminated soils into groundwater may be minimized by the presence of lead carbonate in the soil and by maintaining a soil pH of 8–10 (Mundell et al. 1989). Tetraalkyl lead compounds, such as tetraethyl lead, are considered insoluble in water. In an aqueous media, tetraalkyl lead compounds are first degraded to their respective ionic trialkyl lead species and are eventually mineralized to inorganic lead (Pb^{2+}) by biological and chemical degradation processes (Ou et al. 1995). Tetraethyl lead can be transported through a soil column when it is present in a migrating plume of gasoline (Mansell et al. 1995).

Plants and animals may bioconcentrate lead but biomagnification has not been detected. In general, the highest lead concentrations are found in aquatic and terrestrial organisms that live near lead mining, smelting, and refining facilities; storage battery recycling plants; areas affected by high automobile and truck traffic; sewage sludge and spoil disposal areas; sites where dredging has occurred; areas of heavy hunting (lead source from spent shot); and in urban and industrialized areas. Lead may be present on plant surfaces as a result of atmospheric deposition; its presence in internal plant tissues indicates biological uptake from the soil and leaf surfaces. Although the bioavailability of lead in soil to plants is limited because of the strong absorption of lead to soil organic matter, the bioavailability increases as the pH and the organic matter content of the soil are reduced. Lead is not biomagnified in aquatic or terrestrial food chains. It may contaminate terrestrial plants as a result of atmospheric deposition and uptake from soil, and animals as a result of inhalation of contaminated ambient air or ingestion of contaminated plants. Older organisms tend to contain the greatest body burdens of lead. In aquatic organisms, lead concentrations are usually highest in benthic organisms and algae, and lowest in upper trophic level predators (e.g., carnivorous fish). Exposure of a freshwater fish to several sublethal concentrations of lead for a period of 30 days showed significant accumulation of lead in the blood and tissues. The lead accumulation in tissues was found to increase with lead in water up to a concentration of 5 mg/L (µg/mL); at concentrations of 10 and 20 mg/L, the lead accumulation in the tissues, although indicating an increase, was not proportional to the lead concentration in water (Tulasi et al. 1992). High bioconcentration factors (BCFs) were determined in studies using oysters (6,600 for *Crassostrea virginica*), freshwater algae (92,000 for *Senenastrum capricornutum*) and rainbow trout (726 for *Salmo gairdneri*). However, most median BCF values for aquatic biota are significantly lower: 42 for fish, 536 for oysters, 500 for insects, 725 for algae, and 2,570 for mussels (Eisler 1988). Lead is toxic to all aquatic biota, and organisms higher on the food chain may experience lead poisoning as a result of eating lead-contaminated food. Organolead compounds, such as trialkyl and tetraalkyl lead compounds, are more toxic than inorganic forms and have been shown to bioconcentrate in aquatic organisms. Biomagnification of organolead compounds has not been shown and depuration is relatively rapid, with half-life values of 30–45 hours for rainbow trout exposed to tetramethyl lead. Tetraalkyl lead compounds are more toxic than trialkyl lead compounds, and ethyl forms are more toxic than methyl forms (Eisler 1988). Isolation of a *Pseudomonas aeruginosa* strain designated CHL004 which is able to remove lead from solidified media and soil has been reported (Vesper et al. 1996). The rate of uptake of lead nitrate by CHL004 was very rapid initially and then decreased greatly.

Lead may be taken up in edible plants from the soil via the root system, by direct foliar uptake and translocation within the plant, and by surface deposition of particulate matter. The amount of lead in soil that is bioavailable to a vegetable plant depends on factors such as cation exchange capacity, pH, amount of organic matter present, soil moisture content, and the type of amendments added to the soil. Background agricultural soil lead concentrations for major growing areas of the United States have been determined (Holmgren et al. 1993).

Concentrations of lead (wet weight basis) in samples of eleven raw edible plants have been reported for growing areas in the United States that are uncontaminated by human activities other than normal agricultural practices (Wolnik et al. 1983a, 1983b). Results are as follows: plant (mean µg/g wet weight); lettuce (0.013); peanut (0.010); potato (0.009); soybean (0.042); sweet corn (0.0033); wheat (0.037); field corn (0.022); onion (0.005); rice (0.007); spinach (0.045); tomato (0.002).

The influence of various combinations of soil amendments on lead uptake by soybeans was studied for a metal-contaminated alluvial soil (Pierzynski and Schwab 1993). Addition of limestone was found to be most effective in reducing the bioavailability of metals (including lead) as indicated by the reduction in labile soil metals, increased yields, and decreased soybean tissue metal content. Uptake of metals by lettuce and radishes grown in a loam soil spiked with cadmium chloride and lead nitrate (from 100 to 1000 mg/kg) was also studied (Nwosu et al. 1995). Results indicated that the mean uptake of lead by lettuce increased as the concentration of lead rose in the soil mixture. However, the uptake was small and this finding is inconsistent with other reports. Lead was not bioaccumulated by either plant regardless of soil lead concentrations. The response of kidney bean growth to the concentration and chemical form of lead in soils obtained near a zinc smelter in Japan has been studied (Xian 1989). It was found that the amount of lead in the total plant (approximately 35 to 80 µg) correlated strongly with the concentration of lead in the soil (0 to 240 mg/kg). The best relationship was found between the amount of metal uptake and the concentration of exchangeable and carbonate forms of lead in the soil.

Other factors such as absorption of lead from cooking water and cookware can influence the amount of lead in cooked vegetables. The degree to which lead is released from plant tissue once the vegetable or fruit is consumed also influences a person’s uptake of lead.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Information available regarding the chemistry of lead in air is limited. Before the ban on sales of leaded gasoline, lead particles were emitted to the atmosphere from automobiles as lead halides (mostly PbBrCl) and as double salts with ammonium halides (e.g., $2PbBrCl \cdot NH_4Cl$, $Pb_3[PO_4]_2$, and $PbSO_4$ [Biggins and Harrison 1979; Ter Haar and Bayard 1971]). After 18 hours, approximately 75% of the bromine and 30–40% of the chlorine disappeared, and lead carbonates, oxycarbonates and oxides were produced. These lead oxides are subject to further weathering to form additional carbonates and sulfates (Olson and Skogerboe 1975). Lead particles are emitted from mines and smelters primarily in the form of the lead-sulfur compounds, $PbSO_4$, $PbO \cdot PbSO_4$, and PbS (EPA 1986a). In the atmosphere, lead exists primarily in the form of $PbSO_4$ and $PbCO_3$. It is not completely clear how the chemical composition of lead changes during dispersion (EPA 1986a). Monitoring studies indicate that tetraalkyl lead, at one time present in both urban and rural air, may react with hydroxyl ions to form ionic trialkyl and dialkyl species that are more stable in the atmosphere. Urban air in England that is advected to rural areas may contain up to 5% of the total lead as alkyl lead; this percentage may increase to 20% for maritime air, with trialkyl lead being the predominant species (Hewitt and Harrison 1987).

Tetraalkyl lead compounds, once added to gasoline, are no longer present in significant quantities in the air. However, their degradation products are still present. Based on the vapor pressure of tetraethyl lead (0.26 mm Hg at 20 EC) and tetramethyl lead (26.0 mm Hg at 20 EC), these two compounds exist almost entirely in the vapor phase in the atmosphere (Eisenreich et al. 1981). When exposed to sunlight, they decompose rapidly to trialkyl and dialkyl lead compounds, and eventually to inorganic lead oxides by a combination of direct photolysis, reaction with hydroxyl radicals, and reaction with ozone. The half-life of tetraethyl lead in summer atmospheres is approximately 2 hours, and the half-life for tetramethyl lead is about 9 hours. In the winter, both compounds have half-lives of up to several days (DeJonghe and Adams 1986). Trialkyl compounds occur almost entirely in the vapor phase, and dialkyl compounds occur almost entirely in particulate form. Because of the relatively high water solubility of trialkyl and dialkyl lead compounds, washout in wet deposition was probably a major process for removing these compounds from air. In addition, the dialkyl lead compounds were significantly removed by dry deposition. Adsorption of tetraethyl and tetramethyl lead to atmospheric particles does not appear to be an important fate process (DeJonghe and Adams 1986; EPA 1985a).

5.3.2.2 Water

The chemistry of lead in aqueous solution is highly complex because this element can be found in a multiplicity of forms. Lead has a tendency to form compounds of low solubility with the major anions found in natural waters. The amount of lead in surface waters is dependent on the pH and the dissolved salt content of the water. The dissolved salt content, in turn, is dependent on the pH and the partial pressure of CO_2 as well as the water temperature. In the environment, the divalent form (Pb^{2+}) is the stable ionic species of lead. Hydroxide, carbonate, sulfide, and, more rarely, sulfate may act as solubility controls in precipitating lead from water. At a pH <5.4, lead sulfate limits the concentration of lead in solution, while at a pH >5.4, lead carbonates limit the lead concentrations (EPA 1979d). The relatively volatile organolead compound, tetramethyl lead, may form as a result of biological alkylation of organic and inorganic lead compounds by microorganisms in anaerobic lake sediments; however, if the water over the sediments is aerobic, volatilization of tetramethyl lead from the sediments is not considered to be important because the tetramethyl lead will be oxidized (EPA 1979d).

In water, tetraalkyl lead compounds are subject to photolysis and volatilization with the more volatile compounds being lost by evaporation. Degradation proceeds from trialkyl lead to dialkyl lead to inorganic lead. Tetraethyl lead is susceptible to photolytic decomposition in water. Triethyl and trimethyl lead are more water-soluble and therefore more persistent in the aquatic environment than tetraethyl or tetramethyl lead. The degradation of trialkyl lead compounds yields small amounts of dialkyl lead compounds. Removal of tetraalkyl lead compounds from seawater occurs at rates that provide half-lives measurable in days (DeJonghe and Adams 1986).

5.3.2.3 Sediment and Soil

Lead in its naturally-occurring mineral forms is a very minor component of many soils in the United States. Additional lead is added through processes such as wet and dry deposition from the atmosphere and via surface water flows. Now that lead in gasoline is banned, the major sources on the national level are industrial processes (58% of total estimated emissions in 1995) (EPA 1996h). Smelters in Pennsylvania, Missouri, and Nebraska are among the top 10 emitters. Lead particles emitted from mining operations and smelters are primarily in the form of lead-sulfur compounds $PbSO_4$, $PbO \cdot PbSO_4$, and PbS (EPA 1986a). In the atmosphere, lead probably exists primarily in the form of $PbSO_4$ and $PbCO_3$ and impacts the soil in this form. Organic tetraalkyl lead compounds, once used extensively in motor fuel, are emitted from

automobiles primarily in the form of lead bromochloride. The organolead compounds undergo photolysis and other reactions in the atmosphere to form lead carbonates, oxycarbonates, and oxides. Once these compounds encounter components of the soil, further reactions can occur to produce lead sulfate. Divalent lead ion also has a strong affinity for humic acids in soil and thus usually combines to form stable Pb-organic complexes.

Now that lead additives in motor fuels for highway use are banned, emissions of lead from this source have diminished to very low levels. However, the deposited organolead compounds and their transformation products are still in the soil. Limited data indicate that tetraethyl and tetramethyl lead are converted into water-soluble lead compounds in soil. Although tetraethyl and tetramethyl lead are not expected to leach significantly through soil, their highly water-soluble metabolites, the trialkyl lead oxides, may be subject to leaching (EPA 1985a). Recent laboratory studies have sought to explain how chemical degradation and biological metabolism of two ionic ethyl-lead species, triethyllead and diethyllead, occur in soil (Ou et al. 1995).

In a study of lead migration in forest soils in Vermont, Miller and Friedland (1994) used lead deposition time series and measurements of organic soil horizon lead content made in 1966, 1980, and 1990 to compute dynamic response times for lead storage in several types of soil. The authors concluded that maximum lead concentrations in organic soil occurred around 1980, with concentrations of about 85 μg/g in soils of the northern hardwood forests of the study area and about 200 μg/g in soils of the spruce-fir forests. The large surge of atmospheric lead deposited in these forests during the time when leaded gasoline was routinely used in motor vehicles is being redistributed in the soil profile rather than being retained in the organic horizon. Based on an analysis of lead transit times through mineral soil horizons, the pulse of lead may begin to be released to upland streams sometime in the middle of the next century (Miller and Friedland 1994).

Many plants commonly take up lead from soil, and lead will eventually be returned to soil when these plants decay unless they are harvested (to possibly enter the food chain) or removed (EPA 1986a).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to lead depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on lead

levels monitored or estimated in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable.

5.4.1 Air

Lead levels in the ambient air have been monitored in a number of remote, urban, and nonurban areas of the United States and other countries (EPA 1986a). Atmospheric lead concentrations vary widely but usually decrease with vertical and horizontal distance from emission sources; they are generally 0.3–0.8 times lower indoors than outdoors, with an average ratio of 0.5. Levels of lead in ambient air range from $7.6x10^{-5}$ μg/m^3 in remote areas such as Antarctica (Maenhaut et al. 1979) to >10 μg/m^3 near stationary sources such as smelters, with an average annual concentration of below 1.0 μg/m^3 for urban monitoring sites. Monitoring data from a composite of 147 sampling sites throughout the United States indicate that the maximum quarterly average lead levels in urban air were 0.36 μg/m^3 during 1984 and 0.2–0.4 μg/m^3 during 1986 (EPA 1988f, 1989h). Between 1979 and 1983, atmospheric lead concentrations in precipitation in Minnesota decreased from 29 to 4.3 μg/L at urban locations and from 5.7 to 1.5 μg/L at rural locations, indicating a reduction in lead emissions of more than 80%. This reduction resulted primarily from the decreased use of leaded gasoline (down 56%) and the use of more efficient emission controls on other sources (Eisenreich et al. 1986).

Since 1979, elemental concentrations of fine particles have been monitored in remote areas of the United States in networks operated for the National Park Service (NPS) and the EPA (Eldred and Cahill 1994). Lead at all sites decreased sharply through 1986, corresponding to the shift to unleaded gasoline, but has since leveled off at 1–2 ng/m^3 (0.001–0.002 μg/m^3), which is approximately 18% of the 1982 mean. The elevated lead concentrations (up to 5 ng/m^3) since 1986 at three of the twelve sites are probably associated with mining activity.

In the 1960s, the National Air Surveillance Network (NASN) was established to monitor ambient air quality levels of total particulate solids and trace metals, including lead, at sites in larger American cities. In 1981 some old sites were eliminated and new ones were added to give 139 urban sites for air monitoring purposes. In 1988, the average lead concentration for all 139 sites was 0.085 μg/m^3, well below the National Ambient Air Quality Standard of 1.5 μg/m^3, quarterly average concentration, that has been established for lead (EPA 1996h). In 1988, the average concentration of 18 point-source sites was 0.4 μg/m^3, down from 2.9 μg/m^3 in 1979, and the average concentration for urban sites was 0.1 μg/m^3,

down from 0.8 μg/m^3 in 1979 (EPA 1990c). This decrease was undoubtedly caused by decreased use of leaded gasolines in the period leading up to its total ban after December 1995. Composite urban air measurements of lead for 1989 and 1991 were 0.11 and 0.08 μg/m^3 (EPA 1996h). Although urban lead concentrations in air continue to decline, there are indications that the rate of decline has slowed. Between 1976 and 1995, ambient concentrations of lead in the United States declined by 97%. Between 1994 and 1995, national average lead concentrations remained unchanged at 0.04 μg/m^3 even though lead emissions declined 1% (EPA 1996h).

5.4.2 Water

Lead has been monitored in surface water, groundwater, and drinking water throughout the United States and other countries. The concentration of lead in surface water is highly variable depending upon sources of pollution, lead content of sediments, and characteristics of the system (pH, temperature, etc.). Levels of lead in surface water and groundwater throughout the United States typically range between 5 and 30 μg/L, although levels as high as 890 μg/L have been measured (EPA 1986a). Mean levels of lead in surface water measured at 50,000 surface water stations throughout the United States are 3.9 μg/L (based on 39,490 occurrences) (Eckel and Jacob 1988). Lead is estimated to be present in sea water at approximately 0.005 μg/L (EPA 1982f). Lead concentrations in surface water are higher in urban areas than in rural areas (EPA 1982f).

Based on a survey of 900 public water supply systems, EPA (1988b) estimated that 99% of the 219 million people in the United States using public water supplies are exposed to drinking water with levels of lead <5 μg/L and approximately 2 million people are served by drinking water with levels of lead greater than 5 μg/L. A survey of 580 cities in 47 states indicated that the national mean concentration of lead in drinking water was 29 μg/L after a 30-second flushing period (EPA 1988f, 1989h); however, it was estimated that in 1988 the average lead content of drinking water was 17 μg/L (Cohen 1988b). In 1986, the Safe Drinking Water Act Amendments banned the use of lead solder or flux containing more than 0.2% lead and the use of lead pipes or fittings that contained more than 8% lead (EPA 1988f, 1989h).

In a more recent Federal Register notice (EPA 1991d), EPA examined the occurrences of lead in source water and distributed water. By resampling at the entry point to the distribution system, few samples were found to contain lead at levels above 5 μg/L. EPA now estimates that approximately 600 groundwater systems may have water leaving the treatment plant with lead levels above 5 μg/L. Based on several data

sets, it is estimated that less than 1% of the public water systems in the United States have water entering the distribution system with lead levels above 5 µg/L. These systems are estimated to serve less than 3% of the population that receives drinking water from public systems (EPA 1991d).

Lead levels ranging between 10 and 30 µg/L can be found in drinking water from households, schools, and office buildings as a result of plumbing corrosion and subsequent leaching of lead. The combination of corrosive water and lead pipes or lead-soldered joints in either the distribution system or individual houses can create localized zones of high lead concentrations that exceed 500 µg/L (EPA 1989f).

Quantitative data on the nationwide range of lead levels in drinking water drawn from the tap (which would include lead corrosion by-product) were insufficient to assign a national value at the time of the 1991 EPA publication. One set of data comprised of 782 samples taken in 58 cities in 47 states shows that the average lead level in tap water was 13 µg/L with 90% of the values below 33 µg/L (EPA 1991d).

According to EPA's National Compliance Report for calendar year 1996 (EPA 1998g), the vast majority of people in the nation received water from systems that had no reported violations of the maximum contaminant level and treatment technique requirements or significant monitoring and reporting requirements. Lead has a maximum permissible level of 15 µg/L delivered to any user of a public water system. Lead and copper are regulated in a treatment technique that requires systems to take tap water samples at sites with lead pipes or copper pipes that have lead solder and/or are served by lead service lines. The water system is required to take treatment steps if the action level (15 µg/L for lead) is exceeded in more than 10% of tap water samples. For calendar year 1996, nearly 6 million people in the United States were served by community water systems that reported maximum contaminant level and treatment technique violations of the Lead and Copper Rule (EPA 1998g).

A survey of 1,484 drinking water samples taken from various districts of the American Water Works Service Company showed that average lead levels in a 1-L first-draw sample for copper, galvanized, and plastic pipes were 9, 4.2, and 4.5 µg/L, respectively. These data show that even plumbing that did not use lead solder for copper pipes (e.g., plastic pipes) contained significant levels of lead, primarily from the brass faucet fixtures which are used in almost all plumbing. The brass fixtures may account for approximately one-third of the lead in the first-draw water (Lee et al. 1989). Lead levels are also known to increase when tap water is heated in boiling kettles that contain lead in their heating elements.

Concentrations of lead in water at NPL sites can be at much higher levels. For example, in 1986, an NPL hazardous waste site was identified in Genesee County, Michigan, that contained a landfill and nine surface impoundments. The facility had accepted sludge and residual waste from a chemical warehouse as well as other hazardous wastes. Water samples taken from the impoundments had a maximum lead concentration of 25 mg/L (EPA 1986d).

5.4.3 Sediment and Soil

Sediments contain considerably higher levels of lead than corresponding surface waters. Concentrations of lead in river sediments have been estimated at about 23 mg/kg (EPA 1982f; Fitchko and Hutcheson 1975), and concentrations of lead in coastal sediments range from 1 mg/kg to 912 mg/kg with a mean value of 87 mg/kg (EPA 1982f; Nriagu 1978). Data from the STORET (1973–1979) database of Eastern and Midwestern river basins indicates maximum lead concentrations in river sediments of 440–1,000 mg/kg, and mean lead concentrations of 27–267 mg/kg (EPA 1980, 1982f). Surface sediment concentrations in Puget Sound ranged from 13 µg/g to 53 µg/g (Bloom and Crecelius 1987). An analysis of sediments taken from 10 lakes in Pennsylvania indicated that the elevated lead values were not derived from leaching of lead from the native rocks as a result of acid deposition, but rather originated from anthropogenic lead deposition (probably from automotive emissions) on the soil surface and subsequent runoff of soil particulates into the lake (Case et al. 1989).

The natural lead content of soil derived from crustal rock, mostly as galena (PbS), typically ranges from <10 to 30 µg/g soil. However, the concentration of lead in the top layers of soil varies widely due to deposition and accumulation of atmospheric particulates from anthropogenic sources. The concentration of soil lead generally decreases as distance from contaminating sources increases. The estimated lead levels in the upper layer of soil beside roadways are typically 30–2,000 µg/g higher than natural levels, although these levels drop exponentially up to 25 m from the roadway (EPA 1986a). Soil adjacent to a smelter in Missouri had lead levels in excess of 60,000 µg/g (Palmer and Kucera 1980). Soils adjacent to houses with exterior lead-based paints may have lead levels of >10,000 µg/g (EPA 1986a). As a result of lead reactions with the soil, extractable lead in surface soil samples (0–5 cm depth) from an agricultural area near a car battery manufacturing plant (taken at 0.3 km from the source) decreased from 117 µg/g

to 1 µg/g within 1 year after the plant stopped operating (Schalscha et al. 1987). Soil collected by scraping the top 2.5 cm of soil surface near homes and streetside in Louisiana and Minnesota contained median lead concentrations of greater than 840 µg/g in New Orleans and 265 µg/g in Minneapolis. In contrast, the small towns of Natchitoches, Louisiana, and Rochester, Minnesota, had soil lead concentrations of less than 50 µg/g and 58 µg/g, respectively. These data suggest that lead-contaminated soil is a major source of lead exposure in urban areas (Mielke 1992).

Studies carried out in Maryland and Minnesota indicate that within large light-industrial urban settings such as Baltimore, the highest soil lead levels generally occur in inner-city areas, especially where high traffic flows have long prevailed (Mielke et al. 1983, 1985, 1989) and that the amount of lead in the soil is correlated with the size of the city (Mielke 1991). In 1981, soil lead levels in the Minneapolis/St. Paul inner-city area were 60 times higher (423 µg/g) than levels found in rural Minnesota (6.7 µg/g), with almost all the increase (95%) resulting from the combustion of leaded gasoline. A study conducted in Minneapolis, Minnesota, after the lead content of gasoline has been significantly reduced, found that median soil lead levels taken from the foundations of homes, in yards, and adjacent to the street were 700 µg/g, 210 µg/g, and 160 µg/g, respectively; median soil lead concentrations in comparable samples from the smaller city of Rochester, Minnesota, did not exceed 100 µg/g at any location tested (Mielke et al. 1989). The Minneapolis data showed that average lead levels were elevated in soil samples taken from the foundations of homes, but that lead levels were low (<50 µg/g) in areas where children could be expected to play, such as parks that were located away from traffic but were higher in play areas around private residences. Soil samples taken from around the foundations of homes with painted exteriors had the highest lead levels (mean concentrations of 522 µg/g) but levels around homes composed of brick or stucco were significantly lower (mean concentration 158 µg/g) (Schmitt et al. 1988). Severely contaminated soils (levels #20,136 µg/g) were located near house foundations adjacent to private dwellings with exterior lead-based paint. Elevated soil lead concentrations were found in larger urban areas with 27, 26, 32, and 42% of the soil samples exceeding 300 µg/g lead in Duluth, inner-city North Minneapolis, inner-city St. Paul, and inner-city South Minneapolis, respectively. Only 5% of the soil samples taken from the smaller urban areas of Rochester and St. Cloud, Minnesota, had lead levels in excess of 150 µg/g. It has been suggested that the higher lead levels associated with soils taken from around painted homes in the inner city are the result of greater atmospheric lead content, resulting from the burning of leaded gasoline in cars and the washdown of building surfaces to which the small lead particles adhere by rain (Mielke et al. 1989). A

state-wide Minnesota study concluded that exterior lead-based paint was the major source of contamination in severely contaminated soils located near the foundations of private residences and that aerosol lead accounted for virtually all of the contamination found in soils removed from the influence of lead-based paint. Contamination due to lead-based paint was found to be highly concentrated over a limited area, while contamination due to aerosol lead was found to be less concentrated but more widespread (Minnesota Pollution Control Agency 1987).

In a study of associations between soil lead levels (PbSs) and childhood PbB levels in urban New Orleans and rural Lafourche Parish in Louisiana, childhood PbB levels appeared more closely associated with PbS than with age of housing. In the study, over 2,600 PbS and 6,000 PbB samples were paired by their median values and pre-1940 housing percentages for 172 census tracts. Census tracts with low median PbS were associated with new housing, but census tracts with high median PbS were split evenly between old and new housing. The same pattern was also observed for childhood PbB levels. High PbS was associated with high PbB, and low PbS was associated with low PbB. Risk factors for lead exposure were found to be low in Lafourche Parish, where there was no census tract in which median PbB was above 9 µg/dL and no indication of a statistical association between median PbB and either median PbS or age of housing (Mielke et al. 1997).

In the state of Maine, soil samples taken from areas of high risk (within 1–2 feet of a foundation of a building more than 30 years old) indicated that 37% of the samples had high lead concentrations (>1,000 µg/g). In 44% of the private dwellings, high lead levels were found in the soil adjacent to the foundation; high levels were found in only 10% of the public locations (playgrounds, parks, etc.). In addition, the largest percentage (54%) of highly contaminated soil was found surrounding homes built prior to 1950; homes built after 1978 did not have any lead contamination in the soil (Krueger and Duguay 1989).

In environmental health studies conducted near four NPL sites (plus a comparison area for each), ATSDR collected lead concentration data from both environmental media and human body fluids to estimate low-level exposure risk and to document the magnitude of human exposure to lead near those sites. Environmental samples collected at participants' homes included drinking water, yard soil, house dust, and house paint; body fluids collected from participants included venous blood and urine specimens. For the four sites, mean concentrations of lead in soil ranged from 317 to 529 mg/kg, and mean concentrations of lead in dust ranged from 206 to 469 mg/kg (ATSDR 1995).

In 1972, household dust samples taken near nonferrous ore smelters in El Paso, Texas, which were known to emit 1,012 metric tons of lead per year, had lead levels of 22,191 µg/g (geometric mean) and 973 µg/g at distances from the smelter of 1.6 km and 6.4 km, respectively (Landrigan and Baker 1981).

Lead was measured in soil from a port facility where galena ore concentrate and smelter dross arriving by rail were offloaded, stored, and reloaded onto seagoing vessels from 1974 through 1985. The lead concentrations ranged from 1,900 to 183,000 mg/kg (µg/g) (Ruby et al. 1994).

In 1986, an NPL hazardous waste site that contained a landfill and nine surface impoundments was identified in Genesee County, Michigan. The facility had accepted sludge and residual waste from a chemical warehouse as well as other hazardous wastes. Lead was present in sludge samples taken from the impoundments at a maximum concentration of 11.6 mg/L, in sediment samples at a maximum concentration of 4,770 mg/kg dry weight, and in soil samples at 1,560 mg/kg (EPA 1986d). Thirty of 97 soil samples taken at a former foundry site in Dubuque, Iowa, which was on the NPL, had lead concentrations exceeding 5.0 mg/L as determined using the extraction procedure (EP) toxicity test (the maximum total lead concentration was 4,890 mg/kg). Most of the positive samples were from soil depths of less than 2.5 feet (Mundell et al. 1989).

5.4.4 Paint

Weathering of lead-based paint can contribute to the lead content of dust and soil. A 1974 study indicated that elevated PbB levels in children were most likely a result of ingesting lead-contaminated soil, and that the most likely source was lead-based paint rather than lead from automotive exhaust (Ter Haar and Aronow 1974). A state-wide Minnesota study concluded that exterior lead-based paint was the major source of contamination in severely contaminated soils located near the foundations of private residences (Minnesota Pollution Control Agency 1987). A soil lead study in Minneapolis, Minnesota, found that soil samples taken from around the foundations of homes with painted exteriors had a mean concentration of 522 µg/g while soil samples taken from around the foundations of brick or stucco had a mean concentration of 158 µg/g (Schmitt et al. 1988). Lead-based paint, removed from surfaces by burning (gas torch or hot air gun), scraping, or sanding have been found to result, at least temporarily, in higher levels of exposure for families residing in these homes.

5.4.5 Other Sources

Lead has been detected in a variety of foods. Typical concentrations of lead in various foods are (EPA 1986a):

Food group	Concentration (µg/g)
Dairy products	0.003–0.083
Meat, fish, and poultry	0.002–0.159
Grain and cereal products	0.002–0.136
Vegetables	0.005–0.649
Fruit and fruit juices	0.005–0.223
Oils, fats, and shortenings	0.002–0.028
Sugar and adjuncts	0.006–0.073
Beverages	0.002–0.041 (µg/L)

Canning foods in lead-soldered cans may increase levels of lead 8–10-fold; however, the impact of canning appears to be decreasing as a result of a decrease in the use of lead-soldered cans. The use of three-piece lead-soldered cans ceased in 1991; however, older lead-soldered cans may still be present in some households. In 1974, for example, the lead level in evaporated milk in lead-soldered cans was 0.12 µg/g; in 1986, after these cans were phased out, the lead level in evaporated milk dropped to 0.006 µg/g (Capar and Rigsby 1989). The lead content in canned foods dropped from an overall mean of 0.31 ppm in 1980 to 0.04 ppm in 1988 (NFPA 1992). A 1982 Canadian study found average lead concentrations in dairy milk of 0.00112 µg/g and lead levels in various infant formulas that ranged from 0.0026 µg/g for bottled water to 0.0737 µg/g in infant formula powders (Dabeka and McKenzie 1987). Additional exposure to lead through dietary intake by people living in an urban environment is estimated to be approximately 28 µg/day for adults and 91 µg/day for children, all of which can be attributed to atmospheric lead (dust). Atmospheric lead may be added to food crops in the field or garden (through uptake from soil and from direct deposition onto crop surfaces), during transport to market, processing, and kitchen preparation (EPA 1986a).

The U.S. Fish and Wildlife Service reported on the concentration of metals in a total of 315 composite samples of whole fish sampled from 109 stations nationwide from late 1994 to early 1985. For lead, the geometric mean, maximum, and 85th percentile concentrations (µg/g wet weight) were 0.11, 4.88, and 0.22. The mean concentration of lead was significantly lower than in the 1980–1981 survey. Lead concentrations in fish have declined steadily from 1976 to 1984, suggesting that reductions of leaded gasoline and controls

on mining and industrial discharges have reduced lead in the aquatic environment (Schmitt and Brumbaugh 1990).

In order to reduce lead exposure from consumption of lead-contaminated fish and shellfish, consumption advisories are issued by states recommending that individuals restrict their consumption of specific fish and shellfish species from certain waterbodies where lead concentrations in fish and shellfish tissues exceed the human health level of concern. This level of concern is set by individual state agencies and used to issue advisories recommending no consumption, or restricted consumption, of contaminated fish and shellfish from certain waterbody types (e.g., lakes and/or rivers). In 1995, the EPA Office of Water issued guidance to states on sampling and analysis procedures to use in assessing the health risks from consuming locally caught fish and shellfish. The risk assessment method proposed by EPA was specifically designed to assist states in developing fish consumption advisories for recreational and subsistence fishers (EPA 1995b). These two groups within the general population consume larger quantities of fish and shellfish than the general population and frequently fish the same waterbodies routinely. Because of this, these populations are at greater risk of exposure to lead and other chemical contaminants if the waters they fish are contaminated. In 1997, 10 advisories restricting the consumption of lead-contaminated fish and shellfish were in effect in 5 states (2 in Missouri, 4 in Ohio, 1 in Louisiana, 1 in Tennessee (rescinded), and 1 in Hawaii) and 1 territory (1 in American Samoa) (EPA 1998).

Elevated levels of lead in the blood of cattle grazing near a lead smelter have been reported, although no implications regarding lead in beef were made. The mean lead levels for the herd were highest near the smelter and decreased with distance. Ingestion of soil along with the forage was thought to be a large source of additional metal (Neuman and Dollhopf 1992). Evidence has also been shown for transfer of lead to milk and edible tissue in cattle poisoned by licking the remains of storage batteries burned and left in a pasture (Oskarsson et al. 1992). Levels of lead in muscle of acutely sick cows which were slaughtered ranged from 0.23 to 0.5 mg/kg (wet weight basis). Normal lead levels in bovine meat from Swedish farms are <0.005 mg/kg. For eight cows that were less exposed, levels of lead in milk taken 2 weeks after the exposure were 0.08±0.04 mg/kg. The highest lead level found in the milk of eight cows studied for 18 weeks was 0.22 mg/kg. Lead in most milk samples decreased to values <0.03 mg/kg 6 weeks after exposure. Two affected cows delivered a calf at 35 and 38 weeks after the exposure. There was a high lead level in the blood of the cows at the time of delivery, which suggests mobilization of lead in connection with the latter stages of gestation and delivery. Lead levels in colostrum were increased as compared to

mature milk samples taken 18 weeks after exposure. The concentration of lead in milk produced after delivery decreased rapidly with time and was almost down to the limit of detection in mature milk.

Many non-Western folk remedies used to treat diarrhea or other ailments may contain substantial amounts of lead. Examples of these include: Alarcon, Ghasard, Alkohl, Greta, Azarcon, Liga, Bali Goli, Pay-loo-ah, Coral, and Rueda. In addition, an adult case of lead poisoning was recently attributed to an Asian remedy for menstrual cramps known as Koo Sar. The pills contained lead at levels as high as 12 ppm (CDC 1998). The source of the lead was thought to be in the red dye used to color the pills.

Tamarindo jellied fruit candy from Mexico, and lozeena, a bright orange powder from Iraq used to color rice and meat, have been implicated in lead poisoning (CDC 1998). The lozeena, containing 7.8–8.9% lead, was purchased in Iraq and brought into the United States. Tamarindo candy and jam products, restricted from importation into the United States since 1993, were purchased by a woman visiting her family in Mexico. Although no product was available for testing, several commercial retail lots of tamarindo and tejocote jellied fruit candy were embargoed by the state of California in 1993 because of high lead levels. The fruit candies were packaged in stoneware or ceramic jars. The lead-based glazing applied to the jars appeared to have been the major source of the lead, although some of the fruits from plastic-lined jars also contained substantial amounts of lead.

Lead may leach from lead crystal decanters and glasses into the liquids they contain. Port wine that contained an initial concentration of 89 µg/L lead was stored for 4 months in crystal decanters containing up to 32% lead oxide. At the end of 4 months lead concentrations in the port were 5,331, 3,061, and 2,162 µg/L in decanters containing 32%, 32%, and 24% lead oxide, respectively. Lead was also found to elute from lead crystal wine glasses within minutes. Mean lead concentrations in wine contained in 12 glasses rose from 33 µg/L initially to 68, 81, 92, and 99 µg/L after 1, 2, 3, and 4 hours, respectively (Graziano and Blum 1991).

Lead is also present in tobacco at concentrations of approximately 2.5–12.2 µg/cigarette, of which approximately 2–6% may actually be inhaled by the smoker (WHO 1977).

Hair dyes and some cosmetics may contain lead compounds (Cohen and Roe 1991). Hair dyes formulated with lead acetate may have lead concentrations 3 to 10 times the allowable concentration in paint. Measured lead concentrations of 2,300 to 6,000 µg of lead per gram of product have been reported (Mielke

et al. 1997b). Lead acetate is soluble in water and easily transferred to hands and other surfaces during and following application of a hair dye product. Measurements of 150–700 µg of lead on each hand following application have been reported (Mielke et al. 1997b). In addition to transfer of lead to the hand-to-mouth pathway of the person applying the product, lead is transferred to any other surface (comb, hair dryer, outside of product container, counter top, etc.) that comes into contact with the product. It is also on the hair it is applied to and the hands applying it. Objects coming into contact with hair dyed with a lead-containing product also become contaminated. A dry hand passed through dry hair dyed with a lead-containing product in cream form has been shown to pick up about 786 µg of lead. A dry hand passed through dry hair dyed using foam or liquid lead-containing hair dye products picked up less lead: 69 µg/hand for foam products and 73 µg/hand for liquid products (Mielke et al. 1997b).

Cases of lead poisoning have been related to less common sources of exposure. Illicit "moonshine" whiskey made in stills composed of lead-soldered parts (e.g., truck radiators) may contain high levels of lead. Detectable levels of lead with a maximum concentration of 5.3 mg/L were found in 7 of 12 samples of Georgia moonshine whiskey (Gerhardt et al. 1980). So-called recreational drug users who “sniff” leaded gasoline vapors are also at risk of reaction to organolead compounds as well as the hydrocarbon components of gasoline (Edminster and Bayer 1985). Use of lead ammunition may result in exposure to lead dust generated during gun or rifle discharge at levels up to 1,000 µg/m^3 (EPA 1985c), from lead pellets ingested or imbedded in animals that are used as food sources, and from lead pellets imbedded in humans from shooting incidents (Johnson and Mason 1984).

Lead poisoning has been caused by ingestion of a Chinese herbal medicine to which metallic lead was added to increase its weight and sales price (Wu et al. 1996). Lead contaminants also are present in some calcium supplements. Fourteen of 25 brands tested had lead ingestion rates greater than the provisional total tolerable daily intake of 6 µg. The highest found was 25.1 µg per day based on a calcium dosage of 1,000 mg, an amount commonly ingested by children (Bourgoin et al. 1993). A lead poisoning hazard for young children exists in imported vinyl miniblinds that have had lead added to stabilize the plastic. Over time, the plastic deteriorates to produce lead dust that can be ingested when the blinds are touched by children who then put their hands in their mouths (CPSC 1996). The U.S. Consumer Product Safety Commission (CPSC) has requested that manufacturers change the manufacturing process to eliminate the lead. As a consequence, vinyl miniblinds should now be lead-free. The CPSC recommends that consumers with young children remove old vinyl miniblinds from their homes and replace them with new miniblinds made without added lead or with alternative window coverings.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to lead is most likely to occur through the ingestion of contaminated food and drinking water, and by the inhalation of lead particulates in ambient air. Direct inhalation of lead accounts for only a small part of the total human exposure; however, lead that is adsorbed to soil may be inhaled as dust and reentrainment of lead-contaminated dust is common. Fruits, vegetables, and grains may contain levels of lead in excess of background levels as a result of plant uptake of lead from soils and direct deposition of lead onto plant surfaces (EPA 1986a). Between 1979 and 1989, lead-soldered food cans were virtually eliminated as a source of lead contamination of canned food. The CDC has concluded that the most common source of lead exposure for children (Section 5.6) is lead-based paint that has deteriorated into paint chips and lead dusts and that the most common sources of lead exposure for adults are occupational (CDC 1997b).

Those who use recreational shooting ranges may be exposed to lead and soluble lead compounds, such as carbonates and sulfates, in soil. Surface
lead concentrations at a range in Michigan were 10 to 100 times greater than background level of 25 mg/kg; mobilization of lead appeared to be occurring and may present a threat to ground and surface waters (Murray et al. 1997).

Exposure may also result from engaging in hobbies that use lead. For example, molten lead can be used in casting ammunition and making fishing weights or toy soldiers; leaded solder is used in making stained glass; leaded glazes and frits are used in making pottery; artists' paints may contain lead; lead compounds are used as coloring agents in glassblowing; and lead may be present in platinum printing and screen printing materials (Grabo 1997).

In 1982–1983, the baseline value for daily intake of lead by inhalation in a nonurban environment was estimated to be 0.5 µg/day for a 2-year-old child, 1.0 µg/day for an adult working indoors, and 2.0 µg/day for adults working outdoors; these figures are based on an average atmospheric lead concentration of 0.1 $\mu g/m^3$ and an indoor/outdoor lead concentration ratio of 0.5. In an urban environment, the indoor/outdoor ratio was assumed to be approximately 0.8, giving a lead exposure estimate of 1.0 $\mu g/m^3$ for adults assuming a 2-hour/day exposure to an outside lead concentration of 0.75 $\mu g/m^3$, a 20-hour/day exposure to an indoor lead concentration of 0.6 $\mu g/m^3$, a 2-hour/day exposure to 5 $\mu g/m^3$ in high traffic, and an average daily intake of air by an adult of 20 m^3. These estimates indicate that urban and nonurban residents inhaled approximately the same amount of lead dust (EPA 1986a). Drastic reductions in the lead content of

gasoline since 1986 have resulted in a 64% decrease in lead emissions to the atmosphere (see Section 5.4.1).

In 1991 the composite average concentration of lead in air at EPA National Air Monitoring Systems sites was 0.053 μg/m^3, the same as the "all sites" average. The average lead concentration at point-source oriented sites was 0.7 μg/m^3; the average urban site concentration in 1991 was 0.1 μg/m^3 (EPA 1992b). For 1991 data, if the indoor/outdoor ratio is again assumed to be 0.8 for urban atmospheres and the 2-hour exposure in high traffic of 5 μg/m^3 is replaced by 0.1 μg/m^3, then the average intake by an adult can be calculated as 20 hours at 0.08 μg/m^3 and 4 hours at 0.1 μg/m^3 for a weighted average intake of 0.083 μg/m^3, or 2 μg/day. This exposure is significantly lower than the 1.0 μg/m^3 estimated to be inhaled in an urban setting in 1982–1983 and is comparable to what an adult breathed in a rural setting in 1982–1983.

Between 1979 and 1989 there was a virtual elimination of the use of lead-soldered food cans, with a concomitant drop in lead levels in food. Average daily intakes of lead for adults, based on an analysis of 27 market basket samples taken nationwide for a 1980–1982 Total Diet Study, were as follows (Gartrell et al. 1986b):

Food group	Average adult intake (μg/day)
Dairy products	4.54
Meat, fish, and poultry	4.09
Grain and cereal products	9.84
Potatoes	1.39
Leafy vegetables	0.94
Legume vegetables	9.18
Root vegetables	1.39
Garden fruits	4.44
Fruits	10.00
Oils and fats	1.23
Sugar and adjuncts	2.34
Beverages	6.86
Total lead intake	56.50

This value is only slightly higher than the estimated lead intake of 54 μg/day found in a Canadian 24-hour duplicate diet study conducted during 1981. The average lead content of the 10 food groups used in the Canadian study ranged from 0.088 μg/g for drinking water to 0.654 μg/g for cheese (Dabeka et al. 1987).

Based on data from the FDA's Total Diet Food Studies, baseline values for average daily intake of lead by consumption of food, water, and beverages are presented in Table 5-3. The estimates of lead intake presented in Table 5-3 are based on measurements of lead in foods prepared for consumption and on consumption patterns for those foods (or food groups) from dietary surveys in which survey participant data were grouped by age and sex. The Total Diet Food Studies conducted between 1982 and 1988 determined daily intakes of a variety of pesticides, industrial chemicals, and elements for eight age and sex groups. In 1984, lead residues were found in 193 of the 201 foods analyzed. A comparison of daily intakes of lead by age group (6 months, 2 years, and adult) showed that lead intakes dropped by approximately 50% for each group between 1980 and 1984 (Gunderson 1988) and continued to decrease through 1990 for all age and sex groups (Bolger et al. 1991; FDA 1992b). Data from the 1990–1991 Total Diet Survey indicate that dietary lead intake now ranges from 1.8 to 4.2 µg/day for all age groups combined, primarily as a result of reduced lead solder in cans and the phase-out of leaded gasoline. Further reductions in lead exposure will be more difficult to identify and achieve (Bolger et al. 1991, 1996).

Plastic food wrappers may be printed with pigments that contain lead chromates. Plastic wrappers used for 14 different national brands of bread collected in New Jersey contained a mean concentration of 26 mg of lead for a bag size of 2,000 cm^2. A survey of 106 homemakers who buy such breads indicated that 39% of them reused the bags and 16% of the respondents turned the bags inside out to reuse them, suggesting that the potential exists for lead leaching from the paint into the stored food (Weisel et al. 1991).

Another source of dietary lead is the use of inadequately glazed or heavily worn earthenware vessels for food storage and cooking. Due to the number of incidences of lead poisoning that have resulted from the use of earthenware vessels, the FDA has established action levels of 0.5 µg/mL lead for pitchers to 5.0 µg/mL for cups and mugs soaked for 24 hours in a 4% acetic acid solution (FDA 1992a). However, inadequately glazed pottery manufactured in other countries continues to pose a significant health hazard. Likewise, homemade or craft pottery and porcelain-glazed vessels have been found to release large quantities of lead, particularly if the glaze is chipped, cracked, or improperly applied. In addition, glaze on vessels that are washed repeatedly may deteriorate, and a vessel that previously met FDA standards may become unsafe (CDC 1985; EPA 1986a).

Blood lead levels measured as a part of the National Health and Nutrition Examination Surveys (NHANES) revealed that between 1976 and 1991, the mean PbB levels of the U.S. population aged from 1 to 74 years dropped 78%, from 12.8 to 2.8 µg/dL. The prevalence of PbB levels $10 µg/dL also decreased sharply from 77.8% to 4.3%. The major cause of the observed decline in PbB levels is most likely

Table 5-3. Daily Average Intake of Lead (µg lead/day)

Age	Sex	1980	1982	1984	1986	1988	1990
6–11 months	Male/female	≈34	20	16.7	10	5	3.8
2 years	Male	≈45	25.1	23.0	12.8	5.0	4.3
	Female	No data	No data	No data	No data	No data	No data
14–16 years	Female	No data	No data	28.7	15.2	6.1	6.1
14–16 years	Male	No data	No data	40.9	21.8	8.2	8.5
25–30 years	Female	No data	32.0	28.7	14.8	7.9	6.7
25–30 years	Male	84	45.2	40.9	21.2	10.0	8.5
60–65 years	Female	No data	No data	30.4	15.6	No data	2.2
60–65 years	Male	No data	No data	37.6	19.1	No data	8.1

Source: Derived from Bolger et al. 1991; FDA 1992b; Gunderson 1988

the removal of 99.8% of lead from gasoline and the removal of lead from soldered cans (Pirkle et al. 1994). PbB levels were consistently higher for younger children than for older children, for older adults than for younger adults, for males than for females, for blacks than for whites, and for central-city residents than for non-central-city residents. PbB levels also correlated with low income, low educational attainment, and residence in the Northeast region of the United States. Data from Phase 2 of NHANES III (conducted during October 1991 to September 1994) indicate that PbB levels in the U.S. population aged $1 year continued to decrease and that PbB levels among children aged 1–5 years were more likely to be elevated among those who were poor, non-Hispanic black, living in large metropolitan areas, or living in older housing (CDC 1997b). During 1991–1994, the overall geometric mean PbB of the population aged $1 year was 2.3 µg/dL. Among those aged 1–5 years, approximately 4.4% had PbB levels of 10 µg/dL, representing an estimated 930,000 children with levels high enough to be of concern (CDC 1997b).

Information on occupational exposure to lead is obtained primarily from the National Occupational Exposure Survey (NOES) and industry surveys of workers. While occupational exposure is widespread, environmental monitoring data on levels of exposure in many occupations are not available. OSHA has established a permissible exposure limit (PEL) for lead of 50 µg/m^3 for workplace air (OSHA 1991). NIOSH has estimated that more than 1 million American workers were occupationally exposed to inorganic lead in more than 100 occupations (NIOSH 1977a, 1978a). According to NOES, conducted by NIOSH between 1980 and 1983, an estimated 25,169 employees were exposed to tetraethyl lead (not used in gasoline since December 31, 1995); approximately 57,000 employees were exposed to various lead oxides mostly in non-ferrous foundries, lead smelters, and battery plants; 3,902 employees were exposed to lead chloride; and 576,579 employees were exposed to some other form of lead in the workplace in 1980 (NIOSH 1990). Workers who operate and maintain solid waste incinerators are also exposed to air lead levels as high as 2,500 µg/m^3 (Malkin 1992).

Potentially high levels of lead may occur in the following industries: lead smelting and refining industries, battery manufacturing plants, steel welding or cutting operations, construction, rubber products and plastics industries, printing industries, firing ranges, radiator repair shops and other industries requiring flame soldering of lead solder, and gas stations (EPA 1986a; Feldman 1978; Goldman et al. 1987; NIOSH 1978a). In these work areas, the major routes of lead exposure are inhalation and ingestion of lead-bearing dusts and fumes. In the smelting and refining of lead, mean concentrations of lead in air can reach 4,470 µg/m^3; in the manufacture of storage batteries, mean airborne concentrations of lead from 50 to 5,400 µg/m^3 have been recorded; and in the breathing zone of welders of structural steel, an average lead concentration of 1,200 µg/m^3 has been found (Fu and Boffeta 1995). Evaluations by NIOSH from 1979 to 1990 in radiator repair shops found that 68% of the workers sampled had airborne lead exposures exceeding the OSHA

standard of 0.05 mg/m^3 (Tharr 1993). Also, past studies of PbB levels of 56 radiator shop mechanics in the Boston area revealed that 80% had PbB levels greater than 30 µg/dL and 16 had PbB levels exceeding 50 µg/dL (Tharr 1993).

Studies have been conducted to determine exposure of firearm instructors to lead at outdoor firing ranges when either nonjacketed (pure lead) or jacketed (copper-coated) bullets were used. Instructors are likely to have higher exposure than shooters because they spend more time at the range. In studies at an outdoor range in Virginia, the mean breathing zone lead level when nonjacketed bullets were fired was 67.1 µg/m^3 for one instructor and 211.1 µg/m^3 for another (Tripathi et al. 1991). When jacketed bullets were used, breathing zone levels decreased to 8.7 µg/m^3 or less. PbB levels of the instructors did not exceed the OSHA return standard of 1.93 µmol/L (40 µg/dL) or removal standard of 2.4 µmol/L (50 µg/dL) in either case. When shooters fired conventional lead bullets, their mean exposures to airborne lead were 128 µg/m^3 in the personal breathing zone and 68 µg/m^3 in the general area. When totally copper-jacketed lead bullets were fired, the mean breathing zone and general area air sample concentrations were 9.53 and 5.80 µg/m^3, respectively (Tripathi et al. 1990). At an outdoor uncovered range in Los Angeles, instructors who spent an average of 15 to 20 hours per week behind the firing line were found to be exposed to breathing zone lead concentrations of 460 and 510 µg/m^3 measured as 3-hour, time-weighted averages. The PbB of one instructor reached 3.38 µmol/L (70 µg/dL). After reassignment to other duties, repeat testing indicated his PbB had dropped to 1.35 µmol/L (28 µg/dL) (Goldberg et al. 1991).

In 1991, NIOSH conducted a survey of the Federal Bureau of Investigations (FBI) Firearms Training Unit firing ranges and related facilities to determine occupational lead exposures among FBI and Drug Enforcement Agency (DEA) firing range personnel (NIOSH 1996). Sixty-one personal breathing-zone and 30 area samples for airborne lead were collected. Exposures ranged up to 51.7 µg/m^3 (mean 12.4 µg/m^3), 2.7 µg/m^3 (mean 0.6 µg/m^3), and 4.5 µg/m^3 (mean 0.6 µg/m^3) for range instructors, technicians, and gunsmiths, respectively. Exposure of custodians ranged from non-detectable to 220 µg/m^3 during short-term cleaning of a large indoor range. Carpet dust sampling of dormitory rooms of students who practiced at the firing ranges revealed statistically significant ($p<0.0005$) higher dust-lead concentrations when compared to non-student dormitories (dust-lead concentration range of 116 to 546 µg/g with a geometric mean of 214 µg/g in the student's rooms versus a dust-lead concentration range of 50 to 188 µg/g with a geometric mean of 65 µg/g for the non-student rooms). This suggested that the students were contaminating their living quarters with lead.

Field surveys of three radiator repair shops in the Cincinnati area revealed that local exhaust ventilation (LEV) systems are effective in controlling airborne lead levels. The highest concentration of airborne lead

measured during a brief period of continuous soldering in a shop equipped with an LEV was only 7.1 µg/m^3. In a shop where no LEV was used, the 13 personal samples averaged 209 µg/m^3 with a maximum of 810 µg/m^3 measured for a 56-minute sample worn while tearing down and resoldering a single radiator (Tharr 1993).

Airborne dusts settle onto food, water, clothing, and other objects, and may subsequently be transferred to the mouth. A more recent study suggests that lead, applied to the skin as lead acetate or lead nitrate, was rapidly absorbed through the skin and was detected in sweat, blood, and urine within 6 hours of application (Stauber et al. 1994). In this study, 4.4. mg of lead was applied to the skin under a covered wax/plastic patch on the forearms of human subjects; of the applied dose, 1.3 mg of lead was not recovered from skin washings. The amount that actually remained in (or on) the skin and the mass balance of the fate of this lead was not determined; it may have been dermally absorbed or eliminated from the skin by exfoliation of epidermal cells. Thus, while this study provides evidence for dermal absorption of lead, it did not quantify the fraction of applied dose that was absorbed. The quantitative significance of the dermal absorption pathway as a contributor to lead body burden remains uncertain.

In these occupational areas, good housekeeping and good ventilation have a significant impact on the extent of worker exposure. Workers who were (or are) involved in the production of gasoline additives, tetraethyl lead and tetramethyl lead (now banned from highway use in the United States) are exposed to both inorganic lead and alkyl lead. The major potential hazard to these workers appears to be from dermal exposure since alkyl leads may be absorbed through the skin (Bress and Bidanset 1991; EPA 1986a). Others who may be occupationally exposed to lead are artists and crafts persons who may be exposed to lead used in paints, ceramic glazes, and lead solder for sculpture and stained glass (Fischbein et al. 1992; Hart 1987) and welders where lead concentrations in the welding fumes generated by gas metal arc welding of carbon steel ranged from 1.0 to 17.6 µg/m^3, well below the established PEL for the workplace (Larson et al. 1989). A study conducted at two lead battery factories in Taiwan revealed a high correlation between ambient air concentration of lead and PbB levels in workers; improvement of hygienic practices proved to be more effective at lowering PbB levels than reducing the ambient air lead concentration (Lai et al. 1997).

Lead exposure is frequently monitored by biological testing (e.g., determination of urinary lead levels, PbB levels, urinary coproporphyrin levels, or δ-aminolevulinic acid [ALA] levels) rather than monitoring the workplace environment for lead concentrations (EPA 1986a; NIOSH 1978a). A recent employer survey of California industries that use lead indicated that 229,434 employees were potentially exposed to lead in the workplace; of these workers, 59,142 (25%) had received routine biological monitoring (i.e., determination of PbB levels), and only 24,491 (10%) were in positions where environmental monitoring (workplace air

lead levels) had ever been conducted. In addition, approximately 12% of the potentially exposed individuals were in the construction industry, which has only recently required air or blood monitoring (OSHA 1993; Rudolph et al. 1990).

Workers in an electronic components plant that makes ceramic-coated capacitors and resistors using leaded glass for the ceramic coating were found to be exposed to ambient lead levels ranging from 61 to 1,700 μg/m^3, and to have PbB levels ranging from 16 to 135 μg/dL. Approximately 30% of the workforce was found to be on medical leave as a result of their PbB levels exceeding 40 μg/dL. An analysis of PbB levels among family members of the exposed workers gave mean levels of 10.2 μg/dL compared with 6.2 μg/dL for families of nonexposed workers, indicating possible secondary occupational exposure from workers to their families (Kaye et al. 1987).

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in Section 2.6, Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, and breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

The American Academy of Pediatrics (AAP) (1998) has concluded that although monitoring data demonstrate a decline in the prevalence of PbB levels, lead remains a common, preventable, environmental health threat. The AAP supports the CDC guidelines endorsing universal screening in certain areas and targeted screening for children at high risk (CDC 1997c). Many children continue to be at risk for ingestion of lead-based paint and of soil and dust contaminated through the deterioration of lead-based paint and the residues from combustion of leaded gasoline. A 1974 study indicated that elevated PbB levels in children were most likely a result of ingesting lead-contaminated soil, and that the most likely source was lead-based paint rather than lead from automotive exhaust (Ter Haar and Aronow 1974). However, subsequent data

have shown that children with the highest PbB levels live in areas with high traffic flow where lead particles in the air may fall directly to the soil or adhere to the outer surfaces of building and wash to the soil with rain (Mielke et al. 1989). Studies of children in Minnesota showed that PbB levels in children were correlated with soil lead levels, which were highest in inner-city areas; soil lead levels and blood lead levels were not correlated with the age of housing, although the presence of lead-based paint or lead abatement procedures may be of significance for individual children (Mielke et al. 1989). The CDC has concluded that the most common source of lead exposure for children is lead-based paint that has deteriorated into paint chips and lead dusts (CDC 1997b).

FDA estimated that in 1990, toddlers (2-year-olds) received 16% of their total lead exposure from food (5 µg/day), 1% from soil, 7% from water, and 75% from dust. EPA estimated that in 1990 lead intake from U.S. drinking water would be 11.9 µg/day for a 6-year-old child and 7.5 µg/day for an infant less than 1 year old (Cohen 1988b). A study of lead in the diet of Canadian infants found an average intake by children 0–1 years of age to be 16.5 µg/day when both food and water ingestion were considered (Dabeka and McKenzie 1988).

Lead intoxication has been observed in children, but rarely in adults, in residential settings (Sedman 1989). The geometric mean blood lead level (GM PbB) for children has dropped dramatically since the late 1970's. Results of the CDC NHANES II and NHANES III, Phases I and II, study of blood lead levels for children aged 1–5 are summarized below (CDC 1997b, 1997d).

	NHANES II	NHANES III Phase I	NHANES III Phase II
Children Aged 1–5 Years	1976–1980	1988–1991	1991–1994
GM PbB	15.0 µg/dL	3.6 µg/dL	2.7 µg/dL
PbB $ 10 µg/dL	88.2%	8.9%	4.4%

The NHANES II and NHANES III, Phase I, results showed that from 1976 to 1991, PbB levels were consistently higher for younger children than for older children (Pirkle et al. 1994). In general, PbB levels also correlated with low income, low educational attainment, and residence in the Northeast region of the United States. Data from Phase 2 of NHANES III (conducted during October 1991 to September 1994) indicate that PbB levels in the U.S. population aged $1 year continued to decrease and that PbB levels among children aged 1–5 years were more likely to be elevated among those who were poor, non-Hispanic black, living in large metropolitan areas, or living in older housing (with potential exposure to lead from

lead-based paint) (CDC 1997b). During 1991–1994, the overall geometric mean PbB of the population aged $1 year was 2.3 µg/dL. Among those aged 1–5 years, approximately 4.4% had PbB levels $10 µg/dL, representing an estimated 930,000 children in the general population with levels high enough to be of concern (CDC 1997b). In addition, 1.3% of children aged 1–5 years had PbB levels $15 µg/dL, and 0.4% had PbB levels $20 µg/dL. For the NHANES III, Phase II data, the GM PbB levels were higher for children aged 1–2 years (3.1 µg/dL) than for children aged 3–5 years (2.5 µg/dL). (CDC 1997b).

In 1982–1983, the baseline value for daily intake of lead by inhalation in a nonurban environment was estimated to be 0.5 µg/day for a 2-year-old child. The baseline value was based on an average atmospheric lead concentration of 0.1 $\mu g/m^3$ and an indoor/outdoor lead concentration ratio of 0.5. In an urban environment, the indoor/outdoor ratio was assumed to be approximately 0.8 (EPA 1986a). Drastic reductions in the lead content of gasoline since 1986 have resulted in a 64% decrease in lead emissions to the atmosphere (see Section 5.4.1).

The lead content of dusts can be a significant source of exposure, especially for young children. Baseline estimates of potential human exposure to dusts, including intake due to normal hand-to-mouth activity, are 0.2 g/day for children 1–6 years old versus 0.1 g/day for adults when both indoor and outdoor ingestion of soil including dust is considered (EPA 1989c). For children who engage in pica behavior, the ingestion rate of soil can be as high as 5 g/day. Although ingestion of lead-containing paint may lead to elevated PbB levels in young children, the major source of moderately elevated PbB levels (30–80 µg/dL) in inner city children is mostly likely to be contaminated household dust and subsequent hand contamination and repetitive mouthing (Charney et al. 1980). Weathering of lead-based paint can contribute to the lead content of dust and soil. Lead levels of indoor dust and outdoor soil were found to be strongly predictive of PbB levels in over 200 urban and suburban infants followed from birth to 2 years of age; however, the PbB levels were not correlated with indoor air or tap water lead levels, nor the size of nearby roadways. Indoor dust lead levels and soil lead levels in the homes of children with high PbB levels (>8.8 µg/dL) were 72 µg/wipe (window sill dust) and 1,011 µg/g, respectively; children with low PbB levels (<3.7 µg/dL) were exposed to 22 µg/wipe and 380 µg/g, respectively. In addition, 79% of the homes of children with high PbB levels had been renovated, while only 56% of the homes of children with low PbB levels had been renovated, suggesting that renovating the interior of homes previously painted with leaded paint may increase, at least temporarily, a child's exposure to lead dust (Rabinowitz et al. 1985).

Lanphear et al. (1996a, 1996b, 1997, 1998b) studied factors affecting PbB levels in urban children and found the following independent predictors of children's PbB levels: dust lead loading in homes, African-American race/ethnicity, soil lead levels, ingestion of soil or dirt, lead content and condition of painted

surfaces, and water lead levels (Lanphear et al. 1996a). Differences in housing conditions and exposures to lead-containing house dust appear to contribute to the racial differences in urban children's PbB levels. In addition, white children were more likely to put soil in their mouths (outdoor exposure) and suck their fingers, and African-American children were more likely to put their mouths on window sills (indoor exposure) and to use a bottle. Exterior lead exposures were more significant for white children, and interior lead exposures were more significant for African-American children (Lanphear et al. 1996b). Mouthing behaviors are an important mechanism of lead exposure among urban children (Lanphear et al. 1997). Community characteristics such as residence within a city, proportion African Americans, lower housing value, housing built before 1950, higher population density, higher rates of poverty, lower percent of high school graduates, and lower rates of owner-occupied housing have been used to identify children with elevated blood levels (Lanphear et al. 1998b). An analysis of children's PbB levels and multiple measures of lead concentrations in household dust, water, soil, and paint has been used to predict the effect of changing concentrations of lead in environmental media on children's PbB levels. An increase in dust lead loading from background to 200 μg/ft^2 was estimated to produce an increase of 23.3% in the percentage of children estimated to have a PbB level >10 μg/dL; an increase in water lead concentration from background to 15 μg/L was estimated to produce an increase of 13.7% in the percentage of children estimated to have a PbB level >10 μg/dL; and an increase in soil lead concentration from background to 400 μg/g was estimated to produce an increase of 11.6% in the percentage of children estimated to have a PbB level >10 μg/dL (Lanphear et al. 1998a)

Outdoor lead dust was found to be a more potent contaminant of children's hands than indoor lead dust at day care centers in New Orleans; boys, in general, had higher hand lead levels than girls. The conclusions were based on lead analysis of hand wipe samples taken before and after children played outdoors at four different day care centers (a private inner-city site, a private outer-city site, a public inner-city site, and a public outer-city site). The private inner-city site had a severely contaminated outdoor play area with measured soil lead concentrations ranging from 287 to 1,878 mg/kg. The outdoor play area at the public inner-city site, where children exhibited the lowest hand lead measurements of any site in the study, had been completely paved over with concrete or rubberized asphalt and had well-maintained equipment (Viverette et al. 1996).

In addition to the ingestion of hand soil/dust through normal hand-to-mouth activity, some children engage in pica behavior (consumption of non-food items), which can put them at increased risk through ingestion of large amounts of soil contaminated with lead. It has been estimated that an average child may ingest between 20 and 50 mg of soil per day and that a pica child may ingest 5,000 mg or more of soil per day (LaGoy 1987; Mielke et al. 1989). If the soil contains 100 μg/g of lead, an average child may be exposed to

5 µg of lead per day from this source alone (Mielke et al. 1989), and a pica child may be exposed to more than 100 times that amount. At the EPA's *Soil Screening Guidance* concentration of 400 mg Pb/kg soil, a 13 kg child who consumes 5 g of soil during a pica episode would have a dose from soil of 0.2 mg Pb/kg of body weight, which is 10 times the nonlethal toxic dose (Calabrese et al. 1997b; Stuik 1974). Yard soil containing lead concentrations >500 mg/kg has been associated with a mean PbB $10 µg/dL in children 6 to 71 months of age in a multi-site study (ATSDR 1995).

Fetuses are at even greater risk. As discussed in Section 2.8, lead can readily cross the placenta; therefore, exposure of women to lead during pregnancy results in uptake by the fetus. Furthermore, since the physiological stress of pregnancy may result in mobilization of lead from maternal bone, fetal uptake of lead can occur from a mother who was exposed to lead before pregnancy, even if no lead exposure occurs during pregnancy. Prenatal exposure may be related to postnatal mental retardation, impaired postnatal neurobehavioral development, and reduced birth weight and gestational age (EPA 1986a).

Maternal PbB levels during pregnancy were significantly higher for a group of 1,428 immigrant women (geometric mean 2.3 µg/dL) than for a group of 504 non-immigrant women (geometric mean 1.9 µg/dL) in a study conducted at a medical center in South Central Los Angeles, one of the most economically depressed regions in California. Immigrant PbB levels were strongly dependent on time elapsed since immigration to the United States, with PbB levels being highest in those women who had immigrated most recently. Elevated PbB levels in immigrant women were also associated with engagement in pica and with low dietary calcium during pregnancy (Rothenberg et al. 1999b).

Lead concentrations in maternal and umbilical cord blood have been reported by Greek researchers for 50 parturient women at delivery. Twenty-five of the women lived in industrial areas with high air pollution, and twenty-five lived in agricultural areas with low air pollution. The mean lead concentrations (expressed as mean ± standard deviation) for the women living in areas with high air pollution were 37.2±4.7 µg/L in maternal blood and 20±3.4 µg/L in umbilical cord blood (correlation coefficient, r = 0.57). The mean lead concentrations for the women living in areas with low air pollution were 20.5±5.6 µg/L in maternal blood and 12.9±3.6 µg/L in umbilical cord blood (correlation coefficient, r = 0.70). The authors conclude that the placenta demonstrates a dynamic protective function that is amplified when maternal PbB levels are raised (Vasilios et al. 1997).

Concentrations of lead in umbilical cord blood of two groups of women giving birth in a Boston Hospital in 1980 and 1990 have also been reported. Mean lead concentration of umbilical cord blood was 6.56±3.19 µg/dL for the 1980 group and 1.19±1.32 µg/dL for the 1990 group (Hu et al. 1996).

In a study of blood samples collected from 113 mothers of 23 different nationalities and from their neonates (cord blood), mean maternal PbB levels were 14.9±2.14 µg/dL (range, 6.6–27.8 µg/dL) and mean cord PbB levels were 13±2.5 µg/dL(range, 6.0–30 µg/dL). Sixteen percent of mothers and nearly 10% of cord blood samples had PbB levels >20 µg/dL (Al Khayat et al. 1997b).

Improper removal of lead from housing known to contain lead-based paint can significantly increase lead levels in dust, thus causing lead toxicity in children living in the home during the lead-removal process. Four such cases have been documented (Amitai et al. 1987). In January 1995, the New York State Department of Health identified 320 children in 258 households in New York State (excluding New York City) with PbB levels $20 µg/dL that were considered to be attributable to residential renovation and remodeling (CDC 1997d). PbB levels in children have been found to increase during the summer months when children play outdoors and soil dust is more common. After interior and exterior lead dust cleanup procedures were instituted around areas known to have high soil lead levels, the PbB levels dropped in 52% of the children (Mielke et al. 1992). Authors of a study of PbB levels in children in Toronto, Canada, before and after abatement of lead-contaminated soil and house dust found they could neither strongly support nor refute beneficial effects of abatement. The failure to reach a definite conclusion from the results of the study, which included data from 12 cross-sectional blood-screening surveys that were conducted over an 8-year period, was due in part to a low response rate (32–75%) to questionnaires used to determine behavioral, household, lifestyle, neighborhood, and environmental factors relating to study participants (Langlois et al. 1996).

EPA conducted the Urban Soil Lead Abatement Demonstration Project (USLADP), also known as the "Three City Lead Study," in Boston, Baltimore, and Cincinnati (EPA 1996i). The purpose was to determine whether abatement of lead in soil could reduce PbB levels of inner-city children. No significant evidence was found that soil abatement had any direct impact on children's PbB levels in either the Baltimore or Cincinnati studies. In the Boston study, however, a mean soil lead reduction of 1,856 ppm resulted in a mean decline of 1.28 µg/dL PbB at 11 months post-abatement (Weitzman et al. 1993). Phase II extended the study to 2 years and included soil abatement of the two comparison areas from Phase I (Aschengrau et al. 1994). Combined results from Phase I and II suggested a higher impact of soil remediation on PbB levels (2.2 to 2.7 µg/dL). EPA reanalyzed the data from the USLADP in an integrated report (EPA 1996i). They concluded that when soil is a significant source of lead in the child's environment, under certain conditions, the abatement of that soil will result in a reduction in exposure and consequently, PbB level. Crump (1997) criticized the Boston data, including EPA's integrated report, for poor selection of statistical methods, failure to adequately examine confounding variables, selective interpretation of results, and lack of control group in phase II of the study. Regardless, his reevaluation of the data, based on randomization

analysis, resulted in a significant, yet modest effect of soil abatement (1.37 µg/dL) consistent with the conclusions of Weitzman et al. (1993) (1.28 µg/dL). Clearly, the results of the USLADP suggest that a number of factors are important in determining the influence of soil remediation on PbB levels in children. These include the site-specific exposure scenario, the magnitude of the remediation, and the magnitude of additional sources of lead exposure.

A study by Davis et al. (1992, 1994) used electron microprobe analysis of soil and waste rock from Butte, Montana, to help explain the low PbB levels observed in young children living in that mining community. They hypothesized that, if soils were ingested, the lead bioavailability would be constrained by alteration and encapsulation of the lead-bearing minerals of the Butte ore body (galena, anglesite, cerrusite, and plumbojarosite), which would limit the available lead-bearing surface area. Kinetic limitations relative to the residence time of soil in the gastrointestinal tract also affect the bioavailability of lead (Ruby et al. 1992). The inherent chemical properties of soil-lead adsorption sites may reduce the bioavailability of soil-lead compared to soluble lead salts and lead compounds ingested without soil (Freeman et al. 1992). It has been shown that lead in impacted unleaded and leaded automobile exhaust particulate matter is readily leachable, but lead in paint may not be as leachable (Que Hee 1994). Thus, the differential availability may cause differential lead bioaccessibility and hence bioavailability. The extent of absorption of lead into the tissues of young Sprague-Dawley rats has been determined (Freeman et al. 1992). The animals were fed various concentrations of lead-contaminated mining waste soil mixed with a purified diet for 30 days. The overall percentage bioavailability values, based on lead acetate as the standard, were: 20% based on blood data; 9% based on bone data; and 8% based on liver data. These low bioavailabilties agree favorably with the low blood levels (average 3.5 µg/dL) found in children in Butte, Montana (Freeman et al. 1992). EPA (1989c) uses 0.2 g/day as a typical soil ingestion rate (including both dirt and dust) for children 1–6 years of age.

Trace metals, including lead, have been detected in human breast milk, so breast-feeding could deliver lead to an infant. Levels of lead in human milk vary considerably depending on the mother's exposure and occupation. For example, levels of lead in the milk of a mother who had worked in a battery factory for the first 6 months of pregnancy varied from 63 to 4 µg/L in samples taken soon after the birth of the child up to 32 weeks later. These concentrations were similar to those in control samples even though the PbB of the mother was about 3 times higher than the that of the control subject. The pharmacokinetic model for lead may be complex since more than 90% of the lead body burden is stored in bone tissue and lead is strongly bound to hemoglobin, which may impede its partition to milk (Wolff 1983). On the other hand, an analysis of 210 human milk samples taken across Canada showed a mean lead level of 1.01 µg/L (1.04 ng/g; range, <0.05–15.8 ng/g). Women who resided in homes that were more than 30 years old, lived in high-traffic

areas for more than 5 years, or had drunk 3 or more cups of coffee in the preceding 24 hours prior to taking the milk sample, had higher lead levels. The increased lead levels resulting from coffee drinking were thought to be the result of mobilization by the coffee of the lead stored in tissues and bone (Dabeka et al. 1988). In a paper by Abadin et al. (1997b), results of several additional studies of lead in human milk are summarized and discussed from a public health perspective. Among other citations, the median lead in milk concentrations from 41 volunteers in Sweden was 2 µg/L (Larsson et al. 1981); the mean value for urban residents of Germany in 1983 was 9.1 µg/L (Sternowsky and Wessolowski 1985); and the concentration in 3-day postpartum milk samples from 114 women in Malaysia averaged 47.8 µg/L (Ong et al. 1985).

Gulson et al. (1998) used measured lead isotope ratios ($^{207}Pb/^{206}Pb$ and $^{206}Pb/^{204}Pb$) in mothers' breast milk and in infants' blood to establish that, for the first 60-90 days postpartum, the contribution from breast milk to blood lead in the infants varied from 36% to 80%. Maternal bone and diet appear to be the major sources of lead in breast milk. Mean lead concentration (± standard deviation) in breast milk for participants in the study was 0.73±0.70 µg/kg.

In a review of data on occupational chemicals that may contaminate breast milk (Byczkowski et al. 1994), it is stated that lead may be excreted in milk in amounts lethal to the infant and that the metal may be mobilized from bone stores to milk during the lactation period. Even when the concentration of lead in mother’s milk is low, the absorption of metals into the systemic circulation of infants is generally high when they are on a milk diet. To better understand the sensitivity of the nursing infant to chemicals, epidemiological studies, chemical monitoring, and model development and application are needed.

Lead has also been reported in home-prepared reconstituted infant formula. Two of forty samples collected in a Boston-area study had lead concentrations >15 µg/L. In both cases, the reconstituted formula had been prepared using cold tap water run for 5 to 30 seconds, drawn from the plumbing of houses >20 years old. Three preparation practices for infant formula should be avoided: (1) excessive water boiling, (2) use of lead-containing vessels, and (3) morning (first-draw) water (Baum and Shannon 1997). Gulson et al. (1997a) measured lead in household water throughout the day when the plumbing system of an unoccupied test house was not flushed. Water concentration data ranged from 119 µg/L for the initial (first-draw) sample to 35–52 µg/L for hourly samples to 1.7 µg/L for a fully flushed sample. The water concentration data were used in the EPA's Integrated Exposure Uptake and BioKinetic (IEUBK) Model for Lead in Children to predict PbB levels in infants drinking water (or formula reconstituted using water) drawn from the same tap. Predicted PbB levels in infants only exceeded 10 µg/L when 100% of the water consumed contained 100 µg Pb/L (Gulson et al. 1997a).

Lead-containing ceramic ware used in food preparation has also been associated with childhood lead exposure in children of Hispanic ethnicity in San Diego County, California. One study (Gersberg et al. 1997) used the IEUBK to determine that dietary lead exposure from beans prepared in Mexican ceramic bean pots may account for a major fraction of blood lead burden in children whose families use such ceramic ware.

Workers occupationally exposed to lead apparently carry lead home on clothing, bodies, or tools. PbB levels of children in households of occupationally exposed workers were almost twice those of children in neighboring homes whose parents were not occupationally exposed to lead (median ranges were 10–14 and 5–8 µg/dL, respectively) (Grandjean and Bach 1986). Young children (<6 years old) of workers exposed to high levels of lead in workplace air at an electronic components plant (61–1,700 µg lead/m^3 ambient concentrations) had significantly elevated PbB levels (13.4 µg/dL) compared with children from the same locale whose parents did not work in the electronics plant (7.1 µg/dL) (Kaye et al. 1987). Exposures of lead workers' families have been identified in nearly 30 different industries and occupations. Industries in which exposure of family members has been reported most often include lead smelting, battery manufacturing and recycling, radiator repair, electrical components manufacturing, pottery and ceramics, and stained glass making (NIOSH 1995). Children of lead-exposed construction workers may also be at increased risk (Whelan et al. 1997).

Children may be exposed to lead because of activities associated with certain hobbies and artistic activities practiced by adults in the home. Some of the more obvious hobbies and activities involving use of lead-containing materials (casting, stained glass, pottery, painting, glassblowing, screenprinting) are discussed in Section 5.5. Activities involving use of lead-containing materials should always be done in an area well-ventilated with outdoor air and should never be done with children in the same room or in close proximity.

Children may be exposed to lead from other hobby or recreational activities that are not as obviously dangerous. For example, two case studies (one in North Carolina and one in Arizona) of lead poisoning in children from homes in which environmental surveys indicated no identifiable lead hazards have been reported. More extensive investigations revealed that both children had been observed on several occasions with pool cue chalk in their mouths. Subsequent chemical analysis of 23 different types of pool cue chalk identified three types as having lead concentrations in excess of 7,000 mg/kg (Miller et al. 1996). Accidental or intentional ingestion of folk remedies containing lead (discussed in Section 5.5) represents another source for potential lead-poisoning in children. Acute lead encephalopathy in early infancy has been reported in a Middle Eastern study for 14 infants following the use of *Bint al Thahab*, a traditional medicine containing 91% lead monoxide, and for 5 infants following application of lead-containing

kohl/surma, a preparation used as eye makeup (Al Khayat et al. 1997a). Hair dyes formulated with lead acetate represent a potential source for lead-poisoning both by accidental ingestion and by hand-to-mouth activity following contact with lead-contaminated surfaces, including dyed hair of adults (Mielke et al. 1997b).

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to workers exposed to lead in the workplace, several other population groups at risk for potential exposure to high levels of lead can be identified: preschool-age children and fetuses (see Section 5.6), white males between 40 and 59 years of age (EPA 1986d), and those persons ("sniffers") who purposely inhale leaded gasoline vapors. Individuals living near sites where lead was produced or sites where lead was disposed, and individuals living near one of the 1,026 NPL hazardous waste sites where lead has been detected in some environmental media (EPA 1986d; HazDat 1998) also may be at risk for exposure to high levels of lead.

General population exposure is most likely to occur through the ingestion of food and water that are contaminated with lead; however, some individuals and families may be exposed to additional sources of lead in their homes. This is particularly true of older homes that may contain lead-based paint. In an attempt to reduce the amount of exposure due to deteriorating leaded paint, the paint is commonly removed from homes by burning (gas torch or hot air gun), scraping, or sanding. These activities have been found to result, at least temporarily, in higher levels of exposure for families residing in these homes. In addition, those individuals involved in the paint removal process (i.e., do-it-yourself renovators and professionals who remove lead) can be exposed to such excessive levels that lead poisoning may occur (Chisolm 1986; Feldman 1978; Fischbein et al. 1981; Rabinowitz et al. 1985).

Special populations at risk of high exposure to tetraethyl lead include workers at hazardous waste sites and those involved in the manufacture and dispensing of tetraethyl lead (Bress and Bidanset 1991). Recreational drug "sniffers" of leaded gasoline are also at risk (Edminster and Bayer 1985).

Populations living near any of the 1,026 NPL sites that were identified as having lead present in the environmental media may be at risk for exposure to high levels of lead (HazDat 1998). However, the available data are insufficient to allow characterization of the sizes of these populations or intake levels of lead to which they may be exposed.

5.8 ADEQUACY OF THE DATABASE

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

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

5.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of lead and its compounds are sufficiently well defined to allow an estimation of the environmental fate of lead to be made (Howe 1981; HSDB 1996; Lide 1996; Merck 1989; Sax 1984; Sax and Lewis 1987). Availabilities of the various forms need to be modeled and the connectivities to bioaccessabilities and bioavailabilities determined.

Production, Import/Export, Use, and Release and Disposal. Lead is produced and imported for widespread use in the United States. Therefore, the potential for human exposure in the workplace, the home, the environment, and at waste sites may be substantial.

Lead is produced from both primary (i.e., mined ore) and secondary (i.e., scrap metal and wastes) sources, and is imported by the United States. In 1997, production from primary and secondary sources was 343,000 metric tons and 1.1 million metric tons, respectively (Smith 1998), and imports reached 265,000 metric tons (Larrabee 1998; Smith 1998). Approximately 1.6 million metric tons of lead were consumed in the United States in 1997 (Smith 1998). Of lead used in 1997, 86.9% was used for storage batteries, 7.8% was used in metal products, and 5.3% was used in miscellaneous applications (Smith 1998). Because of the adverse health effects associated with exposure to lead, its use in paints, ceramic products, gasoline additives (now banned), and solder has declined dramatically in recent years. In 1997, exports of

lead metal totaled 37,400 metric tons, and exports of lead waste and scraps totaled 88,400 metric tons (Larrabee 1998; Smith 1998).

Although certain uses of lead preclude recycling (e.g., use as a gasoline additive), lead has a higher recycling rate than any other metal (Larrabee 1998). An estimated 90–95% of the lead consumed in the United States is considered to be recyclable. In the United States, 77.1% of the lead requirements were satisfied by recycled lead products (mostly lead-acid batteries) in 1996. This compares to 69.5% in 1990 and 55.2% in 1980 (Larrabee 1997, 1998).

Industrial wastes, as well as consumer products, containing lead are disposed of in municipal and hazardous waste landfills. Current information on the amounts being disposed of is needed to evaluate the potential for exposure to lead.

The federal government regulates the release and disposal of lead. EPA has established national ambient air quality standards for lead. Under the Safe Drinking Water Act, EPA limits the level of lead in drinking water. Industrial emissions are regulated by the Clean Water Act. Lead and certain of its compounds are designated hazardous substances; CERCLA requires that the person in charge of a vessel or facility notify the National Response Center immediately when there is a release of a hazardous substance in an amount equal to or greater than the reportable quantity for that substance. Such data should be useful in determining potential for exposure and relating it to health effects.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1996 became available in May of 1998 This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Environmental Fate. Lead released to the atmosphere partitions to surface water, soil, and sediment (EPA 1986a; Getz et al. 1977; Mundell et al. 1989; NAS 1980; Nielsen 1984; NSF 1977). Lead is transported in the atmosphere and in surface water. Organolead compounds are transformed in the atmosphere by photodegradation (DeJonghe and Adams 1986); however, the atmospheric transformation of inorganic lead compounds is not completely understood (EPA 1986a). Organolead compounds are transformed in surface waters by hydrolysis and photolysis (EPA 1979d). Inorganic lead compounds may be strongly sorbed to organic matter in soils and sediments (EPA 1986a). Lead is a naturally occurring element and is extremely persistent in the environment. Additional information on the atmospheric

transformations of organic and inorganic lead compounds in the atmosphere would provide a basis for determining the lead compounds to which humans are most likely to be exposed. Modeling the availability of lead compounds needs to be done.

Bioavailability from Environmental Media. Available pharmacokinetic data indicate that lead is absorbed by humans following inhalation of particulate lead in ambient air and ingestion of contaminated foods, drinking water, and soil (Chamberlain et al. 1978; EPA 1986a; Morrow et al. 1980). In addition, children may ingest paint chips that contain lead. The bioavailability of lead from soil or dust on the hand after mouthing activity needs to be modeled. Absorption following dermal exposure is much more limited, although absorption of organolead compounds through the skin occurs (Kehoe and Thamann 1931; Laug and Kunze 1948; Moore et al. 1980).

Food Chain Bioaccumulation. Lead is bioaccumulated by terrestrial and aquatic plants and animals (Eisler 1988). However, lead is not biomagnified in terrestrial or aquatic food chains (Eisler 1988). No additional information is needed.

Exposure Levels in Environmental Media. Environmental monitoring data are available for lead in ambient air, indoor air, surface water, groundwater, drinking water, sediments, soils, and foodstuffs (Eckel and Jacob 1988; EPA 1982f, 1986a, 1988b, 1988f, 1989f, 1989h, 1990c; Lee et al. 1989; Maenhaut et al. 1979; Mielke 1992; Mielke et al. 1983, 1985, 1989); however, these data are not current and additional monitoring data on lead levels in all environmental media, particularly data gathered after EPA lowered and eventually banned the lead content of gasoline, would be helpful in determining current exposure levels. Estimates of human intake from inhalation of ambient air and ingestion of contaminated foods and drinking water are available (Dabeka et al. 1987; EPA 1986a, 1991d; Gartrell et al. 1986b; Gunderson 1988). Additional information on the concentrations of lead compounds in environmental media, particularly at hazardous waste sites, and an estimate of human intake would be helpful in establishing human exposure to lead. Absorption of lead through the skin may be a significant exposure pathway (Stauber et al. 1994) and may be deserving of further study.

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

Exposure Levels in Humans. Lead can be measured in human blood, hair, perspiration, teeth, bones, feces, and urine (Aguilera de Benzo et al. 1989; Batuman et al. 1989; Blakley and Archer 1982; Blakley et al. 1982; Christoffersson et al. 1986; Delves and Campbell 1988; Ellen and Van Loon 1990; Exon et al. 1979; Hu et al. 1989, 1990, 1991; Jason and Kellogg 1981; Manton and Cook 1984; NIOSH 1977a, 1977d, 1977e, 1977f, 1977g 1977h; Que Hee and Boyle 1988; Que Hee et al. 1985a; Wielopoiski et al. 1986). The most common method of assessing human exposure involves measurement of lead in blood (PbB) (Aguilera et al. 1989; Delves and Campbell 1988; Manton and Cook 1984; NIOSH 1977a, 1977d, 1977e, 1977f, 1977g 1977h; Que Hee et al. 1985a). PbB levels have been correlated with ambient air exposure levels and dust, and dietary intake levels (Rabinowitz et al. 1985). Additional information on the biological monitoring of populations living in the vicinity of hazardous waste sites would be helpful in estimating exposure of these populations to lead compounds. The relationships between the major biological monitoring media should be determined. Alkyl lead compounds can be measured in exhaled breath and the diethyllead metabolite of tetraethyl lead can be measured in urine. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. Estimates are available for intake by children through ingestion of contaminated soils, dust, paint chips (EPA 1989c), and breast milk (Wolff 1983). However, some of these estimates are not current or well understood. To better understand the sensitivity of the nursing infant to chemicals such as lead, epidemiological studies, chemical monitoring, and model development and application are needed (Byczkowski et al. 1994). The bioavailability of lead from soil or dust on the hand after mouthing activity needs to be modeled.

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

5.8.2 Ongoing Studies

Ongoing studies regarding potential for environmental exposure to lead were reported in the Federal Research in Progress File (FEDRIP 19968) database. Table 5-4 presents a summary of these studies.

Table 5-4. Ongoing Studies on Potential Environmental Exposure to Lead

Investigator	Affiliation	Research description
K.M. Franken, W.L. Cornell	Bureau of Mines Rolla Research Center, Rolla, MO	Developing methods for treating lead-bearing wastes to render them non-hazardous
J.L. Gardea-Torresda	University of Texas at El Paso	Developing methods for recovery of toxic heavy metals from contaminated water supplies using plants
K.B. Kidd, F.E. Dierberg	Tpl, Inc., Albuquerque, NM; *Aqua Chem Analyses, Inc., Palm* Bay, FL	Investigating the use of plants for *remediation of wastes contaminated with* lead
R.L. Chaney	Beltsville Agricultural Research Center, Beltsville, MD	Evaluating the use of composts for reduction of the bioavailability and phytoavailability of lead and other heavy metals in contaminated soils
D. Heil, A. Hansen	New Mexico State University, Las Cruces, NM	Evaluating the use of solvent extraction as a technique for the remediation of soils contaminated with lead
R. Wang, A.N. Clarke	Wamax, Inc., Bellevue, WA; Eckenenfelder, Inc., Nashville, TN	Developing new lead fixation technologies
D. Leppert	Teague Mineral Products, Salem, OR	Evaluating the naturally occurring mineral clinoptilolite for removal of lead from drinking water
W.F. Bleam	University of Wisconsin, Madison, WI	Determining the soil conditions where lead binds to soils
J.H. Graziano	Columbia University, New York, NY	Conducting a study to determine the bioavailability of lead in soils for representative sites in the U.S.
J.J. Hassett	University of Illinois, Urbana, IL	Determining the relationships between soil lead concentrations and soil characteristics to develop management strategies for reducing bioavailability of lead in soil that would serve as alternatives to removal and disposal of lead-contaminated soils
J.W. Odor	Auburn University, Auburn, AL	Determining the occurrence, accumulation, and plant bioavailability of lead and other metals in acid ultisols.
L.M. Schuman	University of Georgia, Griffin, GA	Investigating the equilibrium of lead and other metals in soils and the effects on water quality

Table 5-4. Ongoing Studies on Potential Environmental Exposure to Lead (continued)

Investigator	Affiliation	Research description
J.H. Peverly	Cornell University, Ithaca, NY	Characterizing trace element chemistry in soil and waste to predict plant uptake and movement of trace elements in soils
G.A. O'Connor, Q. Ma	University of Florida, Gainesville, FL	
G.M. Pierzynski, T.J. Logan	Kansas State University, Manhattan, KS; Ohio State University, Columbus, OH	Chemistry and bioavailability of waste constituents in soils
J.H. Peverly, J.L. Hutson	Cornell University, Ithaca, NY	Determining the fate and movement of nutrients and metals in representative plant/soil systems amended with sewage sludge, composts, and other wastes
C.D. Pepper	Boston University	Performing research to determine why high blood levels continue to occur in bridge construction workers despite government regulations and industry recommendations
H.J. Simpson	Mount Sinai School of Medicine	Conducting a study to identify previously unrecognized urban sources of environmental lead using dated environmental samples
P.J. Landrigan	Mount Sinai School of Medicine	Heading a collaborative, multidisciplinary, Superfund Hazardous Substances Basic Research Program to study the current urban sources, environmental distribution, and toxic effects on human health of lead
J.W. Gillett	Cornell University, Ithaca, NY	Conducting Superfund basic research on the bioavailability and impact of hazardous substances in human health and ecological risk as well as remediation of sites containing heavy metals such as lead
T.E. Ford	Harvard School of Public Health, Boston, MA	Evaluating the interrelationships between the microbial and metal pollutants in the New Bedford Harbor area, an EPA-designated Superfund Site
M.H. Conklin	University of Arizona, Tucson, AZ	Investigating the transport of trace metals, including lead, in a polluted aquifer in Pinal Creek, AZ, a state Superfund site

Table 5-4. Ongoing Studies on Potential Environmental Exposure to Lead (continued)

Investigator	Affiliation	Research description
K. Belitz	Dartmouth College, Hanover, NH	Evaluating the importance of subsurface physical and chemical heterogeneity on the transport of metals, including lead, in geologically complex materials
A.J. Friedland	Dartmouth College, Hanover, NH	Identifying sources and determining mobility of lead in soil, groundwater, and vegetation

Source: FEDRIP 1998

6. ANALYTICAL METHODS

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

6.1 BIOLOGICAL SAMPLES

Blood, Urine, Serum, Cerebrospinal Fluid. There are several methods for the analysis of lead in biological samples. The most common methods currently used are flame atomic absorption spectrometry (AAS), graphite furnace atomic absorption spectrometry (GFAAS), anode stripping voltametry (ASV), inductively coupled plasma-atomic emission spectroscopy (ICP/AES), and inductively coupled plasma mass spectrometry (ICP/MS). Spectrophotometric methods also exist and were commonly used in the past; however, they are not as sensitive or reliable as the newer methods. According to Grandjean and Olsen (1984) and Flegal and Smith (1995), GFAAS and ASV are the methods of choice for the analysis of lead. In order to produce reliable results, background correction, such as Zeeman background correction that minimizes the impact of the absorbance of molecular species, must be applied. Limits of detection for lead using AAS are on the order of μg/mL (ppm) and for GFAAS are generally in the low ng/mL (ppb) range (Flegal and Smith 1995). Other specialized methods for lead analysis are X-ray fluorescence spectroscopy (XRFS), neutron activation analysis (NAA), differential pulse anode stripping voltametry, and isotope dilution mass spectrometry (IDMS). The most reliable method for the determination of lead at low concentrations is IDMS (EPA 1986a; Grandjean and Olsen 1984), but due to the technical expertise required and high cost of the equipment, this method is not commonly used. It is primarily used for the development of certified standard reference materials by which other methods can determine their reliability since results of lead analyses from numerous laboratories often do not agree (Fell 1984). Details of several methods used for the analysis of lead in biological samples are presented in Table 6-1.

Concentrations of lead in blood, urine, serum, and cerebrospinal fluid have been used as indicators of exposure to lead. Measurement of lead in blood is the most common method of assessing exposure. Blood lead is also considered the most useful tool for screening and diagnostic testing (Moore 1995); the half-life of lead in blood is approximately 36 days (Todd et al. 1996). A second half-life is generally considered to be approximately 4 years (Graziano 1994) and reflects the replenishment of lead in the blood from the bone storage compartment. Sample preparation usually consists of wet ashing (digesting) the sample with strong acid and heat, and redissolving the residue in dilute acid prior to analysis so that all lead species are converted quantitatively to the same lead compound (NIOSH 1977a, 1977d, 1977e, 1977g, 1977h). Preparation methods not requiring wet ashing have also been used with good results (Aguilera de Benzo et al. 1989; Delves and Campbell 1988; Manton and Cook 1984; NIOSH 1977f; Que Hee et al. 1985a; Zhang et al. 1997). For samples analyzed by ICP/MS, ASV, AAS, and GFAAS, sensitivity is in the low- to sub-ppb (0.1–15 ppb) with good accuracy and precision (Aguilera de Benzo et al. 1989; Delves and Campbell 1988; NIOSH 1977d, 1977e, 1977f, 1977g, 1977h; Que Hee et al. 1985a; Zhang et al. 1997). The presence of phosphate, ethylenediaminetetraacetic acid (EDTA) and oxalate can sequester lead and cause low readings in flame AAS (NIOSH 1984). A comparison of IDMS, ASV, and GFAAS showed that all three of these methods can be used to reliably quantify lead levels in blood (Que Hee et al. 1985a). ACGIH recommends quantification of blood lead by GFAAS. ESA, Inc., has introduced a simple to use, portable device for performing blood lead measurements using a finger stick or a venous sample (ESA 1998). Results can be obtained in about 3 minutes. For analysis of urine, chelation and solvent extraction, followed by atomic absorption for quantification is the recommended method (ACGIH 1986). Estimated accuracy reported for an IDMS technique was excellent (Manton and Cook 1984). Sensitivity and precision were not reported by the authors, but they are generally considered to be excellent (EPA 1986a; Grandjean and Olsen 1984).

In a recent article by Dyatlov et al. (1998), a method for the determination of Pb^{+2} and Ca^{+2} in intracellular fluids was described. In this method, a fluorescent, calcium indicator (fluo-3) was used. This dye fluoresces after binding Pb^{+2} and Ca^{+2}; lead is considered an interferant to the determination of calcium by this approach. However, by complexing the divalent lead ion with the heavy metal chelator TPEN (N,N,N',N'-tetrakis(2-pyridylmethyl)ethylene-diamine) prior to the addition of the fluo-3, the fluorescent

Table 6-1. Analytical Methods for Determining Lead in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample limit detection	Percent recovery	Reference
Blood	Wet ashing with acid mixtures; residue dissolution in dilute $HClO_4$	ASV with mercury-graphite electrode (NIOSH method P&CAM 195)	40 µg/L	95–105	NIOSH 1977d
Blood	Wet ashing with HNO_3; residue dissolution in dilute HNO_3	GFAAS (NIOSH method P&CAM 214)	100 µg/L	No data	NIOSH 1977g
Blood	Dilution with Triton X-100®; addition of nitric acid and diammonium phospate	GFAAS	2.4 µg/L	93–105	Aguilera et al. 1989
Blood	Dilution of sample with ammonium solution containing Triton X-100	ICP/MS	15 µg/L	96–111	Delves and Campbell 1988
Blood	Dilution of sample in 0.2% Triton X-100 and water	GFAAS	≈15 µg/L	97–150	Que Hee et al. 1985a
Blood	wet ashing, dilution	ICP/MS	0.1 ppb	94–100	Zhang et al. 1997
		GFAAS	4 ppb	90–108	
Blood and urine	Mixing of urine sample with HNO_3; filtration, chelation of lead in whole blood or filtered urine with APDC, extraction with MIBK	AAS (NIOSH Method 8003)	0.05 µg/g (blood) or 10 µg/mL (urine)	99 (±10.8%)	NIOSH 1984
Blood and urine	Wet ashing of sample with HNO_3, complexation with diphenylthio-carbazone, and extraction with chloroform	Spectrophotometry (NIOSH method P&CAM 102)	30 µg/L (blood); 12 µg/L (urine)	97 97	NIOSH 1977a
Blood and urine	^{206}Pb addition and sample acid digestion; lead coprecipitation by addition of $Ba(NO_3)_2$, followed by electrodeposition on platinum wire	IDMS	No data	98–99	Manton and Cook 1984

Table 6-1. Analytical Methods for Determining Lead in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample limit detection	Percent recovery	Reference
Blood and tissue	Digestion of sample with HNO_3 / $HclO_4$ / H_2SO_4; heat	ICP/AES (Method P&CAM 8005)	0.01 µg/g (blood) 0.2 µg/g (tissue)	113	NIOSH 1985a
Blood	Addition of 50 µL of blood into reagent, mixing, and transferring to sensor strip (commercial test kit)	Gold electrode sensor	1.4 µg/dL	No data	ESA 1998
Urine	Extraction of sample with polydithio-carbamate resin and NaOH; filtration on cellulose ester membrane; neutralization with NaOH; ashing; dissolution and heating; dilution with distilled water	ICP/AES (Method P&CAM 8310)	0.005 µg/mL	100	NIOSH 1984
Serum blood, and urine	Filtration of sample if needed; blood requires digestion in a Parr bomb; dilution of serum or urine with acid or water	ICP/AES	10–50 µg/L	85 (serum) >80 (urine, blood)	Que Hee and Boyle 1988
Urine	Wet ashing of sample with acid mixture and dissolution in dilute $HClO_4$	ASV with mercury-graphite electrode (Method P&CAM 200)	4 µg/L	90–110	NIOSH 1977e
Urine (δ-aminolevulinic acid)	Dilution of sample; reaction with ethylacetoacetate and ethylacetate to form δ-amino-levulinic acid-pyrrole; reaction with Erhlich's reagent	Spectrophotometry	No data	No data	Tomokuni and Ichiba 1988
Urine (δ-aminolevulinic acid)	Acidification of sample; separate δ-aminolevulinic acid on HPLC; reaction with formaldehyde and acetylacetone	HPLC/FL	10 µg/L	No data	Tabuchi et al. 1989
Plasma, Urine (δ-aminolevulinic acid)	Derivatization of δ-aminolevulinic acid with formaldehyde and acetylacetone to form fluorescent compounds; separation using HPLC	HPLC/FL	3 µg/L	No data	Oishi et al. 1996

Table 6-1. Analytical Methods for Determining Lead in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample limit detection	Percent recovery	Reference
Serum and cerebrospinal fluid	^{206}Pb addition and sample acid digestion; lead isolation by ion-exchange, elution, and deposition onto platinum wire	IDMS	No data	80–120	Manton and Cook 1984
Feces	Dessication and pulverization of sample; digestion with hot acid in Paar bomb	ICP/AES	10–50 µg/L	>86	Que Hee and Boyle 1988
Testes, liver, spleen, kidney	Dicing of sample and digestion in hot acid in a Paar bomb; evaporation; redissolution in HCl/HNO_3	ICP/AES	10–50 µg/L	>80	Que Hee and Boyle 1988
Spleen, liver, and kidney; Liver, kidney, muscle	Wet digestion of sample with HNO_3-$HClO_4$ mixture; Bomb digestion of sample with acid and heat or digestion with acid and dry ashing; dissollution in acid; dilution with water	GFAAS GFAAS DPASV	No data 20 µg/g (bomb); 5 µg/g (dry ashing) No data	No data 85–107 (bomb); 75–107 (dry ashing) 82–120	Blakley and Archer 1982; Ellen and Van Loon 1990
Tissues (brain, heart, lung, kidney, liver, and testes)	Dry ashing of sample; dissolution in HNO_3	AAS	No data	No data	Exon et al. 1979
Tissues	Freeze drying of samples; subjection to thermal neutron irradiation; chemical separation of elements	NAA	No data	No data	Hewitt 1988
Brain	Wet ashing of sample with mixture of acids, mixing with Metex® and analysis	ASV	No data	No data	Jason and Kellogg 1981
Bone	Partially polarized photon directed at second phalanx of left forefinger (noninvasive technique)	K-XRF	20 µg/g	No data	Christoffersson et al. 1986

Table 6-1. Analytical Methods for Determining Lead in Biological Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample limit detection	Percent recovery	Reference
Bone	Partially polarized photon directed at anteromedial skin surface of mid-tibia (non-invasive technique)	L-XRF	20 µg/g	No data	Wielopolski et al. 1986
Teeth	Cleaning and sectioning of tooth; digestion with HNO_3; evaporation; redissollution in buffer solution	ASV	No data	83–114	Rabinowitz et al. 1989
Teeth	Dry ashing of sample; crushing; dry ashing again; dissollution in HNO_3	AAS	No data	90–110	Steenhout and Pourtois 1981
Hair	Cleaning of sample with acetone/ methanol; digestion with acid mixture and heat; diammonium phosphate addition as matrix modifier	GFAAS	0.16 µg/g	99	Wilhelm et al. 1989
Bone	^{109}Cd gamma-ray irradiation with source at 2.5 cm from skin of proximal tibia	K-XRF	2 µg/g	No data	Hu et al. 1989, 1990, 1991
Hair	Cleaning of sample with hexane, ethanol, and water; wet ashing with HNO_3 and H_2O_2	ICP/AES	No data	No data	Thatcher et al. 1982

AAS = atomic absorption spectroscopy; APDC = ammonium pyrrolidine dithiocarbamate; ASV = anode stripping voltammetry; $Ba(NO_3)_2$ = barium nitrate; ^{109}Cd = cadmium 109 radioisotope; DPASV = differential pulse anodic stripping voltammetry; GFAAS = graphite furnace atomic absorption spectroscopy; H_2O_2 = hydrogen peroxide; HCl = hydrogen chloride; H_2SO_4 = sulfuric acid; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; HPLC/FL = high performance liquid chromatography/fluorimetry; ICP/AES = inductively coupled plasma/atomic emission spectroscopy; ICP-MS = inductively coupled plasma-mass spectrometry; IDMS = isotope dilution mass spectrometry; K-XRF = K-wave X-ray fluorescence; L-XRF = L-wave X-ray fluorescence; MIBK = methyl isobutyl ketone; NAA = neutron activation analysis; NaOH = sodium hydroxide; NIOSH = National Institute for Occupational Safety and Health; P&CAM = physical and chemical analytical methods; ^{206}Pb = lead 206

product was proportional to the concentration of Ca^{+2} and lead was determined by difference. An LOD of 1 pM lead was estimated for cell-free media. This interaction shows how divalent lead can interfere with the actions of other divalent cations such as calcium, an aspect of crucial importance in living organisms (see Chapter 2).

Several biomarkers exist for monitoring exposure to lead. A number of biochemical assays are available for the assessment of lead exposure and toxicity in the human body using standard clinical laboratory techniques. Details of such assays are reported in several reviews (EPA 1986a; Grandjean and Olsen 1984; Stokinger 1981) and are also available in standard clinical laboratory methods manuals. The commonly used assays are coproporphyrin, 1,25-dihydroxyvitamin D, ALA (δ-aminolevulinic acid), and EP (erythrocyte protoporphyrin) concentrations and ALAD (ALA dehydratase) activity. All of these assays are sensitive, reliable, and well established; however, erythrocyte protoporphyrin and ALAD activity appear to be the most useful and sensitive for determining exposure to lead. A recent review (Porru and Alessio 1996) indicated that ALAD activity was proportional to blood lead concentration ranging from 10–40 µg/dL, and EP concentration was proportional to blood lead over the range of 30–80 µg/dL. The EP concentration was said to be useful for assessing exposure experienced over the past 3 to 4 months. Urinary ALA, however, was not proportional to blood lead until the blood concentrations reached 60–70 µg/dL, a concentration too high to be of use for early screening since other clinical symptoms should already be evident. A colorimetric method for detection of ALA in urine, in which the pyrrole from ALA is formed and reacted with Ehrlich's reagent to form a colored end product, has been used successfully (Tomokuni and Ichiba 1988). ALA has also been determined in urine using high-performance liquid chromatography (HPLC) followed by quantification of a fluorescent end product (Tabuchi et al. 1989). A similar approach to ALA determination in blood and urine was described by Oishi et al. (1996) and was more sensitive than the method of Tabuchi et al. (1989). Erythrocyte protoporphyrin bound to zinc has been quantified using hemofluorimetry (Braithwaite and Brown 1987). An HPLC/fluorescent method has been reported for determination of coproporphyrin in urine (Tomokuni et al. 1988). Other biological assays that have been used as indicators of lead exposure are serum immunoglobulins and salivary IgA (Ewers et al. 1982). While all these biological assays are reliable and have been verified for clinical laboratory use, they are not specific for lead.

Tissues. Lead has been quantified in a variety of tissues, including liver, kidney, brain, heart, lung, muscle, and testes. Techniques for measuring lead in tissues are similar to those used for blood and urine. When AAS, GFAAS, or ASV are used for analysis, the samples may be wet ashed, digested with acid, or

bomb digested (Blakley and Archer 1982; Blakley et al. 1982; Ellen and Van Loon 1990; Exon et al. 1979; Jason and Kellogg 1981; Que Hee and Boyle 1988). The information located did not allow an adequate comparison between these methods. Parr bomb digestions are recommended for estimation of metals in biological tissues (Que Hee and Boyle 1988). Sensitivities reported for GFAAS and ICP/AES are in the low ppm (5–20 ppm) (Ellen and Van Loon 1990) and are probably comparable for the other techniques. Differential anodic stripping pulse voltametry (DPASV) and NAA have also been used to analyze tissues for lead. Sample preparation for DPASV is the same as those for AAS, GFAAS, and ASV. Its accuracy and precision are comparable to results using GFAAS, and its sensitivity is slightly greater (Ellen and Van Loon 1990). Determination of lead in tissue samples following freeze drying, neutron irradiation, and chemical separation has been reported. An advantage of this method is that the sample does not have to be dissolved. No further information was reported for the method (Hewitt 1988).

Hair, Teeth, and Bone. Noninvasive methods using X-ray fluorescence can be used for the determination of lead concentration in bones. These methods include L X-rays of the tibia using an X-ray generator (Wielopolski et al. 1986); K X-rays in the second phalanx of the index finger using a cobalt source and a germanium silicon detector (Christoffersson et al. 1986); and *in vivo* tibial K X-ray fluorescence (Batuman et al. 1989; Hu et al. 1989, 1990, 1991). This latter method has the advantage of deeper penetration of the bone (2 cm) to allow for averaging lead concentrations over the whole bone thickness (Wedeen 1990). The better penetration also alleviates errors resulting from the measurement of overlying skin and makes the method relatively insensitive to movement of the subject during the 15-minute sampling period (Landigran and Todd 1994). The level of lead in bone has been reported to be a good indicator of stored lead in body tissue (Ahlgren et al. 1976; Bloch et al. 1976; Rosen et al. 1987; Skerfving et al. 1993). The sensitivity of the technique is in the low ppm and the precision is acceptable. Advantages are that no sample preparation is required and the technique can safely and easily be done on live subjects. Teeth have been analyzed for lead using AAS and ASV (Rabinowitz et al. 1989; Steenhout and Pourtois 1981). Samples must be dry ashed or digested with acid prior to analysis. Precision and accuracy of both AAS and ASV are good. Detection limits were not reported by the authors. A detection limit in the sub-ppm (0.16 ppm) and high accuracy were reported for GFAAS analysis of hair samples (Wilhelm et al. 1989). ICP/AES has also been used to analyze hair for lead, but lack of data prevents a comparison with the AAS method (Thatcher et al. 1982).

The isotopic distribution of lead (IDMS) in shed teeth from children has been shown to be useful in studies of the history of exposure to lead, including the definition of the source of the exposure, e.g., mine dust vs.

food (Gulson and Wilson 1994), so IDMS certainly has important applicability, if not for routine determinations. ICP/MS, however, is easier, more sensitive, allows for multi-element analysis, and provides isotopic data.

6.2 ENVIRONMENTAL SAMPLES

The primary methods of analyzing for lead in environmental samples are AAS, GFAAS, ASV, ICP/AES, and XRFS (Lima et al. 1995). Less commonly employed techniques include ICP/MS, gas chromatography/photoionization detector (GC/PID), IDMS, DPASV, electron probe X-ray microanalysis (EPXMA), and laser microprobe mass analysis (LAMMA). The use of ICP/MS will become more routine in the future because of the sensitivity and specificity of the technique. ICP/MS is generally 3 orders of magnitude more sensitive than ICP/AES (Al-Rashdan et al. 1991). Chromatography (GC, HPLC) in conjunction with ICP/MS can also permit the separation and quantification of organometallic and inorganic forms of lead (Al-Rashdan et al. 1991). In determining the lead concentrations in the atmosphere and water, a distinction between the concentration of lead in the particulate and gaseous or dissolved forms is often necessary. Particulate lead can be separated from either media using a filter technique. The filter collects the particulate matter and allows the dissolved material to pass through for separate analysis of each form. As with the analysis of biological samples, the definitive method of analysis for lead is IDMS. However, most laboratories do not possess the expertise or equipment required for this method. ICP/MS is becoming more available and will probably soon become the major method. Table 6-2 summarizes several methods for determining lead in a variety of environmental matrices.

Air. Various methods have been used to analyze for particulate lead in air. The primary methods, AAS, GFAAS, ICP/AES are sensitive to levels in the low $\mu g/m^3$ range (0.1–20 $\mu g/m^{3)}$ (Birch et al. 1980; EPA 1988b; NIOSH 1977c, 1977g, 1981, 1984, 1994; Scott et al. 1976). Accuracy and precision are generally good. GFAAS is considered to be more sensitive than AAS; however, AAS is not subject to as much interference from matrix effects as GFAAS (NIOSH 1977b, 1977g, 1977i). Detection of particulate lead by generation of the lead hydride has been used to increase the sensitivity of the AAS technique (Nerin et al. 1989). Excellent accuracy and precision was reported for this method. ASV has

Table 6-2. Analytical Methods for Determining Lead in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (particulate lead)	Collection of particulate matter onto membrane filter; digestion with HNO_3 / H_2O_2; dilution with distilled water	GFAAS (Method P&CAM 7105)	2.0 µg/m^3	82–103	NIOSH 1990, 1994
Air (particulate lead)	Collection of particulate matter onto membrane filter; wet ashing with HNO_3 / $HClO_4$ / H_2SO_4; dissolution in acetate buffer	ASV with mercury-graphite electrode (Method P&CAM 191)	0.16 µg/m^3	90–110	NIOSH 1977c
Air (particulate lead)	Collection of particulate matter onto membrane filter; wet ashing with HNO_3	AAS flame (Method 7082)	50 µg/m^3	82–103	NIOSH 1984
Air (particulate lead)	Collection of particulate matter onto cellulose acetate membrane filter; wet ashing with HNO_3 / $HClO_4$	ICP/AES (Method P&CAM 7300)	5 µg/m^3	95–105	NIOSH 1984
Air (particulate lead)	Collection of particulate matter onto filter; extraction with HNO_3 / HCl, heat, and sonication	ICP/AES	No data	No data	EPA 1988a
Air (particulate lead)	Collection of particulate matter onto filter; dry ashing; extraction with HNO_3 / HCl; dilution with HNO_3	AAS AES	0.1 µg/m^3 0.15 µg/m^3	93 102	Scott et al. 1976
Air (particulate lead)	Collection of sample onto cellulose acetate filter; dissolution in HNO_3 with heat; addition of HCl / H_2O_2 and reaction in hydride generator with sodium borohydride to generate lead hydride	AAS	8 ng/L	100–101	Nerin et al. 1989
Air (particulate lead)	Collection of sample onto filter; addition of ^{206}Pb to filter; dissolution of filter in NaOH; acidification; separation of lead by electrodeposition; dissolution in acid	IDMS	0.1 ng/m^3	No data	Volkening et al. 1988
Air (particulate PbS)	Collection of particles onto filter, suspension in THF, recollection onto silver filter	XRD	60 µg/m^3	102.6	NIOSH 1994
Air (particulate lead)	Collection of sample onto nucleopore polycarbonate filter; coating of filter sections with carbon	EPXMA LAMMA	No data No data	No data No data	Van Borm et al. 1990
Air (tetramethyl and tetraethyl lead)	Adsorption of volatile compounds in filtered sample onto XAD-2 resin, desorption with pentane	GC/PID (Method 2534 (TML) and 2537 (TEL))	40 µg/m^3 (TML) 45 µg/m^3 (TEL)	99 105.5	NIOSH 1987
Air (particulate and organolead)	Collection of particulate matter collected onto glass fiber filter; passage of filtered gases through iodine monochloride bubblers; wet ashing of particulate matter; conversion of lead compounds in bubbler solution to dithiazone complex in presence of EDTA-salts and extraction with carbon tetrachloride solution followed by acid extraction	GFAAS	No data (particulate); 0.25 ng/m^3 (gaseous)	No data (particulate); 95–99 (gaseous)	Birch et al. 1980

Table 6-2. Analytical Methods for Determining Lead in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Air (particulate and organolead)	Collection of particulate matter collected onto nucleopore filters; filtered gases cryogenically trapped and thermally desorbed	XRF (particulate) GC/GFAAS (gaseous)	0.3 µg/m^3 0.2 ng/m^3	46–>90 90–100	De Jonghe et al. 1981
Surface contamination (lead and its compounds)	Wiping of defined area surface using a moistened gauze pad; digestion of sample using nitric acid; dilution.	ICP/AES GFAAS	2 µg/sample 0.1 µg/sample	No data	NIOSH 1994
Water (particulate and dissolved lead)	Filtration of water through a 0.45 µm membrane filter (dissolved lead); particulate material dissolved by wet ashing (insoluble lead)	ICP/AES (EPA Method 200.7)	42 µg/L	94–125	EPA 1983a
Water (TAL)	Extraction with hexane	GC/AAS	0.5 µg/L	88–90	Chau et al. 1979
Water (TAL)	Purging of sample with gas followed by cryogenically trapping volatile species onto solid sorbent GC column	GC/AAS	0.5 ng/g	No data	Chau et al. 1980
Water (alkyl lead)	Complexation of sample with diethyldithiocarbamate; extraction with pentane; removal of water; butylation; extraction with nonane	GC/AAS	1.25 ng/L	90–108	Chakraborti et al. 1984
Water (particulate and dissolved lead)	Filtration of water through a 0.45 µm membrane filter (dissolved lead); particulate material dissolved by wet ashing (insoluble lead)	AAS (EPA Method 239.1) GFAAS (EPA Method 239.2)	0.1 mg/L 1 µg/L	99.8–125.7 88–95	EPA 1983a
Water (total lead)	Digestion of sample with acid and heat; dilution with water	AAS	1.0 ng/g	No data	Chau et al. 1979
Water (dissolved or total)	Digestion of water sample followed by filtration, acidification, addition of ammoniacal citrate-cyanide reducing solution; extraction with chloroform containing dithizone.	Measure absorbance at 510 nm (Standard Method 3500-PbD)	0.5 µg/L	98.6% at 10.4 µg/L (6.8% RSD)	Eaton et al. 1995a
Water	Direct introduction of water or of extract following extraction of water with methyl isobutyl ketone containing ammonium pyrolidine dithiocarbamate.	AAS (Standard Method 3111	0.5 mg/L at 283.3 nm	No data (%RSD = 4.7 for direct; 23.5 for extract)	Eaton et al. 1995b
Water and wastewater (dissolved, total)	Addition of matrix modifier, analysis	GFAAS (Standard Method 3113)	1 µg/L at 283.3 nm	117% at 10.4 µg/L (31 %RSD for surface water at 10.4 µg/L	Eaton et al. 1995c

Table 6-2. Analytical Methods for Determining Lead in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water and wastewater (dissolved, total)	Filtration/acidification and analysis for dissolved; digestion followed by analysis for total	ICP/AES (Standard Method 3120)	40 µg/L	104% (12.5 %RSD) at 100 µg/L	Eaton et al. 1995d
Water, extracts or digests of waste	Filtration or digestion as appropriate (depends on matrix, dissolved or total, acid leachable, etc.)	ICP/MS (EPA Method 6020)	No data	71–137% (11–23% RSD) for aqueous solutions; 90–104% (6–28% RSD) for solid samples	EPA 1994e
Water	Filtration; addition of $Ni(NO_3)_2$ and $NH_4H_2PO_4$matrix modifiers	ETAAS	0.14 µg/L	89–101	Xu and Liang 1997
Water (total lead)	Filtration of sample followed by analysis; digestion of filter with acid	ICP/AES	10–50 µg/L	>80	Que Hee and Boyle 1988
Soil	Drying of soil sample followed by sieving; digestion with HNO_3; centrifugation	ICP/AES	0.09 µg/g	97–103	Schmitt et al. 1988
Dust	Wiping of hard surface of known dimension; acid digestion	ICP/AES AAS GFAAS	Varies	No data	ASTM 1998f (ASTM E 1728) ASTM 1998b (ASTM E 1644) ASTM 1998a (ASTM E 1613)
Soil	Drying of soil followed by homogenization, digestion with nitric acid and hydrogen peroxide, dilution	ICP/AES AAS GFAAS	Varies	No data	ASTM 1998e (ASTM E 1727) ASTM 1998d (ASTM E 1726) ASTM 1998a (ASTM E 1613)
Soil	Drying of soil sample followed by sieving, digestion with HNO_3, filtration	AAS	no data	no data	Mielke et al. 1983
Soil	Drying of sample and sieving for XRF; digestion of sieved sample with HNO_3 and heat for AAS	XRF AAS	No data No data	65–98 63–68	Krueger and Duguay 1989
Soil	Drying of sample, dry ashing, digestion with acid, and dilution with water	AAS	2 µg/g	79–103	Beyer and Cromartie 1987

Table 6-2. Analytical Methods for Determining Lead in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Soil	Digestion with HNO_3 and H_2O_2; evaporation; redissolution with HNO_3; filtration	FI-HG-AAS	2 µg/L	98–101	Samanta and Chakraborti 1996.
Soil, wastes, and groundwater	Acid digestion of sample, dilution with water, and filtration	AAS (EPA method 7420) GFAAS (EPA method 7421)	0.1 mg/L 1 µg/L	No data No data	*EPA 1986e*
Soil, dust, and paint	Digestion of sample with hot acid; evaporation of water; redissolution in HNO_3	AAS	12 ng/g	>80	Que Hee et al. 1985b
Sediment	Digestion of sample with hot HNO_3/H_2SO_4	GFAAS	No data	92–95	Bloom and Crecelius 1987
Sediment, fish (TAL)	Homogenization of fish; addition of EDTA to sample; extraction with hexane; centrifugation; isolation off organic layer for analysis.	GC/AAS	0.01 µg/g (sediment) 0.025 µg/g	81–85 72–76	Chau et al. 1979
Sediment, (fish), vegetation (TAL)	Purging of sample with gas followed by cryogenically trapping volatile species onto solid sorbent GC column.	GC/AAS	0.1 ng/g (solid)	No data	Chau et al. 1980
Sediment, fish, vegetation (total lead)	Digestion of sample with acid and heat; dilution with water	AAS	50 ng/g (sediment) 10 ng/g (fish and vege-tation)	No data No data	Chau et al. 1980
Dried paint	Sample collection using heat gun, cold scraping, or coring methods; microwave digestion with nitric acid and hydrochloric acid	ICP/AES AAS GFAAS	Varies	No data	ASTM 1998g (ASTM E 1729) ASTM 1998c (ASTM E 1645) ASTM 1998a (ASTM E 1613)
Milk	Addition of 50 µL $(C_2H_5)_4NOH$ in ethanol to 25 µL milk followed by heating and dilution with water to 125 µL	GFAAS	No data	No data	Michaelson and Sauerhoff 1974
Evaporated milk	Dry ashing of sample; dissolution in HNO_3	ASV	0.005 µg/g	99	Capar and Rigsby 1989
Mussel, tomato	Digestion of sample with acid or acid plus catalyst; generation of lead hydride	GFAAS	4 ng/g	94–95	Aroza et al. 1989
Agricultural crops	Dry ashing of sample with H_2SO_4 and HNO_3; dilution with water	DPASV	0.4 ng/g	85–106	Satzger et al. 1982

Table 6-2. Analytical Methods for Determining Lead in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Grains, milk mussel, fish	Bomb digestion of sample with acid and heat or digestion with acid and dry ashing; dissolution in acid; dilution with water	GFAAS	20 µg/g (bomb); 5 µg/g (dry ash)	85–107	Ellen and Van Loon 1990
			No data	75–107	
		DPASV		82–120	
Edible oils	Microwave digestion with acid mixture; $(NH_4)_2PO_4$ added as matrix modifier	ICP/AES	50 ng/g	75–107	Allen et al. 1998
		GFAAS	30 ng/g	78–117	
Citrus leaves and paint	Chopping or pulverization of sample; digestion with hot acid; evaporation of water; redissolution in acid	ICP/AES	10–50 µg/L	75–82 (citrus leaves); 89–96 (paint)	Que Hee and Boyle 1988

AA = atomic absorption; AAS = atomic absorption spectroscopy; AES = atomic emissions spectroscopy; ASV = anode stripping voltammetry; $(C_2H_5)_4NOH$ = tetraethylammonium hydroxide; DPASV = differential pulse anodic stripping voltammetry; EDTA = ethylenediamine tetraacetic acid; EPA = Environmental Protection Agency; EPXMA = electron probe X-ray micro-analysis; ETAAS = electrothermal atomic absorption spectroscopy; GC = gas chromatography; GFAAS = graphite furnace atomic absorption spectrometry; HCl = hydrochloric acid; $HClO_4$ = perchloric acid; HNO_3 = nitric acid; H_2O_2 = hydrogen peroxide; H_2SO_4 = sulfuric acid; ICP/AES = inductively coupled plasma-atomic emission spectroscopy; IDMS = isotope dilution mass spectrometry; LAMMA = laser microprobe mass analysis; MS = mass spectrometry; NaOH = sodium hydroxide; NG = nanogram; ^{206}Pb = lead 206; P&CAM = physical and chemical analytical methods; PID = photoionization detector; TAL = tetraalkyl leads; TEL = tetraethyl lead; THF = tetrahydrofuran; TML = tetramethyl lead; XRD = X-ray diffraction; XRF = X-ray fluorescence

a wide range as well as high sensitivity. It is relatively inexpensive compared to other methods (NIOSH 1977b). Advantages of ICP/AES are that it has a wide range and allows analysis of several elements at once. However, the technique is expensive in terms of equipment and supplies (NIOSH 1981). XRFS has been used to analyze for particulate lead in air (DeJonghe et al. 1981). While sensitivity was good, recovery was highly variable and relatively low compared to other methods. The highest sensitivity was obtained with IDMS, as expected (Volkening et al. 1988). As previously stated, this is the definitive method for determining lead in environmental, as well as biological samples. Two sophisticated methods, EPXMA and LAMMA, have been used to determine the inorganic lead species present in particulate matter in air (Van Borm et al. 1990).

Determination of lead vapor in air requires prior filtering of the air to exclude particulate lead, and trapping of the gaseous components. Gaseous lead is also referred to as organic lead or alkyl lead, the most common being the tetraalkyl species. Organic lead species may be trapped by liquid or solid sorbents, or cryogenically (Birch et al. 1980; DeJonghe et al. 1981; NIOSH 1978b). Gas chromatography (GC) is used to separate the different alkyl species. Detection by GFAAS and PID have been reported (DeJonghe et al. 1981; NIOSH 1978b). GFAAS detection is more sensitive than PID, but both have good accuracy.

Water. As with air, water can be analyzed for both particulate and dissolved (organic) lead. Particulate lead collected on a filter is usually wet ashed prior to analysis. Comparison of the GFAAS and AAS methods for particulate lead showed the former technique to be about 100 times more sensitive than the latter, although both offer relatively good accuracy and precision (EPA 1983). ICP/MS has been used to determine lead in water (EPA 1994e). Chelation/extraction can also be used to recover lead from aqueous matrices (Eaton 1995b). GC/AAS has been used to determine organic lead, present as various alkyl lead species, in water (Chakraborti et al. 1984; Chau et al. 1979, 1980). Sample preparation for organic lead analysis was either by organic solvent extraction (Chakraborti et al. 1984; Chau et al. 1979) or purge-and-trap (Chau et al. 1980). Sensitivity was in the ppb to ppt range and reliability was similar for all three methods. Total lead can be determined by digesting samples with acid and analyzing by either AAS or the more sensitive GFAAS (Chau et al. 1980; EPA 1982c, 1986e).

Dusts, Sediments, and Soil. Both total and organic lead have been determined in dusts, sediments, and soils. In most cases the sample must be digested with acid to break down the organic matrix prior to analysis (ASTM 1998b, 1998d; Beyer and Cromartie 1987; Bloom and Crecelius 1987; EPA 1982c, 1986e; Krueger and Duguay 1989; Mielke et al. 1983; Que Hee and Boyle 1988; Que Hee et al. 1985b; Samanta

and Chakraborti 1996; Schmitt et al. 1988); however, organic extraction (Chau et al. 1979) and purge-and-trap (Chau et al. 1980) have also been used. The primary detection methods are ICP/AES, AAS or GFAAS, GFAAS being more sensitive, but also more susceptible to interference. When quantification of organic lead is desired, GC is employed to separate the alkyl lead species (Chau et al. 1979, 1980). Precision and accuracy are acceptable for these atomic absorption-based methods (Beyer and Cromartie 1987; Bloom and Crecelius 1987; Chau et al. 1979; EPA 1982c, 1986e; Krueger and Duguay 1989; Que Hee et al. 1985b). ICP/AES is reported to be more sensitive and reliable than atomic absorption techniques (Schmitt et al. 1988), but sample collection and preparation methods have been shown to strongly influence the reliability of the overall method (Que Hee et al. 1985b). Sampling of house dust and hand dust of children requires special procedures (Que Hee et al. 1985b). XRFS appears to provide a simpler method of measuring lead in soil matrices; however, the available data do not permit an assessment of the techniques sensitivity and reliability for soil analysis (Krueger and Duguay 1989). XRFS has been shown to permit speciation of inorganic and organic forms of lead in soil for source elucidation (Manceau et al. 1996).

Other Matrices. Lead has been determined in several other environmental matrices, including paint, fish, vegetation, agricultural crops, and various foods. As with soil, the methods of choice are either ICP/AES, AAS, or GFAAS. Samples may be prepared using one of the methods described for sediment and soil or by wet or dry ashing (Aroza et al. 1989; ASTM 1998d; Capar and Rigsby 1989; Que Hee and Boyle 1988; Que Hee et al. 1985b; Satzger et al. 1982). ASV and DPASV have also been used with good sensitivity (ppb) and reliability to analyze for lead in other environmental media (Capar and Rigsby 1989; Ellen and Van Loon 1990; Satzger et al. 1982).

6.3 ADEQUACY OF THE DATABASE

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

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would

reduce or eliminate the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect Methods are available for measuring inorganic lead in blood, serum, urine, cerebrospinal fluid, tissues, bone, teeth, and hair (Aguilera de Benzo et al. 1989; Batuman et al. 1989; Blakley and Archer 1982; Blakley et al. 1982; Christoffersson et al. 1986; Delves and Campbell 1988; Ellen and Van Loon 1990; Exon et al. 1979; Hu et al. 1989, 1990, 1991; Jason and Kellogg 1981; Manton and Cook 1984; NIOSH 1977a, 1977d, 1977e, 1977f, 1977g, 1977h, 1984; Que Hee and Boyle 1988; Que Hee et al. 1985a; Wielopolski et al. 1986; Zhang et al. 1997). Available methods for determining lead in body fluids are sensitive and reliable for measuring background exposure levels, as well as exposure levels at which health effects have been observed to occur. Blood lead levels have been found to correlate best with exposure concentrations (Rabinowitz et al. 1985; Moore 1995). Methods of quantifying lead in tissues, bone, teeth, and hair are generally reliable, but are only sensitive at relatively high exposure concentrations. There is a need for more sensitive methods of detection for matrices so that correlations between lead levels in these media and exposure concentrations can be more reliably determined. Several nonspecific biomarkers are used to assess exposure to lead. These include ALAD activity and ALA, EP, coproporphyrin, and 1,25-dihydroxyvitamin D concentrations (Braithwaite and Brown 1987; EPA 1986a; Grandjean and Olsen 1984; Oishi et al. 1996; Porru and Alessio 1996; Stokinger 1981; Tabuchi et al. 1989; Tomokuni and Ichiba 1988; Tomokuni et al. 1988). The methods for determining these variables are sensitive, reliable, and well established. No additional research for these biomarkers appears to be needed. There is a need to identify and quantify those molecules responsible for lead transport within the body; the measurement of lead associated with these compounds could provide additional information about exposure.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Numerous analytical methods are available for measuring inorganic and organic lead compounds in air, water, sediments, dust, paint, soil, fish, agricultural products, and foodstuffs (Eaton et al. 1995a, 1995b, 1995c, 1995d; Eckel and Jacob 1988; EPA 1982a, 1986a, 1988b, 1988f, 1989f, 1989h, 1990c, 1994e; Lee et al. 1989; Maenhaut et al. 1979; Mielke 1992; Mielke et al. 1983, 1985, 1989). Most of these are sensitive and reliable for determining background concentrations of lead compounds in the

environment and levels at which health effects might occur. The most frequently used methods are AAS, GFAAS, ASV, and ICP/AES, the methods recommended by EPA and NIOSH (ASTM 1998a; Birch et al. 1980; EPA 1988b; NIOSH 1977c, 1981, 1984; Scott et al. 1976). The definitive method is IDMS, which is used to produce reference standards by which laboratories can determine the reliability of their analyses (Volkening et al. 1988). No additional analytical methods for determining low levels of lead compounds in environmental media are needed. Additional method development work is needed if individual lead species in environmental media are to be accurately determined. ICP/MS based methods should be critically examined.

6.3.2 Ongoing Studies

Ongoing studies regarding analytical methods for lead were reported in the Federal Research in Progress File (FEDRIP 1998) database. Only one had relevance to analytical methods and was related to biomarkers. Dr. Liebelt at Yale University, with funding from the National Center for Research Resources, is investigating erythropoietin production in children with lead poisoning.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding lead in air, water, and other media are summarized in Table 7-1.

ATSDR has not derived MRLs for lead. The EPA has not developed a reference concentration (RfC) for lead. EPA has also decided that it would be inappropriate to develop a reference dose (RfD) for inorganic lead (and lead compounds) because some of the health effects associated with exposure to lead occur at blood lead levels as low as to be essentially without a threshold (IRIS 1999).

EPA has assigned lead a weight-of-evidence carcinogen classification of B2, which indicates that lead is a probable human carcinogen (IRIS 1999). The International Agency for Research on Cancer (IARC) has determined that there is sufficient evidence from animal studies to classify lead and some lead compounds as possibly carcinogenic to humans; group 2B (IARC 1987). The evidence relevant to carcinogenicity from studies of human exposures to lead and some lead compounds is inadequate to permit conclusions regarding the presence or absence of a casual association (IARC 1987). The IARC has determined that organolead compounds are not classifiable as to their carcinogenicity to humans; group 3 (IARC 1987). The American Conference of Governmental Industrial Hygienists (ACGIH) has categorized elemental lead and certain inorganic lead compounds, assessed as lead, as A3 carcinogens: carcinogenic in experimental animals at a relatively high dose not considered relevant to worker exposure. The data obtained from epidemiologic studies suggest that, except for uncommon routes or levels of exposure, these substances are unlikely to cause cancer in humans (ACGIH 1998). The ACGIH has categorized lead chromate, assessed on the basis of both lead and chromium, as an A2 carcinogen. Although substances in this category are carcinogenic in experimental animals at dose levels that are considered relevant to worker exposure, the data from epidemiologic studies are insufficient to confirm an increased risk of cancer in exposed humans (ACGIH 1998).

OSHA requires employers of workers who are occupationally exposed to a toxic or hazardous substance to institute engineering controls and work practices that maintain or reduce their exposure to a level that is at or below the permissible exposure limit (PEL) established for the substance. For occupational exposures to lead, the employer must use engineering controls and work practices to achieve an occupational exposure of 50 $\mu g/m^3$ (0.006 ppm) or lower, based on an 8-hour time-weighted average (TWA) (OSHA 1995). When employee exposures to lead can not be maintained at or below 50 $\mu g/m^3$ through engineering and work practice controls, the employer is required to provide the employees with respirators as a means of supple-

mental control. The specifications for different types of respirators and the conditions for their use are provided in the Code of Federal Regulations at 29 CFR 1910.1025. OSHA specifies 30 µg/m^3 of air as the action level for employee exposure to airborne concentrations of lead (OSHA 1995). Under the requirements for medical surveillance and biological monitoring, the blood lead level of employees exposed to lead above the action level for more than 30 days per year must be determined at least every 6 months. The frequency for sampling an employee's blood for lead levels increases to every 2 months if the results of his previous blood analysis indicated a blood lead level at or above 40 µg/dL (OSHA 1995). OSHA requires continuing the 2-month sampling scenario until the employee's blood lead level measures below 40 µg/dL for 2 consecutive samplings. If an employee is working in an area where exposure to lead is at or above the action level, and the employee's periodic blood test or a follow-up test indicates a blood lead level at or above 50 µg/dL, the employer is required to remove the employee from that work area (OSHA 1995). The relocation of an employee may also be instituted if the average of the 3 most recent blood tests or the average of all blood tests given over the most recent 6 month period indicates a blood lead level at or above 50 µg/dL. If however, the last single blood test taken during this period indicates a blood lead level at or below 40 µg/dL, relocation of the employee may not be required (OSHA 1995). Except for the construction industry and certain aspects of the agricultural industry, more detailed requirements for limiting all occupational exposures to lead, including shipyard employment (OSHA 1996), can be found in 29 CFR 1910.1025 (OSHA 1995). On May 4, 1993, OSHA published an interim final rule which reduced the permitted level of occupational exposure to lead for construction workers from an 8-hour TWA of 200 µg/m^3 to an 8-hour TWA of 50 µg/m^3 (OSHA 1993). As with other industries, the action level for occupational exposure to lead in the construction industry is 30 µg/m^3 (OSHA 1998). More detailed requirements for protecting construction workers from occupational exposures to lead can be found in 29 CFR 1926.62 (OSHA 1998).

The EPA regulates lead under the Clean Air Act (CAA) and has designated lead as a hazardous air pollutant (HAP). The major stationary source categories for which lead emissions are controlled in accordance with promulgated performance standards are secondary lead smelters (EPA 1977), primary copper smelters (EPA 1976a), primary lead smelters (EPA 1976b), glass manufacturing plants (EPA 1980a), lead-acid battery manufacturing (EPA 1982a), metallic mineral processing plants (EPA 1984a), and the synthetic organic chemicals manufacturing industry (EPA 1983b, 1990a, 1993a, 1994f).

In the early 1970s, after determining that lead additives would impair the performance of emission control systems installed on motor vehicles and that lead particle emissions from motor vehicles presented a

significant health risk to urban populations, the EPA began regulating the lead content in gasoline (EPA 1996f). In 1973, EPA instituted a phase-down program designed to minimize the lead content of leaded gasoline over time. By 1988, the total lead usage in gasoline had been reduced to less than 1% of the amount of lead used in the peak year of 1970 (EPA 1996f). The EPA defined unleaded gasoline as gasoline produced without the use of any lead additive and containing not more than 0.05 g of lead per gallon and not more than 0.0005 g of phosphorous per gallon. The 0.05 g criterion was allowed because EPA determined that this maximum trace level would provide adequate protection for catalyst emission control devices (i.e., prevent deterioration in emission control systems) and would be practicable for the petroleum industry. In 1990, Congress added Section 211(n) to the CAA and provided that after December 31, 1995, it would be unlawful to offer, sell, dispense, or transport, for use as fuel in any motor vehicle any gasoline which contains lead or lead additives. The effective date for this prohibition was January 1, 1996 (EPA 1996f). On February 2, 1996, the EPA published a direct final rule revising its regulation for consistency with the CAA prohibitions; however, EPA's definition of unleaded gasoline still allowed the sale of gasoline containing trace amounts of lead up to 0.05 g per gallon. The current definition, however, expressly prohibits the use of any lead additive in the production of unleaded gasoline. The term "lead additive" was defined to include pure lead as well as lead compounds (EPA 1996f).

Lead is regulated by the Clean Water Effluent Guidelines and Standards which are promulgated under the authority of the Clean Water Act (CWA). The regulations provide limitations on pollutant concentrations in wastewater discharges from point source categories and represent the degree of reduction in pollutant concentration that is attainable through demonstrated technologies for new and existing sources. The regulations also provide standards of performance for new sources, and pretreatment standards for new and existing sources. The effluent limitations establish the maximum discharge of pollutants allowed for 1 day and for a monthly average. The regulated point source categories include iron and steel manufacturing (EPA 1982d); nonferrous metals manufacturing (EPA 1984b); steam electric power generation (EPA 1982e); pesticide chemicals (EPA 1978b); battery manufacturing (EPA 1984e); copper forming (EPA 1983b); metal molding and casting (EPA 1985h); and nonferrous metals forming and metal powders (EPA 1985i). For some processes applicable to point source subcategories (such as secondary aluminum smelting, primary lead production, and primary zinc production) lead has a zero discharge limitation (EPA 1984b). Lead has a "no-detectable-amount" criterion for the steam electric power generating point source (EPA 1982e). The CWA establishes the basic structure for regulating the discharge of pollutants to waterways and is designed to ensure that all waters are sufficiently clean to protect public health and/or the environment. However, if waters and their sediments become contaminated from sources such as

atmospheric deposition and discharges from industrial, municipal, or agricultural operations, toxic substances could concentrate in the tissue of fish and wildlife. Advisories have been developed and issued to warn people about the health risks of consuming lead-contaminated fish, shellfish, or wildlife and provide guidance as to the amount of fish or wildlife that can be safely consumed. Each state, Native American Tribe, or U.S. Territory establishes its own criteria for issuing fish and wildlife advisories. A fish or wildlife advisory will specify which waters (lake, rivers, estuaries, or coastal areas) or hunting areas have restrictions. The advisory provides information on the species and size range of the fish or wildlife of concern. The advisory may completely ban eating fish, shellfish, or recommend consumption limits (numbers of fish meals per specified time period) considered to be safe to eat. For example, an advisory may recommend that a person eat a certain type of fish no more than once a month. Advisories may specify the tissues of the fish or wildlife that can be safely eaten or proper preparation and cooking practices to help decrease exposure to lead. The fish or wildlife advisory is typically more restrictive to protect pregnant women, nursing mothers, and young children. Published information in the form of brochures on fish and wildlife advisories is available from state public health departments, natural resources departments, or fish and game departments. Signs may be posted in certain fishing and hunting areas frequently used by recreational fishers and hunters to warn them about specific contamination problems (EPA 1995b). Currently, 10 advisories are in effect in 5 states (Hawaii, Louisiana, Missouri, Ohio, and Tennessee, and one U.S. Territory (American Samoa) restricting the consumption of lead-contaminated fish and shellfish (EPA 1998f). No advisories were issued for wildlife.

In an effort to protect human health by reducing the lead levels in drinking water at consumers' taps to as close to the maximum contaminant level goal (MCLG) of zero, water system authorities are required to: (1) install or improve corrosion control to minimize lead levels at the tap while ensuring that treatment does not cause the water system to violate any national primary drinking water regulation; (2) install treatment to reduce lead in source water entering the distribution system; (3) replace lead service lines when more than 10% of targeted tap samples exceed 0.015 mg/L lead in drinking water if corrosion control and/or source water treatment does not bring lead levels below the lead action level; and (4) conduct public education programs if lead levels are above the action level (EPA 1991a, 1985g).

The EPA also regulates the lead content in hazardous wastes as prescribed by the Resource Conservation and Recovery Act (RCRA). A solid waste may be defined as hazardous if it exhibits any of the four characteristics (ignitability, corrosivity, reactivity, and toxicity) used to identify hazardous wastes. A solid waste containing lead or lead compounds may be defined as a hazardous waste if it exhibits the

characteristic of toxicity. The waste is said to exhibit the toxicity characteristic if the lead concentration in the extract obtained by subjecting a sample of the waste to the Toxicity Characteristic Leaching Procedure (TCLP) exceeds 5.0 mg/L (EPA 1990c). On December 18, 1998, EPA issued a proposed rule under the Toxic Substances Control Act (TSCA) to provide new standards for the management and disposal of lead-based paint debris generated by individuals involved in abatements, renovations, and demolition of target housing and from lead removal and demolition of public and commercial buildings (EPA 1998a). As a result of the proposed rule and to avoid duplication and inconsistency in the management of lead-based paint debris, EPA also issued on the same day a proposed rule which would temporarily suspend the applicability of the toxicity characteristic to these types of debris (EPA 1998b).

The Lead-Based Paint Poisoning Prevention Act, as amended by the National Consumer Information and Health Promotion Act of 1976, mandates that the use of lead-based paint in residential structures constructed or rehabilitated by any federal agency or with federal assistance in any form be prohibited (HUD 1998). By definition, residential structures include non-dwelling facilities operated by the owner and commonly used by children under 6 years old, such as child care centers. The Act also authorized the Department of Housing and Urban Development (HUD) to promulgate regulations to eliminate lead-based paint from HUD-associated housing built prior to 1978. The regulatory definition of lead-based paint is "any paint or other surface coating that contains lead equal to or in excess of 1.0 mg/cm^2 or 0.5 percent by weight" (HUD 1997, 1998) For paints manufactured after June 22, 1977, however, Section 501(3) of the Act defines lead-based as any paint where the nonvolatile content contains 0.06% lead by weight. Purchasers and tenants of HUD-associated housing constructed before 1978 must be notified that the dwelling was constructed prior to 1978 and may contain lead-based paint. Information concerning the hazards of lead-based paint, the symptoms and treatment of lead-based paint poisoning, the precautions to be taken to avoid poisoning, and maintenance and removal techniques must also be provided (HUD 1998). The Residential Lead-Based Paint Hazard Reduction Act of 1992 (also known as Title X of the Housing and Community Development Act) requires sellers, landlords and agents to provide the same type of information to potential purchasers or tenants of other "target housing" (i.e., constructed prior to 1978). Exceptions to these requirements include: housing for elderly or disabled persons unless a child younger than 6 years of age is expected to reside in the dwelling; and dwellings without bedrooms such as studio/efficiency apartments, individual room rentals, dormitories, and military barracks (HUD1998). Title IX also mandates a broad range of interrelated lead exposure activities, some of which require inter-agency collaboration.

In addition to HUD, the primary federal agencies responsible for promulgating regulations implementing the mandates of Title X are the EPA, the Department of Health and Human Services (DHHS) and the Department of Labor's Occupational Safety and Health Administration (OSHA). Title X amends the Toxic Substances Control Act (TSCA) by adding Title IV, entitled "Lead Exposure Reduction." Title IV provides the authority for developing standards that reduce lead-based paint hazards in housing and environmental media (EPA 1998a). Section 402 of Title IV requires the EPA to promulgate regulations for accrediting training programs and certification of persons engaging in "lead-based paint activities" such as for lead abatement and renovation. The aim of the ruling is to ensure that individuals conducting these activities are properly trained and certified. The EPA/HUD training and certification program provides for 5 categories of lead-based paint professionals: supervisors, workers, inspectors, risk assessors, and project designers; and 3 categories of activities: inspection, risk assessment and abatement. Section 403 of Title IV requires EPA to develop standards for lead-based paint hazards in most pre-1978 housing and child-occupied facilities and to address by regulation(s) the definition of "lead-based paint hazards," "lead-contaminated dust," and "lead-contaminated soil." On June 3, 1998, EPA issued several proposed standards in a notice of proposed rulemaking. It was proposed that lead-based paint hazards be described as "paint in poor condition" and defined as more than 10 ft^2 of deteriorated paint on exterior surface areas and more than 2 ft^2 on interior surface areas (EPA 1998b). The proposed standard for a lead-dust hazard is an average level of lead in dust that equals or exceed 50 $\mu g/ft^2$ on uncarpeted floors and 250 $\mu g/ft^2$ on interior window sills (EPA 1998b). For soils, an average concentration of 400 ppm/yard was the proposed standard at which the public should be made aware of the risk associated with exposure to lead (EPA 1998b).

Section 404 of Title IV concerns the authorization requirements for state and tribal programs. States and Indian tribes can seek authorization from EPA to implement their own lead training, accreditation, and certification programs. On August 26, 1996, EPA published the final rule establishing the requirements That state or tribal programs must meet for authorization to administer and enforce the standards and regulations promulgated in accordance with Title IV (EPA 1998e). According to "The Lead Listing" provided by the National Lead Service Providers Listing System, as of July 1, 1998, 22 states have established operational lead programs that actively certify lead service providers. A list of these states is provided in Table 7-1. Local, certified (licensed) lead-based paint inspectors, risk assessor, and laboratories can be located by calling the National Lead Information Center and Clearinghouse (1-800-LEAD-FYI [1-800-532-3394]) or through the Internet at http://www.leadlisting.org (HUD 1997). The Lead Listing is operated by a private entity for HUD's Office of Lead Hazard Control.

Section 406 of Title IV directs the EPA to develop consumer information concerning the hazards of exposure to lead and procedures to be followed during housing renovations or remodeling. On June 1, 1998, the EPA issued its final rule on the requirements for lead hazard education prior to conducting renovations in target housing (EPA 1998a. It is important to note that while the federal disclosure program requires property owners to make others aware of the potential lead hazards in or on their property, the program does not require the property owner to conduct inspections or risk assessments prior to selling or leasing property. Regulations responding to the mandates of Title IV are codified at 40 CFR 745; Lead-Based Paint Poisoning Prevention In Certain Residential Structures.

Lead also appears on the FDA's list of poisonous and deleterious substances which was established to control levels of contaminants in human food and animal feed. The action levels established for these substances represent limits at or above which the FDA will take legal action to remove the affected consumer products from the market (FDA 1994). The foods for which the FDA has established action levels for lead are fruit beverages (80 μg/kg), and foods packaged in lead-soldered cans (250 μg/kg) (FDA 1994). Lead solders are alloys of metals which contain lead and are used in the construction of metal food cans. The FDA considers any food packaged in containers that use lead in can solders to be adulterated and in violation of the Federal Food, Drug, and Cosmetic Act (FDA 1995). As of February 8, 1996, the FDA considers wine in bottles capped with tin-coated lead foil capsules to be adulterated (FDA 1996). Tin-coated lead foil has been used as a covering applied over the cork and neck areas of wine bottles to prevent insect infestations, as a barrier to oxygen, and for decorative purposes. Because it can be reasonably expected that lead could become a component of the wine, the use of these capsules is also a violation of the Federal Food, Drug, and Cosmetic Act (FDA 1996). The FDA has reviewed several direct human food ingredients and has determined them to be "generally recognized as safe"when used in accordance with current good manufacturing practices. Some of these ingredients contain an allowable concentrations of lead ranging from 0.1 to 10 parts per million (ppm) (FDA 1998).

The Lead Contamination Control Act of 1988 mandates that the Consumer Product Safety Commission (CPSC) (1) require the repair or recall of drinking water coolers containing lead in parts that come in contact with drinking water, (2) prohibit the sale of drinking water coolers that are not lead-free, (3) require that states establish programs to assist educational agencies in testing and remediating lead contamination of drinking water in schools, and (4) require that EPA certify testing laboratories and provide for coordination by the Center for Disease Control and Prevention (CDC) of grants for additional lead screening and referral programs for children and infants (Congressional Record 1988a, 1988b). The CPSC has declared paints and similar surface coating having a lead content which exceeds the 0.06% by weight limit to be "banned hazardous products" (CPSC 1977a). Paints and surface coatings with lead concentrations exceeding the

0.06% limit are defined as “lead-containing paint.” Except for applications to motor vehicles and boats, once lead-containing paints are applied to toys or other articles intended for use by children and articles of furniture manufactured for consumer use, these items also become “banned hazardous products” (CPSC 1977a). These products may be exempt from the ban if, at a minimum, the main label on the product includes the single word “Warning” and the statement: “Contains Lead. Dried Film of This Paint May Be Harmful If Eaten or Chewed” (CPSC 1977a).

The CDC determined in 1991 that blood lead levels of >10 µg/dL in children were to be considered elevated (CDC 1991). In its annual publication of threshold limit values (TLVs) and biological exposure indices (BEIs), the ACGIH notes that women of child-bearing age who have blood lead levels exceeding the CDC guideline value are at risk of delivering children with a blood lead levels greater than 10 µg/dL (ACGIH 1998). In its report to Congress, NIOSH summarizes occupational exposure information and provides recommendations for workers (NIOSH 1997b).

The ACGIH also notes that if a child’s blood lead level remains elevated, the child may be at increased risk of cognitive deficits (ACGIH 1998). The ACGIH has adopted BEIs for various substances. The BEI for a substance is an industrial hygiene reference value to be used in evaluating potential health hazards. It is important to note that BEIs are guideline values, and that they are not intended for use as measures of adverse effects or for diagnosis of occupational illness (ACGIH 1998). They represent the level of substance most likely to be observed in specimens (e.g., blood or urine) collected from a healthy worker who has been exposed to a chemical at its threshold limit value (TLV). The TLV refers to the airborne concentration of a substance at which nearly all workers may be repeatedly exposed, day after day, without adverse health affects. BEIs apply to 8-hour exposures occurring 5 days per week. The BEI for lead is 30 µg/dL (ACGIH 1998). The recommended exposure level (REL) for lead in the air adopted by the National Institute of Occupational Safety and Health (NIOSH) is 0.1 mg/m^3 (NIOSH 1997a). NIOSH also recommends maintaining air concentrations so that worker blood lead remains at less than 60 µg/dL (NIOSH 1997a).

Table 7-1. Regulations and Guidelines Applicable to Lead

Agency	Description	Information	References
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenic classification:		
	Elemental lead and inorganic lead compounds	Group 2B[a]	IARC 1987
	Organolead	Group 3[b]	
WHO	Drinking water guidelines	0.05 mg/L	WHO 1984
	Blood lead level of concern	20 μg/dL	WHO 1986
NATIONAL			
Regulations:			
a. Air:			
OSHA	Occupational Safety and Health Standards		
	Lead	Yes	29 CFR 1910.1025
	PEL TWA (8-hour average)		OSHA 1978
	inorganic lead	0.05 mg/m^3	
	action level	0.03 mg/m^3	
	Lead exposure in construction interim final rule was promulgated in 1993	50 μg/m^3	29 CFR 1926.62 OSHA 1998 58 FR 26590 OSHA 1993
EPA OAR	Hazardous Air Pollutants	Yes	Clean Air Act Amendments U.S. Congress 1990
	Standards of Performance for New Stationary Sources		
	Secondary lead smelters— standards for particulate matter		40 CFR 60, Subpart L EPA 1977
	blast (cupola) or reverberatory furnace	<50 mg/dscm (0.022 gr/dscf) <20% opacity	
	pot furnace	<10% opacity	
	Primary copper smelters	Yes	40 CFR 60, Subpart P EPA 1976a
	Primary lead smelters—		40 CFR 60, Subpart R
	particulate matter	<50 mg/dscm (0.022 gr/dscf)	EPA 1976b
	sulfur dioxide	<0.065% by volume	
	opacity	<20%	
	Glass manufacturing plants	Yes	40 CFR 60, Subpart CC EPA 1980a

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Lead-acid battery manufacturing plants-lead content in gases discharged to the atmosphere from:		40 CFR 60, Subpart KK EPA 1982a
	grid-casting facilities paste-mixing facility three-process operation facility	<0.40 mg/m^3 of exhaust (0.000176 gr/dscf) <1.0 mg/m^3 of exhaust (0.00044 gr/dscf)	
	lead oxide manufacturing facility	<1.0 mg/m^3 of exhaust (0.00044 gr/dscf)	
	lead reclamation facility	<5.0 mg/kg of lead feed (0.101 lb/ton) <4.5 mg/m^3 of exhaust (0.00198 gr/dscf)	
	other lead-emitting operation	<1.0 mg/m^3 of exhaust (0.00044 gr/dscf)	
	affected facilities other than lead-reclamation	0% opacity	
	lead reclamation facilities	<5% opacity	
	Metallic Mineral Processing Plants	Yes	40 CFR 60, Subpart LL EPA 1984a
	Standards of performance for Equipment Leaks of VOC in the Synthetic Organic Chemicals Manufacturing Industry (SOCMI)—chemicals produced by affected facilities (tetra ethyl lead, tetramethyl lead)	Yes	40 CFR 60.489 EPA 1983b
	Standards of Performance for VOC Emissions from SOCMI— distillation operation (tetra (methyl-ethyl) lead, tetramethyl lead)	Yes	40 CFR 60.667 EPA 1990a
	Standards of Performance for VOC Emissions from SOCMI—reactor processes (tetra (methyl-ethyl) lead, tetramethyl lead)	Yes	40 CFR 60.707 EPA 1993a
	National Emission Standards for Hazardous Air Pollutants for Source Categories		
	SOCMI chemicals	Yes	40 CFR 63.106 EPA 1994f
	Regulation of Fuels and Fuel Additives		

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	General provisions--definition of unleaded gasoline	Up to 0.05 g of lead per gallon	40 CFR 80.2 EPA 1973a
	test methods	Yes	40 CFR 80.3 EPA 1982b
	Controls and Prohibitions (40 CFR 80.22)	Yes	61 FR 3832 EPA 1996f
	Reformulated Gasoline—Fuel certification procedures	Yes	40 CFR 80.40 EPA 1994g
	Test Methods for Lead in Gasoline Method 1-Standard method test for lead in gasoline by atomic absorption spectrometry	Yes	40 CFR 80, App. B EPA 1974
	Method 2-Automated method test for lead in gasoline by atomic absorption spectrometry		
	Method 3-Test for lead in gasoline by X -ray spectrometry		
b. Water:			
EPA ODW	Regulated under SDWA of 1986	Yes	FSTRAC 1988
	Action level in drinking water	0.015 mg/L	EPA 1996g
	National Primary Drinking Water Regulations Definitions	Yes	40 CFR 141.2 EPA 1975
	Public notification	Yes	40 CFR 141.32 EPA 1987b
	Special monitoring for corrosivity characteristics	Yes	40 CFR 141.42 EPA 1990b
	Prohibition on use of lead pipes, solder, and flux	Yes	40 CFR 141.43 EPA 1987c
	Control of Lead and Copper	Yes	40 CFR 141, Subpart I EPA 1991a
	National Primary Drinking Water Regulations Implementation Records and reports kept by States	Yes	40 CFR 142.14-142.15 EPA 1976c
	Review of State implementation of regulations for lead and copper	Yes	40 CFR 142.19 EPA 1991b

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
EPA OW	Designation of Hazardous Substances—List of hazardous substances	Yes	40 CFR 116.4 EPA 1978a
	Guidelines Establishing Test Procedures for the Analysis of Pollutants—Identification of test procedures	Yes	40 CFR 136.3 EPA 1973c
	Designated as a toxic pollutant under Section 307(a)(1) of the Federal Water Pollution Control Act	Yes	40 CFR 401.15 EPA 1979b
	Iron and Steel Manufacturing Point Source Category--BAT, BPT, NSPS, PSES, and PSNS	Yes	40 CFR 420, Subparts B-L EPA 1982d
	Nonferrous Metals Manufacturing Point Source Category--BAT, BPT, NSPS, PSES, and PSNS	Yes	40 CFR 421, Subpart C-H *EPA 1984b* 40 CFR 421, Subpart I EPA 1985e 40 CFR 421, Subpart P-AB, and AE EPA 1985h 40 CFR 421, Subparts J, K, and M EPA 1984c
	Steam Electric Power Generating Point Source—BAT, NSPS, PSES, and PSNS for 126 priority pollutants	No detectable amount	40 CFR 423, App. A EPA 1982e
	Pesticide Chemicals—Organic pesticide chemicals manufacturing subcategory applicability	Yes	40 CFR 455.20 EPA 1978b

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	BAT and NSPS effluent limitations for priority pollutants for direct discharge point sources that use end-of-pipe biological treatment (total lead)	Yes	40 CFR 455.50, Table 4 EPA 1993e
	BAT and NSPS effluent limitations for priority pollutants for direct discharge point sources that do not use end-of-pipe biological treatment (total lead)	Yes	40 CFR 455.50, Table 5 EPA 1993e
	PSES and PSNS for priority pollutants	Yes	40 CFR 455.50, Table 6 EPA 1993e
	Battery Manufacturing Point Source Category—BAT, BPT, NSPS, PSES, and PSNS for lead subcategory	Yes	40 CFR 461.31-461.35 EPA 1984e
	Metal Molding and Casting Point Source Category—BAT, BPT, NSPS,PSES, and PSNS	Yes	40 CFR 464 EPA 1985 h
	Copper Forming Point Source Category—BAT, BPT, NSPS,PSES, and PSNS for copper forming subcategory	Yes	40 CFR 468.11-468.15 EPA 1983c
	Nonferrous Metals Forming and Metal Powder Point Source Category—BAT, BPT, NSPS,PSES, and PSNS for lead tin-bismuth forming subcategory	Yes	40 CFR 471 EPA 1985i
c. Food:			
FDA	Action Levels for Poisonous or Deleterious Substances in Human Food and Animal Feed–Lead		FDA 1994
	Fruit beverages (juices, nectars, and drinks) packed in lead-soldered cans	80 μg/kg	
	Foods (other than fruit beverages) packed in lead-soldered cans	250 μg/kg	
	Leaching solution for ceramicware flatware (average of 6 units)	3.0 μg/mL	
	Leaching solution for small hollowware (any 1 of 6 units)	2.0 μg/mL	
	Leaching solution for large hollowware (any 1 of 6 units)	1.0 μg/mL	

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Leaching solution for cups and mugs (any 1 of 6 units)	0.5 μg/mL	FDA 1994
	Leaching solution for pitchers (any 1 of 6 units)	0.5 μg/mL	
	Silver-plated hollowware-products intended for use by adults (average of 6 units)	7.0 μg/mL	
	Product intended for use by infants and children (any 1 of 6 units)	0.5 μg/mL	
	Substances prohibited from indirect addition to human food through food-contact surfaces	Lead solder	29 CFR 189.240 FDA 1995
d. Other:			
CPSC	Paint is declared banned from household use and interstate commerce if the lead content exceeds	0.06% total weight of solids or paint film	CPSC 1973 16 CFR 1500.17 EPA 1973c
EPA OSW	Criteria for Classification of Solid Waste Disposal Facilities and Practices Maximum contaminant levels (MCLs)	0.05 mg/L	40 CFR 257, App. I EPA 1993b
	Criteria for Municipal Solid Waste Landfills Maximum contaminant levels (MCLs)	0.05 mg/L	40 CFR 258.40 EPA 1993d
	Constituents for detection monitoring (total lead)	Yes	40 CFR 258, App. I EPA 1993c
	List of hazardous inorganic and organic constituents	*Yes*	*40 CFR 258, App. II* EPA 1993c
	Identification and Listing of Hazardous Waste Definition of hazardous waste--generic exclusion levels for K061 and K062 nonwastewater HTMR residues	0.15 mg/L (maximum for any single composite sample TCLP	40 CFR 261.3 EPA 1992
	Exclusions	Yes	40 CFR 261.4 EPA 1980b
	Special requirements for hazardous waste generated by conditionally exempt small quantity generators	Yes	40 CFR 261.5 EPA 1986c
	Requirements for recyclable materials	Yes	40 CFR 261.6 EPA 1985d

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
	Toxicity characteristic; maximum concentration of contaminants for the toxicity characteristic (Hazardous Waste No. D008)	5.0 mg/L	40 CFR 261.24, Table 1 EPA 1990c
	temporary suspension of toxicity characteristic rule for specified lead-based paint debris	Yes	63 FR 70233 EPA 1998d
	Hazardous waste from specific sources–hazardous waste codes K046, K052, K065, K069, and K100	Yes	40 CFR 261.32 EPA 1981a
	Discarded commercial chemical products, off-species, container residues, and spill residues–hazardous waste codes P110, (tetraethyl lead), U144 (lead acetate), U145 (lead phosphate), and U146 (lead subacetate)	Yes	40 CFR 261.33 EPA 1980c
	Basis for listing hazardous waste–hazardous waste code F035, K002, K003, K005, K046, K048, K049, K051, K052, K061, K062, K064, K064, K065, K069, K086, and K100	Yes	40 CFR 261, App. VII EPA 1981b
	Hazardous constituents: lead lead compounds (not otherwise specified) lead acetate lead phosphate lead subacetate	Yes	40 CFR 261, App. VIII EPA 1988b
	Waste excluded under 40 CFR 260..20 and 260.22	Yes	40 CFR 261, App. IX EPA 1984d
	Standard for Owners and Operators of Hazardous Waste Treatment, Storage, and Disposal Facilities—		40 CFR 264.94 EPA 1982c
	Releases from solid waste management units; concentration limits (lead)	0.05 mg/L	
	Groundwater monitoring list (lead)	Yes	40 CFR 264, Appendix IX EPA 1987a
	Reference air concentration lead tetraethyl lead	 9.0E-02 $\mu g/m^3$ 1.0E-04 $\mu g/m^3$	40 CFR 266, App. IV EPA 1991c
	Health-based limits for exclusion of waste-derived residues–TCLP extract concentration limits for metals (lead)	5 mg/L	40 CFR 266, App. VII EPA 1991c
	Land Disposal Restrictions— Definitions	Yes	40 CFR 268.2 EPA 1990d
	Waste specific prohibitions–Third third waste (hazardous waste codes)	Yes	40 CFR 268.35 EPA 1990e

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information		References
NATIONAL (cont.)				
	Treatment standards for hazardous waste expressed as concentrations in waste extract or expressed as specified technologies	Yes		40 CFR 268.40 EPA 1994h
	Technology codes and description of technology-based standards	Yes		40 CFR 268.42 EPA 1994i
	Universal treatment standards (lead)	Wastewater (mg/L) 0.69	Nonwastewater (mg/L) 0.37 (TCLP)	40 CFR 268.48 EPA 1994j
	Metal bearing waste prohibited from dilution in a combustion unit according to 40 CFR 268.3(c)	D008, K069, K100, P110, and U145		40 CFR 268, App. XI EPA 1996d
EPA OERR	Designation, Reportable Quantities, and Notification—List of hazardous substances and reportable quantities	Yes		40 CFR 302.4 EPA 1989a
	Reportable Quantity Adjustment for Lead Metal, Lead Compounds, Lead-containing Hazardous Wastes, and Methyl Isocyanate-Final rule (40 CFR 117, 302, and 355)	Statutory RQ lbs.	Final RQ lbs. (kg)	58 FR 35314 EPA 1993f
	lead	1	10 (4.54)	
	lead acetate	*5,000*	*10 (4.54)*	
	lead arsenate	5,000	1 (0.454)	
	lead and compounds	1	not assigned	
	lead chloride	5,000	10 (4.54)	
	lead fluoroborate	5,000	10 (4.54)	
	lead fluoride	1,000	10 (4.54)	
	lead iodide	5,000	10 (4.54)	
	lead nitrate	5,000	10 (4.54)	
	lead phosphate	1	10 (4.54)	
	lead stearate	5,000	10 (4.54)	
	lead subacetate	1	10 (4.54)	
	lead sulfate	5,000	10 (4.54)	
	lead sulfide	5,000	10 (4.54)	
	lead thiocyanate	5,000	10 (4.54)	
	tetraethyl lead	100	10 (4.54)	
	Toxic chemical release reporting; Community right-to-know	Yes		40 CFR 372.65 EPA 1988a
EPA OPPTS	Lead-based Paint Poisoning Prevention In Certain Residential Structures	Yes		40 CFR 745 (61 FR 9064) EPA 1996e
	Title IV-Lead Exposure Reduction	Yes		Toxic Substance Control Act (TSCA)--. PL 102-550 U.S. Congress 1992a

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
EPA/HUD	Residential Lead-Based Paint Hazard Reduction Act of 1992-42 U.S. Code 4852d Lead-Based Paint Poisoning and Prevention Act of 1992- 42 U.S. Code 4822	Yes	Housing and Community Development Act of 1992, Title X U.S. Congress 1992b
HUD	Requires testing and elimination of lead-based paint in federally funded housing and housing rehabilitation programs, public housing, and Indian housing	Yes	HUD 1987a, 1987b
	Action level for lead-based paint	1 mg/m^3 (XRF) or 1 mg/cm^2 (AAS or ICP-AES)	HUD 1987a, 1987b
Guidelines:			
a. Air:			
ACGIH	TLV TWA		
	lead elemental and inorganic as Pb	0.05 mg/m^3	ACGIH 1998
	lead arsenate	0.15 mg/m^3	
	lead chromate as Pb	0.05 mg/m^3	
NIOSH	REL	<0.1 mg/m^3	NIOSH 1994
OAQPS	NAAQS	1.5 $\mu g/m^3$	40 CFR 50.12 EPA 1987d
b. Water:			
EPA ODW	Maximum Contaminant Level Goals (MCLGs) for Inorganic contaminants	0 mg/L	40 CFR 141.51 EPA 1985g
EPA OWRS	Ambient Water Quality Criteria for Protection of Human Health	50 $\mu g/L$	45 FR 79318 EPA 1980d
	Ambient Water Quality Criteria for Protection of Aquatic Organisms		
	Freshwater:		50 FR 30784
	Acute (1-hour average)	82 $\mu g/L$	EPA 1985f
	Chronic (4-day average)	3.2 $\mu g/L$	
	Marine		
	Acute (1-hour average)	140 $\mu g/L$	
	Chronic (4-day average)	5.6 $\mu g/L$	
c. Other:			
ACGIH	Biological Exposure Indices		
	In blood	30 $\mu g/100$ mL	ACGIH 1998
	Cancer Classification		
	Elemental lead and inorganic as Pb	A3[d]	
	Lead chromate as Pb	A2[e]	
CDC	Blood lead level of concern in children	10 $\mu g/dL$	CDC 1991

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
NATIONAL (cont.)			
EPA	RfD	No data[f]	IRIS 1999
	Cancer classification (inorganic lead)	Group B2	
	Unit risk (inhalation)	No data	
	Unit risk (oral)	No data	
NIOSH	Recommended worker blood level to be maintained through air concentrations	<0.060 mg Pb per 100 grams of whole blood	NIOSH 1997
NTP	Cancer classification may reasonably be anticipated to be carcinogens	lead acetate and lead phosphate	NTP 1998
OSHA	Blood lead level of concern (all occupations; including the construction industry)	40 µg/dL	29 CFR 1910.1025 OSHA 1995 and 29 CFR 1926.62
	Medical Removal	50 µg/dL	OSHA 1998
STATE			
Regulations and Guidelines:			
a. Air:	Acceptable Ambient Air Concentrations		NATICH 1992
	Lead Acetate		
MA	24-hour	6.80E+03 µg/m^3	
ND	NA	0.00 BACT	
NY	1-year	3.00E-02 µg/m^3	
	Lead Arsenate		
TX	30-min.	2.00E-02 µg/m^3	
	Annual	2.00E-03 µg/m^3	
WA-SWEST	24-hour	5.00E-01 µg/m^3	
	Lead Chromate		
CT	8-hour	5.00E-01 µg/m^3	
ND	NA	0.00 BACT	
NV	8-hour	1.00E-03 mg/m^3	
TX	30-min.	1.20E-01 µg/m^3	
	Annual	1.20E-02 µg/m^3	
VA	24-hour	5.00E-01 µg/m^3	
WA-SWEST	24-hour	2.00E-01 µg/m^3	

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
STATE (cont.)			
	Lead Oxide		
AZ	1-hour	4.50 $\mu g/m^3$	
	24-hour	1.50 $\mu g/m^3$	
	Lead Phosphate		
ND	NA	0.00 BACT	
	Lead Powder		
CT	8-hour	3.00 $\mu g/m^3$	
FL-Pinella	8-hour	1.5 $\mu g/m^3$	
	24-hour	3.60E-01 $\mu g/m^3$	
	Annual	9.00E-02 $\mu g/m^3$	
KS	Annual	3.57E-01 $\mu g/m^3$	
MA	24-hour	1.40E-01 $\mu g/m^3$	
	Annual	7.00E-02 $\mu g/m^3$	
	Lead Powder		
ND	8-hour	7.00E-02 $\mu g/m^3$	
NV	8-hour	1.50E-03 mg/m^3	
PA-Phil	1-year	4.00E-03 mg/m^3	
	Annual	1.5 $\mu g/m^3$	
VA	24-hour	1.5 $\mu g/m^3$	
VT	3-month	2.5 $\mu g/m^3$	
		1.5 $\mu g/m^3$	
	Lead Subacetate		
MA	24-hour	1.40E-01 $\mu g/m^3$	
	Annual	1.00E-02 $\mu g/m^3$	
	Lead2 Arsenate		
FL-Ftldle	8-hour	1.50E-03 mg/m^3	
FL-Tampa	8-hour	1.50E-03 mg/m^3	
NY	1-year	5.00E-01 $\mu g/m^3$	
SC	24-hour	7.50E-01 $\mu g/m^3$	
TX	30-min.	1.5 $\mu g/m^3$	
	Annual	1.50E-01 $\mu g/m^3$	
	Lead3 Arsenate	3.00 $\mu g/m^3$	
CT	8-hour	1.50E-03 mg/m^3	
ND	8-hour	4.00E-03 mg/m^3	
NV	8-hour	5.00E-01 $\mu g/m^3$	
NY	1-year	2.5 $\mu g/m^3$	
	Lead4 Arsenate		
SC	24-hour	7.50E-01 $\mu g/m^3$	
	Tetraethyl Lead		
AZ	1-hour	2.50 $\mu g/m^3$	
	24-hour	5.90E-01 $\mu g/m^3$	
CT	8-hour	1.5 $\mu g/m^3$	
FL-Pinella	8-hour	7.50E-01 $\mu g/m^3$	
	24-hour	1.80E-01 $\mu g/m^3$	
	Annual	1.00E-04 $\mu g/m^3$	

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
STATE (cont.)			
IN	8-hour	5.0 $\mu g/m^3$	
ND	8-hour	1.00E-03 mg/m^3	
NV	8-hour	2.00E-03 mg/m^3	
OK	24-hour	1.00 $\mu g/m^3$	
TX	30-min.	7.50E-01 $\mu g/m^3$	
	Annual	7.50E-02 $\mu g/m^3$	
VA	24-hour	1.7 $\mu g/m^3$	
WA-SWEST	24-hour	3.00E-01 $\mu g/m^3$	
	Tetramethyl Lead		
CT	8-hour	1.50 $\mu g/m^3$	
FL-Pinella	8-hour	7.50E-01 $\mu g/m^3$	
	24-hour	1.80E-01 $\mu g/m^3$	
ND	8-hour	1.50E-03 mg/m^3	
NV	8-hour	4.00E-03 mg/m^3	
TX	30-min.	7.50E-01 $\mu g/m^3$	
	Annual	7.50E-02 $\mu g/m^3$	
VA	24-hour	2.50 $\mu g/m^3$	
WA-SWEST	24-hour	5.00E-01 $\mu g/m^3$	
	Designated as a hazardous air pollutant and subject to regulations		CELDS 1990b
Iowa		Yes	
Montana		Yes	
Utah		Yes	
	Ambient air emissions limitations for Class I areas		CELDS 1990a
Kentucky	(3-month)	0.1 $\mu g/m^3$	
Montana	(24-hour)	0.1 $\mu g/m^3$	
	Permit required to construct and operate an air contamination source project if yearly emissions exceed		CELDS 1990a
Arizona		0.6 ton	
Connecticut		0.6 ton	
Missouri		0.6 ton	
New York		0.6 ton	
Virginia		0.6 ton	
	Prevention of significant deterioration: Sources exempt from air monitoring requirements if net emissions increase is:		CELDS 1990a
Delaware	(24-hour average)	<0.1 $\mu g/m^3$	
Louisiana	(24-hour average)	<0.1 $\mu g/m^3$	
Oregon	(24-hour average)	<0.1 $\mu g/m^3$	
Wisconsin	(24-hour average)	<0.1 $\mu g/m^3$	
b. Water:	Drinking water quality guidelines and standards (Lead)		FSTRAC 1995
AL	Standard	20 $\mu g/L$	
AZ	Standard	50 $\mu g/L$	
IL	Standard (source water)	50 $\mu g/L$	
ME	Guideline	20 $\mu g/L$	
MN	Guideline	20 $\mu g/L$	

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
STATE (cont.)			
	MCL in drinking water		
AL		0.02 mg/L	CELDS 1990a
IA		0.05 mg/L	CELDS 1990b
TX		0.05 mg/L	CELDS 1990a
AZ	Permit requirement for operation of stationary source emitting	>5 tons/year	CELDS 1990a
CA	Toxic materials limitations objectives for protection of marine aquatic wildlife		CELDS 1990b
	6-month median	2 μg/L	
	Daily maximum	8 μg/L	
	Instantaneous maximum	20 μg/L	
IA	Surface water quality criteria		IAC 1986a
	Class B waters[g]	0.1 mg/L	
	Class C waters[h]	0.05 mg/L	
IL	Water quality standards		IEPA 1988a
	General use	100 μg	
	Public and food processing water supply	50 μg	
	Lake Michigan	50 μg	
	Secondary contact and indigenous aquatic life	100 μg	IEPA 1988b
	General effluent standards	0.2 mg/L	
IN	Constituent comprising groundwater protection standards	Yes	CELDS 1990b
KY	Domestic water supply source criteria	0.05 mg/L	401KAR 5:03 NREPC 1987
	Maximum groundwater contaminant level	0.05 mg/L	401KAR 30:020
	Significant emission levels of toxic air pollution	3.83×10^{-5} pounds/hour	NREPC 1988 401KAR 63:021
	Interim primary drinking water standards	0.05 mg/L	NREPC 1986 401KAR 35:31NREPC 1988
NY	Effluent standards: Maximum allowable concentrations into saturated or unsaturated zones	0.05 mg/L	CELDS 1990a
	Allowable concentration limits for Class GA waters	0.025 mg/L	CELDS 1990a
NV	Water quality criteria		CELDS 1990b
	Irrigation	<5.0 mg/L	
	Watering of livestock	<0.1 mg/L	
	Propagation of wildlife	<0.1 mg/L	
	Municipal or domestic water supply	0.05 mg/L	
	Ground water standards		
NM		0.05 mg/L	CELDS 1990b
UT		0.05 mg/L	CELDS 1990a

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
STATE (cont.)			
WI	Public health groundwater quality standards: Enforcement standard Preventative action limit	 50 μg/L 5 μg/L	WAC 1985
c. Other:			
CA	Chemical parameter for leachate monitoring	Yes	CELDS 1990b
IA	Land application of sludge and solid waste from publicly owned treatment center: No permit required if lead level does not exceed	1,000 mg/kg	IAC 1986b
KY	Defined as hazardous waste	Yes	401KAR 31:040 NREPC 1988
	Fish and Shellfish Advisories	Number of Advisories Issued	EPA 1998f
AS	Marine	1	
HI	Freshwater	1	
LA	Freshwater	1	
MO	Freshwater	2	
OH	Freshwater	4	
TN	Freshwater	1	
	States with Adult Blood Lead Level Registries	Reporting Level (μg/dL)	
AL	Alabama Department of Public Health, Division of Epidemiology	15	
AZ	Arizona Department of Health, Office of Environmental Health	10	
CA	California Department of Health Services Occupational Lead Poisoning Prevention Program	25	
CO	Colorado Department of Health	25 (< 18 years) 10 (18 years or older)	
CT	Connecticut Department of Health, Environmental Epidemiology & Occupational Health	10	
FL	Florida Department of Health and Rehabilitative Service	10	
GA	Epidemiology and Prevention Branch	10	
IN	Indiana State Department of Health Epidemiology Resource Center	None	
IA	Iowa Department of Public Health, Bureau of Environmental Health, State Lead Coordinator	All Levels	

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
STATE (cont.)			
KY	Kentucky Injury Prevention and Research Center, Occupational Injury Prevention Program Manager	25	
ME	Maine Bureau of Health, Occupational Health Program	25	
MD	Maryland Department of the Environment, Office of Environmental Health Coordination	25 (18 years or older)	
MA	Massachusetts Department of Labor & Industries, Division of Occupational Hygiene	15	
MI	Michigan Department of Community Health, Childhood lead Poisoning Prevention Project	All Levels	
MN	Minnesota Department of Health	All Levels	
MS	Missouri Department of Health, Lead Poisoning Program	25	
NE	Department of Health & Human Service	10	
NH	Department of Health and Human Services, Public Health Services, Bureau of Risk Assessment	All Levels	
NJ	New Jersey Department of Health, Occupational Disease Prevention Program	25	
NM	New Mexico Department of Health, Division of Epidemiology, Evaluation & Planning	All Levels	
NY	New York State Department of Health	All Levels	
NC	Department of environmental Health & Natural Resources, Occupation Health Section/Epidemiology Division	40	
OH	Ohio State Department of Health	All Levels	
OK	Oklahoma State Department of Health, Maternal and Child Health	10	
OR	Oregon Health division	25 (>18 years) 10 (<18 years)	
PA	Pennsylvania Department of Health, Division of Environmental Health Assessment	15 or more (≤6 years) 25 or more (>6 years and pregnant females)	
RI	Rhode Island Department of Health, office of Occupational and Radiological Health	25	

Table 7-1. Regulations and Guidelines Applicable to Lead (continued)

Agency	Description	Information	References
STATE (cont.)			
SC	Department of Health & Environmental Control, Division of Health Hazard Evaluations	40 (>6 years) 10 (≤6 years)	
TX	Texas Department of Health, Bureau of Epidemiology	40	
UT	Utah Department of Health, Bureau of Epidemiology	15	
VT	Vermont Department of Health, Division of Epidemiology and Health Promotion	10 (>6 years) All Levels (≤6 years)	
WA	Washington State Department of Labor & Industries, Safety & Health Assessment & Research Program	All Levels	
WI	Division of Health, Bureau of Public Health	10 or more	
WY	Wyoming Department of Health	All Levels	

[a] Group 2B: Possible Human Carcinogen
[b] Group 3: Not classifiable as to their carcinogenicity to humans
[c] Final Draft of Air Quality Criteria Document (600/8-83-028F) declines to derive an air quality criterion for lead.
[d] A3: Animal carcinogen; carcinogenic in experimental animals at a relatively high dose that is not considered relevant to worker exposure.
[e] A2: Suspected human carcinogen; carcinogenic in experimental animals at dose levels that are considered relevant to worker exposure.
[f] Interested parties are referred to the 1986 Air Quality Criteria for Lead (EPA-600/8-83/028a-dF)and its 1990 Supplement (EPA/600/8-89/049F)
[g] Protected for wildlife, fish, aquatic and semiaquatic life and secondary contact water uses
[h] Protected as a raw water source of potable water supply

AAS = atomic absorption spectroscopy; ACGIH = American Conference of Governmental Industrial Hygienists; ADI = Acceptable Daily Intake; BACT = Best Available Control Technology; BAT = Best Available Technology Economically Achievable; BPT = Best Practicable Control Technology Currently Available; CDC = Centers for Disease Control; CNS = central nervous system; CPSC = Consumer Product Safety Commission; dL = deciliter; dscm = dry cubic meter at standard conditions; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; gpg = grams per gallon; gr/dscf = grains/dry cubic feet at standard conditions; HUD = Department of Housing and Urban Development; IARC = International Agency for Research on Cancer; ICP-AES = Inductively Coupled Plasma-Atomic Emission Spectroscopy; MCL = Maximum Contaminant Level; MCLG = Maximum Contaminant Level Goal; NAAQS = National Ambient Air Quality Standard; NAS = National Academy of Sciences; NIOSH = National Institute for Occupational Safety and Health; NSPS = New Source Performance Standards; OAQPS = Office of Air Quality Planning and Standards; ODW = Office of Drinking Water; OAR = Office of Air and Radiation; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OWRS = Office of Water Regulations and Standards; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; PSES = Performance Standards Existing Sources; PSNS = Performance Standards New Sources; RfC = Reference Concentration; RfD = Reference Dose; SDWA = Safe Drinking Water Act; TLV = Threshold Limit Value; TWA = Time-Weighted Average; WHO = World Health Organization; XRF = X-Ray Fluorescence

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9. GLOSSARY

Absorption—The taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD)—is usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a BMD_{10} would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

Benchmark Dose Model—is a statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

Cancer Effect Level (CEL)—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report—describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

Case Series—describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

Ceiling Value—A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs—substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—the quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and in utero death.

Environmental Protection Agency (EPA) Health Advisory—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Epidemiology—refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity—a specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—a measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

Immediately Dangerous to Life or Health (IDLH)—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

Incidence—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunological Effects—are functional changes in the immune response.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

In Vitro—Isolated from the living organism and artificially maintained, as in a test tube.

In Vivo—Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level (MRL) —An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a chemical.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio—a means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound—a phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40 hour workweek.

Pesticide—general classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

Pharmacokinetic Model—is a set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—is a type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information 4such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study--a type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*—The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m^3 for air).

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—the possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

Time-Weighted Average (TWA)—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose$_{(50)}$ (TD$_{50}$)—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Toxicokinetic—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty

in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

Xenobiotic—any chemical that is foreign to the biological system.

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (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 for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX A

MRL WORKSHEETS

No MRLs were derived for lead.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper- bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse- Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

(1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

(2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).

(4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.

(7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

(8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

(9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.

(10) Reference The complete reference citation is given in chapter 8 of the profile.

(11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.

(12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.

(14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.

(15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).

(17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

(18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1*).

(19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 6

TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 6 INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 6 Systemic	9	9	9	9	9		9
4 6 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					9		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

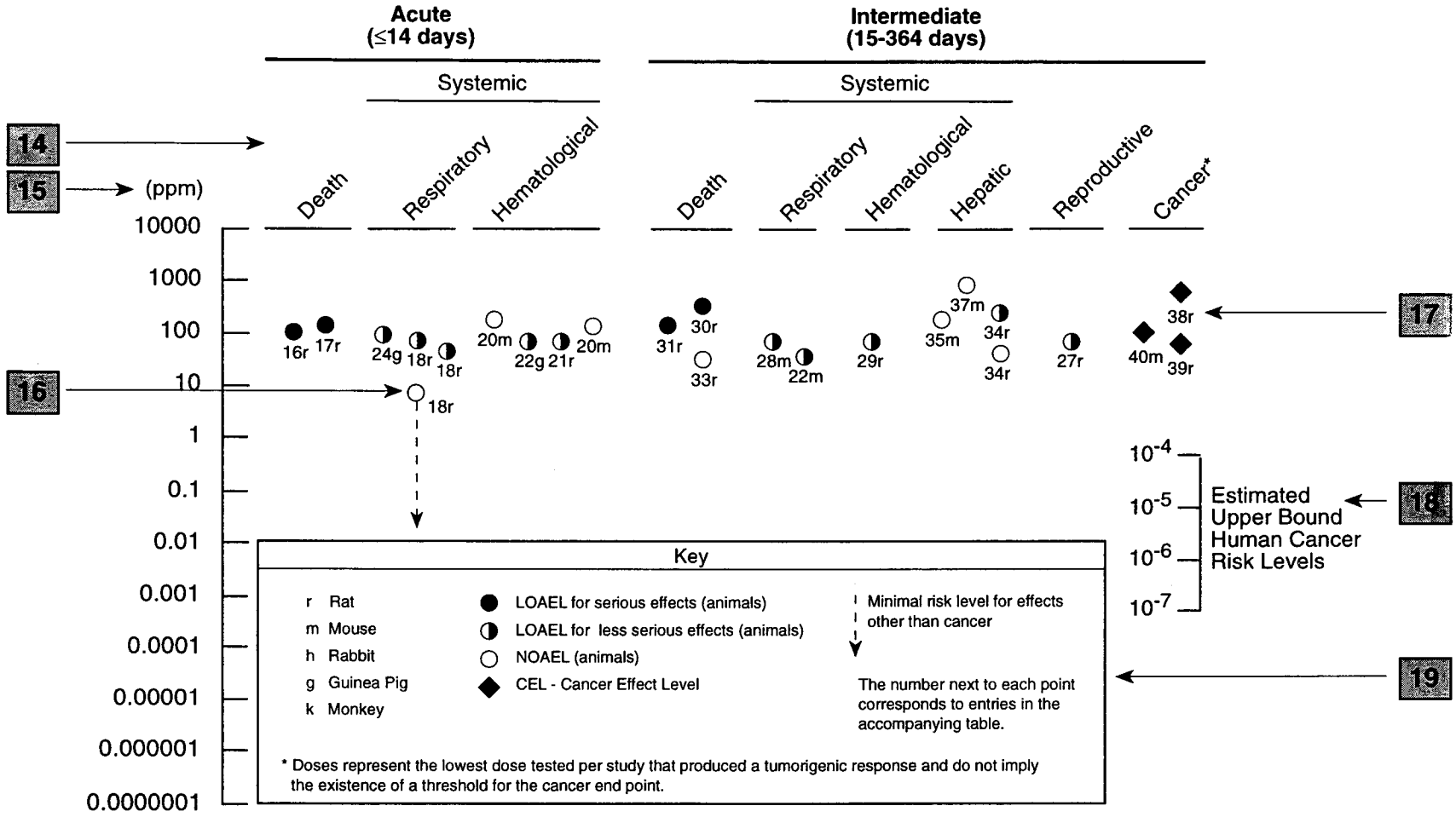
[a] The number corresponds to entries in Figure 2-1.

12 6 [b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = days(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BLL	Blood Lead Level
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code

DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie

MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water

OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short-term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to

=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
µm	micrometer
µg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

A FRAMEWORK TO GUIDE PUBLIC HEALTH ASSESSMENT DECISIONS AT LEAD SITES

ABSTRACT

The Agency for Toxic Substances and Disease Registry (ATSDR) provides health consultations and assessments at hazardous waste sites. Many of these sites have potentially significant levels of lead contamination for which the Agency must assess the health implications of exposure. Typically, environmental data are used to predict blood lead (PbB) levels in order to determine at which sites, if any, follow-up action is needed. Estimating blood lead levels from environmental lead concentrations, however, can be problematic. Several approaches have been developed, including classical ingestion rate determinations and comparison to animal studies, prevalence studies extrapolated to comparable sites, regression analysis of known exposure followed by slope factor estimates of similar levels of exposure, and the Environmental Protection Agency's (EPA) Integrated Exposure Uptake Biokinetic Model (IEUBK). Uncertainty is attendant to each of these approaches due, in part, to the limited nature of the environmental sampling data and the various site-specific factors . In this manuscript we describe an approach ATSDR developed to utilize regression analysis with multi-route uptake parameters to estimate blood lead levels.

The profound toxicity of lead has been acknowledged for many years. Developmental effects associated with female lead workers and wives of lead workers were well known during the 18th and 19th centuries, and much of what is taken for granted today regarding lead poisoning in children has been known for more than ninety years. None the less, production of lead compounds, mining and smelting of lead ore and secondary lead sources, and widespread use of lead-containing products continued to increase during the 20th century. These manufacturing, mining, and smelting activities resulted in the contamination of many industrial and residential areas. In addition, leaded gasoline and lead-based paint contributed to the dispersal of lead throughout the environment. During the 1970s and 1980s, federal agencies targeted programs and resources to reduce lead exposure in the United States. These primary prevention activities resulted in regulations governing air emissions, drinking water standards, the phase-out of lead in gasoline, and the banning of lead-based paint and leaded solder. Although these efforts have all contributed to reducing lead exposure to the general population, past uses have resulted in the contamination of many areas, many of which still have the potential for adversely affecting the public health.

Introduction

One of the mandates of the Agency for Toxic Substances and Disease Registry (ATSDR) (under the Comprehensive Environmental Response, Compensation, and Liability Act, Section 104(i)(3), or Superfund) is to address the potential for adverse effects on public health resulting from lead exposure. Lead has been identified as a contaminant in at least 1,026 of the National Priorities List (NPL) sites and is currently ranked first on the Priority List of Hazardous Substances (ATSDR 1996a). Consequently, ATSDR must address public health concerns regarding lead exposure at hazardous waste sites. ATSDR's specific responsibilities related to blood lead screening at lead-contaminated hazardous waste sites include: (1) evaluation of site-specific environmental lead exposure information, (2) identification of populations potentially exposed to lead, (3) decision about whether or not to conduct blood lead screening, (4) evaluation of blood lead screening results, and (5) determination of whether the U.S. Environmental Protection Agency's (EPA) proposed site remediation plans are sufficient to protect public health.

Evaluation of these environmental data is associated with a high level of biomedical judgment regarding appropriate public health actions. In this manuscript, we describe a framework developed to guide such judgment and one that can be used to evaluate the need for a site-specific public health action, which may include blood lead screening. This approach utilizes regression analysis along with uptake parameters and potential results of exposure in an effort to estimate blood lead levels in at-risk populations.

Superfund specifically directs ATSDR to ascertain significant human exposure levels for hazardous substances. Minimal risk levels (MRLs) were developed as part of the strategy to address this mandate. An MRL is "an estimate of the daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse, noncancerous effects over a specified duration of exposure" (ATSDR 1996b) and is analogous to the reference doses and the reference concentrations developed by EPA. MRLs are derived from no-observed-adverse-effect levels or lowest-observed-adverse-effect levels and are intended to assist in determining the safety of communities near hazardous waste sites. For example, an exposure level below the MRL suggests that there is little likelihood of adverse, noncancer human health effects occurring, whereas an exposure level exceeding the MRL alerts the health assessor that a more detailed evaluation using site-specific and chemical-specific information is required. Although the database for lead is large, empirical data from which to obtain a threshold for the effects of lead are lacking. With no observable threshold yet identified, the derivation of conventional health assessment tools such as MRLs is not feasible (De Rosa et al. 1991). In addition, a great deal of the human health effects data are expressed in terms of blood lead (PbB) levels rather than exposure dose, the usual comparison value. Using more traditional methodologies would overlook this significant body of literature, as well as the Centers for Disease Control (CDC, now the Centers for Disease Control and Prevention) guidelines[1]. A predictive tool relating environmental levels to PbB levels is needed.

In response to this mandate, the Agency has been seeking ways to further refine the tools necessary for assessing the public health implications from exposure to hazardous substances. MRLs provide a guidance for single routes of exposure to a single substance. But, clearly, multi-route, multi-substance exposure considerations are needed not only for lead but for other substances. To this end, a framework for determining significant human exposure levels was developed (Mumtaz et al. 1995). The development of health-based guidance for lead is consistent with this concept. It should be noted that this effort and others to associate environmental levels with PbB levels and consequently make health decisions are simply screening tools. Many issues must be considered on a site-by-site basis and used in conjunction with this guidance. Some of these issues are outlined below.

Exposure and Bioavailability Issues. Primary routes of exposure to lead are via inhalation and ingestion. Lead exposure occurs through inhalation of airborne lead particles with deposition rates in adults of 30%-50% depending on factors such as particle size and ventilation rate (EPA 1986). Once deposited in the lower respiratory tract, lead appears to be almost completely absorbed (Morrow et al. 1980).

Oral intake of lead is a more important route of exposure for children and can occur from ingestion of contaminated food, soil, dust, water, or lead-based paint chips. For young children (1-6 years of age), soil and dust are important pathways for exposure. Ingestion of soil and dust can occur through normal hand-to-mouth activity. Lead-based paint, often found in older homes, and flaking or peeling off walls, can also contribute significantly to exposure in young children. Through normal aging and weathering, intact lead-based paint can contribute to the contamination of dust or soil

[1]The weight of evidence suggests that PbB levels of "10-15 µg/dL and possibly lower" are the levels of concern (ATSDR 1993; Davis 1990; EPA 1986). The Department of Health and Human Services (DHHS) has determined that primary prevention activities should begin at blood lead levels of 10 µg/dL in children (CDC 1991).

The extent and rate of gastrointestinal absorption of lead is mediated by several factors including fasting, physical and chemical form of lead, and dietary status of the individual (Aungst et al. 1981; Grobler et al. 1988; Baltrop and Meek 1979; Chamberlain et al. 1978; Mahaffey et al. 1982; Rabinowitz et al. 1976).

Animal studies indicate that nutritional deficiencies in a number of essential elements (e.g., calcium, iron, zinc, copper, phosphorus) may impact the toxicokinetic and toxicological behavior of lead (ATSDR 1993; Chaney et al. 1989). In infants and children, lead retention has been shown to be inversely correlated with calcium intake (Johnson and Tenuta 1979; Sorrell et al. 1977; Ziegler et al. 1978). Zinc has been shown to have a protective effect against lead toxicity in a number of animal species (Goyer 1986; Haeger-Aronsen et al. 1976; Brewer et al. 1985; Cerklewski and Forbes 1976).

The physical and chemical characteristics of the lead/soil matrix and the particular lead species have also been shown to affect the bioavailability of lead. Studies measuring lead concentration at various soil and dust particle sizes have shown that higher lead concentrations are often found in the smaller-sized fractions. The results of these studies have been summarized by Duggan and Inskip (1985). This is particularly important for young children because smaller particles (<100 µm in diameter) also tend to adhere more readily to hands. Additionally, lead from smaller particles is more readily absorbed from the gastrointestinal tract (Barltrop and Meek 1979). It has been suggested that lead at mining waste sites is less bioavailable and therefore poses less of a human health hazard than lead found at smelter sites or in urban areas (Hemphill et al. 1991; Steele et al. 1990). These differences in bioavailability have been attributed to these biochemical/ biophysical differences of the lead source. Lead particles at mining sites are typically of larger size and consist of the less soluble lead sulfides. However, recent data suggest that this may not always be the case and that a site-by-site evaluation is necessary to determine the lead hazards to the surrounding populations (Gulson et al. 1994; Mushak 1991). See Mushak (1991) for a review of physical/chemical issues regarding lead bioavailability.

Age is also an important factor in that young children absorb lead more efficiently than adults (50% versus 15%) (Chamberlain et al. 1978). Fasting has a significant effect on absorption of lead. Retention of ingested lead is about 60% under fasting conditions compared with 4% when lead is ingested with a balanced meal (James et al. 1985).

Behavioral factors must also be considered. The normal hand to mouth activity of young children results in an increase in lead intake from hand soil/dust particles. In addition, children who exhibit pica behavior are at increased risk because they may ingest more lead-contaminated soil/dust. Health assessors should also be aware of distinct sources of lead within a household or community, such as certain hobbies that would expose one to lead (e.g. using molten lead for casting ammunition, leaded solder for making stained glass, leaded glazes for pottery), the use of folk remedies or lead-glazed pottery, or eating imported canned foods that might contain elevated lead from lead solder used in the can seams.

Approach

Numerous longitudinal and cross-sectional studies have attempted to correlate environmental lead levels with blood lead levels (Table 1). These studies have provided a number of regression analyses and corresponding slope factors (δ) for various media including air, soil, dust, water, and food. The specifics of each of these have been extensively discussed and evaluated elsewhere (Brunekreef 1984; Duggan and Inskip 1985; EPA 1986; Reagan and Silbergeld 1989; Xintaras 1992). In an attempt to use this valuable body of data, ATSDR has developed an integrated exposure regression analysis (Abadin and Wheeler, 1993). This approach utilizes slope values from select studies to integrate all exposures from various pathways, thus providing a cumulative exposure estimate expressed as total blood lead.

Table 1. Summary of blood slope factors from various environmental media.

Population	Slope	Comments	Reference
Air Slope Factors:	µg/dL per µg Pb/m^3		
Adults; N = 43	1.75 ± 0.35	Experimental study; EPA analysis	Griffin et al. 1975
Adults; N=5	1.59–3.56	Experimental study; EPA analysis	Rabinowitz et al. 1976
Adults; N=10	2.7	Experimental study; EPA analysis	Chamberlain et al. 1978
Children; 1–18 years of age; N=831; 1,074 blood samples	1.92 ± 0.60	Omaha cross-sectional study; smelter	Angle et al. 1984
Children; N=148	2.46 ± 0.58	Belgium cross-sectional study; smelter; EPA analysis	Roels et al. 1980
Children; N=880	1.53 ± 0.064	Kellogg/Silver Valley cross-sectional study; EPA analysis; smelter	Yankel et al. 1977
Adult males; 5 groups, 30/group	2.57 ± 0.04	Cross-sectional study;air concentrations of 1 µg/m^3	Azar et al. 1975
Adult males; 5 groups, 30/group	1.12	Reanalysis of Azar 1975 by Snee 1982; at air concentration of 1 µg/m^3	Azar et al. 1975
Adult males; 5 groups, 30/group	1–2.39	Analysis of Azar 1975 by EPA; at 1 µg/m^3	Azar et al. 1975
Adults; N=44	1.14	Occupational longitudinal study over 30 months; air concentration <30 µg/m^3	Hodgkins et al. 1992

Table 1. Summary of blood slope factors from various environmental media (continued).

Population	Slope	Comments	Reference
Water Slope Factors:	µg/dL per µg Pb/L		
Infants, N=131	0.26 at <15 µg/L 0.04 at >15 µg/L	Scottish study of infants; EPA analysis	Lacey et al. 1985
Children, N=495	0.16 at <15 µg/L 0.03 at >15 µg/L	Scottish study; EPA analysis	Laxen et al. 1987
Adult males, N=7,735	0.06	24 British towns sampled; water lead levels <100 µg/L	Pocock et al. 1983
Adult Females, N=114	0.03	Duplicate diet study; Ayr, Scotland; EPA analysis	Sherlock et al. 1982
Diet Slope Factors:	µg/dL per µg Pb/day		
Infants and toddlers; N=29	0.24	Breast-fed and formula-fed; EPA analysis	Ryu et al. 1983; EPA 1990
Adults; N=31	0.034--females	Duplicate diet study; Ayr, Scotland	Sherlock et al. 1982
Adults; N=15	0.014–0.017--males 0.018–0.022--females	Experimental study; blood leads were not allowed to equilibrate	Stuik et al. 1974
Adult males; N=15	0.027	Experimental study	Cools et al. 1976

Table 1. Summary of blood slope factors from various environmental media (continued).

Population	Slope	Comments	Reference
Soil Slope Factors:	µg/dL per mg Pb/kg		
Mixed	0.002–0.016	Review of the literature	Reagan and Silbergeld 1989
Children; 1–18 years of age; N=831; 1,074 blood samples	0.0068 ± 0.00097	Omaha study; urban/suburban	Angle et al. 1984
Children; 1–72 months of age; N=377; 926 blood leads	-0.00016–0.00223 (near house) 0.00073–0.0023 at curb)	New Haven, CT; EPA analysis. The largest slopes were from the children under 1 year	Stark et al. 1982
Children; N=880	0.0011 (avg. for all ages) 0.0025 (for 2–3 year olds)	Kellogg/Silver Valley cross-sectional study; smelter; EPA analysis	Yankel et al. 1977
U.S. males age 18–65 years old (NHANES III)	0.001–0.003	Slope derived from Monte Carlo analysis	Stern 1996
Dust Slope Factors:	µg/dL per mg Pb/kg		
Children; 1–18 years of age; N=831; 1074 blood samples	0.00718 ± 0.00090	Omaha study; urban/suburban; housedust	Angle et al. 1984
Children; 1–6 years of age; N=32	0.008	Homes of lead workers; housedust	Baker 1977
Children; 2 years of age; N=82	0.004	Area of high lead soil; housedust	Baltrop et al. 1974
Adults and children; N=80	0.0086–0.0096 (housedust); 0.0021–0.0067 (outside dust)	Smelter	Roberts et al. 1974
Children; N=377; 1–72 months of age; 926 blood lead levels	0.00402 ± 0.0017 (0–1 year old); 0.00182 ± 0.00066 (2–3 years old) 0.00022±0.00077 (4–7 years old)	New Haven, CT; EPA analysis	Stark et al. 1982

Source: adapted from Duggan and Inskip 1985; EPA 1986, 1989

The general form of the model is:

$$PbB=\delta_S TPb_S + \delta_D TPb_D + \delta_W TPb_W + \delta_{AO} TPb_{AO} + \delta_{AI} TPb_{AI} + \delta_F TPb_F$$

where,

Pb_S=soil lead concentration
Pb_D=dust lead concentration
Pb_W=water lead concentration
Pb_{AO}=outside air lead concentration
Pb_{AI} = inside air concentration
Pb_F=food lead concentration
T=relative time spent
δ=the respective slope factor for specific media

A worktable that can be used to calculate a cumulative exposure estimate on a site-specific basis is provided in Table 2. To use the table, environmental levels for outdoor air, indoor air, food, water, soil, and dust are needed. In the absence of such data (as may be encountered during health assessment activities), default values can be used. In most situations, default values will be background levels unless data are available to indicate otherwise. Based on the U.S. Food and Drug Administration's (FDA's) Total Diet Study data, lead intake from food for infants and toddlers is about 5 Fg/day (Bolger et al. 1991). In some cases, a missing value can be estimated from a known value. For example, EPA (1986) has suggested that indoor air can be considered 0.03 x the level of outdoor air. Suggested default values are listed in Table 3.

Empirically determined and/or default environmental levels are multiplied by the percentage of time one is exposed to a particular source and then multiplied by an appropriate regression slope factor. This assumes slope factor studies were based upon continuous exposure. The slope factors can be derived from regression analysis studies that determine PbB levels for a similar route of exposure. Typically, these studies identify standard errors describing the regression line of a particular source of lead exposure. These standard errors can be used to provide an upper and lower confidence limit contribution of each source of lead to PbB. The individual source contributions can then be summed to provide an overall range estimate of PbB. While it is known that such summing of standard errors can lead to errors of population dynamics, detailed demographic analysis (e.g., Monte Carlo simulations) would likely lead to a model without much utility. As a screening tool, the estimates provided here have much greater utility than single value central tendency estimates, yet still provide a simple-to-use model that allows the health assessor an easy means to estimate source contributions to PbB.

As an example, Table 4 provides environmental monitoring data for a subset of data from the Multisite Lead and Cadmium Exposure Study (ATSDR 1995). Default values are used for air and dietary lead. The data are input as described in equation 1 with suggested slope factors from Table 2. The resulting media-specific contributions to PbB, the range of predicted PbB levels, and the actual PbB levels are given in Table 5.

The purpose of screening tools, such as MRLs or estimates derived from this approach, is to alert health assessors to substances that may pose risk to the exposed population. In addition, these approaches economize the use of resources by eliminating substances for which there is little likelihood of human

Table 2. Worktable for calculation of PbB from environmental and dietary lead.

Media	Concentration	Relative Time Spent	Slope Factor	Blood Lead	
				Low	High
Outdoor Air					
Indoor Air					
Food					
Water					
Soil					
Dust					
Total					

Table 3. Suggested default values to be used for missing data.

Media	Default	Reference
Outdoor Air	0.1-0.2 Fg/m^3	Eldred and Cahill 1994
Indoor Air	0.03-0.06 Fg/m^3 (0.3 x outdoor concentration)	EPA 1986
Food	5 Fg/day	Bolger et al. 1991
Water	4 Fg/L	EPA 1991
Soil	10-70 mg/kg	Shacklette and Boerngen 1972
Dust	10-70 mg/kg	Shacklette and Boerngen 1972

Table 4. Media concentrations for three sites: A, B, and C.

	SITE		
Media	A	B	C
Soil (mg/kg)	290	768	580
Dust (mg/kg)	383	580	560
Air (Fg/m^3)	0.06-0.2	0.06-0.2	0.06-0.2
Water (Fg/L)	1	1	1
Food (Fg/day)	5	5	5

Table 5. Contribution of environmental lead to blood lead for three sites: A, B, and C.

	SITE		
Media	**A** contribution to PbB (Fg/dL)	**B** contribution to PbB (Fg/dL)	**C** contribution to PbB (Fg/dL)
Soil	1.1-2.8	3-7.4	2.3-5.6
Dust	1.7-3.8	2.6-5.7	2.5-5.5
Air	0.1-0.2	0.1-0.2	0.1-0.2
Water	0.26	0.26	0.26
Food	1.2	1.2	1.2
Predicted range of PbB (Fg/dL)	4.4-8.3	7-14.8	6.4-12.8
Actual PbB	4.8	10.6	13.1

Slope values used were based on Angle et al. (1984): soil = 0.0068 ± 3SE; dust = 0.00718 ± 3SE; air = 1.92 ± 3SE.
Slope value for water was 0.26, based on Lacey et al. 1985 (reanalyzed by EPA 1986).
Slope value for food was 0.24, based on Ryu et al. 1983 (reanalyzed by Marcus in EPA 1990).
Default concentrations were used for air and food.

health effects so that efforts can be concentrated on those compounds of importance. Interpretation of the results from Table 5 would indicate that the potential exists that children at sites B and C have elevated PbB levels as defined by the CDC guidelines. Further action on these sites would, therefore, be warranted based on the individual site-specific demographic information and the CDC recommended follow-up services. These might include education, follow-up testing, and social services (CDC 1997). Results from site A, however, would indicate to the health assessor that the environmental data would not likely adversely affect PbB levels of resident children; resources can then be shifted to the other substances at the site.

Summary and Discussion

A number of methods and models have been used at sites to estimate potential risks from exposure to lead. One method is the use of prevalence data for estimating PbB levels. In this case, PbB measurements can be made at a site and extrapolated to other sites with similar environmental and demographic data. Limitations of this method include site-to-site variability with respect to, among other things, children's behavioral patterns, age, and bioavailability issues. Estimation of past exposures can be problematic because of redistribution of Pb out of the blood compartment since PbB is only an indicator of recent exposure (<90 days).

More traditional approaches have calculated exposure doses from a particular medium via a specific route (ATSDR, 1992). Such exposure doses can then be compared with a reference value derived for the same substance via the same route of exposure. Usual assumptions are ingestion rates of 100 mg dust/day and 200 mg soil/day, child body weight of 15 kg, and continuous exposure scenarios. This approach assumes a threshold for the effects of lead and does not reflect the fullest possible use of the wealth of human data on PbB levels.

Pharmacokinetic models have been developed that attempt to relate environmental levels to PbB levels (Leggett 1993; O'Flaherty 1995). The Integrated Exposure Uptake Biokinetic Model (IEUBK) developed by EPA is one of the most extensive efforts to date to make population-based predictions of PbB levels based upon environmental data. The model incorporates both exposure/uptake parameters and a biokinetic component to estimate the PbB distribution in the exposed population (EPA 1994).

The framework described here provides a useful screening tool. Preliminary efforts to test its predictive power have shown promise (unpublished data). The framework's strengths lie in its simplicity and flexibility to take into consideration environmental and biological variability between sites through the selection of slope factors from similar sites. For example, slope factors from a lead mining study can be used to address concerns at a mining community or, as more refined regression coefficients become available, they can be used in a site-specific manner to assist in making appropriate decisions. The framework also offers a simple approach that allows the health assessor to readily identify factors that may be contributing to elevated PbB levels. In this manner, it provides for multi-media evaluation of all source contributions and utilizes a basic approach for determining significant human effect levels. This helps the health assessor determine source contributions of most significance and suggests plausible remediation avenues. These insights, coupled with biomedical judgment, can serve as valuable screening tools to identify those sites meriting further evaluation.

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