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 2005. This edition supersedes any previously released draft or final profile.

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

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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 is being 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 ATSDR to prepare toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on December 7, 2005 (70 FR 72840). 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); October 28, 1992 (57 FR 48801); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014); and November 7, 2003 (68 FR 63098). 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: Relevance to Public Health: The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

Chapter 3: Health Effects: Specific health effects of a given hazardous compound are reported by type of health effect (death, systemic, immunologic, reproductive), by route of exposure, 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 3.7	**Children's Susceptibility**
Section 6.6	**Exposures of Children**

Other Sections of Interest:

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

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636)
1-888-232-6348 (TTY)
Fax: (770) 488-4178
E-mail: cdcinfo@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@AOEC.ORG • Web Page: http://www.aoec.org/.

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, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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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 Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.

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

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PEER REVIEW

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

1. Philip Landrigan, M.D., Ethel H. Wise, Professor of Community and Preventive Medicine and Professor of Pediatrics, Director, Division of Environmental and Occupational Medicine, Mount Sinai School of Medicine, New York, New York;

2. Deborah Cory-Slechta, Ph.D., Director, Environmental and Occupational Health Sciences Institute, Chair, Department of Environmental and Occupational Medicine, Robert Wood Johnson Medical University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey; and

3. Howard Hu, M.D., M.P.H., Professor of Occupational and Environmental Medicine, Harvard School of Public Health, Boston, Massachusetts.

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.

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 to it.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. Lead has been found in at least 1,272 of the 1,684 current or former NPL sites. Although the total number of NPL sites evaluated for this substance is not known, the possibility exists that the number of sites at which lead is found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure and exposure to this substance may harm you.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be 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 will determine whether you will 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 any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1.1 WHAT IS LEAD?

Lead is a heavy, low melting, bluish-gray metal that occurs naturally in the Earth's crust. However, it is rarely found naturally as a metal. It is usually found combined with two or more other elements to form lead compounds.

Metallic lead is resistant to corrosion (i.e., not easily attacked by air or water). When exposed to air or water, thin films of lead compounds are formed that protect the metal from further attack. Lead is easily molded and shaped. Lead can be combined with other metals to form alloys. Lead and lead alloys are commonly found in pipes, storage batteries, weights, shot and

ammunition, cable covers, and sheets used to shield us from radiation. The largest use for lead is in storage batteries in cars and other vehicles.

Lead compounds are used as a pigment in paints, dyes, and ceramic glazes and in caulk. The amount of lead used in these products has been reduced in recent years to minimize lead's harmful effect on people and animals. Tetraethyl lead and tetramethyl lead were once used in the United States as gasoline additives to increase octane rating. However, their use was phased out in the United States in the 1980s, and lead was banned for use in gasoline for motor vehicles beginning January 1, 1996. Tetraethyl lead may still be used in gasoline for off-road vehicles and airplanes. It is also still used in a number of developing countries. Lead used in ammunition, which is the largest non-battery end-use, has remained fairly constant in recent years. However, even the use of lead in bullets and shot as well as in fishing sinkers is being reduced because of its harm to the environment.

Most lead used by industry comes from mined ores ("primary") or from recycled scrap metal or batteries ("secondary"). Lead is mined in the United States, primarily in Alaska and Missouri. However, most lead today is "secondary" lead obtained from lead-acid batteries. It is reported that 97% of these batteries are recycled.

For more information on the physical and chemical properties of lead, please see Chapter 4. For more on the production and use of lead, please see Chapter 5.

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. Environmental levels of lead have increased more than 1,000-fold over the past three centuries as a result of human activity. The greatest increase occurred between the years 1950 and 2000, and reflected increasing worldwide use of leaded gasoline. Lead can enter the environment through releases from mining lead and other metals, and from factories that make or use lead, lead alloys, or lead compounds. Lead is released into the air during burning coal, oil, or waste. Before the use of leaded gasoline was banned, most of

the lead released into the U.S. environment came from vehicle exhaust. In 1979, cars released 94.6 million kilograms (208.1 million 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 (4.8 million pounds) 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. Before the 1950s, lead was used in pesticides applied to fruit orchards. Once lead gets into the atmosphere, it may travel long distances if the lead particles are very small. Lead is removed from the air by rain and by particles falling to land or into surface water.

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, bridges, and other structures. Landfills may contain waste from lead ore mining, ammunition manufacturing, or other industrial activities such as battery production. Disposal of lead-containing products contribute to lead in municipal landfills. Past uses of lead such as its use in gasoline are a major contributor to lead in soil, and higher levels of lead in soil are found near roadways. Most of the lead in inner city soils comes from old houses with paint containing lead and previous automotive exhaust emitted when gasoline contained lead.

Once lead falls onto soil, it sticks strongly to soil particles and remains in the upper layer of soil. That is why past uses of lead such as lead in gasoline, house paint, and pesticides are so important in the amount of lead found in soil.

Small amounts of lead may enter rivers, lakes, and streams when soil particles are moved by rainwater. Small amounts of lead from lead pipe or solder may be released into water when the water is acidic or “soft”. Lead may remain stuck to soil particles or sediment in water for many years. Movement of lead from soil particles into groundwater is unlikely unless the rain falling on the soil is acidic or "soft". Movement of lead from soil will also depend on the type of lead 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 lead compounds are changed into other forms of lead by sunlight, air, and water. However, elemental lead 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. Chapter 6 contains more information about what happens to lead in the environment.

1.3 HOW MIGHT I BE EXPOSED TO LEAD?

Lead is commonly found in soil especially near roadways, older houses, old orchards, mining areas, industrial sites, near power plants, incinerators, landfills, and hazardous waste sites. 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 dust or dirt that contain lead. People may be exposed to lead by eating food or drinking water that contains lead. Drinking water in houses containing lead pipes may contain lead, especially if the water is acidic or “soft”. If one is not certain whether an older building contains lead pipes, it is best to let the water run a while before drinking it so that any lead formed in the pipes can be flushed out. People living in areas where there are old houses that have been painted with lead paint may be exposed to higher levels of lead in dust and soil. Similarly, people who live near busy highways or on old orchard land where lead arsenate pesticides were used in the past may be exposed to higher levels of lead. People may also be exposed to lead when they work in jobs where lead is used or have hobbies in which lead is used, such as making stained glass.

Foods may contain small amounts of lead. However, since lead solder is no longer used in cans, very little lead is found in food. Leafy fresh vegetables grown in lead-containing soils may have lead-containing dust on them. 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. Cigarette smoke may also contain small amounts of lead. The amount of lead found in canned foods decreased 87% from 1980 to 1988 in the United States, which indicates that the chance of exposure to lead in canned food from lead-soldered containers has been greatly reduced. Lead-soldered cans are still used in some other nations. In the most recent studies, lead was not detectable in most foods and the average dietary intake of lead was about 1 microgram (a microgram is a millionth of a gram) per kilogram of body weight per day. Children may be exposed to lead by hand-to-mouth contact after exposure to lead-containing soil or dust.

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 be dissolved and to enter the water we drink. Public water treatment systems are now required to use control measures to make water less acidic. Plumbing that contains lead may be found in public drinking water systems, and in houses, apartment buildings, and public buildings that are more than 20 years old. However, as buildings age, mineral deposits form a coating on the inside of the water pipes that insulates the water from lead in the pipe or solder, thus reducing the amount of lead that can leach into the water. Since 1988, regulations require that drinking water coolers must not contain lead in parts that come into contact with drinking water.

Breathing in, or swallowing airborne dust and dirt, is another way you can be exposed to lead. 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 for motor vehicles. 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 nonferrous (brass and bronze) foundries. Lead released into air may also come from burning of solid waste that contains lead, windblown dust, volcanoes, exhaust from workroom air, burning or weathering of lead-painted surfaces, fumes and exhaust from leaded gasoline, and cigarette smoke.

Skin contact with dust and dirt containing lead occurs every day. Recent data have shown that inexpensive cosmetic jewelry pieces sold to the general public may contain high levels of lead which may be transferred to the skin through routine handling. However, not much lead can get into your body through your skin.

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, cosmetics, 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 and demolition 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. Painters who sand or scrape old paint may be exposed to lead in dust. 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. For more information on the potential for exposure to lead, please refer to Chapter 6.

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.

Larger particles that are too large to get into your lungs can be coughed up and swallowed. You may also swallow lead by eating food and drinking liquids that contain it. 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. 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 5% 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. Children absorb about 50% of ingested lead.

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. You can, however, accidentally swallow lead that is on your hands when you eat, drink, smoke, or apply cosmetics (for example, lip balm). 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" and organs (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 (e.g., 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 of the lead that enters the body will be eliminated, and this may result in accumulation of lead in body tissues, especially bone. For more information on how lead can enter and leave your body, please refer to Chapter 3.

1.5 HOW CAN LEAD AFFECT MY HEALTH?

Scientists use many tests to protect the public from harmful effects of toxic chemicals and to find ways for treating persons who have been harmed.

One way to learn whether a chemical will harm people is to determine how the body absorbs, uses, and releases the chemical. For some chemicals, animal testing may be necessary. Animal testing may also help identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method for getting information needed to make wise decisions that protect public health. Scientists have the responsibility to treat research animals with care and compassion. Scientists must comply with strict animal care guidelines because laws today protect the welfare of research animals.

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 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. Lead exposure also causes small increases in blood pressure, particularly in middle-aged and older people. Lead exposure may also cause anemia. At high levels of exposure, lead can severely damage the brain and kidneys in adults or children and ultimately

cause death. 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.

We have no conclusive proof that lead causes cancer (is carcinogenic) in humans. Kidney tumors have developed in rats and mice that had been given large doses of some kind of lead compounds. The Department of Health and Human Services (DHHS) has determined that lead and lead compounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from animal studies, and the EPA has determined that lead is a probable human carcinogen. The International Agency for Research on Cancer (IARC) has determined that inorganic lead is probably carcinogenic to humans. IARC determined that organic lead compounds are not classifiable as to their carcinogenicity in humans based on inadequate evidence from studies in humans and in animals. See Chapters 2 and 3 for more information on the health effects of lead.

1.6 HOW CAN LEAD AFFECT CHILDREN?

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

Studies carried out by the Centers 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 result is because lead is banned from gasoline, residential paint, and solder used for food cans and water pipes. However, about 310,000 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 level targeted for elimination among young children in the Unites States by 2010.

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 contains as much as 50% lead. Also, compared with adults, a bigger proportion of the amount of lead swallowed will enter the blood in children.

Children are more sensitive to the health effects of lead than adults. No safe blood lead level in children has been determined. Lead affects children in different ways depending on how much lead a child swallows. A child who swallows large amounts of lead may develop anemia, kidney damage, colic (severe "stomach ache"), muscle weakness, and brain damage, which ultimately can kill the child. 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. If a child swallows smaller amounts of lead, such as dust containing lead from paint, much less severe but still important effects on blood, development, and behavior may occur. In this case, recovery is likely once the child is removed from the source of lead exposure, but there is no guarantee that the child will completely avoid all long-term consequences of lead exposure. 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 also may slow mental development and cause lower intelligence later in childhood. There is evidence that these effects may persist beyond childhood.

Children with high blood lead levels do not have specific symptoms. However, 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 type of test, however, is not routine. More information regarding children's health and lead can be found in Section 3.5.

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

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

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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, but paint chips and lead-containing dust may still be in the yard soil. Decaying, peeling, or flaking paint can introduce lead into household dust and the area where this is occurring should be repainted. If your paint is decaying or your child has symptoms of lead poisoning, you may want to have your house tested for lead. In some states, homeowners can have the paint in their homes tested for lead by their local health departments. The National Lead Information Center (1-800-532-3394) has a listing of approved risk assessors (people who have met certain criteria and are qualified to assess the potential risks of a site) and of approved testing laboratories (for soil, paint, and dust).

Sanding surfaces painted with lead-based paint or using heat to peel the paint may cause exposure to high levels of lead. Many cases of lead poisoning have resulted from do-it-yourself

home renovations. Therefore, any renovations should be performed by a licensed contractor who will minimize exposure to household members. It is important for the area being renovated to be isolated from the rest of the house because of lead-containing dust. The federal government requires that contractors who test for or remove lead must be certified by the EPA or an EPA-approved state program. Ask to see certifications of potential contractors. Your state health department or environmental protection division should be able to identify certified contractors for you. The National Lead Abatement Council (P.O. Box 535; Olney, MD 20932; telephone 301-924-5490) can also send you a list of certified contractors.

Families can lower the possibility of children swallowing paint chips by discouraging their children from chewing or putting these painted surfaces in their mouths and making sure that they wash their hands often, especially before eating. Lead can be found in dirt and dust. Areas where levels of lead in dirt might be especially high are near old houses, highways, or old orchards. Some children have the habit of eating dirt (the term for this activity is pica). Discourage your children from eating dirt and other hand-to-mouth activity.

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. If you give your children these substances or if you are pregnant or nursing, you may expose your children to lead. It is wise to know the ingredients of any medicines that you or your children use.

Older homes that have plumbing containing lead may have higher amounts of lead in drinking water. Inside plumbing installed before 1930 is most likely to contain high levels of lead. Copper pipes have replaced lead pipes in most residential plumbing. You cannot see, taste, or smell lead in water, and boiling your water will not get rid of lead. If you have a water-lead problem, EPA recommends that anytime water in a particular faucet has not been used for 6 hours or longer, you should flush your cold water pipes by running water until it is cold (5 seconds–2 minutes). Because lead dissolves more easily in warm water than in cold water, you should only use cold water for drinking, cooking, and preparing baby formula. You can contact your local health department or water supplier to find out about testing your water for

lead. If your water tests indicate a significant presence of lead, consult your water supplier or local health department about possible remedies.

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.

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 entering the home 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.

Lead-containing dust may be deposited on plant surfaces and lead may be taken up in certain 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. Vegetables should be well washed before eating to remove surface deposits. 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 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.

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.

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 shows if you have been recently exposed to lead. Lead can be measured in teeth or bones by x-ray techniques, but these methods are not widely available. These tests show long-term exposures to lead. The primary screening method is measurement of blood lead. Exposure to lead also 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). These tests usually require special analytical equipment that is not available in a doctor's office. However, your doctor can draw blood samples and send them to appropriate laboratories for analysis. For more information on tests to measure lead in the body, see Chapters 3 and 7.

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. The EPA, the Occupational Safety and Health

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

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

Recommendations and regulations are also updated periodically 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. CDC recommends that the states test children:

- at ages 1 and 2 years;
- at ages 3–6 years if they have never been tested for lead;
- if they receive services from public assistance programs for the poor such as Medicaid or the Supplemental Food Program for Women, Infants, and Children;
- 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; and/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. Many states or local programs provide intervention to individual children with blood lead levels equal to or greater than 10 µg/dL. Medical evaluation and environmental investigation and remediation should be done for all children with blood lead levels equal to or greater than 20 µg/dL. Medical treatment (i.e., chelation therapy) 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.

Under the Lead Copper Rule (LCR), EPA requires testing of public water systems, and if more than 10% of the samples at residences contain lead levels over 0.015 milligrams per liter (mg/L), actions must be taken to lower these levels. Testing for lead in drinking water in schools is not required unless a school is regulated under a public water system. The 1988 Lead Contamination Control Act (LCCA) was created to help reduce lead in drinking water at schools and daycare centers. The LCCA created lead monitoring and reporting requirements for schools, as well as the replacement of fixtures that contain high levels of lead. However, the provisions in the LCCA are not enforceable by the federal government and individual states have the option to voluntarily comply with these provisions or create their own.

To help protect small children, the Consumer Product Safety Commission (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 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 $\mu g/m^3$ for an 8-hour workday. If a worker has a blood lead level of 50 µg/dL or higher, then OSHA requires that the 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 unsafe. 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 such foil is also a violation of the Federal Food, Drug, and Cosmetic Act. FDA has reviewed several direct human food ingredients (i.e., food dyes) 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 ppm.

Please see Chapter 8 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 contact ATSDR at the address and phone number below.

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

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

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

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

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

2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO LEAD IN THE UNITED STATES

Lead is a naturally occurring metal found in the Earth's crust at about 15–20 mg/kg. In comparison to the two most abundant metals in the Earth, aluminum and iron, lead is a relatively uncommon metal. Lead rarely occurs in its elemental state, but rather its +2 oxidation state in various ores throughout the earth. The most important lead containing ores are galena (PbS), anglesite ($PbSO_4$), and cerussite ($PbCO_3$). The world's reserves of lead are estimated at $7.1x10^7$ tons, with over one third located in North America. Levels of lead in the environment (not contained in ore deposits) have increased over the past three centuries as a result of human activity. Human exposure to lead is common and results from the many uses of this metal due to its exceptional properties. The largest industrial use of lead today is for the production of lead batteries, largely used in the automobile industry. Other uses of lead include the production of lead alloys, use in soldering materials, shielding for x-ray machines, and in the manufacture of corrosion and acid resistant materials used in the building industry (see Chapter 5 for more details regarding lead usage).

The greatest potential for human exposure to lead arises from its previous use as an additive in gasoline, which resulted in its widespread dispersal throughout the environment, and its use as a pigment in both interior and exterior paints. Although the use of lead as a gasoline additive has been gradually phased out and completely banned by 1995 in the United States and its use in paints was banned in 1978, human exposure to lead continues because unlike organic chemicals released to the environment, lead does not degrade to other substances. Leaded paint is still prevalent in many older homes in the United States, and peeling or flaking paint contributes to indoor and outdoor dust levels. Prior to World War II, lead-arsenic compounds were used as pesticides, especially in orchards. Because lead does not degrade and is strongly absorbed to soil, the lead released from past uses still remains in the soil. Since the ban on the use of leaded gasoline took effect, lead emissions to the atmosphere have decreased significantly. According to the EPA, atmospheric emissions of lead decreased 93% over the 21-year period of 1982–2002. The atmospheric concentration of lead varies greatly, with the highest levels observed near stationary sources such as lead smelters. Levels of lead in ambient air range from about $7.6x10^{-5}$ $\mu g/m^3$ in remote areas such as Antarctica to >10 $\mu g/m^3$ near point sources. The EPA national ambient air quality standard for lead is 1.5 $\mu g/m^3$.

The amount of lead contained in pipes and plumbing fittings have been strictly regulated since 1988; however, human exposure to lead from drinking water still occurs as a consequence of leaching of lead from corroding pipes and fixtures or lead containing solder. Based on several data sets, it is estimated that <1% of the public water systems in the United States have water entering the distribution system with lead levels above 5 µg/L. Copper pipes have replaced lead pipes in most residential plumbing. Section 1417 of the Safe Drinking Water Act, which took effect in August 1998, requires that all pipes, fixtures, and solder be lead-free. However, lead-free means that solders and flux may not contain >0.2% lead, while pipes, pipe fittings, and well pumps may not contain >8% lead. The EPA requires public water distribution systems to reduce the corrosivity of water if >10% of the water samples exceed 15 µg/L of lead.

Occupational exposure to lead occurs for workers in the 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. In these occupations, 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.

Certain populations may be exposed to lead from other sources. Several non-western folk medicines can contain substantial levels of lead. Lead glazing that is applied to some pottery and ceramic ware may leach lead into foods or liquids that are stored in them (see Section 6.4.5 for more information). The FDA regulates the amount of leachable lead from food containers (see Table 8-1).

Blood lead levels (PbB) in the general population of the United States have been decreasing over the past 3 decades as regulations regarding lead paint, leaded fuels, and lead-containing plumbing materials have reduced exposure. PbBs measured as a part of the National Health and Nutrition Examination Surveys (NHANES) indicated that from 1976 to 1991, the mean PbBs of the U.S. population aged from 1 to 74 years dropped 78%, from 12.8 to 2.8 µg/dL. The prevalence of PbBs ≥10 µg/dL also decreased sharply from 77.8 to 4.3%. Data from NHANES III, phase II (1991–1994) showed that 4.4% of children aged 1–5 years had PbBs ≥10 µg/dL, and the geometric mean PbBs for children 1–5 years old was 2.7 µg/dL. From the most recent sampling data conducted for 1999–2002, 1.6% of children aged 1–5 years had PbBs ≥10 µg/dL, with a geometric mean PbBs of 1.9 µg/dL (see Section 6.5 for greater

detail). The Centers for Disease Control and Prevention (CDC) action level for children ≤7 years of age is 10 µg/dL. A tiered approach is recommended for managing lead-exposed children (see Section 3.9).

Analysis of lead in whole blood is the most common and accurate method of assessing lead exposure. Erythrocyte protoporphyrin (EP) tests can also be used, but are not as sensitive at low blood lead levels (≤20 µg/dL); the screening test of choice is blood lead levels. X-ray fluorescence techniques (XRF) can be used for the determination of lead concentration in bones. Lead partitions to the bone over a lifetime of exposure; therefore, bone lead measurements are a good indicator of cumulative exposure, whereas measurements of lead in blood are more indicative of recent exposure. However, XRF is primarily used in the research area and is not widely available (see Sections 3.3 and 3.6.1 for greater detail).

2.2 SUMMARY OF HEALTH EFFECTS

An enormous amount of information is available on the health effects of lead on human health. In fact, the toxic effects of lead have been known for centuries, but the discovery in the past few decades that levels of exposure resulting in relatively low levels of lead in blood (e.g., <20 µg/dL) are associated with adverse effects in the developing organism is a matter of great concern. Most of the information gathered in modern times regarding lead toxicity comes from studies of workers from a variety of industries and from studies of adults and children in the general population. The most sensitive targets for lead toxicity are the developing nervous system, the hematological and cardiovascular systems, and the kidney. However, due to the multi-modes of action of lead in biological systems, lead could potentially affect any system or organs in the body.

Studies of lead workers suggest that long-term exposure to lead may be associated with increased mortality due to cerebrovascular disease. The same was found in a study of adults from the general population who were hospitalized for lead poisoning during childhood. Population studies suggest that there is a significant association between bone-lead levels and elevated blood pressure. Blood lead levels (PbBs) also have been associated with small elevations in blood pressure. Between the two biomarkers, bone lead appears to be the better predictor. Lead also affects kidney functions; glomerular filtration rate appears to be the function affected at the lowest PbBs. Decreased glomerular filtration rate has been consistently observed in populations with mean PbB <20 µg/dL and two studies have reported effects at PbB <10 µg/dL. Lead may alter glomerular filtration rate by several mechanisms.

Lead has long been known to alter the hematological system by inhibiting the activities of several enzymes involved in heme biosynthesis. Particularly sensitive to lead action is δ-aminolevulinic acid dehydratase (ALAD). Inhibition of ALAD activity occurs over a wide range of PbBs beginning at <10 μg/dL. The anemia induced by lead is primarily the result of both inhibition of heme synthesis and shortening of erythrocyte lifespan, but lead also can induce inappropriate production of the hormone erythropoietin leading to inadequate maturation of red cell progenitors, which can contribute to the anemia.

A recent study in children 8–10 years of age suggested that lead accelerates skeletal maturation, which might predispose to osteoporosis in later life. Lead also has been associated with increased occurrence of dental caries in children and periodontal bone loss, which is consistent with delayed mineralization in teeth observed in studies in animals. Current mean PbBs in these cohorts were <5 μg/dL; however, the cross-sectional nature of the studies precluded assessment of the exposure history.

Changes in circulating levels of thyroid hormones, particularly serum thyroxine (T_4) and thyroid stimulating hormone (TSH), generally occurred in workers having mean PbB ≥40–60 μg/dL. Altered serum levels of reproductive hormones, particularly follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone have been observed at PbB ≥30–40 μg/dL. Lead also has been shown to decrease circulating levels of the active form of vitamin D, 1,25-dihydroxyvitamin D, in children with moderate to high PbB (30–60 μg/dL), but not in children with low to moderate PbB (average lifetime PbB between 4.9 and 23.6 μg/dL, geometric mean, 9.8 μg/dL). Normal levels of vitamin D are important for maintaining calcium homeostasis.

Altered immune parameters have been described in lead workers with PbB in the range of 30–70 μg/dL. Reported effects included changes in some T-cell subpopulations, response to T-cell mitogens, and reduced chemotaxis of polymorphonuclear leukocytes. Several studies of children reported significant associations between PbB and increases in serum IgE levels. IgE is the primary mediator for type-I hypersensitivity and is involved in various allergic diseases such as asthma. These findings in children along with results from studies in rodents exposed *in utero* have led some to suggest that lead may be a risk factor for childhood asthma, although a recent relatively large study (4,634 children) found that PbB was less a predictor of asthma than was race.

Exposure to high amounts of lead resulting in PbBs of 100–120 μg/dL in adults or 70–100 μg/dL in children produce encephalopathy, a general term that describes various diseases that affect brain function.

Symptoms develop following prolonged exposure and include dullness, irritability, poor attention span, epigastric pain, constipation, vomiting, convulsions, coma, and death. Lead poisoning in children can leave residual cognitive deficits that can be still detected in adulthood. Neurobehavioral effects including malaise, forgetfulness, irritability, lethargy, headache, fatigue, impotence, decreased libido, dizziness, weakness, and paresthesia have been reported in lead workers with PbBs in the range of 40–80 μg/dL. Also, PbBs between 40 and 80 μg/dL have been associated with neuropsychological effects in lead workers. A recent study of lead workers reported that higher tibia lead was associated with increased prevalence and severity of white matter lesions, as assessed by brain MRI. Studies of older populations with current mean PbBs <10 μg/dL have reported associations between PbB and/or bone lead and poorer performance in neurobehavioral tests. Lead also has been shown to affect nerve conduction velocity and postural balance in workers with PbB in the range of 30–60 μg/dL. Alterations of somatosensory evoked potentials also have been reported in lead workers with mean PbBs in the range of 30–50 μg/dL.

As previously mentioned, one of the major concerns regarding lead toxicity is the cognitive and neurobehavioral deficits that are observed in children exposed to lead. Prospective studies have provided the greatest amount of information. Analyses of these and other studies suggest that an IQ decline of 1–5 points is associated with an increase in PbB of 10 μg/dL. Of special interest and concern are the results of recent studies that have reported neurobehavioral deficits in children associated with PbBs <10 μg/dL and an apparent lack of threshold down to even the lowest PbBs recorded in these studies. Lead also has caused neurobehavioral alterations in developing animals, and at PbBs similar to those reported in children. Studies in animals, particularly in monkeys, have provided key information for the interpretation of a cognitive basis for IQ changes. Studies of children also have shown associations between PbB and growth, delayed sexual maturation in girls, and decreased erythropoietin production.

Some studies of humans occupationally or environmentally exposed to lead have observed associations between PbB and abortion and preterm delivery in women and alterations in sperm and decreased fertility in men. On the other hand, there are several studies that found no significant association between lead exposure and these end points. At least for the effects in males, the threshold PbB appears to be in the range of 30–40 μg/dL. Studies have shown that lead can affect the association of protamines with DNA in sperm cells from exposed males. Lead does so by competing or reducing zinc in protamine P2 *in vivo*, which would leave sperm chromatin and DNA open to damage from other exposures.

In vitro mutagenicity studies in microorganisms have yielded mostly negative results for lead, but lead is a clastogenic agent, as shown by the induction of chromosomal aberrations, micronuclei and by sister

chromatid exchanges in peripheral blood cells from lead workers. Studies of cancer in lead workers have been inconclusive. A meta-analysis of eight major occupational studies on cancer mortality or incidence in workers with high lead exposure concluded that there is some limited evidence of increased risk of lung cancer and stomach cancer, although there might have been confounding with arsenic exposure in the study with highest relative risk of lung cancer. The results also showed a weak evidence for an association with kidney cancer and gliomas. In the only study of the general population available, there was suggestive evidence for an increase risk of cancer mortality in women, but not men, with a threshold PbB of 24 μg/dL. This study used data from the Second National Health and Nutrition Survey (NHANES II) Mortality Study. Lead has produced primarily renal tumors in rodents by a mechanism not yet elucidated. Some nongenotoxic mechanisms that have been proposed for lead-induced cancer include inhibition of DNA synthesis and repair, alterations in cell-to-cell communication, and oxidative damage.

The Department of Health and Human Services (DHHS) has determined that lead and lead compounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from animal studies. The EPA has determined that lead is a probable human carcinogen based on sufficient evidence from studies in animals and inadequate evidence in humans. The International Agency for Research on Cancer (IARC) has determined that inorganic lead is probably carcinogenic to humans based on sufficient evidence from studies in animals and limited evidence of carcinogenicity from studies in humans. IARC also determined that organic lead compounds are not classifiable as to their carcinogenicity in humans based on inadequate evidence from studies in humans and animals.

A discussion of the most sensitive end points for lead toxicity, neurodevelopmental, cardiovascular/renal, and hematological, is presented below. The reader is referred to Chapter 3, Health Effects, for information on additional effects.

Neurodevelopmental Effects. Lead can impair cognitive function in children and adults, but children are more vulnerable than adults. The increased vulnerability is due in part to the relative importance of exposure pathways (i.e., dust-to-hand-mouth) and differences in toxicokinetics (i.e., absorption of ingested lead). Although the inhalation and oral routes are the main routes of exposure for both adults and children, children are more likely to have contact with contaminated surfaces due to playing on the ground and to hand-to-mouth activities. Furthermore, children absorb a larger fraction of ingested lead than adults. However, perhaps more important is the fact that the developing nervous system is especially susceptible to lead toxicity. During brain development, lead interferes with the

trimming and pruning of synapses, migration of neurons, and neuron/glia interactions. Alterations of any of these processes may result in failure to establish appropriate connections between structures and eventually in permanently altered functions. Because different brain areas mature at different times, the final outcome of the exposure to lead during development (i.e., *in utero* vs. pediatric exposure) will vary depending on the time of exposure. This has been demonstrated in studies in animals. The time of exposure-specific response appears to have contributed to the failure to identify a "behavioral signature" of lead exposure in children. Other factors that may affect individual vulnerability are certain genetic polymorphisms, such as that for the vitamin D receptor, the lead-binding enzyme ALAD, or the APOE genotype. One important additional factor shown to influence the toxicity of lead is the characteristics of the child's rearing environment, a modifying factor. It has been argued that effect modification is a property of a true association and should be distinguished from confounding. Effect modification can explain inconsistencies in findings, and if it exists, failure to address it will lead to an error in inference. For example, if social class is an effect modifier of the association between PbB and IQ, and differs between two cohorts, the strength of the association based on these two studies will necessarily be different.

Despite the many factors that can potentially work against finding agreement among studies, the preponderance of the evidence indicates that lead exposure is associated with decrements in cognitive function. Meta-analyses conducted on cross-sectional studies or a combination of cross-sectional and prospective studies suggest that an IQ decline of 1–5 points is associated with an increase in PbB of 10 μg/dL. Most importantly, no threshold for the effects of lead on IQ has been identified. This has been confirmed by a series of recent studies in children that found significant inverse associations between cognitive function and PbBs <10 μg/dL. Moreover, these and other studies have shown that the slope of the lead effects on cognitive variables is steeper (the effect is greater) at lower than at higher PbBs (supra-linear dose-response relationship). However, there is not complete agreement on the interpretation of the lack of linearity in the dose-response relationship among the scientific community. Some have argued, based on a theoretical statistical analysis, that the supra-linear slope is a required outcome of correlations between data distributions where one is log-normally distributed and the other is normally distributed. Perhaps the strongest evidence for nonlinearity is provided by an international pooled analysis of seven prospective studies (details in Section 3.2.4). After testing several models, these investigators determined that the shape of the dose-response was nonlinear insofar as the quadratic and cubic terms for concurrent PbB were statistically significant ($p<0.001$, $p=0.003$, respectively). Additional support for the steeper slope at low PbB was provided by plotting the individual effects estimates for each of the seven cohorts, adjusted for the same covariates. The plot showed that the studies with the lowest mean PbBs had a

steeper slope compared with studies with higher PbBs. Yet further evidence for nonlinearity was presented when the data were divided at two cut-points *a priori* (maximal PbB above and below 10 μg/dL and above and below 7.5 μg/dL). The investigators then fit separate linear models to the data in each of those ranges and compared the PbB coefficients for the concurrent PbB index. The stratified analyses showed that the effects estimate for children with maximal PbB <7.5 μg/dL was significantly greater (p=0.015) than those with a maximal PbB ≥7.5 μg/dL. Similar results were seen at the cut-off point of 10 μg/dL. A reanalysis of the pooled studies found that a log-linear relationship between PbB and IQ was a better fit within the ranges of PbBs in the studies than was a linear relationship (p<0.009). Collectively, the results of the pooled analysis and of additional studies provide suggestive evidence of lead effects on cognitive functions in children at PbBs <10 μg/dL and, possibly as low as 5 μg/dL. It should be stressed, however, that the effects of lead on IQ and other neurobehavioral scores are very small compared with the effects of other factors such as parents' IQ, but is also important to stress that lead exposure, unlike most of those other factors, is highly preventable.

The other aspect that has been questioned regarding the nonlinear shape of the dose-response relationship is the apparent lack of a biological mechanism that could produce this result, and this clearly represents a data need. To explain the nonlinear shape of the dose-response, it was proposed that "the initial damage caused by lead may reflect the disruption of different biological mechanisms than the more severe effects of high exposures that result in encephalopathy or frank mental disability. This might explain why, within the range of exposures not producing overt clinical effects, an increase in PbB beyond a certain level might cause little *additional* impairment in children's cognitive function."

While measurements of IQ are convenient in that they allow comparison across populations of different demographic and cultural characteristics, and help define the extent of the public health issue, they only partially advance our understanding of the problem of lead-induced behavioral toxicity. It is important to elucidate the underlying basis of the deficits in IQ as well as the behavioral mechanisms that account for them. It was noted that "the answers are critical not only to further define neurobiological mechanisms associated with learning deficits, but also to determine behavioral or neurochemical therapeutic approaches to alleviate them." Studies in animals have provided answers to some of these questions. Studies in animals have great utility because the possibility of confounding is reduced with the controlled experimental design and genetic factors. In addition, they address specific domains of cognitive function and allow determination of critical periods of exposure. Results of behavioral tests performed primarily in rats and monkeys exposed to lead have suggested that the impaired performance is the result, at least in part, of a combination of distractibility, inability to inhibit inappropriate responding, and perseveration in

behaviors that are no longer appropriate. Evaluation of children exposed to lead with different subscales of IQ tests in conjunction with assessments of behavior on teacher's rating scales on young school-age children suggest that increased distractibility, impulsivity, short attention span, and inability to follow simple and complex sequences of directions are associated with increased lead body burden. The similarity between neurobehavioral effects in lead-exposed children and in animals, and the fact that the deficits are observed at similar PbBs should stimulate continued research to elucidate the biochemical and morphological substrates that underlie specific behaviors.

Although the decrement of IQ points in children associated with lead exposure is generally small, lead neurotoxicity may have major implications for public health when exposure is considered in terms of large populations and its preventable nature. One study quantified the economic benefits from projected improvements in worker productivity resulting from the reduction in children's exposure to lead in the United States since 1976. Based on data from NHANES (a study designed to provide national estimates of the health and nutritional status of the U.S. civilian noninstitutionalized population aged 2 months and older) and meta-analyses, it was estimated that mean PbBs declined 15.1 μg/dL between 1976 and 1999 and that IQ scores increased between 0.185 and 0.323 points for each 1 μg/dL blood lead concentration. It was further estimated that each IQ point raises worker's productivity by 1.76–2.38%, and that the economic benefit for each year's cohort of 3.8 million 2-year-old children ranges from $110 to $319 billion. In another study, using an environmentally attributable fraction model, it was estimated that the present value of economic losses in the United States attributable to lead exposure in amounts to $43.4 billion per year in each annual birth cohort. More recently, one study estimated that mild mental retardation and cardiovascular outcomes resulting from exposure to lead amounts to almost 1% of the global burden of disease, with the highest burden in developing regions.

A related and important issue is whether lead-lowering interventions, such as with chelators, are paralleled by improvement in health outcomes reportedly altered by lead. In one study, improvement in cognitive functions was related to decreases in blood lead but not to chelation treatment. In a multi-center study of 780 children, chelation therapy lowered blood lead by a mean of 4.5 μg/dL during the 6 months after initiation of treatment, but it did not improve scores on tests of cognition, behavior, or neuro-psychological function in children with PbB below 45 μg/dL. Re-analysis of these data showed that improvement in test scores was associated with greater falls in PbB only in the placebo group. A further evaluation of this cohort showed that chelation therapy lowered blood lead, but produced no benefits in cognitive, behavioral, or neuromotor end points. The conclusion of this series of studies reached by the investigators was that chelation therapy is not indicated in children with moderate blood lead levels.

Thus, it appears that lead abatement must remain the primary approach in the public health management of lead poisoning.

Cardiovascular/Renal Effects. Although lead has been shown to produce various cardiovascular and renal effects in animals, end points of greatest concern for humans at low exposures and low PbB are elevations in systemic blood pressure and decrements in glomerular filtration rate. These effects may be mechanistically related and, furthermore, can be confounders and covariables in epidemiological studies. Decrements in glomerular filtration rate may contribute to elevations in blood pressure, and elevated blood pressure may predispose people to glomerular disease.

Effects on Blood Pressure. Numerous covariables and confounders affect studies of associations between PbB and blood pressure, including, age, body mass, race, smoking, alcohol consumption, ongoing or family history of cardiovascular/renal disease, and various dietary factors. Varying approaches and breadth of inclusion of these may account for some of the disparity of results that have been reported. Including confounders in a regression model will attenuate the apparent association between lead exposure and the measured health outcome. Measurement error may also be an important factor. Blood pressure estimates based on multiple measurements or, preferably, 24-hour ambulatory measurements, are more reproducible than single measurements. Few studies have employed such techniques and, when used, have not found significant associations between PbB and blood pressure.

An additional limitation of blood lead studies, in general, is that PbB may not provide the ideal biomarker for long-term exposure to target tissues that contribute a hypertensive effect of lead. Bone lead appears to be a better predictor of lead-induced elevations in blood pressure than PbB. In a recent prospective analysis of the Normative Aging Study, higher tibial lead levels, but not PbBs, were associated with higher systolic blood pressure and abnormalities in electrocardiographic conduction.

Chronic lead exposure increases blood pressure in rats through diverse mechanisms that include alterations in neurohumoral control of peripheral vascular resistance, heart rate, and cardiac output (see Section 3.4.2). Studies conducted in animal models provide strong evidence for the plausibility of lead elevating blood pressure in humans. Meta-analyses of the epidemiological findings have found a persistent trend in the data that supports a relatively weak, but significant association. Quantitatively, this association amounts to an increase in systolic blood pressure of approximately 1 mmHg with each doubling of PbB. The results of more recent epidemiology studies indicate that the lead contribution to elevated blood pressure is more pronounced in middle age than at younger ages. A longitudinal study of

males, mean age 67 years, found positive associations between systolic blood pressure and bone lead concentrations, and increased risk of hypertension in association with increased bone lead concentration. Based on this study, an increase in patella bone lead from the midpoint of the lowest quintile (12.0 μg/g) to the highest quintile (53.0 μg/g) was associated with a 1.71-fold increase in hypertension risk (rate-ratio, 95%; confidence interval [CI], 1.08–2.71). A case-control study of women, ages >55 years, found increased risk of hypertension in association with increased bone lead concentration. In this study, an increase in patella bone lead from 6 to 31 μg/g was associated with a 1.86-fold (odds ratio [OR], 95%; CI, 1.09–3.19) increase in risk of hypertension. A large-scale cross-sectional analysis of the NHANES III data on males and females, age 40–59 years, found increasing risk for hypertension in association with increasing PbB, with higher risks in postmenopausal women than in premenopausal women. Risks of diastolic hypertension for pre- and postmenopausal women, combined, who were in the highest blood lead quartile (mean, 6.4 μg/dL; range, 3.0–31.1) was predicted to be 3.4-fold higher (OR, 95%; CI, 1.3–8.7) than that of women in the lowest quartile (mean, 1 μg/dL; range, 0.5–1.6); corresponding risks for postmenopausal women were 8.1 times greater (OR, 95%; CI, 2.6–24.7) (highest vs. lowest quartile). The results of two analyses of the NHANES III data on adult subjects provides evidence for an association between increasing PbB and increasing blood pressure that is more pronounced in blacks than whites. Lead exposures during infancy and childhood (reflected in PbB) have been associated with increased blood pressure and altered responses to acute pressor stresses in childhood. Lead poisoning in childhood has also been associated with hypertension during adulthood in the absence of clinically significant renal disease and discernable elevations in PbB.

Effects in Renal Glomerular Filtration. Classic lead nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and interstitial fibrosis and related functional deficits, including enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate. In humans, the overall dose-effect pattern suggests an increasing severity of nephrotoxicity associated with increasing PbB, with effects on glomerular filtration evident at PbBs below 10 μg/dL, enzymuria and proteinuria becoming evident above 30 μg/dL, and severe deficits in function and pathological changes occurring in association with PbB exceeding 50 μg/dL. Thus, the renal effects of greatest concern, at low exposures (i.e., low PbB), are on glomerular filtration.

The results of epidemiological studies of general populations have shown a significant effect of age on the relationship between glomerular filtration rate (assessed from creatinine clearance of serum creatinine concentration) and PbB (see Section 3.2.2. Renal Effects). Furthermore, as noted previously, hypertension can be both a confounder in studies of associations between lead exposure and creatinine

clearance as well as a covariable with lead exposure. Another important complication in the assessment of associations between lead exposure and adverse effects on glomerular filtration is the potential confounding effect of decrements in glomerular filtration rate and increased lead body burden. Lead exposure has also been associated with increases in glomerular filtration rate. This may represent a benign outcome or a potentially adverse hyperfiltration, which may contribute to subsequent adverse renal effects. Increases in glomerular filtration rate have been observed in the early phases of development of chronic renal injury in rats. When age and other covariables that might contribute to glomerular disease are factored into the dose-response analysis, decreased glomerular filtration rate has been consistently observed in populations that have average PbBs <20 μg/dL, with some studies finding effects at PbBs <10 μg/dL (see Section 3.2.2, Table 3-4). Two studies provide evidence for an effect at lead concentrations below 10 μg/dL. A longitudinal study found a significant relationship between increasing serum creatinine concentration and increasing PbB below 10 μg/dL. A cross-sectional analysis of data from the NHANES III found increased risk of chronic renal disease (defined as severely depressed glomerular filtration rate) in association with PbB <6 μg/dL. The confounding and covariable effects of hypertension are also relevant to the interpretation of the regression coefficients reported in these studies. Given the evidence for an association between lead exposure and hypertension, and that decrements in glomerular filtration rate can be a contributor to hypertension, it is possible that the reported hypertension-adjusted regression coefficients may underestimate the actual slope of the PbB relationship with serum concentration of creatinine or creatinine clearance.

Hematological Effects. The adverse hematological effects of lead are mainly the result of its perturbation of the heme biosynthesis pathway. The activity of ALAD, an enzyme occurring early in the heme synthesis pathway, is negatively correlated with PbBs between 5 and 95 μg/dL. Although inhibition of ALAD occurs 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. Nevertheless, because the impairment of heme synthesis has a far-ranging impact not limited to the hemopoietic system, there is concern that developing organisms might be particularly susceptible.

A potential consequence of the inhibition of heme synthesis is a decreased formation of mixed function oxidases in the liver resulting in impaired metabolism of endogenous compounds, as well as impaired detoxification of xenobiotics. Mitochondrial cytochrome oxidase is another heme-requiring protein that could be affected by heme synthesis inhibition. In addition, tryptophan pyrrolase, a hepatic heme-requiring enzyme system, is inhibited via the reduction in the free hepatic heme pool. This could ultimately lead to increased levels of the neurotransmitter serotonin in the brain and increased aberrant

neurotransmission in serotonergic pathways. Inhibition of heme synthesis also results in increased levels of δ-aminolevulinic acid (ALA), which has a structure similar to that of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), and therefore, interferes with GABA neurotransmission. Finally, a prospective study of children with moderate PbB (25–40 µg/dL) and hemoglobin levels within normal limits found that serum erythropoietin (EPO) was positively associated with PbB at ages 4.5 and 6.5 years, but the magnitude of the association gradually declined from 4.5 to 12 years. EPO is a glycoprotein hormone produced in the kidney that regulates both steady-state and accelerated erythrocyte production. This suggested that in nonanemic children with moderate PbB, hyperproduction of EPO is necessary to maintain normal hemoglobin concentrations. The decline in slope with age suggested that the compensatory mechanism gradually begins to fail due to direct lead-induced inhibition of EPO production or indirectly through toxic effects of lead on the kidney. Inhibition of EPO production may contribute to lead-induced anemia. Anemia occurs at PbBs of ≥20 µg/dL.

2.3 LEAD DOSE-RESPONSE RELATIONSHIPS

MRLs were not derived for lead because a clear threshold for some of the more sensitive effects in humans has not been identified. In addition, deriving an MRL would overlook the significant body of PbB literature. These data suggest that certain subtle neurobehavioral effects in children may occur at very low PbBs. 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 PbBs (see Appendix D).

Epidemiological studies and clinical observations provide evidence for a progression of adverse health effects of lead in humans that occur in association with PbBs ranging from <10 to >60 µg/dL (Table 2-1). At the low end of the blood lead concentration range, adverse effects include delays and/or impaired development of the nervous system, delayed sexual maturation, neurobehavioral effects, increased blood pressure, depressed renal glomerular filtration rate, and inhibition of pathways in heme synthesis. Although fewer studies have examined associations between health outcomes and bone lead concentrations, recent studies provide evidence for adverse effects occurring in association with bone lead concentrations in excess of 10 µg/g (e.g., cardiovascular/renal, neurobehavioral effects).

The timing of exposure, in addition to the exposure intensity, appears to be an important variable in the exposure-response relationship for lead. Exposures that occur during pre- and postnatal development, which result in PbBs of 10 µg/dL or less, produce delays or impairments of neurological and sexual

Table 2-1. Blood and Bone Lead Concentrations Corresponding to Adverse Health Effects

Age	Effect	Blood lead[a] (µg/dL)	Bone lead[a] (⏭g/g)
Children	Depressed ALAD	<5	ND
Children	Neurodevelopmental effects	<10	ND
Children	Sexual maturation	<10	ND
Children	Depressed vitamin D	>15	ND
Children	Elevated EP	>15	ND
Children	Depressed NCV	>30	ND
Children	Depressed hemoglobin	>40	ND
Children	Colic	>60	ND
Adults (elderly)	Neurobehavioral effects	>4	>30
Adults	Depressed ALAD	<5	ND
Adults	Depressed GFR	<10	>10
Adults	Elevated blood pressure	<10	>10
Adults	Elevated EP (females)	>20	ND
Adults	Enzymuria/proteinuria	>30	ND
Adults	Peripheral neuropathy	>40	ND
Adults	Neurobehavioral effects	>40	ND
Adults	Altered thyroid hormone	>40	ND
Adults	Reduced fertility	>40	ND
Adults	Depressed hemoglobin	>50	ND

[a]Concentration range associated with effect.

ALAD = δ-aminolevulinic acid dehydratase; EP = erythrocyte protoporphyrin; GFR = glomerular filtration rate; NCV = nerve conduction velocity; ND = no data

development. Cognitive deficits, hypertension, and depressed glomerular filtration rate have been observed in older adults (>60 years and/or postmenopause) in association with PbBs <10 µg/dL. This may reflect a higher vulnerability with age and/or the effects of cumulative life-time exposures that are less evident in younger populations that have lower time-integrated exposures.

The epidemiological literature provides a basis for associating specific biomarkers (e.g., PbB, bone lead concentration) with adverse health effects. Prediction of health outcomes that might result from any given environmental exposure requires an understanding of the relationships between environmental exposure (level, frequency, duration), human physiology and behaviors that result in intake of lead (e.g., ingestion of dust, drinking water, inhalation), and lead biokinetics. Models that predict PbBs corresponding to specific exposure scenarios have been used in this context for the purpose of assessing lead health risks. Two general approaches have been explored: (1) integrated exposure-biokinetics models that simulate lead exposure, intake, absorption, tissue distribution, and excretion of lead in humans; and (2) slope factor models that predict PbB based on an empirically-derived linear parameter relating exposure level, or rate of lead absorption, to PbB. Descriptions of exposure-biokinetics and slope factor models that have been used or have potential use in assessing exposure-effect relationships in human populations are described in Section 3.3.5 and in Appendix D.

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3. HEALTH EFFECTS

3.1 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 on the toxicology of lead. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

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

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 toxic effects of alkyl lead are mediated through metabolism to inorganic lead and that during the combustion of gasoline 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. 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 contribution by the oral route. Because the toxic effects of lead are the same regardless of the route of entry into the body, the profile will not attempt to separate human dose data by routes of exposure. The dose data for humans are generally expressed in terms of absorbed dose and not in terms of external exposure levels, or milligrams per kilogram per day (mg/kg/day). The most common metric of absorbed dose for lead is the concentration of lead in the blood (PbB), although other indices, such as lead in bone, hair, or teeth also are available (further information regarding these indices can be found in Section 3.3.2 and Section 3.6.1). The concentration of lead in blood reflects mainly the exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of lead in bone. Lead in bone is considered a biomarker of cumulative or long-term

exposure to lead because lead accumulates in bone over the lifetime and most of the lead body burden resides in bone. For this reason, bone lead may be a better predictor than blood lead of some health effects.

The database on effects of lead in animals is extensive and, in general, provides 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. In this profile, animal studies will be discussed only to the extent that they support the findings in humans.

Due to the extent of the lead database, it is impossible to cite all, or even most, of the studies on a specific topic. ATSDR acknowledges that all studies that add a new piece of information are valuable, but the relative impact on the overall picture regarding lead toxicity varies among studies. Given that the goal of Chapter 3 is to provide an overall perspective on the toxicology of lead, some sections focus on studies that have provided major contributions to the understanding of lead toxicity over those that only add a small piece of information into a very big puzzle or that only reiterate findings previously published. Health outcomes associated with internal lead doses from selected studies are presented in Table 3-1.

3.2 DISCUSSION OF HEALTH EFFECTS

3.2.1 Death

Mortality studies for workers exposed occupationally to lead as well as studies of the general population are available (see also Section 3.2.8, Cancer). 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 (Cooper 1988; Cooper et al. 1985). Overall mortality and standardized mortality ratios (SMRs) were determined. From 1947 through 1972, mean PbBs 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

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Cardiovascular [a]					
519 males, 67 years old (mean)	General population	20.3 ppm (mean tibia Pb)	Increased risk of hypertension; no significant association with PbB or patella lead	Longitudinal study (Normative Aging Study). Covariates: age and body mass index; race; family history of hypertension; education; tobacco smoking and alcohol consumption; and dietary intakes of sodium and calcium. Subjects were free from definite hypertension at baseline.	Cheng et al. 2001
667 pregnant females, 15–44 years old	General population	10.7 ppm (mean calcaneus Pb)	Hypertension; a 10 ppm increase in calcaneus Pb was associated with a 0.70 mmHg increase in systolic blood pressure and 0.54 mmHg diastolic blood pressure	Longitudinal study of pregnancy. Co-variates: age and body mass index, parity, postpartum hypertension, tobacco smoking, and education.	Rothenberg et al. 2002b
496 adults, 56 years old (mean)	Occupational	4.6 µg/dL (mean PbB at baseline) 14.7 ppm (mean tibia Pb at year 3 of study)	Increase in systolic blood pressure associated with PbB and tibia Pb	Longitudinal study. Covariates: age and body mass index; diagnosis of diabetes, arthritis, or thyroid disease; education; and blood pressure measurement interval.	Glenn et al. 2003
294 females, 61 years old (mean)	General population	17.3 ppm (mean patella Pb)	Increased risk of hypertension; no significant association with tibia Pb or PbB	Case-control study (Nurses Health Study). Covariates: age and body mass index, dietary sodium intake, and family history of hypertension.	Korrick et al. 1999

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
146 males, 67 years old (mean)	General population	24 ppm (mean tibia Pb)	Increased risk of hypertension; an increase in tibia Pb from 8 to 37 ppm associated with a 1.5 odds ratio for hypertension	Case-control study. Covariates: body mass index and family history of hypertension.	Hu et al. 1996a
13,781 males and females, >20 years old	General population	2.1–4.2 µg/dL median PbB in white and black males and females	Bordeline association between PbB and systolic BP in black males and significant association in black females; no association in whites	NHANES III analysis. Covariates: age and body mass index; hematocrit, total serum calcium, and protein concentrations; tobacco smoking; alcohol and coffee consumption; dietary calcium, potassium, and sodium intakes; diabetes; and use of antihypertensive drugs.	Den Hond et al. 2002
543 females, 50 years old (mean)	General population	6.4 µg/dL (mean PbB) 4.0–31 µg/dL (range)	Increased risk of diastolic hyper-tension	NHANES III analysis. Co-variates: race, age, and body mass index; tobacco smoking, and alcohol consumption.	Nash et al. 2003
508 males and females, 19–24 years old	General population	>10 ppm (tibia Pb)	Increase in systolic and diastolic blood pressure	Cohort follow-up study of Bunker Hill children. Covariates: gender, age, and body mass index; blood hemoglobin and serum albumin concentrations; education; tobacco smoking and alcohol consumption; current use of birth control pills; income; and current PbB.	Gerr et al. 2002

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
775 males, 68 years old (mean)	General population	22.2 ppm (mean tibia Pb)	Significant association with EKG changes and conduction defects. Less strong association with patella Pb; no association with PbB	Cross-sectional study (Normative Aging Study). Covariates: age, body mass index, diastolic blood pressure, fasting blood glucose level, alcohol consumption, and serum HDL concentration.	Cheng et al. 1998
122 children, 9 years of age	General population	1.98 µg/dL (mean PbB prenatal); 4.62 µg/dL (mean PbB at evaluation)	Higher prenatal PbB associated with higher resting systolic BP; higher childhood PbB associated with greater peripheral resistance response to stress	Covariates included in the models were: maternal age, education, IQ, SES, HOME score, health and nutrition, substance use during pregnancy, and infant and childhood characteristics.	Gump et al. 2005
Gastrointestinal					
Children	General population	60–100 µg/dL (PbB range)	Colic	Compilation of unpublished data.	NAS 1972
Hematological					
159 adults	General population and occupational	5–95 µg/dL (PbB range)	Decreased ALAD activity	Four groups of subjects were analyzed. One unexposed group and three worker groups.	Hernberg and Nikkanen 1970
579 children, 1–5 years old	Residence near lead ore smelter	PbB >20 µg/dL	Anemia	Anemia defined as hematocrit <35%. Iron status was not available.	Schwartz et al. 1990
143 children, 10–13 years old	Residence near lead smelter	5–40 µg/dL (PbB range)	Decreased ALAD activity	There was no obvious threshold for ALAD-PbB relationship. A threshold for elevation of EP was evident between 15 and 20 µg/dL PbB.	Roels and Lauwerys 1987

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Musculoskeletal					
290 children, 6–10 years old	General population	2.9 µg/dL (mean PbB)	Increased caries in urban children	No increase in caries was seen in 253 rural children (PbB, 1.7 µg/dL). Covariates: sex, race, SES, maternal smoking, parental education, and dental hygiene variables.	Gemmel et al. 2002
6,541 children 2–11 years old	General population	2.9 µg/dL (geometric mean PbB for 2–5-year-olds); 2.1 µg/dL for 6–11-year-olds)	Increasing PbB associated with increased number of dental caries in both groups	NHANES III analysis. Covariates included age, gender, race-ethnicity, poverty income ratio, exposure to tobacco smoke, geographic region, parental education, carbohydrate and calcium intake, and dental visits.	Moss et al. 1999
10,033 males and females 20–69 years old	General population	2.5 µg/dL (geometric mean PbB)	Increasing PbB associated with periodontal bone loss	NHANES III analysis. Covariates included age, gender, race/ethnicity, education, SES, age of home, smoking, and periodontal disease.	Dye et al. 2002
Renal [b]					
744 males, 64 years old (mean)	General population	8 µg/dL (mean PbB) <4–26 µg/dL (range)	Decrease in GFR; an increase in PbB of 10 µg/dL was associated with a decrease in creatinine clearance rate of 10.4 mL/minute	Cross-sectional study (Normative Aging Study). Covariates: age and body mass index; systolic and diastolic blood pressure; alcohol consumption and tobacco smoking; and analgesic or diuretic medications.	Payton et al. 1994
459 males, 57 years old (mean)	General population	10 µg/dL (mean PbB) 0.2–54 µg/dL (range)	Decrease in GFR; a 10-fold increase in PbB was associated with a significant increase in serum creatinine	Longitudinal study (Normative Aging Study). Covariates: age and body mass index; hypertension; alcohol consumption and tobacco smoking; and education.	Kim et al. 1996a

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
707 males, 62 years old (mean)	General population	6.5 µg/dL (mean PbB) 21 ppm (mean tibia Pb)	Decrease in GFR; PbB and tibia, but not patella Pb, predicted increases in serum creatinine in men with diabetes and hypertension	Prospective study (Normative Aging Study). Covariates: age and body mass index; diabetes and hypertension; alcohol consumption and tobacco smoking; and education.	Tsaih et al. 2004
4,813 males and females, >20 years old	General population	4.2 µg/dL (mean PbB)	Decrease in GFR in subjects with hypertension	NHANES III analysis. Covariates: age, gender, and body mass index; systolic blood pressure; cardiovascular disease and diabetes mellitus; alcohol consumption and cigarette smoking; and household income, marital status, and health insurance.	Muntner et al. 2003
1,981 males and females, 48 years old (mean)	General population	11 µg/dL (mean PbB), 2–72 µg/dL (range in men); 7.5 µg/dL (1.7–60 µg/dL range in women)	Decrease in GFR; a 10-fold increase in PbB associated with decrease of 10–13 mL/minute in creatinine clearance	Cross-sectional study (Cadmibel Study). Covariates: age and body mass index; urinary glutamyltransferase activity; diabetes mellitus; and analgesic or diuretic therapy.	Staessen et al. 1992
803 males and females, 18–65 years old	Occupational	32 µg/dL (mean PbB) 37 ppm (mean tibia lead)	Increasing tibia lead associated with increased serum creatinine and uric acid; increasing PbB associated with increasing BUN	Cross-sectional study of Korean workers. Associations significant only for >46-year-old workers. Covariates included age, gender, body mass index, current/former exposed status, and hypertension.	Weaver et al. (2003a, 2005a)

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Endocrinological					
75 men	Occupational	50–98 µg/dL (PbB range)	Decreased serum T_3 and T_4	No significant correlation for FT_4 and TSH in this PbB range. TSH, T3, FT4, and T4 increased in the range 8–50 µg/dL.	López et al. 2000
58 males, mean age 31.7 years	Occupational	51.9 µg/dL (mean PbB)	TSH significantly higher than in controls (mean PbB 9.5 µg/dL in controls)	Cross-sectional study. The association between PbB and TSH was independent of employment length. T3 was lower in a subgroup of 17 workers employed for 17.5 years than in those employed for 2.4 years.	Singh et al. 2000a
68 children, 11 months–7 years old	General population	2–77 µg/dL (PbB range) 25 µg/dL (mean PbB)	No effect on serum T_4 or FT_4	Covariates: sex, race, SES, and hemoglobin; 56% of the children had PbB <24 µg/dL.	Siegel et al. 1989
30 children, 1–5 years old	General population	33–120 µg/dL (PbB range)	Decreased serum Vitamin D levels	15 children with mean PbB of 18 µg/dL served as a comparison group.	Rosen et al. 1980
Immunological					
38 children, 3–6 years old	General population	PbB >10 µg/dL	Increased IgE and decreased IgG and IgM in females	35 children with PbB <10 µg/dL served as controls. No such effect was seen in males or in the combined analysis of males and females.	Sun et al. 2003
279 children, 9 months–6 years old	General population	1–45 µg/dL (PbB range)	Increased serum IgE	No other parameter of cellular or humoral immunity showed a significant association with PbB. Covariates: age, race, sex, nutrition, and SES.	Lutz et al. 1999

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Neurological					
172 children, 5 years old	General population	7.7 µg/dL (lifetime average PbB)	7.4 IQ points decline with PbB increase 1–10 µg/dL	Children tested with Stanford-Binet Intelligence Scale. Covariates: sex, birth-weight, iron status; mother's IQ, education, race, smoking, income, and HOME score.	Canfield et al. 2003
4,853 children, 6–16 years old	General population	1.9 µg/dL (geometric mean PbB)	PbB <5 µg/dL associated with decrease in arithmetic and reading skills	NHANES III (1988–1994). Covariates: sex, race, iron status, exposure to second-hand smoke, region of the United States, marital status, country, parental education, poverty index, and birth weight. Exposure history was unknown.	Lanphear et al. 2000a
237 children, 7.5 years old	General population	5.4 µg/dL (current mean PbB)	PbB associated with decrements in domains of attention, executive, function, visual-motor integration, social behavior, and motor skills	Associations were present at PbB as low as 3 µg/dL; 19 variables were controlled for in addition to alcohol and drug use.	Chiodo et al. 2004
780 children, 7 years old	General population	8 µg/dL (mean PbB at age 7)	Concurrent PbB always has the strongest association with IQ	Children had been treated for elevated PbB (20–44 µg/dL at 2 years of age and were followed until 7 years of age with serial IQ tests.	Chen et al. 2005

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
146 children, 12 and 24 months old	General population	6.1 µg/dL (mean maternal PbB during first trimester of pregnancy)	One SD (0.014 µg/dL) in first trimester plasma Pb associated with a reduction of 3.5 points in MDI score at 24 months of age	Study of women in Mexico City. Potential confounders included child's sex, PbB at 24 months, height for age and weight, and maternal age and IQ.	Hu et al. 2006
294 children, 12 and 24 months old	General population	PbB <10 µg/dL	24-month PbB inversely associated with MDI and PDI scores at 24 months; 12-month PbB associated with PDI scores at 12 months	MDI and PDI scores of the BSID II were evaluated at 12 and months. Conditions for inclusion included PbB <10 µg/dL, gestation age ≥37 weeks, and birth weight >2,000 g.	Téllez-Rojo et al. 2006
736 older adults	General population	4.5 µg/dL (mean PbB) 29.5 ppm (mean patella Pb)	Impaired cognitive test performance	Associations were found for both PbB and bone lead. Age, education, and alcohol intake were included in regression models.	Wright et al. 2003c

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
Reproductive					
74 adult men	Occupational	46.3 µg/dL (mean PbB)	Decreased fertility	Wife's variables controlled for included parity, time since previous birth, age, birth cohort, employment status, and education. Husband's variables included smoking, alcohol intake, education, and parameters reflecting exposure intensity and duration.	Gennart et al. 1992b
251 men	Occupational	10–40 µg/dL (PbB range)	Weak evidence of decreased fertility	Only couples with one pregnancy were included in study. Association existed only with younger maternal age (<30 years).	Sallmén et al. 2000b
98 men	Occupational	36.7 µg/dL (mean PbB)	Significantly higher alterations in sperm density, motility, viability, and indicators of prostate function than in a reference group	Cross-sectional study. Reference group consisted of 51 men with mean PbB of 10.3 µg/dL. Exposed and controls were comparable in age, smoking status, and alcohol consumption.	Telisman et al. 2000
121 women	General population	≥5.1 µg/dL (cord blood PbB)	Increased pre-term births	The effect was evident only among primiparous, but not multiparous women.	Torres-Sánchez et al. 1999
Developmental					
329 infants, 1 month old	General population	5.6 µg/dL (mean infant PbB at 1 month) 15.3 ppm (maternal patella Pb)	Infant PbB at 1 month and maternal patella bone inversely associated with weight gain	Infant age, sex, breast feeding practices, and infant health were included in regression models. Maternal variables: age, parity, maternal anthropometry, education, and hospital of recruitment.	Sanín et al. 2001

Table 3-1. Internal Lead Doses Associated with Health Effects from Selected Studies

Population studied	Exposure	Biomarkers	Effect	Comments	Reference
233 infants, 1 month old	General population	7.0 µg/dL (mean cord blood Pb) 14.1 ppm (maternal patella Pb)	Cord PbB associated with low birth length; patella lead associated with low head circumference	Variables included in models were maternal height, calf circumference, smoking, parity, reproductive history, age and education, hospital of delivery, infant sex, and gestational age.	Hernández-Avila et al. 2002
4,391 children, 1–7 years old	General population	1–72 µg/dL (PbB range)	Decrease of 1.57 cm in stature and 0.52 cm in head circumference per 10 µg/dL increase in PbB	Data from NHANES III. Models included: age, sex, ethnicity, and poverty-income ratio. Models also considered head of household education, exposure to cigarette smoke, nutrient intake, iron status, anemia, history of anemia, previous testing for high PbB, and previous treatment for lead poisoning.	Ballew et al. 1999
1,706 girls, 8–16 years old	General population	1–22 µg/dL (PbB range)	Delayed sexual maturation	Data from NHANES III. Covariates: race/ ethnicity, age, family size, residence in metropolitan area, poverty-income ratio, and body mass index.	Wu et al. 2003b
2,741 girls, 8–18 years old	General population	3 µg/dL (geometric mean PbB)	Delayed sexual maturation	Data from NHANES III. Covariates: age, height, body mass index, history of tobacco smoking or anemia, dietary intake of iron, vitamin C, calcium, and family income.	Selevan et al. 2003

[a]See also Table 3-2.
[b]See also Table 3-3.

ALAD = δ-aminolevulinic acid dehydratase; BP = blood pressure; BUN = blood urea nitrogen; EKG = electrocardiogram; EP = erythrocyte protoporphyrin; GFR glomerular filtration rate; HDL = high density lipoprotein; Ig = immunoglobin; NHANES III = Third National Health and Nutrition Examination; NM = not measured; SES = socioeconomic status; TSH = thyroid stimulating hormone

hypertension and nephritis; and "ill-defined" causes. Three additional studies provided suggestive evidence of increased mortality due to cerebrovascular disease in lead workers (Fanning 1988; Malcolm and Barnett 1982; Michaels et al. 1991). Malcolm and Barnett (1982) studied causes of death between 1921 and 1976 among lead acid battery plant workers and found a significant increase in deaths due to cerebrovascular disease among workers 65–69 years of age. In addition, a marginally significant increase in the incidence of deaths due to nephritis and nephrosis was observed in the lead workers during 1935–1958, but not at later periods, compared to workers with no lead exposure. Fanning (1988) 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 and found a significant increase in deaths due to cerebrovascular disease among workers who died between 1946 and 1965 as compared to controls. No other cause produced an excess of deaths in lead workers. Environmental lead levels and biological monitoring for body lead burdens were not available for the entire period. 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. Michaels et al. (1991) followed a cohort of 1,261 white male newspaper printers (typesetters) from January 1961 through December 1984. These workers had little or no occupational exposure to any other potentially toxic agents. 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 fewer 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 >30 years. Since there was no excess of arteriosclerotic heart disease, it appeared that lead exposure selectively increased cerebrovascular disease.

Few studies of the general population have been conducted. McDonald and Potter (1996) studied the possible effects of lead exposure on mortality in a series of 454 children who were hospitalized for lead poisoning at Boston's Children Hospital between 1923 and 1966 and who were traced through 1991. 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. A total of 86 deaths were observed, 17 of these cases were attributed to lead poisoning. Although the distribution of causes of mortality generally agreed with expectations, there was a statistically significant excess of death from

cardiovascular disease (observed/expected [O/E], 2.1; 95% confidence interval [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; 95% CI, 1.1–36.2) and two from non-Hodgkin's lymphoma (O/E, 13.0; 95% CI, 1.5–46.9).

Lustberg and Silbergeld (2002) used data from the Second National Health and Nutrition Examination Survey (NHANES II) to examine the association of lead exposure and mortality in the United States. A total of 4,292 blood lead measurements were available from participants aged 30–74 years who were followed up through December 31, 1992. After adjusting for potential confounders, individuals with PbB between 20 and 29 μg/dL had 46% increased all-cause mortality, 39% increased circulatory mortality, and 68% increased cancer mortality compared with those with PbB <10 μg/dL. The results also showed that nonwhite subjects had significantly increased mortality at lower PbB than did white subjects, and that smoking was associated with higher cancer mortality in those with PbB of 20–29 μg/dL compared with those with PbB <20 μg/dL. Recently, Schober et al. (2006) used data from NHANES III (1988–1994) to determine relative risk of mortality from all causes, cancer, and cardiovascular disease in 9,757 participants who were ≥40 years of age. After adjusting for covariates, relative to PbBs <5 μg/dL, the relative risks of mortality from all causes for those with PbB 5–9 and ≥10 μg/dL were 1.24 (95% CI, 1.05–1.48) and 1.59 (95% CI, 1.28–1.98), respectively. Similar observations were reported for deaths due to cardiovascular disease and cancer, and tests for trend were statistically significant ($p<0.01$) for both causes of death. Of interest also is a study that describes trends in lead poisoning-related deaths in the United States between 1979 and 1998 (Kaufmann et al. 2003). Reviews of death certificates revealed that approximately 200 lead poisoning-related deaths occurred from 1979 to 1998. The majority were among males (74%), African Americans (67%), adults of age ≥45 years (76%), people living in the South region of the United States (70%), and residents in cities with populations <100,000 habitants (73%). Lead poisoning was the underlying cause of death in 47% of the deaths. The authors also found that alcohol (moonshine ingestion) was a significant contributing cause for 28% of adults.

In summary, the information available suggests a potential association between lead exposure and cerebrovascular disease. There is no information from studies in animals that would support or refute the existence of a possible association between lead exposure and mortality due to cerebrovascular disease.

3.2.2 Systemic Effects

Respiratory Effects. Very limited information was located regarding respiratory effects in humans associated with lead exposure. A study of 62 male lead workers in Turkey reported significant alterations in tests of pulmonary function among the workers compared to control subjects (Bagci et al. 2004). The cohort consisted of 22 battery workers, 40 exhaust workers, and 24 hospital workers with current PbB of 37, 27, and 15 µg/dL, respectively. Workers and controls were matched for age, height, weight, and smoking habit. No association was found between PbB and duration of employment. No information was provided regarding exposure levels, medical histories of the workers or potential exposure to other chemicals. No relevant information was located from studies in animals.

Cardiovascular Effects. Although lead has been shown to produce various cardiovascular effects in animals (Vaziri and Sica 2004), end points of greatest concern for humans at low exposures and low PbBs are elevations in systemic blood pressure and decrements in glomerular filtration rate. These effects may be mechanistically related and, furthermore, can be confounders and covariables in epidemiological studies. Decrements in glomerular filtration rate may contribute to elevations in blood pressure, and elevated blood pressure may predispose people to glomerular disease. Effects of lead on glomerular filtration are discussed in Section 3.2.2, Renal Effects. Other cardiovascular changes have been noted in association with increasing lead body burdens and/or lead exposures in humans that include changes in cardiac conduction and rhythm (Böckelmann et al. 2002; Cheng et al. 1998; Kirkby and Gyntelberg 1985; Kosmider and Petelenz 1962), which may be secondary to lead-induced impairment of peripheral nerve conduction (see Section 3.2.4, Neurological Effects).

Effects on Blood Pressure. Numerous epidemiological studies have examined associations between lead exposure (as indicated by PbB or bone lead concentration) and blood pressure. Meta-analyses of the epidemiological findings have found a persistent trend in the data that supports a relatively weak, but significant association. Quantitatively, this association amounts to an increase in systolic blood pressure of approximately 1 mmHg with each doubling of PbB (Nawrot et al. 2002; Schwartz 1995; Staessen et al. 1994). The results of more recent epidemiology studies indicate that the lead contribution to elevated blood pressure is more pronounced in middle age than at younger ages. Numerous covariables and confounders affect studies of associations between PbB and blood pressure, including age, body mass, race, smoking, alcohol consumption, ongoing or family history of cardiovascular/renal disease, and various dietary factors (e.g., dietary calcium). Including confounders in a regression model will attenuate the apparent association between lead exposure and the measured health outcome (e.g., Moller and

Kristensen 1992). For example, adjusting for alcohol consumption will decrease the apparent association between blood lead concentration and blood pressure, if alcohol consumption contributes to lead intake and, thereby, blood lead concentration (Bost et al. 1999; Hense et al. 1993; Hertz-Picciotto and Croft 1993; Wolf et al. 1995). Conversely, failure to account for important effect modifiers (e.g., inherited disease) will result in overestimation of the apparent strength of the association. Varying approaches and breadth of inclusion of these may account for the disparity of results that have been reported. Measurement error may also be an important factor. Blood pressure estimates based on multiple measurements or, preferably, 24-hour ambulatory measurements, are more reproducible than single measurements (Staessen et al. 2000). Few studies have employed such techniques and, when used, have not found significant associations between PbB and blood pressure (Staessen et al. 1996b).

An additional limitation of blood lead studies, in general, is that PbB may not provide the ideal biomarker for long-term exposure to target tissues that contribute a hypertensive effect of lead. Bone lead, a metric of cumulative or long-term exposure to lead, appears to be a better predictor of lead-induced elevations in blood pressure than PbB (Cheng et al. 2001; Gerr et al. 2002; Hu et al. 1996a; Korrick et al. 1999; Rothenberg et al. 2002a). In a recent prospective analysis of the Normative Aging Study, higher patellar lead levels, but not PbB, were associated with higher systolic blood pressure and abnormalities in electrocardiographic conduction (Cheng et al. 1998, 2001).

Epidemiology studies, alone, cannot prove cause and effect relationships between lead exposure and blood pressure or cardiovascular disease. However, studies conducted in animal models support the plausibility of blood pressure effects of lead in humans. These studies have shown that long-term lead exposure can elevate blood pressure in nutritionally replete rats (Carmignani et al. 1988; Iannaccone et al. 1981; Khalil-Manesh et al. 1993; Victery et al. 1982a, 1982b), and have identified potential mechanisms for the effect (Carmignani et al. 2000; Ding et al. 1998; Gonick et al. 1997; Purdy et al. 1997; Vaziri and Ding 2001; Vaziri et al. 1999a, 1999b, 2001).

Meta-analyses. A recent meta-analysis of 31 studies published between 1980 and 2001, which included a total of 58,518 subjects (Nawrot et al. 2002), estimated the increase in systolic pressure per doubling of PbB to be 1 mmHg (95% CI, 0.5–1.5) and the increase in diastolic pressure to be 0.6 mmHg (95% CI, 0.4–0.8) (Table 3-2; Figures 3-1 and 3-2). This outcome is similar to two other meta-analyses. A meta-analysis reported by Staessen et al. (1994) included 23 studies (published between 1984 and 1993; 33,141 subjects) and found a 1 mmHg (95% CI, 0.4–1.6) increase in systolic blood pressure and 0.6 mmHg (95% CI, 0.2–1.0) in diastolic pressure per doubling of PbB. Schwartz (1995) conducted a

Table 3-2. Characteristics of the Study Population in Meta-Analyses of Effects of Lead on Blood Pressure

	Reference	No.[a]	Pop.[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (μg/dL)[g]
1[h]	Pocock et al. 1984; Shaper et al. 1981	7,379	GP	100	Y	49 (40–59)	145	82	15.13 (2.07–66.3)[Ae]
2	Kromhout 1988; Kromhout et al. 1985	152	GP	100	Y	67 (57–76)	154	92	18.23 (10.77–27.97)[Ac]
3	Moreau et al. 1982, 1988; Orssaud et al. 1985	431	WC	100	Y	41 (24–55)	131	75	18.23 (8.91–49.94)[Ae]
4	Weiss et al. 1986, 1988	89	WC	100	Y	47 (30–64)	122	83	24.45 (18.65–29.01)[Mx]
5	de Kort and Zwennis 1988; de Kort et al. 1987	105	BC	100	N	40 (25–80)	136	83	29.22 (4.35–83.29)[Ae]
6	Lockett and Arbuckle 1987	116	BC	100	Y	32 (?–?)	119	80	37.5 (14.92–95.52)[Ae]
7	Parkinson et al. 1987	428	BC	100	Y	36 (18–60)	127	80	27.97 (6.01–49.52)[Ac]
8	Rabinowitz et al. 1987	3,851	GP	0	Y	28 (18–38)	121	76	7.04 (3.73–10.15)[Ac]
9	Elwood et al. 1988a, 1988b[i]	1,156	GP	100	Y	56 (49–65)	146	87	12.64 (6.01–26.11)[Gc]
10	Elwood et al. 1988a, 1988b[j]	1,721	GP	50	Y	41 (18–64)	127	78	10.15 (4.56–23.21)[Gc]
11	Gartside 1988; Harlan 1988; Harlan et al. 1985; Pirkle et al. 1985; Ravnskov 1992[k]	6,289	GP	53	Y	30 (10–74)	127	80	13.47 (2.07–95.93)[Ge]
12	Neri et al. 1988[l]	288	BC	100	?	? (?–?)	?	?	45.17 (6.01–65.06)[Ae]
13	Neri et al. 1988[m]	2,193	GP	?	Y	45 (25–65)	?	?	23.41 (0–47.03)[Me]
14	Grandjean et al. 1989, 1991[n]	1,050	GP	48	Y	40 (40–40)	?	?	11.6 (3.94–60.09)[Ae]
15	Reimer and Tittelbach 1989	58	BC	100	?	32 (?–?)	134	81	39.99 (12.85–70.24)[Ac]
16	Apostoli et al. 1990	525	GP	48	Y	45 (21–60)	132	84	13.05 (2.07–28.18)[Ae]
17	Morris et al. 1990	251	GP	58	Y	? (23–79)	?	?	7.46 (4.97–38.95)[Ae]
18	Sharp et al. 1988, 1989, 1990	249	WC	100	N	43 (31–65)	128	83	6.63 (2.07–14.92)[Pe]
19	Staessen et al. 1984[o]	531	WC	75	Y	48 (37–58)	126	78	11.4 (4.14–35.22)[Ge]
20	Møller and Kristensen 1992[p]	439	GP	100	Y	40 (40–40)	?	?	13.68 (4.97–60.09)[Ae]

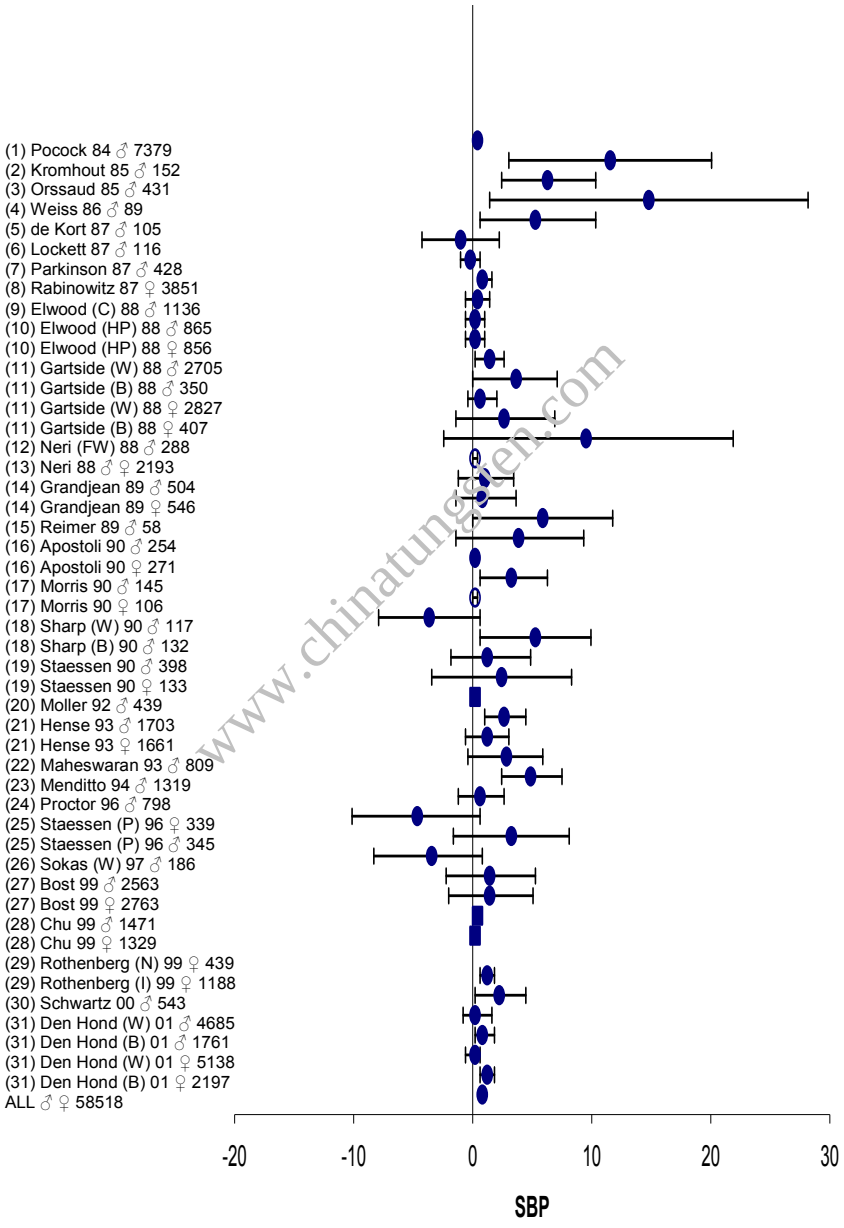
Table 3-2. Characteristics of the Study Population in Meta-Analyses of Effects of Lead on Blood Pressure

	Reference	No.[a]	Pop.[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (μg/dL)[g]
21	Hense et al. 1993	3,364	GP	51	Y	48 (28–67)	129	80	7.87 (1.24–37.09)[Ae]
22	Maheswaran et al. 1993	809	BC	100	Y	43 (20–65)	129	84	31.7 (0–98.01)[Ae]
23	Menditto et al. 1994	1,319	GP	100	Y	63 (55–75)	140	84	11.19 (6.22–24.66)
24	Hu et al. 1996a; Proctor et al. 1996[q]	798	GP	100	Y	66 (43–93)	134	80	5.59 (0.41–35.02)[Pe]
25	Staessen et al. 1996a, 1996b[r]	728	GP	49.3	Y	46 (20–82)	130	77	9.12 (1.66–72.52)[Ge]
26	Sokas et al. 1997[s]	186	BC	99	Y	43 (18–79)	130	85	7.46 (2.07–30.04)[Pe]
27	Bost et al. 1999	5,326	GP	48	Y	48 (16–?)	135	75	63.82 (?–?)[G]
28	Chu et al. 1999	2,800	GP	53	Y	44 (15–85)	123	78	6.42 (0.41–69)[Ae]
29	Rothenberg et al. 1999a, 1999b	1,627	GP	0	Y	27 (?–?)	110	59	2.28 (?–?)[G]
30	Schwartz and Stewart 2000	543	BC	100	Y	58 (41–73)	128	77	4.56 (1.04–20.1)[Ae]
31	Den Hond et al. 2001[t]	13,781	GP	53.2	Y	48 (20–90)	125	73	3.11 (0.62–55.94)[Ge]

[a]No.: Number of persons in whom relevant data were available.
[b]Pop.: Study population: BC = blue collar workers; GP = sample from general population; WC = white collar employees
[c]Men: Percentage of men
[d]HT: Indicates whether the sample included (Y = yes) or did not include (N = no) hypertensive patients.
[e]Age: Mean age or midpoint of age span (range or approximate range given between parentheses).
[f]SBP, DBP: Mean systolic and diastolic blood pressures
[g]Lead: Measure of central tendency: A = arithmetic mean; G = geometric mean; M = midpoint of range; P = P_{50} (median). The spread of blood lead is given between parentheses: c = P_5–P_{05} interval; P_{10}–P_{90} interval, or interval equal to 4 times the standard deviation; e = extremes; x = approximate limits of distribution.
[h]Number refers to reference in Figures 3-1 and 3-2.
[i]Caerphilly Study
[j]Welsh Heart Program
[k]NHANES (National Health and Nutrition Examination Survey)
[l]foundry workers
[m]Canadian Health Survey
[n]Glostrup Population Study, cross-sectional analysis (1976)
[o]London Civil Servants
[p]Glostrup Population Study, longitudinal analysis (1976–1987)
[q]Normative aging study
[r]PheeCad (Public Health and Environmental Exposure to Cadmium) Study
[s]Because of missing information, only the effect in whites is included.
[t]NHANES III Survey

Source: Nawrot et al. 2002

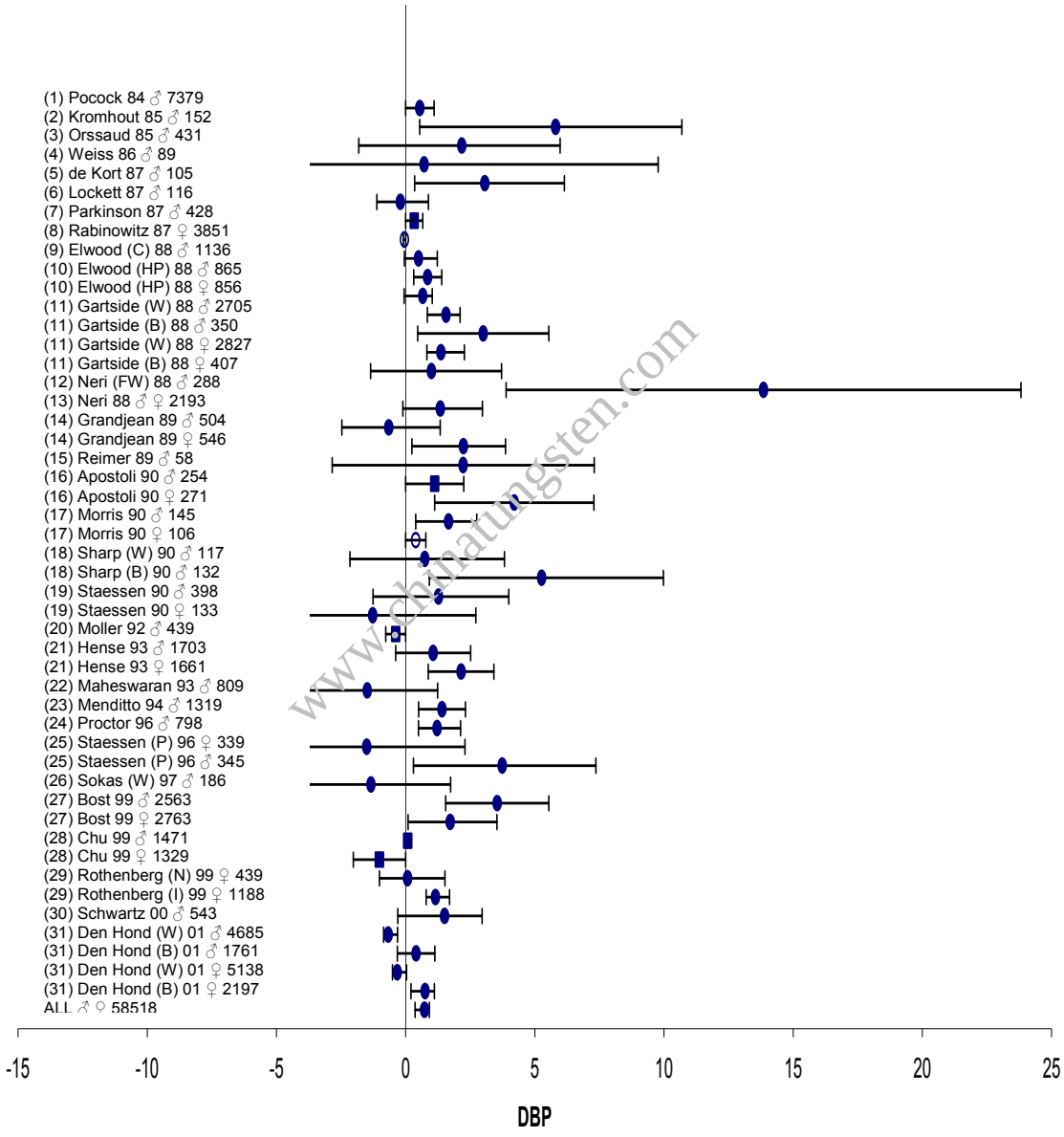
Figure 3-1. Change in the Systolic Pressure Associated with a Doubling of the Blood Lead Concentration*



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 3-2 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; NI = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

Figure 3-2. Change in the Diastolic Pressure Associated with a Doubling of the Blood Lead Concentration*



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 3-2 for more details on study groups.

B = blacks; C = Caerphilly Study; CS = civil servants; FW = foundry workers; HP = Welsh Heart Program; I = immigrants; NI = non-immigrants; P = Public Health and Environmental Exposure to Cadmium Study; W = whites

meta-analysis that encompassed a similar time frame (15 studies published between 1985 and 1993) and found a 1.25 mmHg (95% CI, 0.87–1.63) increase in systolic blood pressure per doubling of PbB (diastolic not reported). The latter analysis included only those studies that reported a standard error on effect measurement (e.g., increase in blood pressure per doubling of PbB). Of the 15 studies included in the Schwartz (1995) analysis, 8 were also included in the Staessen et al. (1994) analysis.

Longitudinal Studies—General Populations—Adults. The Normative Aging Study is a longitudinal study of health outcomes in males, initially enrolled in the Boston area of the United States between 1963 and 1968. At enrollment, subjects ranged in age from 21 to 80 years (mean, 67 years) and had no history of heart disease, hypertension, cancer, peptic ulcer, gout, bronchitis, or sinusitis. Physical examinations, including seated blood pressure and medical history follow-ups, have been conducted at approximately 3–5-year intervals. Beginning in 1991, PbB and bone x-ray fluorescence (XRF) measurements (mid-tibia and patella) were included in the examinations. Data collected for a subset of the study population (840 subjects) observed between 1991 and 1997 were analyzed for associations between blood pressure and blood or bone lead concentrations (Cheng et al. 2001). Mean baseline PbB was 6.1 µg/dL (standard deviation [SD], 4.0) for the entire study group and 5.87 µg/dL (SD, 4.01) in the normotensive group (n=323). Mean bone lead concentrations in the normotensive subjects (n=337) were: tibia, 20.27 µg/g (SD, 11.55); patella, 28.95 (SD, 18.01). Based on a cross-sectional linear multivariate regression analysis of 519 subjects who had no hypertension at the time of first bone and blood lead measurement, covariate-adjusted systolic blood pressure was not significantly associated with PbB or patella lead concentration; however, increasing tibia lead concentration was associated with increasing systolic blood pressure. Follow-up examinations were completed on 474 subjects, allowing a longitudinal analysis of hypertension risk. Covariate-adjusted risk (risk ratio, RR; proportional hazards model) of hypertension (systolic >160 mm Hg or diastolic >95 mm Hg) was significantly associated with patella bone lead concentrations (RR, 1.29; 95% CI, 1.04–1.61), but not with PbB (RR, 1.00; 95% CI, 0.76–1.33) or tibia bone lead concentration (RR, 1.22; 95% CI, 0.95–1.57). Increases in patella lead concentration from 12.0 µg/g (mid-point of lowest quintile) to 53.0 µg/g (mid-point of highest quintile) were associated with a rate ratio of 1.71 (95% CI, 1.08–2.70). Covariates considered in the analyses included age and body mass index; race; family history of hypertension; education; tobacco smoking and alcohol consumption; and dietary intakes of sodium and calcium. A cross-sectional case-control analysis of the Normative Aging Study also found significant associations between bone lead concentration and risk of hypertension (see discussion of Hu et al. 1996a). The observation that risk of hypertension in middle-aged males increased in association with increasing patella bone lead concentration, but not tibia bone lead or PbB, is consistent with a similar finding in middle-aged females, derived from the Nurses Health

Study (Korrick et al. 1999). Associations between PbB and hypertension risk in middle-aged women have been found in larger cross-sectional studies (Nash et al. 2003). These observations suggest that, in some populations, blood pressure increases may be more strongly associated with cumulative lead exposure (reflected in bone lead levels) than more contemporaneous exposures (reflected in blood lead concentrations).

A random sample from the general population of Belgium (728 subjects, 49% male, age 20–82 years old) was studied during the period 1985 through 1989 (baseline; from Cadmibel study, Dolenc et al. 1993) and reexamined from 1991 through 1995 (follow-up) (Staessen et al. 1996b). Multiple seated blood pressure measurements were taken during the baseline and follow-up periods; multiple ambulatory measurements were taken during the follow-up period. The baseline PbB for the study group was 8.7 µg/dL (range, 1.7–72.5). Based on a linear multivariate regression analysis (with log-transformed blood lead concentrations), covariate-adjusted time-integrated systolic or diastolic blood pressure, or changes in systolic or diastolic blood pressure (follow-up compared to baseline) were not significantly associated with PbB or zinc photoporphyrin (ZPP) concentrations. The covariate adjusted risk for hypertension of doubling of the baseline PbB was not significantly >1. Covariates considered in the above analyses included gender, age, and body mass index; menopausal status; smoking and alcohol consumption; physical activity; occupational exposure to heavy metals; use of antihypertensive drugs, oral contraceptives, and hormonal replacement therapy; hematocrit or blood hemoglobin concentration; and urinary sodium, potassium, and γ-glutamyltransferase activity.

A random sample of the general population of Denmark (451 males, 410 females, age 40 years) was studied in 1976 (baseline) and reexamined in 1981 (Grandjean et al. 1989). Baseline and follow-up observations included sitting blood pressure measurements, physical examination and health histories, and PbB measurements. The median baseline PbB was 13 µg/dL (90^{th} percentile, 20) and 9 µg/dL (90^{th} percentile, 13) in males and females, respectively. Covariate adjusted linear regression coefficients for relating systolic or diastolic blood pressure with PbB (log-transformed) were not statistically significant in males or females. Covariates considered in the analysis included height-adjusted weight index, exercise, smoking, alcohol intake, occupation, blood hemoglobin, serum cholesterol, and serum triglycerides. Similar conclusions were reported from a prospective study of this same population; adjustment for cardiovascular risk factors (i.e., body mass index, tobacco smoking, alcohol consumption, physical fitness) attenuated an apparent association between PbB and systolic and diastolic blood pressure (Moller and Kirstensen 1992).

Longitudinal Studies—General Population—Pregnancy. A longitudinal study examined associations between blood pressure and lead exposure during pregnancy and postpartum (Rothenberg et al. 2002b). The study included 667 subjects (age 15–44 years) registered at prenatal care clinics in Los Angeles during the period 1995–2001, and who had no history of renal or cardiovascular disease, postnatal obesity (body mass index >40), or use of stimulant drugs (e.g., cocaine, amphetamines). Measurements of sitting blood pressure and PbB were made during the third trimester and at 10 weeks postnatal. Tibia and calcaneus bone lead concentrations (XRF) were measured at the postnatal visit. Mean (geometric) PbBs were 1.9 µg/dL (+3.6/-1.0, geometric standard deviation [GSD]) during the third trimester and 2.3 µg/dL (+4.3/-1.2, GSD) postnatal. Mean (arithmetic) bone lead concentrations were 8.0 µg/g (11.4, SD) in tibia and 10.7 µg/g (11.9, SD) in calcaneus. Covariate-adjusted risk (odds ratio, OR) of hypertension (≥140 mmHg systolic or ≥90 mmHg diastolic) in the third trimester was significantly associated with increasing calcaneous bone lead concentration (OR, 1.86; 95% CI, 1.04–3.32). A 10 µg/g increase in calcaneous bone lead concentration was associated with a 0.77 mmHg (95% CI, 0.04–1.36) increase systolic blood pressure in the third trimester and a 0.54 mmHg (95% CI, 0.01–1.08) increase in diastolic blood pressure. Covariates included in the final model were age and body mass index, parity, postpartum hypertension, tobacco smoking, and education.

Longitudinal Studies—General Population—Children. Possible associations between blood pressure and lead exposure in young children were studied as part of a prospective study of pregnancy outcomes (Factor-Litvak et al. 1996). The study group consisted of 281 children, age 5.5 years, from the Kosovo, Yugoslavia prospective study (see Section 3.2.4 for more details on this cohort). Approximately half of the children (n=137) lived in a town with heavy lead contamination (exposed group) and the other half (n=144) were from a relatively uncontaminated town (reference group). Mean PbBs were 37.3 µg/dL in the exposed group and 8.7 µg/dL in the reference group. Covariate-adjusted linear regression coefficients relating blood pressure and PbB at 5.5 years of age were not significantly >0: systolic, 0.054 (95% CI, -0.024–0.13); diastolic, -0.042 (95% CI, -0.01–0.090). Regression coefficients for the integrated average PbB (assessed every 6 months from birth) were similar in magnitude: systolic, 0.047 (95% CI, -0.037–0.13), diastolic, 0.041 (95% CI, -0.016–0.098). Covariates included in the analysis were gender, height and body mass index, birth order, and ethnicity.

A prospective study designed to assess various environmental factors on development examined possible associations between PbB and blood pressure in a group of 122 children (66 females) at 9 years of age (Gump et al. 2005). The mean PbB at the time of evaluation was 4.62 µg/dL (SD±2.51). Outcomes measured included heart rate, diastolic and systolic blood pressure, stroke volume, cardiac output, and

total peripheral resistance; these were assessed at rest and following an acute pressor stress (arm immersion in ice water). General linear models were used to explore associations between PbB and outcomes. Increasing cord PbB was significantly associated with increasing covariate-adjusted resting systolic blood pressure (β, 12.16; Standard error [SE], 4.96; p= 0.016). Increasing childhood PbB was significantly associated with an increased total peripheral vascular resistance in response to the acute pressor stress (β, 0.88 dyn-s/cm^5 per µg/dL; 95% CI, 0.024–0.152; p=0.007). Covariates considered in the models included: maternal age, education, IQ, socioeconomic status (SES), HOME score, health, nutrition; substance use during pregnancy; infant birth characteristics (e.g., gestational age, birth weight, head circumference, Ballard score); and childhood characteristics (e.g., body mass index, SES).

Longitudinal Studies—Occupational. A population of 496 current and former employees of an organic lead manufacturing facility (mean age, 55.8 years) located in the eastern United States, was studied during the period 1994–1996 with follow-up examinations at approximately 4–14-month intervals through 1998 (Glenn et al. 2003). Multiple seated blood pressure measurements were taken at each examination. PbB was measured at the initial examination (baseline) and tibia bone XRF measurements were taken in 1997. The mean PbB was 4.6 µg/dL and the mean tibia bone lead concentration was 14.7 µg/g. Based on a generalized estimating equation model, covariate-adjusted systolic blood pressure was significantly associated with baseline PbB or tibia bone lead concentration. A one standard deviation increase in PbB was associated with a 0.64 mmHg (95% CI, 0.14–1.14) increase in systolic blood pressure and a 0.009 (95% CI, -0.24–0.43) increase in diastolic blood pressure. A one standard deviation increase in tibia bone lead concentration was associated with a 0.73 mmHg (95% CI, 0.23–1.23) increase in systolic blood pressure and a 0.07 mmHg (95% CI, -0.29–0.42) increase in diastolic blood pressure. Covariates considered in the analyses included race; age and body mass index; diagnosis of diabetes, arthritis, or thyroid disease; education; and blood pressure measurement interval.

A population of 288 foundry workers was studied during the period 1979–1985, during which multiple blood pressure and PbB measurements were taken (Neri et al. 1988). Linear regression coefficients were estimated for the relationship between PbB and systolic or diastolic blood pressure, for each of 288 subjects. The average covariate (age and body weight) adjusted regression coefficient (mmHg per µg/dL blood lead) was 0.210 (SE, 0.139, p=0.064) for systolic pressure and 0.298 (SE, 0.111, p<0.05) for diastolic pressure.

A population of 70 Boston policemen was studied during the period 1969–1975, during which multiple seated blood pressure measurements were taken (years 2–5) and PbB measurements were taken in

year 2 (Weiss et al. 1986, 1988). Covariate adjusted linear regression coefficients (mmHg per μg/dL) were determined, with exposure represented as low (20–29 μg/dL) or high (≥30 μg/dL). After adjusting for covariates, high PbB was a significant predictor of subsequent elevation in systolic blood pressure of 1.5–11 mmHg in the working policemen with normal blood pressure. Low PbB (20–29 μg/dL) was not a predictor of subsequent systolic blood pressure elevations. Diastolic pressure was unrelated to PbB. Covariates retained in the model were previous systolic blood pressure, body mass index, age, and cigarette smoking.

Case-control Studies—General Population. A case-control study examined potential associations between blood pressure and blood and bone lead concentrations in a population of middle-aged women (mean age, 61 years; Korrick et al. 1999). Cases (n=89) and age-matched controls (n=195) were a subset of women who resided in the Boston area of the United States (recruited during the period 1993–1995) who were enrolled in the National Nurses Health Study (NHS). Cases were selected based on self-reported physician diagnosis of hypertension as part of the NHS. Potential controls were excluded from consideration if they had a history of hypertension or other cardiovascular disease, renal disease, diabetes, malignancies, obesity, or use of antihypertensive or hypoglycemic medication. Controls were stratified based on measured blood pressure: low normal (<115 mm Hg systolic and <75 mmHg diastolic), or high normal (>134 and <140 mmHg systolic or >85 and <90 mmHg diastolic). Multiple sitting blood pressure measurements, PbB, and tibia and patella bone lead concentration measurements were taken at the beginning of the study. Self-reported information on medical history was provided as part of the NHS every 2 years. The mean PbB (cases and controls combined) was 3 μg/dL (range, <1–14 μg/dL). Mean bone lead concentrations were: tibia, 13.3 μg/g and patella, 17.3 μg/g. Risk of hypertension was assessed using a logistic regression model. Covariate-adjusted risk of hypertension (defined as systolic pressure ≥140 mm Hg or diastolic ≥90 mm Hg) was significantly associated with increasing patella lead concentration, but not with tibia bone concentration or PbB. An increase from the 10^{th} to the 90^{th} percentile of patella bone lead concentration (from 6 to 31 μg/g) was associated with an increase in the odds of hypertension of 1.86 (95% CI, 1.09–3.19). Covariates considered in the regression models included: age and body mass index; dietary calcium and sodium intakes; alcohol consumption and tobacco smoking, and family history of hypertension. Of these, age and body mass index, dietary sodium intake, and family history of hypertension were included in the final model. The OR (odds of being a case/odds of being in control group) of hypertension with increasing patella lead concentration was 1.03 (95% CI, 1.00–1.05). When stratified by age, the ORs were 1.04 (95% CI, 1.01–1.07) in the >55 years of age groups and 1.01 (95% CI, 0.97–1.04) in the age group ≤55 years. Stratification by menopausal status resulted in ORs of 1.04 (95% CI, 1.01–1.06) for the postmenopausal group and

0.98 (95% CI, 0.91–1.04) for the premenopausal group (78 of 89 of the cases, 93%, were postmenopausal). The observation that risk of hypertension in women increased in association with increasing patella bone lead concentration, but not tibia bone lead or PbB, is consistent with a similar finding in men, derived from the longitudinal Normative Aging Study (Cheng et al. 2001). Associations between PbB and hypertension risk in postmenopausal women also have been found in larger cross-sectional studies (Nash et al. 2003; see below).

As part of the Normative Aging Study, a case-control study examined potential associations between blood pressure and blood and bone lead concentrations in a population of middle-aged males (mean age, 66 years; Hu et al. 1996a). The Normative Aging Study is a longitudinal study of health outcomes in males, initially enrolled in the Boston area of the United States between 1963 and 1968. At enrollment, subjects ranged in age from 21 to 80 years (mean, 67 years) and had no history of heart disease, hypertension, cancer, peptic ulcer, gout, bronchitis, or sinusitus. Physical examinations, including seated blood pressure and medical history follow-ups, have been conducted at approximately 3–5-year intervals. Beginning in 1991, PbB and bone x-ray fluorescence (XRF) measurements (mid-tibia and patella) were included in the examinations. Cases (n=146) and age-matched controls (n=444) were a subset of the study group who resided in the Boston area of the United States (recruited during the period 1993–1995) who were observed between 1991 and 1994. Hypertension cases were taking daily medication for the management of hypertension and/or had a systolic blood pressure >160 mmHg or diastolic pressure ≥96 mmHg. The mean PbBs in cases and controls were 6.9 µg/dL (4.3, SD) and 6.1 µg/dL (4.0, SD), respectively. Mean bone lead concentrations in cases and controls were: tibia, 23.7 µg/g (14.0, SD) and 20.9 µg/g (11.4, SD), respectively; and patella, 35.1 µg/g (19.5, SD) and 31.1 µg/g (18.3, SD), respectively. Risk of hypertension (OR) was assessed using a logistic regression model. Covariate-adjusted risk of hypertension was significantly associated with increasing tibia lead concentration, but not with patella bone concentration or PbB. An increase in tibia bone lead concentration from the mid-point of the lowest quintile (8 µg/g) to the mid-point of the highest quintile (37 µg/g) was associated with an OR of 1.5 (95% CI, 1.1–1.8). Covariates in the final regression model included body mass index and family history of hypertension. A longitudinal analysis of the Normative Aging Study also found significant associations between bone lead concentration and risk of hypertension (see discussion of Cheng et al. 2001).

A case-control study examined the association between PbB and hypertension risk in middle-aged and menopausal women (Al-Saleh et al. 2005). Hypertension cases (n=100; age, 47–92 years) and controls (n=85; age, 45–82 years) were selected from the King Faisal Hospital Hypertension Clinic (Saudi Arabia)

during the period 2001–2002. Hypertension case inclusion criteria were: taking medication, or >160 mm Hg systolic pressure, or >95 mm Hg diastolic pressure. Control inclusion criteria were: average systolic/diastolic pressure <120/80 mm Hg, and no record of >130/85 mm Hg). Mean PbB of the case group was 4.8 µg/dL (range, 1.4–28) and of the control group was 4.6 µg/dL (range, 1.2–18). Covariate adjusted ORs in association with a median PbB ≥3.86 µg/dL was 5.27 (95% CI, 0.93–30; p=0.06).

Cross-sectional Studies—General Population. Several analyses of possible associations between blood pressure and PbB have been conducted with data collected in the NHANES (II and III). The NHANES III collected data on blood pressure and PbB on approximately 20,000 U.S. residents during the period 1988–1994. The results of two analyses of the NHANES III data on adult subjects provides evidence for an association between increasing PbB and increasing blood pressure that is more pronounced in blacks than whites (Den Hond et al. 2002; Vupputuri et al. 2003). Den Hond et al. (2002) analyzed data collected on 13,781 subjects of age 20 years or older who were white (4,685 males; 5,138 females) or black (1,761 males; 2,197 females). Median PbBs (µg/dL, inter-quartile range) were: white males, 3.6 (2.3–5.3); white females, 2.1 (1.3–3.4); black males, 4.2 (2.7–6.5); and black females, 2.3 (1.4–3.9). Based on multivariate linear regression (with log-transformed blood lead concentration), the predicted covariate-adjusted increments in systolic blood pressure per doubling of PbB (95% CI) were: white males, 0.3 (95% CI, -0.2–0.7, p=0.29); white females, 0.1 (95% CI, -0.4–0.5, p=0.80); black males, 0.9 (95% CI, 0.04–1.8, p=0.04); and black females, 1.2 (95% CI, 0.4–2.0, p=0.004). The predicted covariate-adjusted increments in diastolic blood pressure per doubling of PbB (95% CI) were: white males, -0.6 (95% CI, -0.9– -0.3, p=0.0003); white females, -0.2 (95% CI, -0.5– -0.1, p=0.13); black males, 0.3 (95% CI, -0.3–1.0, p=0.28); and black females, 0.5 (95% CI, 0.01–1.1, p=0.047). Covariates included in the regression models were: age and body mass index; hematocrit, total serum calcium, and protein concentrations; tobacco smoking; alcohol and coffee consumption; dietary calcium, potassium, and sodium intakes; diabetes; and use of antihypertensive drugs. Poverty index was not included as a covariate in the above predictions because its independent effect was not significant; however, when included in the regression model for black males, the effect size was not significant.

Vupputuri et al. (2003) analyzed the NHANES III subset of 14,952 subjects of age 18 years or older who were white (5,360 males; 5,188 females) or black (2,104 males; 2,197 females). Mean PbBs (µg/dL, ±SE) were: white males, 4.4±0.1; white females, 3.0±0.1; black males, 5.4±0.2; and black females, 3.4±0.1. Based on multivariate linear regression, the predicted covariate-adjusted increments in systolic blood pressure per one standard deviation increase of PbB (95% CI) were: white males, 0.29 (95% CI, -0.24–0.83, p≥0.05); white females, 0.34 (95% CI, -0.49–1.17, p≥0.05); black males, 0.83 (95% CI, 0.19–

1.44, p<0.05); and black females, 1.55 (95% CI, 0.47–2.64, p<0.010). The predicted covariate-adjusted increments in diastolic blood pressure per one standard deviation increase in PbB (95% CI) were: white males, 0.01 (95% CI, -0.38–0.40, p≥0.05); white females, -0.04 (95% CI, -0.56–0.47, p≥0.05); black males, 0.64 (95% CI, -0.08–1.20, p<0.05); and black females, 1.07 (95% CI, 0.37–1.77, p<0.01). Covariates included in the regression models were: age and body mass index; alcohol consumption; dietary calorie, potassium, and sodium intakes; and physical activity. The analyses of Den Hond et al. (2002) and Vupputuri et al. (2003) suggest an association between blood pressure and PbB in blacks but not in whites; among blacks, the association was significant for women and or borderline significance for men.

A more recent analysis of the NHANES III data focused on females between the ages of 40 and 59 years (Nash et al. 2003). The study group (n=2,165) had a mean age of 48.2 years and mean PbB of 2.9 µg/dL (range, 0.50–31.1). Based on multivariate linear regression, covariate-adjusted systolic and diastolic blood pressure was significantly associated with increasing PbB. Increasing PbB from the lowest (0.5–1.6 µg/dL) to highest (4.0–31.1 µg/dL) quartile was associated with a 1.7 mmHg increase in systolic pressure and a 1.4 mmHg increase in diastolic pressure. The study group was stratified by blood lead concentration (quartile), and into pre- and postmenopausal categories. Increased risk of diastolic (but not systolic) hypertension (systolic ≥140 mmHg diastolic ≥90 mmHg) was significantly associated with increased blood lead concentration. When stratified by menopausal status, the effect was more pronounced in the postmenopausal group. Covariates included in the models were race, age, and body mass index; tobacco smoking, and alcohol consumption. The Nursing Health Study (Korrick et al. 1999) found significant associations between hypertension risk and patella lead concentration in postmenopausal women, but not with PbB. However, the Nash et al. (2003) study included 850 postmenopausal subjects, compared to 78 in the Korrick et al. (1999) case-control study.

The NHANES II collected data on PbB and blood pressure during the period 1976–1980. In general, PbBs were higher in the NHANES II sample than in NHANES III sample (Pirkle et al. 1998), providing a means to explore possible associations between blood pressure and higher PbB than is possible with the NHANES III data. While various analyses have yielded somewhat conflicting results (Gartside 1988; Harlan 1988; Harlan et al. 1985; Landis and Flegal 1988; Pirkle et al. 1985; Schwartz 1988), they support the general findings of the more recent longitudinal and case-control studies (including those of the NHANES III) that increasing PbB is associated with increasing blood pressure in middle-aged adults.

An analysis of the NHANES II data on white males (40–59 years of age, n=564) found a significant association between increasing systolic or diastolic blood pressure and increasing PbB, after accounting for significant covariates (Pirkle et al. 1985). Covariates considered in the analysis included 87 nutritional and diet variables, cigarette smoking, alcohol consumption, socioeconomic status, and family history of hypertension. Those included in the final linear regression model for diastolic blood pressure were age and body mass index; blood hemoglobin concentration and serum albumin concentration; and dietary potassium and vitamin C intakes. Additional covariates included in the systolic blood pressure model were dietary riboflavin, oleic acid, and vitamin C. Blood lead statistics for the study group were not reported; however, the association appeared to have been evaluated over a range of 7–38 μg/dL. Lead was also a significant predictor of diastolic hypertension (≥90 mm Hg). Gartside (1988) stratified the NHANES II data into age and race categories and also found significant associations between systolic (but not diastolic) blood pressure and PbB in white males in age categories between 36 and 55 years. In these age categories, doubling PbB was associated with an increase in systolic blood pressure of approximately 4 mmHg. The statistical model used was a forward linear regression; however, the covariates retained in the final models were not reported. 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 in middle-aged white males remain significant when sampling site is included as a variable in multiple regression analyses. Accuracy of blood pressure data in the NHANES II has been challenged (e.g., digit preference by people recording the measurements, differing variability among survey sites). When these sources of variability are accounted for, the magnitude of the covariate-adjusted PbB—blood pressure relationship decreases; however, it remains significant, and strongest, for white males in the 49–50-year-old group (Coate and Fowles 1989).

Relationships between PbB and hypertension were evaluated in a survey of 7,731 males, aged 40–59 years, from 24 British towns in the British Regional Heart Study (BHRS) (Pocock et al. 1984, 1988). The PbB distributions in the study group were approximately: <12.4 μg/dL, 27%; 12.4–16.6 μg/dL, 45%; 18.6–22.8 μg/dL, 19%; and >24.9 μg/dL, 8%. The most recent, multivariate analysis of the data from this survey (Pocock et al. 1988), found that covariate-adjusted systolic blood pressure increased by 1.45 mmHg and diastolic blood pressure increased by 1.25 mmHg for every doubling in PbB. Covariates included in the regression model included age, body mass index, alcohol consumption, cigarette smoking, and socioeconomic factors. Covariate-adjusted risk of ischemic heart disease (OR) was not significantly associated with PbB. PbBs in cases (n=316) of ischemic heart disease were not statistically different,

when compared to those of the rest of the study group, after adjustment was made for age, number of years smoking cigarettes, and town of residence.

A more recent survey conducted in Great Britain (Health Survey for England, HSE) collected data annually on blood pressure and PbB. An analysis of the HSE data collected in 1995 included 2,563 males (mean age, 47.5 years) and 2,394 females (mean age, 47.7) (Bost et al. 1999). Multiple seated blood pressure measurements were taken. Mean (geometric) PbBs were 3.7 µg/dL in males and 2.6 µg/dL in females. Based on multivariate linear regression (with log-transformed PbB), increasing covariate-adjusted diastolic blood pressure was significantly associated with increasing PbB in males, but not in females. Covariates included in the above model were: age and body mass index, alcohol consumption and tobacco smoking, socioeconomic status, and region of residence; subjects who were on antihypertensive agents were excluded.

A cross-sectional study of potential associations between blood and bone lead, and blood pressure in older adults was conducted as part of the longitudinal Baltimore Memory Study (Martin et al. 2006). The study group consisted of 964 adults (age, 50–70 years, 65% female) who were evaluated for blood pressure and PbB during the period 2001–2002, and tibia lead during the period 2002–2004. Mean PbB concentration in the study group was 3.5 µg/dL (SD±2.3) and tibia lead was 18.8 µg/g (SD±12.4). Increasing PbB (but not tibia lead) was significantly associated (linear regression model) with increasing covariate-adjusted systolic (β, 0.99 mm Hg per µg/dL; 95% CI, 0.47–1.51; $p<0.01$) and diastolic blood pressure (β, 0.51; 95% CI, 0.24–0.79; $p<0.01$). Covariates included in the model included age, gender, body mass index, sodium and potassium intakes, SES, and race/ethnicity). Covariate-adjusted ORs for hypertension (>140 mm Hg systolic pressure or >90 mmHg diastolic pressure) were significantly associated with tibia lead (but not PbB) only when the multivariate logistic model excluded SES (OR, 1.21; 95% CI, 1.02–1.43; $p=0.03$) or SES and race/ethnicity (OR, 1.24; 95% CI, 1.05–1.47; $p=0.01$) from the model. When SES and race/ethnicity were included in the model, the odds ratios were not significant for tibia lead (OR, 1.16; 95% CI, 0.98–1.77; $p=0.09$) or PbB (OR, 1.01; 95% CI, 0.86–1.19).

The potential effects of childhood exposure to lead on bone lead—blood pressure relationships in adulthood have been examined in a cohort study (Gerr et al. 2002). The exposed cohort consisted of 251 people (ages 19–24 years in 1994), who resided in any of five towns near the former Bunker Hill smelter in Silver Valley, Idaho and were between the ages of 9 months and 9 years during the period 1974–1975, when uncontrolled emissions from the smelter resulted in contamination of the region and elevated PbB in local children. The reference cohort consisted of 257 Spokane, Washington residents in

the same age range as the exposed cohort. Individuals were excluded from participating in the study if they were black, pregnant, had a history of hypertension or chronic renal failure, or had a PbB exceeding 15 μg/dL at the initial examination. Subjects were given a physical examination, which included medical history, multiple measurements of sitting blood pressure, PbB measurement, and XRF measurement of tibia bone lead concentration. Relationships between blood pressure and bone lead were assessed using the general linear model, in which bone lead was expressed categorically (μg/g): <1, 1–5, >5–10, and >10. Covariate-adjusted systolic and diastolic blood pressures were significantly higher in the highest bone lead category compared to the lowest category; the differences being 4.26 mmHg (p=0.014) systolic pressure and 2.80 mmHg (p=0.03) diastolic pressure. Covariates retained in the final models included gender, age and body mass index; blood hemoglobin and serum albumin concentrations; education; tobacco smoking and alcohol consumption; current use of birth control pills; income; and current PbB. While residence (exposed vs. reference) was not a significant variable in predicting blood pressure, 82% of subjects in the highest bone lead group were members of the exposed group (i.e., residents of the contaminated towns in 1974–1975). Mean PbB during the exposure period, 1974–1975, was also higher in the high bone lead group (65 μg/dL) compared to the lower bone lead groups (2–2.4 μg/dL). Similar findings were reported by Hu et al. (1991a) in a pilot study of subjects with well-documented lead poisoning in 1930–1942 in a Boston area. Exposed subjects (mean current age, 55 years; mean current PbB, 6 μg/dL) and controls were matched for age, race, and neighborhood. Comparison of 21 matched pairs showed that the risk of hypertension was significantly higher in subjects who had experienced plumbism (RR, 7.0; 95% CI, 1.2–42.3). Kidney function, evaluated by measurements of creatinine clearance rate was significantly higher in subjects with plumbism than in controls, but serum creatinine was not significantly different than in controls subjects. The results from these two studies (Gerr et al. 2002; Hu 1991a) suggest the possibility that high childhood exposures to lead may contribute to higher blood pressure in adulthood. However, epidemiological studies of children have not found significant associations between increasing PbB and blood pressure (Factor-Litvak et al. 1996; Friedlander 1981; Rogan et al. 1978; Selbst et al. 1993).

Studies in Animal Models. Early studies in experimental animals suggested that long-term lead exposure could elevate blood pressure in nutritionally replete rats (Carmignani et al. 1988; Iannaccone et al. 1981; Khalil-Manesh et al. 1993; Victery et al. 1982a, 1982b). These observations have been corroborated with more recent studies, as well as studies that have identified numerous potential mechanisms for the effect that are relevant to humans (Carmignani et al. 2000; Ding et al. 1998; Gonick et al. 1997; Purdy et al. 1997; Vaziri and Ding 2001; Vaziri et al. 1999a, 1999b, 2001).

Other Cardiovascular Effects. Several studies have explored possible associations between lead exposure and cardiovascular disease mortality and morbidity. In a multivariate analysis of the data from the British Regional Heart Study (7,731 males, age 40–59 years; 8% of cohort had PbB >24.9 μg/dL), covariate-adjusted risk of ischemic heart disease (OR) was not significantly associated with PbB (Pocock et al. 1988). Cooper (1988) reported significantly elevated SMRs for "other hypertensive disease" (i.e., malignant hypertension, or essential benign hypertension, or hypertensive renal disease) among male battery plant workers (n= 4,519; mean PbB, 63 μg/dL) and lead production workers (n=2,300; mean PbB, 80 μg/dL). The study did not explore associations between SMRs and biomarkers of lead exposure (e.g., PbB). SMRs for cardiovascular disease were not elevated among 1,987 male lead smelter workers who worked at the Bunker Hill smelter facility in northern Idaho (i.e., who were hired between 1950 and 1965 and who worked at least 1 year) (Selevan et al. 1985, 1988). The study did not explore associations between SMRs and biomarkers of lead exposure (e.g., PbB). SMRs for ischemic heart disease were significantly elevated (SMR, 1.72; 95% CI, 1.16–1.79) among male smelter workers (n=644) who worked for at least 3 months during the period 1942–1987; however, the SMRs were across time-integrated PbB quartiles (Gerhardsson et al. 1995a).

Data from a subset of the Normative Aging Study were analyzed to assess possible associations between electrocardiographic abnormalities and body lead burdens (Cheng et al. 1998). The Normative Aging Study is a longitudinal study of health outcomes in males, initially enrolled in the Boston area of the United States. Subjects enrolled in the study, between 1963 and 1968, ranged in age from 21 to 80 years (mean, 67; SD, 7), and had no history of heart disease or hypertension. Physical examinations, including electrocardiograms and medical history follow-ups, have been conducted at approximately 3–5-year intervals. Beginning in 1991, PbB and bone XRF measurements (midtibia and patella) were included in the examinations. Data collected for a subset of the study population (775 subjects) observed between 1991 and 1995 and for whom complete data were acquired, were analyzed for associations between blood and bone lead concentrations and electrocardiographic abnormalities (e.g., heart rate, conduction defects, arrhythmia). The mean age of the subjects at the time of evaluation was 68 years (range, 48–93). Lead levels were: blood, 5.79 μg/dL (SD, 3.44); tibia bone, 22.19 μg/g (SD, 13.36); and patella bone, 30.82 μg/g (SD, 19.19). The study group was stratified by age (<65 or ≥65 years) for multivariate regression (linear and logistic) analyses. Covariate-adjusted QT and QRS intervals were significantly associated with tibia bone lead in subjects <65 years of age. A 10 μg/g increase in tibia lead concentration was associated with a 5.01 millisecond increase in the QT interval and 4.83 millisecond increase in QRS interval. Covariates included in the analyses were age, body mass index, diastolic blood pressure, fasting blood glucose level, and alcohol consumption. Covariate-adjusted OR for

intraventricular conduction defect was significantly associated with increasing tibia bone lead in the <65 year-age group; ORs were not significant for the older age group. In the age group ≥65 years, the OR for atrioventricular conduction defect with increasing tibia bone lead concentration was 1.22 (95% CI, 1.02–1.47; p=0.03), and for patella bone lead concentration, 1.16 (95% CI, 1.00–1.29; p<0.01); ORs were not significant for the younger age group. Covariates included in the models were age and serum HDL concentration. Risk of arrhythmia was not significantly associated with blood or bone lead concentrations.

A study of 95 lead smelter workers and matched (age, occupational status, duration of employment) unexposed reference group found a significantly higher incidence of ischemic ECG changes (20%) in the lead workers than in the reference group (6%) (Kirkby and Gyntelberg 1985). Mean PbB was 53 µg/dL in the exposed group and 11 µg/dL in the reference group.

A cross-sectional analysis of the NHANES (for the period 1999–2000) data found a significant association between PbB and risk of peripheral artery disease (Navas-Acien et al. 2004). The analysis included 2,125 subjects (1,055 females, 1,070 males) whose ages were ≥40 years. Geometric mean PbB was 2.1 µg/dL (25^{th}–75^{th} percentile range, 1.5–2.9). The increasing PbB was significantly associated with increasing covariate-adjusted OR for peripheral artery disease (ankle brachial index <0.9 in one or both legs). For the upper quartile PbB (>2.9 µg/dL), the ORs were 4.07 (95% CI, 1.21–13.73), without adjustment for smoking status and 2.52 (95% CI, 0.75–8.51) with adjustment for smoking. Other covariates included in the analysis were age, gender, race, education, body mass index, alcohol consumption, hypertension, diabetes, hypercholesterolemia, glomerular filtration, and C-reactive protein.

As part of the Baltimore-Washington Infant Study, a case-control study examined possible associations between lead exposure and risk of total anomalous pulmonary venous return (TAPVR), a rare congenital malformation in which pulmonary veins deliver oxygenated blood to the right atria rather than the left atria (Jackson et al. 2004). Cases (n=54) were recruited during the period 1981–1989. Controls (n=522) consisted of a stratified random sample of live-born infants without birth defects (excluding twins, low birth weight infants, and infants whose race was other than black or white). Subjects were classified as having been exposed to lead (or not) during critical maternal (i.e., from 3 months prior to conception through third trimester) or paternal (i.e., within 6 months prior to conception) periods based on self-reporting of occupational or environmental exposures, reported in an administered questionnaire. Prevalence of maternal lead exposure was 17% among cases and 11% among controls; prevalence of paternal lead exposure was 61% among cases and 46% among controls. The OR for TAPVR in

association with any maternal lead exposure during the critical maternal period was 1.57 (95% CI, 0.64–3.47; p=0.27); the OR for any paternal lead exposure was 1.83 (95% CI, 1.00–3.42, p=0.045).

Several small-scale studies have reported changes in peripheral hemodynamics in association with occupational exposures to lead. Effects observed in these studies may represent effects of lead on either the cardiovascular and/or autonomic nervous systems. A study conducted in Japan compared the results of finger plethysmographic assessments in 48 male workers in a lead refinery and 43 male controls who had no occupational lead exposure (Aiba et al. 1999). Ages of the exposed and reference groups were similar (mean±SD; 46±15 and 49±11 years, respectively). Mean PbB in the exposed group was 43.2 µg/dL (25.2, SD), PbBs for the control group were not measured. Covariate-adjusted acceleration plethysmography parameters were significantly different in the exposure group compared to the reference group and were significantly associated with PbB. The prevalence of abnormal parameter values (<25th percentile value) was significantly higher in the exposure group and prevalence increased with increasing duration of employment or increasing PbB. A study of ceramic painters in Japan evaluated postural changes in finger blood flow in relation to PbB (Ishida et al. 1996). Subjects of the study were 50 males (age, 55±12 years) and 78 females (age, 52±8 years) who were not currently receiving pharmacological treatment. Finger blood flow parameters evaluated were the percent change in finger blood flow in response to standing from a supine position, and the rate of decrease in blood flow in response to standing. The mean (geometric) PbB was 16.5 µg/dL (2.1, SD; range, 3.5–69.5 µg/dL) in males and 11.1 µg/dL (1.7, SD; range, 2.1–31.5 µg/dL) in females. Both percent change in blood flow and rate of decrease in blood flow significantly decreased with increasing PbB in both males and females. Covariate-adjusted postural change in finger blood flow was significantly associated with PbB. Covariates included in the regression model were age, body mass index total blood cholesterol concentration, skin temperature, alcohol consumption and tobacco smoking.

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 PbBs of 100–200 µg/dL, they have sometimes been noted in workers whose PbBs were between 40 and 60 µg/dL (Awad El Karim 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; Pagliuca et al. 1990; Pollock and Ibels 1986; Rosenman et al. 2003; 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 alter the hematological system. The anemia induced by lead is microcytic and hypochromic and results primarily from both inhibition of heme synthesis and shortening of the erythrocyte lifespan. Lead interferes with heme synthesis by altering the activities of 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 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).

Studies of lead workers have shown that ALAD activity correlated inversely with PbB (Alessio et al. 1976; Gurer-Orhan et al. 2004; Hernberg et al. 1970; Meredith et al. 1978; Schuhmacher et al. 1997; Tola et al. 1973; 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 PbBs 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, with no threshold yet apparent. ALAD activity was inversely correlated with PbB 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; Roels and Lauwerys 1987; adults—Roels et al. 1976). Studies of children in India and China also have reported significant decreases in ALAD activity associated with PbB ≥10 µg/dL (Ahamed et al. 2005; Jin et al. 2006). Inverse correlations between PbB and ALAD activity were found in mothers (at delivery) and their newborns (cord blood). PbB ranged from approximately 3 to 30 µg/dL (Lauwerys et al. 1978). In a study in male volunteers exposed to particulate lead in air at 0.003 or 0.01 mg lead/m^3 for 23 hours/day for 3–4 months mean PbB increased from 20 µg/dL (pre-exposure) to 27 µg/dL at the 0.003 mg/m^3 exposure level and from 20 µg/dL (pre-exposure) 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. 1975). Similar observations were made in a study of volunteers who ingested lead acetate at 0.02 mg lead/kg/day every day for 21 days (Stuik 1974). The decrease in erythrocyte ALAD could be noticed by day 3 of lead ingestion and reached a maximum by day 14. Mean PbB was approximately 15 µg/dL before exposure and increased to approximately 40 µg/dL during exposure. Cools et al. (1976) reported similar results in a study of 11 volunteers who ingested lead acetate that resulted in a mean PbB of 40 µg/dL; the mean pre-exposure PbB was 17.2 µg/dL.

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 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 and log urinary ALA in workers. Some of these studies indicated that correlations can be seen at PbB 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 PbBs >40 µg/dL. In a study of 98 occupationally exposed subjects (mean PbB, 51 µg/dL) and 85 matched referents (mean PbB, 20.9 µg/dL), it was found that log ZPP and log ALA in urine correlated well with PbB (Gennart et al. 1992a). In the exposed group, the mean ZPP was 4 times higher than in the comparison group, whereas urinary ALA was increased 2-fold.

Correlations between PbBs and urinary ALA similar to those observed in occupationally exposed adults have also been reported in nonoccupationally 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 >35 µg/dL in women and >45 µg/dL in men (Roels and Lauwerys 1987). A significant linear correlation between PbB and log ALA was obtained for data in children 1–5 years old with PbBs 25–75 µg/dL. The correlation was seen primarily at PbBs >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 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 PbBs 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 of 95 mother-infant pairs from Toronto showed a significant inverse correlation between maternal and umbilical cord lead levels and FEP (Koren et al. 1990). Most (99%) infants had cord PbBs 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.

The threshold PbB 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 PbBs 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 of 51 μg/dL, the mean hemoglobin concentration was not significantly different than in an unexposed group of 85 subjects (mean PbB, 21 μg/dL). However, four exposed workers, but no controls, had hemoglobin levels below the level considered as the limit value for defining anemia (13 μg/dL) (Gennart et al. 1992a). Similar lack of correlation between PbB and hemoglobin was reported in a study of 94 Israeli lead workers with a mean PbB of 38.1 μg/dL (range, 6–113 μg/dL) (Froom et al. 1999). 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 El Karim et al. 1986; Pagliuca et al. 1990). In a study of workers with a relatively low mean PbB of 8.3 μg/dL (range, 2–25 μg/dL), it was found that PbB did not correlate with either hemoglobin or hematocrit; however, patellar lead significantly correlated with a decrease in hemoglobin and hematocrit

even after adjusting a number of confounders (Hu et al. 1994). 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). In a pilot study of subjects who suffered lead poisoning in 1930–1942 in a Boston area, hemoglobin and hematocrit were significantly decreased compared to unexposed matched controls (Hu 1991a). The mean current age of the subjects was 55 years and the mean current PbB was 6 µg/dL. No difference was noticed in red blood cell size or shape between exposed and control subjects. Hu et al. (1991a) suggested that the effect observed may have represented a subclinical effect of accumulated bone lead stores on hematopoiesis.

Other studies have shown that adverse effects on hematocrit may occur at even lower PbBs 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 PbBs and hematocrit. Between 20 and 100 µg/dL, the decrease in hematocrit was greater than proportional to the increase in PbB. The effect was strongest in the youngest children. The analysis also revealed that at PbBs of 25 µg/dL, there is a dose-related depression of hematocrit in young children. Similar results also have been reported by others (Kutbi et al. 1989).

Lead also inhibits the enzyme pyrimidine-5'-nucleotidase within the erythrocyte, which results in an accumulation of pyrimidine nucleotides (cytidine and uridine phosphates) in the erythrocyte or reticulocyte and subsequent destruction of these cells. This has been reported 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). PbBs 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 PbBs. A significant negative linear correlation between pyrimidine-5'-nucleotidase and PbB level was seen in 21 children with PbBs ranging from 7 to 80 µg/dL (Angle and McIntire 1978). Similar results were seen in another study with 42 children whose PbB ranged from <10 to 72 µg/dL (Angle et al. 1982). Additional findings included a direct correlation between cytidine phosphate levels and PbBs (log-log). There was no indication of a threshold for these effects of lead in these two studies.

In summary, of all the parameters examined, ALAD activity appears to be the most sensitive indicator of lead exposure. In studies of the general population, ALAD activity was inversely correlated with PbBs

over the entire range of 3–34 µg/dL. In contrast, the threshold PbB for increase in urinary ALA in adults is 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 PbBs for decreased hemoglobin levels in adults and children have been estimated at 50 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 PbBs ≥30 µg/dL that the assay cannot distinguish between moderate and severe exposure.

Studies in animals, in general, support the findings in humans and indicate that the effects depend on the chemical form of lead, duration of exposure, and animal species. Of particular interest are the results of a study in a cohort of 52 monkeys administered lead acetate orally for up to 14 years (Rice 1996b). PbB was dose-related and ranged between 10 and 90 µg/dL. Decreased hematocrit and hemoglobin was observed in monkeys at 7 (PbB 25 µg/dL) and 11 years (PbB 90 µg/dL) of age; hemoglobin also was decreased at 6 years of age when PbB was 23 µg/dL. All changes that occurred were within normal ranges, which led Rice (1996b) to conclude that under the conditions of the study, there were no lead-related hematological effects.

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). Rosenman et al. (2003) described musculoskeletal effects (frequent pain/soreness and/or muscle weakness) in lead workers with PbB ≥40 µg/dL.

A study of the association between lead exposure and bone density in children was recently published (Campbell et al. 2004). The cohort consisted of 35 African American children 8–10 years of age from Monroe County, New York State. The cohort was divided into two groups, one (n=16) with mean cumulative PbB of 6.5 µg/dL (low-exposure group) and the other (n=19) with mean cumulative PbB of 23.6 µg/dL (high-exposure group). The groups were similar by sex, age, body mass index, socio-economic status, physical activity, or calcium intake. Contrary to what was expected, subjects with high cumulative exposure had a higher bone mineral density than subjects with low-lead cumulative exposure. Among 17 bony sites examined, four were significantly different ($p<0.05$). Campbell et al. (2004)

speculated that lead accelerates skeletal maturation by inhibiting proteins that decrease the rate of maturation of chondrocytes in endochondral bone formation. A lower peak bone mineral density achieved in young adulthood might predispose to osteoporosis in later life.

A limited number of 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; Gruber et al. 1997; Hamilton and O'Flaherty 1994, 1995; Ronis et al. 2001). These data, all from intermediate-duration studies in 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. In general, rats appear to be less sensitive than humans to lead effects in bone. A recent study in mice reported that lead delays fracture healing at environmentally relevant doses and induces fibrous nonunions at higher doses by the progression of endochondral ossification (Carmouche et al. 2005). In studies in cultured osteoblast-like cells, lead disrupted the modulation of intracellular calcium by 1,25-dihydroxyvitamin D in a biphasic manner (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).

The studies that have examined relationships between lead exposure, as reflected by PbB, and the occurrence of dental caries in children have, for the most part, found a positive association (Campbell et al. 2000a; Gemmel et al. 2002; Moss et al. 1999). Moss et al. (1999) conducted a cross-sectional analysis of measurements of PbB and dental caries in 24,901 people, including 6,541 children 2–11 years of age, recorded in the NHANES III (1988–1994). Mean (geometric) PbBs were 2.9 µg/dL in children 2–5 years of age and 2.1 µg/dL in children 6–11 years of age. Increasing PbB was significantly associated with increased number of dental caries in both age groups, after adjustment for covariates. An increase in PbB of 5 µg/dL was associated with an adjusted OR of 1.8 (95% CI, 1.3–2.5) for the age group 5–17 years. Covariates included in the models were age, gender, race/ethnicity, poverty income ratio, exposure to cigarette smoke, geographic region, educational level of head of household, carbohydrate and calcium intakes, and dental visits. A retrospective cohort study conducted in Rochester, New York compared the

risk of dental caries among 154 children 7–12 years of age associated with PbB less than or exceeding 10 µg/dL, measured at ages 18 and 37 months of age (Campbell et al. 2000a). The OR (adjusted for age at examination, grade in school, and number of dental surfaces at risk) for caries on permanent teeth associated with a PbB exceeding 10 µg/dL was 0.95 (95% CI, 0.43–2.09; p=0.89) and for deciduous teeth, 1.77 (95% CI, 0.97–3.24; p=0.07). Other covariates examined in the models, all of which had no significant effect on the outcome, were gender, race/ethnicity, SES, parental education and residence in community supplied with fluoridated drinking water, and various dental hygiene variables. Gemmel et al. (2002) conducted a cross-sectional study of associations between PbB and dental caries in 543 children, 6–10 years of age, who resided either in an urban (n=290) or rural (n=253) setting. Increasing PbB was significantly associated with the number of caries in the urban cohort, but not in the rural cohort. The mean PbBs were 2.9 µg/dL (SD, 2.0) in the urban group and 1.7 µg/dL (SD, 1.0) in the rural group. Covariates examined in the models were gender, race/ethnicity, SES, maternal smoking, parental education, and various dental hygiene variables.

Dye et al. (2002) conducted a cross-sectional analysis of measurements of blood lead concentration and indices of periodontal bone loss in 10,033 people, 20–69 years of age, recorded in the NHANES III (1988–1994). Mean (geometric) PbB was 2.5 µg/dL (SE, 0.08). Increasing blood lead concentration was significantly associated with periodontal bone loss, after adjustment for covariates. Covariates examined in the analysis included age, gender, race/ethnicity, education, SES, age of home, smoking, and dental furcation (an indicator of severe periodontal disease) as well as an interaction term for smoking and dental furcation.

Studies in animals also have examined the effect of lead exposure on teeth. For example, young rats whose mothers were exposed to lead since young adults, during pregnancy, and lactation had a significantly higher mean caries score than a control group (Watson et al. 1997). The mean PbB achieved in the dams was 48 µg/dL and in the breast milk 500 µg/dL; PbB in the offspring was not determined. Lead also has been reported to delay mineralization in teeth, resulting in less hard enamel (Gerlach et al. 2002) and eruption rate in hypofunctional teeth (Gerlach et al. 2000).

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. 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). Another study found a significant reduction in 6β-hydroxylation of cortisol in children who had positive urinary excretion of lead

(≥500 µg/24 hours) upon ethylenediamine tetraacetic acid (EDTA) provocative tests compared with an age-matched control group (Saenger et al. 1984). These biochemical transformations are mediated by hepatic mixed-function oxygenases.

The association between lead exposure and serum lipid profile was examined in a study of Israeli workers (Kristal-Boneh et al. 1999). The mean PbB of the 87 workers was 42.3 µg/dL and that of 56 control subjects was 2.7 µg/dL. After adjusting for confounders including nutritional variables, the authors found statistically higher values for total cholesterol (212 vs. 200 mg/dL) and HDL cholesterol (47 vs. 42 mg/dL) in the workers compared to controls; no significant differences were seen for LDL cholesterol and triglycerides. These findings are of dubious biological significance, particularly since the HDL/total cholesterol ratio was the same in the two groups. A study in rats administered lead acetate for 7 weeks that resulted in PbBs of 17 and 32 µg/dL reported a dose-related increase in triglycerides and decrease in HDL cholesterol (Skoczynska et al. 1993). The authors speculated that the increase in serum triglycerides could have been caused by lead-induced inhibition of lipoprotein lipase activity or decreased activity of hepatic lipase; no possible explanation was offered for the decrease in HDL cholesterol.

A study of workers in the United Arab Emirates reported that a group of 100 workers with a mean PbB of 78 µg/dL had significantly higher concentrations of amino acids in serum than 100 controls whose mean PbB was 20 µg/dL (Al-Neamy et al. 2001). Tests for liver function that included serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities found small (≤10%) but statistically significant increases in alkaline phosphatase and lactate dehydrogenase activities in the serum of the workers. A study in rats treated with lead acetate for 4 months found decreased AST and ALT activities in hepatic homogenates, but activities in serum were not monitored (Singh et al. 1994).

Collectively, the information regarding effects of lead on the liver in humans and animals is scarce and does not allow for generalizations.

Renal Effects. Lead nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis and interstitial fibrosis (Diamond 2005; Goyer 1989; Loghman-Adham 1997). Functional deficits in humans that have been associated with excessive lead exposure include enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed glomerular filtration rate. A few studies have revealed histopathological features of renal injury in humans, including intranuclear inclusion bodies and cellular necrosis in the proximal tubule and interstitial fibrosis (Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979).

A large number of studies of lead nephropathy in humans have been published (Table 3-3). Most of these studies are of adults whose exposures were of occupational origin; however, a few environmental and/or mixed exposures are represented and a few studies of children are also included (Bernard et al. 1995; Fels et al. 1998; Verberk et al. 1996). In most of these studies, PbB was the biomarker for exposure, although more recent epidemiological studies have explored associations between toxicity and bone lead concentrations. These studies provide a basis for establishing blood lead, and in some cases, bone lead concentration ranges associated with specific nephrotoxicity outcome. The studies are sorted in Figure 3-3 by the central tendency blood lead concentration reported in each study; details about the subjects and exposures are provided in Table 3-3. End points of kidney status captured in this data set include various measures of glomerular and tubular dysfunction. Data on changes in glomerular filtration rate represent measurements of either creatinine clearance or serum creatinine concentration. Measurements of enzymuria represent, mainly, urinary N-acetyl-D-glucosaminidase (NAG), are also represented. Increased excretion of NAG has been found in lead-exposed workers in the absence of increased excretion of other proximal tubule enzymes (e.g., alanine aminopeptidase, alkaline phosphatase, glutamyltransferase) (Pergande et al. 1994). Data points indicating proteinuria refer to total urinary protein, urinary albumin, or urinary LMW protein (e.g., 2μG or RBP). Indices of impaired transport include clearance or transport maxima for organic anions (e.g., p-aminohippurate, urate) or glucose (Biagini et al. 1977; Hong et al. 1980; Wedeen et al. 1975). A few studies have provided histo-pathological confirmation of proximal tubular injury (Biagini et al. 1977; Wedeen et al. 1975, 1979).

Figure 3-3 illustrates a few general trends regarding the relationship between PbB and qualitative aspects of the kidney response. A cluster of observations of decrements in glomerular filtration rate appear at the low end of the PbB range (<20 μg/dL); the significance of these studies is discussed in greater detail below. Outcomes for the various renal toxicity end points are mixed over the PbB range 20–50 μg/dL. Enzymuria or proteinuria were detected in most studies in which these end points were evaluated, whereas indications of depressed glomerular filtration rate were, with only one exception, not observed over this PbB range. At PbBs >50 μg/dL, functional deficits, including enzymuria, proteinuria, impaired transport, and depressed glomerular filtration rate, dominate the observations. The overall dose-effect pattern suggests an increasing severity of nephrotoxicity associated with increasing PbB, with effects on glomerular filtration evident at PbBs below 20 μg/dL, enzymuria and proteinuria becoming evident above 30 μg/dL, and severe deficits in function and pathological changes occurring in association with PbBs exceeding 50 μg/dL.

Table 3-3. Selected Studies of Lead-Induced Nephrotoxicity in Humans[a]

No.	Reference	Exposure type	Number of subjects	Age (year)	Exposure duration (year)	Blood lead concentration (µg/dL)[b]	Biomarker evaluated[c]
1	Muntner at al. 2003	Unknown	4,831	>20	NA	5 (<1–56)	SCr*
2	Hu 1991b	Environmental	22	55	NA	6 (2–11)	CCr*[d]
3	Lin et al. 2001	Unknown	55	57	NA	7 (1–16)	CCr*
4	Staessen et al. 1992	Environmental	1,981	48	NA	8 (~2–70)	CCr*, SCr*
5	Payton et al. 1994	Environmental	744	64	NA	8 (4–26)	CCr*
6	Kim et al. 1996a	Unknown	459	57	NA	10 (<1–54)	SCr*
7	Staessen et al. 1990	Environmental	531	48	NA	10 (<4–35)	SCr*
8	Bernard et al. 1995	Environmental	154	13	NA	12 (3–35)	UNAG*, URBP*
9	Fels et al. 1998	Environmental	62	10	NA	13 (SD=6)	SCr, UE, UP, ULMWP
10	Sonmez et al. 2002	Occupational	13	32	0.14	25 (SD=10)	SCr, UNAG*
11	Chia et al. 1994	Occupational	128	28	3	30 (4–66)	UNAG*
12	Chia et al. 1995a, 1995b	Occupational	137	28	>0.5	30 (4–66)	SCr, $S\beta_2\mu G$*, UAlb, $U\beta_2\mu G$, URBP
13	Weaver et al. 2003a, 2005	Occupational	803	40	1–36	32 (4–86)	BUN*[e], SCr*[e], CCr, UNAG*[e], URBP
14	Mortada et al. 2001	Occupational	43	33	10	32 (SD=17)	SCr, UNAG*, UAlb*
15	Gerhardsson et al. 1992	Occupational	100	37–68	14–32	32 (5–47)	CCr, SCr, $U\beta_2\mu G$*, UNAG*
16	Verberk et al. 1996	Environmental	151	4.6	NA	34 (<5–~110)	UNAG*
17	Factor-Litvak et al. 1999	Environmental	394	6	6	35 (20–40)	UP*
18	Omae et al. 1990	Occupational	165	18–57	0.1–26	37 (9–60)	CCr, CUA, $U\beta_2\mu G$, $C\beta_2\mu G$

Table 3-3. Selected Studies of Lead-Induced Nephrotoxicity in Humans[a]

No.	Reference	Exposure type	Number of subjects	Age (year)	Exposure duration (year)	Blood lead concentration (µg/dL)[b]	Biomarker evaluated[c]
19	Cardozo dos Santos et al. 1994	Occupational	166	33	4.5	37 (16–88)[f]	SCr, UNAG*, UAlb, UP
20	Wedeen et al. 1975	Occupational	4	36	5–8	40 (29–52)	GFR, RPF, TMPAH, HP
21	Hsiao et al. 2001	Occupational	30	38	13	40 (<10–98)	SCr[g]
22	Huang et al. 2002	Occupational	40	30	5	42 (24–63)	$U\beta_2\mu G$, UP
23	Fels et al. 1994	Occupational	81	30	7	42 (21–73)	UP*
24	Pergande et al. 1994	Occupational	82	30	7	42 (21–73)	SCr, UP*, UE*
25	Roels et al. 1994	Occupational	76	44	6–36	43 (26–68)	CCr*[d], UNAG*
26	Kumar and Krishnaswamy 1995	Occupational	22	32.5	NA	43 (30–69)	CCr, $U\beta_2\mu G$*, UNAG*
27	Buchet et al. 1980	Occupational	25	45	13	44 (34–61)	CCr, SCr, $U\beta_2\mu G$, UP
28	de Kort et al. 1987	Occupational	53	42	12	47 (44–51)	SCr, BUN
29	Verschoor et al. 1987	Occupational	155	30–51	<2–>10	47 (34–66)	UNAG*, URPB*
30	Cardenas et al. 1993	Occupational	41	39	14	48 (36–65)	SCr, UP, $U\beta_2\mu G$, UNAG*, UTBX*, UPG*
31	Wedeen et al. 1975	Occupational	1	40	5	48	GFR*, TMPAH*, HP*
32	Gennart et al. 1992	Ocupational	98	38	8	51 (45–70)	SCr, UNAG, $U\beta_2\mu G$, URBP
33	Wedeen et al. 1979	Occupational	15	41	14	52 (20–98)	GFR*, HP*
34	Ehrlich et al. 1998	Occupational	382	41	12	54 (23–110)	SCr,* SUA*
35	Pinto de Almeida et al. 1987	Occupational	52	38	NA	64 (SD=16)	SCr*
36	Hong et al. 1980	Occupational	6	35	7	68 (34–110)	GFR*, TMG*
37	Wedeen et al. 1975	Occupational	3	28	3–5	72 (51–98)	GFR*, RPF*, TMPAH*, HP*

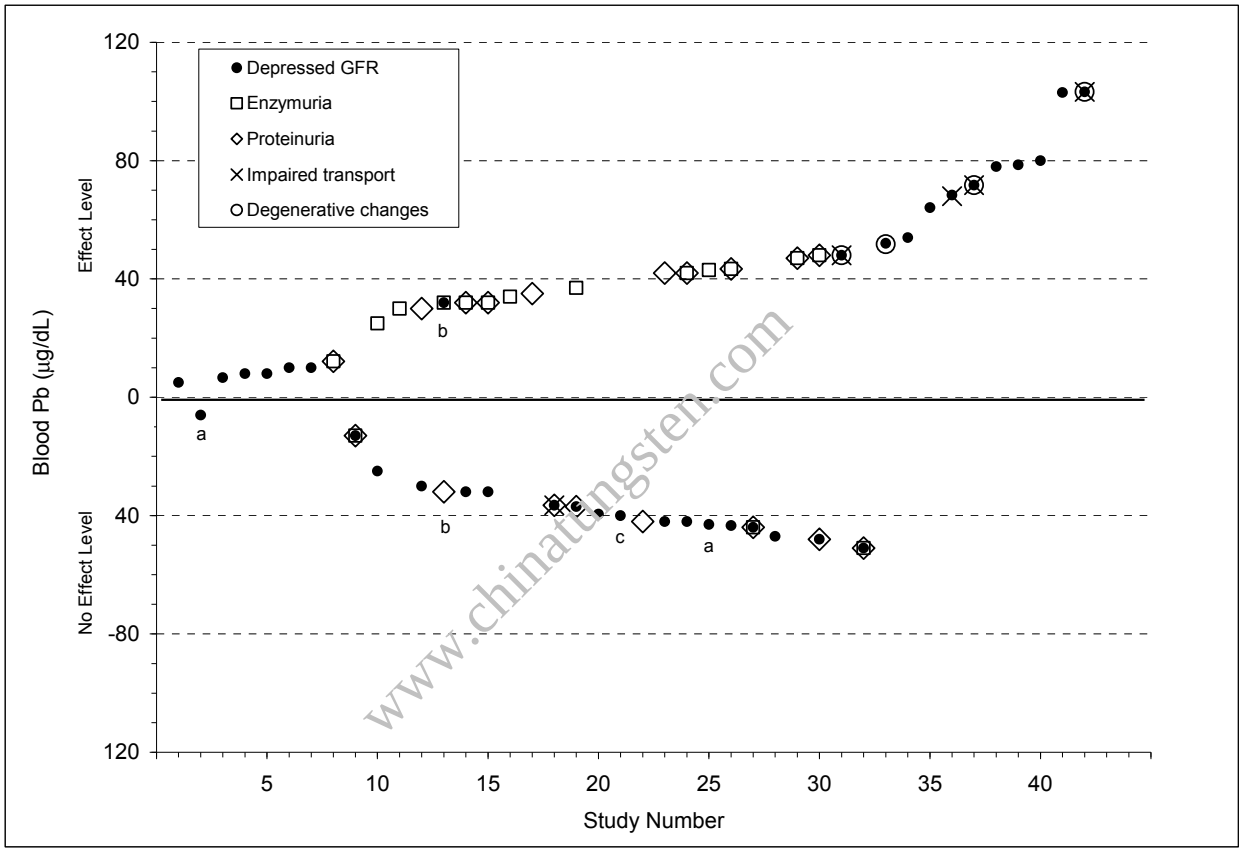
Table 3-3. Selected Studies of Lead-Induced Nephrotoxicity in Humans[a]

No.	Reference	Exposure type	Number of subjects	Age (year)	Exposure duration (year)	Blood lead concentration (µg/dL)[b]	Biomarker evaluated[c]
38	Baker et al. 1979	Occupational	160	29–62	4–31	77 (16–280)	GFR*, BUN*
39	Lilis et al. 1968	Occupational	102	32–61	>10	79 (42–149)	GFR*, SCr*
40	Lilis et al. 1980	Occupational	449	NA	12	80 (<40>80)	SCr*, BUN*
41	Cramer et al. 1974	Occupational	7	45	9	103 (71–109)	GFR*, HP*
42	Biagini et al. 1977	Occupational	11	44	12	103 (60–200)	GFR*, CPAH*, HP*

[a]See Figure 3-3 for graphical representation of lead-induced renal effects.
[b]Blood lead concentrations are reported central tendencies with range or SD in parentheses.
[c]Asterisk indicates association with lead exposure.
[d]Significant increase in creatinine clearance.
[e]Significant in upper age tertile (>46 years).
[f]3rd and 97th percentile.
[g]Significant decrease in serum creatinine concentration.

BUN = blood urea nitrogen, CCr = creatinine clearance; $C\beta_2\mu G$ = $\beta_2\mu G$ clearance, CPAH=p-aminohippurate (PAH) clearance; CUA = uric acid clearance; GFR = glomerular filtration rate; HP = histopathology; $S\beta_2\mu G$ = serum $\beta_2\mu G$; SCr = serum creatinine; SD = standard deviation; SUA = serum uric acid; RPF= renal plasma flow; TMG = transport maximum for glucose; TMPAH = transport maximum for PAH; UAlb = urine albumin; $U\beta_2\mu G$ = urine $\beta_2\mu G$; UE = urine enzymes; ULMWP = urine low molecular weight proteins; UNAG = urine N-acetyl-β-D-glucosaminidase; UP = urine protein; UPG = urine prostaglandins; URBP = urine retinol binding protein; UTBX = urine thromboxane

Figure 3-3. Indicators of Renal Functional Impairment Observed at Various Blood Lead Concentrations in Humans*



*Refer to Table 3-3 for study details (indexed by study number)

a = Increase in creatinine clearance; b = >46 years of age; c = Decrease in serum creatinine; GFR = glomerular filtration rate

Source: Diamond 2005

Inconsistencies in the reported outcomes across studies may derive from several causes. Varying uncertainty also exists, across studies, in exposure history of subjects and in the biomarkers assessed. In addition, occupational studies are subject to a healthy worker bias (i.e., tendency for workers who experience adverse effects to remove themselves, or be removed, from exposure).

Observations made in animal models provide evidence for the plausibility of effects of lead on renal glomerular and tubular function in humans. In rats, proximal tubular injury involves the convoluted and straight portions of the tubule (Aviv et al. 1980; Dieter et al. 1993; Khalil-Manesh et al. 1992a, 1992b; Vyskocil et al. 1989), with greater severity, at least initially, in the straight (S3) segment (Fowler et al. 1980; Murakami et al. 1983). Typical histological features include, in the acute phase, the formation of intranuclear inclusion bodies in proximal tubule cells (see below for further discussion); abnormal morphology (e.g., swelling and budding) of proximal tubular mitochondria (Fowler et al. 1980; Goyer and Krall 1969); karyomegaly and cytomegaly; and cellular necrosis, at sufficiently high dosage. These changes appear to progress, in the chronic phase of toxicity and with sufficient dosage, to tubular atrophy and interstitial fibrosis (Goyer 1971; Khalil-Manesh et al. 1992a, 1992b). Glomerular sclerosis has also been reported (Khalil-Manesh et al. 1992a). Adenocarcinomas of the kidney have been observed in long-term studies in rodents in which animals also developed proximal tubular nephropathy (Azar et al. 1973; Goyer 1993; Koller et al. 1985; Moore and Meredith 1979; Van Esch and Kroes 1969).

Effects on Glomerular Filtration Rate. In humans, reduced glomerular filtration rate (i.e., indicated by decreases in creatinine clearance or increases in serum creatinine concentration) has been observed in association with exposures resulting in average PbBs <20 μg/dL (Figure 3-3, Table 3-3).

The results of epidemiological studies of general populations have shown a significant effect of age on the relationship between glomerular filtration rate (assessed from creatinine clearance of serum creatinine concentration) and PbB (Kim et al. 1996a; Muntner et al. 2003; Payton et al. 1994; Staessen et al. 1990, 1992; Weaver et al. 2003a, 2005b). Furthermore, hypertension can be both a confounder in studies of associations between lead exposure and creatinine clearance (Perneger et al. 1993) and a covariable with lead exposure (Harlan et al. 1985; Muntner et al. 2003; Payton et al. 1994; Pirkle et al. 1985; Pocock et al. 1984, 1988; Tsaih et al. 2004; Weiss et al. 1986). These factors may explain some of the variable outcomes of smaller studies in which the age and hypertension effects were not fully taken into account. When age and other covariables that might contribute to glomerular disease are factored into the dose-response analysis, decreased glomerular filtration rate has been consistently observed in populations that have average PbB <20 μg/dL (Table 3-4). In the Kim et al. (1996a) and Muntner et al. (2003) studies, a

Table 3-4. Summary of Dose-Response Relationships for Effects of Lead Exposure on Biomarkers of Glomerular Filtration Rate

Reference	Exposure	Number of Subjects	Mean PbB (range) (µg/dL)	End point	Change in end point (per 10-fold increase in blood lead)
Payton et al. 1994	Mixed[a]	744 M	8.1 (4–26)	CCr (mL/minute)	-10[b]
Staessen et al. 1992	Environmental	1,016 F 965 M	7.5 (1.7–65)	CCr (mL/minute)	-10 F[c] -13 M
Kim et al. 1996a	Mixed[a]	459 M	9.9 (0.2–54)	SCr (mg/dL)	0.08[d] 0.14[e]
Staessen et al. 1990	Environmental	133 F 398 M	12 (6–35)	SCr (mg/dL)	0.07 M[f]

[a]U.S. Veterans Administration Normative Aging Study
[b]Partial regression coefficient, -0.040 ln mL/minute creatinine clearance per ln µmol/L blood lead concentration.
[c]Partial regression coefficient, -9.51 mL/minute creatinine clearance per log µmol/L blood lead concentration.
[d]Partial regression coefficient, 2.89 µmol/L serum creatinine per ln µmol/L blood lead concentration.
[e]In subjects with blood lead concentrations less than 10 µg/dL, the partial regression coefficient was 5.29 µmol/L serum creatinine per ln µmol/L blood lead concentration.
[f]Reported 0.6 increase in serum creatinine (µmol/L) per 25% increase in blood lead concentration (µmol/L, log-transformed) in males (two subjects with serum creatinine concentrations exceeding 180 µmol/L excluded; regression coefficient not reported for females).

CCr = creatinine clearance; F = females; ln = natural logarithm; M = males; PbB = blood lead concentration; SCr = serum creatinine concentration

significant relationship between serum creatinine and PbB was evident in subjects who had PbB below 10 µg/dL (serum creatinine increased 0.14 mg/dL per 10-fold increase in PbB). Assuming a glomerular filtration rate of approximately 90–100 mL/minute in the studies reported in Table 3-4, a change in creatinine clearance of 10–14 mL/minute would represent a 9–16% change in glomerular filtration rate per 10-fold increase in PbB. Estimating the change in glomerular filtration rate from the incremental changes in serum creatinine concentration reported in Table 3-4 is far less certain because decrements in glomerular filtration do not necessarily give rise to proportional increases in serum creatinine concentrations. A 50% decrement in glomerular filtration rate can occur without a measurable change in serum creatinine excretion (Brady et al. 2000). Nevertheless, the changes reported in Table 3-4 (0.07–0.14 mg/dL) would represent a 6–16% increase, assuming a mean serum creatinine concentration of 0.9–1.2 mg/dL. This suggests at least a similar, and possibly a substantially larger, decrement in glomerular filtration rate. The confounding and covariable effects of hypertension are also relevant to the interpretation of the regression coefficients reported in these studies. Given the evidence for an association between lead exposure and hypertension, and that decrements in glomerular filtration rate can be a contributor to hypertension, it is possible that the reported hypertension-adjusted regression coefficients may underestimate the actual slope of the blood lead concentration relationship with serum creatinine concentration or creatinine clearance.

Another important complication in the assessment of associations between lead exposure and adverse effects on glomerular filtration is the potential confounding effect of decrements in glomerular filtration rate and increased lead body burden. Lead exposure has also been associated with increases in glomerular filtration rate (Hsiao et al. 2001; Hu 1991b; Roels et al. 1994). This may represent a benign outcome or a potentially adverse hyperfiltration, which may contribute to subsequent adverse renal effects. Increases in glomerular filtration rate have been observed in the early phases of development of chronic renal injury in rats (Khalil-Manesh et al. 1992a).

The observations suggestive of a relationship between PbB and decrements in glomerular filtration rate derived from the studies presented in Table 3-3 are consistent with those of a smaller prospective clinical study in which progression of renal insufficiency was related to higher lead body burden among patients whose PbB was <15 µg/dL (Lin et al. 2001; Yu et al. 2004). Mean PbB in a high lead body burden group (EDTA provocation test yielded >600 µg excreted/72 hours) were 6.6 µg/dL (range, 1.0–15 µg/dL) compared to 3.9 µg/dL (1–7.9 µg/dL) in a low body burden group.

The above observations suggest that significant decrements in glomerular filtration rate may occur in association with PbB below 20 µg/dL and, possibly, below 10 µg/dL (Kim et al. 1996a; Muntner et al. 2003). This range is used as the basis for estimates of lead intakes that would place individuals at risk for renal functional deficits.

Longitudinal Studies—General Population. Three studies of glomerular function and lead exposure were conducted as part of the Normative Aging Study, a longitudinal study of health outcomes in 2,280 males, initially enrolled in the Boston area of the United States between 1963 and 1968. At enrollment, subjects ranged in age from 21 to 80 years (mean, 67), and had no history of heart disease, hypertension, cancer, peptic ulcer, gout, bronchitis, or sinusitus. Physical examinations, including seated blood pressure and medical history follow-ups, were conducted at approximately 3–5-year intervals. Beginning in 1987, participants were requested to provide 24-hour urine samples for analysis, including urine creatinine; and beginning in 1991, blood and bone concentrations were included in the examinations. Data collected from a subset of the study population (744 subjects, observed between 1988 and 1991) were analyzed for associations between serum creatinine, renal creatinine clearance, and blood lead concentrations (Payton et al. 1994). Mean age of the study group was 64.0 years (range, 43–90). Mean baseline PbB was 8.1 µg/dL (range, <4–26 µg/dL). Based on multi-variate linear regression (with log-transformed PbB), covariate-adjusted creatinine clearance was significantly associated with blood lead concentration (regression coefficient, -0.0403; SE, 0.0198; p=0.04). A 10-fold increase in PbB was associated with a decrease in creatinine clearance of 10.4 mL/minute. This would represent a decrease in creatinine clearance of approximately 11% from the group mean of 88 mL/minute. Co-variates included in the regression model were age and body mass index; systolic and diastolic blood pressure; alcohol consumption and tobacco smoking; and analgesic or diuretic medications.

In a subsequent longitudinal study, data collected from a random subset of the Normative Aging Study population (459 subjects, observed between 1991 and 1994) were analyzed for associations between serum creatinine and PbB (Kim et al. 1996a). Mean age of the study group was 56.9 years (range, 37.7–87.5). Mean PbB was 9.9 µg/dL (range, 0.2–54.1 µg/dL). Based on multivariate linear regression (with log-transformed PbB), covariate-adjusted serum creatinine concentration (mg/dL) was significantly associated with PbB. A 10-fold increase in PbB was associated with an increase of 0.08 mg/dL in co-variate-adjusted serum creatinine (95% CI, 0.02–0.13). This would represent an increase of approximately 7% from the group mean of 1.2 mg/dL. When subjects were stratified by PbB, the association was significant for three blood lead categories: ≤40, ≤25, and ≤10 µg/dL. In subjects who had PbB ≤10 µg/dL, serum creatinine was predicted to increase 0.14 mg/dL per 10-fold increase in PbB

(approximately 11% increase from the unstratified group mean). Covariates included in the models were age and body mass index; hypertension; alcohol consumption and tobacco smoking; and education.

A prospective study included 707 subjects from the Normative Aging Study who had serum creatinine, blood lead and bone lead measurements taken during the period 1991–1995 (baseline), and a subset of the latter group (n=448) for which follow-up serum creatinine measurements made 4–8 years later (Tsaih et al. 2004). Mean age of the study group was 66 years at the time of baseline evaluation and 72 years at follow-up. Mean PbB was 6.5 μg/dL at baseline and 4.5 at follow-up. Baseline bone lead concentrations were: tibia, 21.5 μg/g and patella, 32.4 μg/g and were essentially the same at follow-up. Associations between covariate-adjusted serum creatinine concentrations and lead measures were significant ($p<0.05$) in the study group only for blood lead and follow-up serum creatinine. Covariates included in the models were age and body mass index; diabetes and hypertension; alcohol consumption and tobacco smoking; and education. When stratified by diabetes and hypertension status, significant associations between serum creatinine concentration and lead measures (blood or bone lead) were found in the diabetic (n=26) and hypertensive groups (n=115), suggesting the possibility of interactions between lead exposure, glomerular function, diabetes, or hypertension. An increase in tibia bone lead concentration from the mid-point of the lowest to the highest quintile (9–34 μg/g) was associated with a significantly greater increment in serum creatinine concentration among diabetics (1.08 mg/dL per 10 years) compared to non-diabetics (0.062 mg/dL per 10 years).

Cross-sectional Studies—General Population. The NHANES III collected data on serum creatinine concentrations and PbB on approximately 20,000 U.S. residents during the period 1988–1994. Muntner et al. (2003) analyzed data collected on 15,211 subjects of age 20 years or older. Subjects were stratified into normotensive (n=10,398) or hypertensive categories (n=4,813; ≥140 mmHg systolic pressure or ≥90 mmHg diastolic pressure). Mean PbB was 3.30 μg/dL in the normotensive group and 4.21 μg/dL in the hypertensive group. Associations between PbB and risk of elevated serum creatinine concentrations or chronic renal disease (i.e., depressed glomerular filtration rate) were explored using multivariate regression. Elevated serum creatinine concentration was defined as ≥1.5 or ≥1.3 mg/dL in non-Hispanic Caucasian males and females, respectively; ≥1.6 mg/dL (males) or 1.4 mg/dL (females) for non-Hispanic African Americans; or ≥1.4 mg/dL (males) or ≥1.2 mg/dL (females) for Mexican Americans. Glomerular filtration rate was estimated from serum creatinine concentration using a predictive algorithm (Levey et al. 1999). Chronic renal disease was defined as glomerular filtration rate <60 mL/minute per 1.73 m^2 of body surface area. Covariate-adjusted ORs were estimated for PbB quartiles 2 (2.5–3.8 μg/dL), 3 (3.9–5.9 μg/dL), and 4 (6.0–56.0 μg/dL), relative to the 1st quartile (0.7–2.4 μg/dL). The ORs for elevated

serum creatinine concentration and chronic renal disease, but not in the normotensive group, exceeded unity in all quartiles of PbB and showed a significant upward trend with PbB. Covariate-adjusted ORs for chronic renal disease were: 2nd quartile, 1.44 (95% CI, 1.00–2.09); 3rd quartile, 1.85 (95% CI, 1.32–2.59); and 4th quartile, 2.60 (95% CI, 1.52–4.45). A 2-fold increase in PbB was associated with an OR of 1.43 (95% CI, 1.20–1.72) for elevated serum creatinine concentration or 1.38 (95% CI, 1.15–1.66) of chronic renal disease. Covariates included in the models were age, gender and body mass index; systolic blood pressure; cardiovascular disease and diabetes mellitus; alcohol consumption and cigarette smoking; and household income, marital status, and health insurance. A stronger association between PbB and depressed glomerular filtration rate (i.e., creatinine clearance) also was found in people who have hypertension, compared to normotensive people, in the smaller prospective study (Tsaih et al. 2004).

An analysis of relationships between PbB and renal creatinine clearance was conducted as part of the Belgian Cadmibel Study (Staessen et al. 1992). The Cadmibel Study was a cross-sectional study, originally intended to assess health outcomes from cadmium exposure. Subjects recruited during the period 1985–1989 resided for at least 8 years in one of four areas (two urban, two rural) in Belgium. One of the urban and rural areas had been impacted by emissions from heavy metal smelting and processing. PbB and creatinine clearance measurements were obtained for 965 males (mean age, 48 years) and 1,016 females (mean age, 48 years). Mean PbB was 11.4 µg/dL (range, 2.3–72.5) in males and 7.4 µg/dL (range, 1.7–6.0) in females. Based on multivariate linear regression (with log-transformed PbB), co-variate-adjusted creatinine clearance was significantly associated with PbB in males. A 10-fold increase in PbB was associated with a decrease in creatinine clearance of 13 mL/minute in males and 30 mL/minute in females. This would represent a decrease in creatinine clearance of approximately 13% from the group mean of 99 mL/minute in males, or 38% from the group mean of 80 mL/minute in females. Covariates included in the regression model were age and body mass index; urinary γ-glutamyl-transferase activity; and diuretic therapy. A logistic regression model was applied to the data to examine the relationship between risk of impaired renal function, defined as less than the 5th percentile value for creatinine clearance in subjects who were not taking analgesics or diuretics (<52 mL/minute in males or 48 mL/minute in females). A 10-fold increase in PbB was associated with a covariate-adjusted risk for impaired renal function of 3.76 (95% CI, 1.37–10.4; p=0.01). Covariates included in the logistic model were age and body mass index; urinary γ-glutamyltransferase activity; diabetes mellitus; and analgesic or diuretic therapy.

A cross-sectional study of civil servants in London examined relationships between PbB and serum creatinine concentration (Staessen et al. 1990). Participants included 398 males (mean age, 47.8 years)

and 133 females (mean age, 47.5 years). Mean PbB was 12.4 µg/dL in males and 10.2 µg/dL in females. Serum creatinine concentration was significantly (p=0.04, linear regression with log-transformed PbB) associated with PbB in males, but not in females. The association was no longer significant after excluding two subjects from the analysis who had serum creatinine concentrations exceeding 180 µmol/L (2 mg/dL). The predicted increase in serum creatinine concentration per 25% increase in PbB was 0.6 µmol/L (95% CI, -0.2–1.36). Although several covariates were considered in the analysis of the blood lead concentration data, covariates included in the regression model for serum creatinine concentration were not reported.

The Agency for Toxic Substances and Disease Registry (1995) conducted a cross-sectional analysis of possible associations between lead exposure and serum creatinine concentration or BUN among residents of four NPL sites (Granite City, Illinois; Galena, Kansas; Joplin, Mississippi; Palmerton, Pennsylvania). The study consisted of a target group of NPL site residents (n=1,645) and a comparison group (n=493) that had similar distributions of gender, age, SES, education, and housing age. Geometric mean blood lead concentrations were 4.26 µg/dL (SD±0.71) in the target group and 3.45 µg/dL (SD±0.74) in the comparison group. Multivariate regression analyses (linear and logistic) of subsets of the study group (e.g., age strata) did not reveal significant associations between PbB and either serum creatinine concentration or BUN.

Cross-sectional Studies—Occupational Exposures. As part of a longitudinal study of health outcomes among Korean lead workers, cross-sectional studies of potential associations between biomarkers of lead exposure (PbB, tibia lead, DMSA evoked urinary lead) have been conducted (Weaver et al. 2003a, 2003b, 2005a, 2005b). The cross-sectional study of the first of three longitudinal evaluations included 803 current and former lead workers (age range, 18–65 years; 639 males) and 135 controls (age range, 22–60 years; 124 males), enrolled in the study during the period 1997–1999 (Weaver et al. 2003a, 2005a). Mean PbB of the lead workers was 32 µg/dL (range, 4–86 µg/dL); mean tibia lead was 37 µg/g (range, -7–338 µg/dL). Significant associations were evident in the upper age tertile (>46 years), but not at younger ages, between increasing covariate-adjusted tibia lead and increasing serum creatinine (β, 0.0008 mg/dL per µg/dL; p<0.01) and increasing serum uric acid concentration (β, 0.0036 mg/dL per µg/dL; p=0.04); and between increasing PbB and increasing BUN (β, 0.0615 mg/dL per µg/dL; p<0.01). Covariates included age, gender, body mass index, current/former exposure status, and hypertension. In a subsequent cross-sectional study of the third evaluation of this same study group (n=652), performed during the period 1999–2001, similar age-dependent outcomes were observed (Weaver et al. 2005b). Significant associations between increasing serum creatinine and increasing tibia lead (β, 0.000451;

p=0.04), patella lead (β, 0.000147; p=0.04), or PbB (β, 0.001266; p=0.02) were evident in the upper age tertile (46 years).

Experimental studies in laboratory animals have shown that exposures to lead that result in blood lead concentrations exceeding 50 µg/dL can depress glomerular filtration rate and renal blood flow and produce glomerular sclerosis (Aviv et al. 1980; Khalil-Manesh et al. 1992a, 1992b).

Endocrine Effects. Occupational studies provide evidence for an association between high exposures to lead and changes in thyroid, pituitary, and testicular hormones. There are a number of inconsistencies in the available findings that are related in part to small sample sizes, possible confounding effects by age, tobacco use, and other factors, responses that remained within reference limits, and differences in laboratory methods of hormonal evaluation. Changes in circulating levels of thyroid hormones, particularly serum thyroxine (T_4) and thyroid stimulating hormone (TSH), generally occurred in workers having mean PbB ≥40–60 µg/dL. Altered serum levels of reproductive hormones, particularly follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone, have been observed at PbB ≥30–40 µg/dL. Some data, mainly results of tests of hormonal stimulation tests, suggest that the changes in thyroid and testicular hormones are secondary to effects of lead on pituitary function.

Decreases in serum T_4 were found in studies of workers with very high PbB (Cullen et al. 1984; Robins et al. 1983). Serum T_4 and estimated free thyroxine (EFT_4) were reduced in three of seven men who had symptomatic occupational lead poisoning and a mean PbB of 87.4 µg/dL (range, 66–139 µg/dL) (Cullen et al. 1984). There were no effects on thyroid binding globulin (TBG), total triiodothyronine (T_3), TSH, or TSH response to thyrotrophin releasing hormone (TRH) stimulation. A clinical study similarly found subnormal (low to borderline) serum T_4 and EFT_4 values in 7 of 12 (58%) foundry workers with a mean PbB of 65.8 µg/dL (Robins et al. 1983). However, in a cross-sectional study of 47 men from the same foundry with PbB <50 µg/dL and a mean employment duration of 5.8 years, only 12 (26%) had evidence of reduced T_4 and EFT_4 (Robins et al. 1983). Serum T_3 and TSH levels (only measured in the clinical study) and thyroid binding capacity (TBC, only measured in the cross-sectional study) were normal, and regression analyses showed no clear correlation between T_4 or EFT_4 and PbB. The thyroid effects in these studies (i.e., reduced T_4 with inappropriately low TSH or poor TRH response) are consistent with a primary pituitary or hypothalamic insufficiency. Evaluation of 176 Kenyan male car battery factory and secondary lead smelter workers (mean PbB, 56 µg/dL; mean lead exposure duration 7.6±5.1 years) showed that serum T_4, FT_4, T_3, and TSH levels were similar in subgroups of 93 workers with PbB ≤56 µg/dL and 83 workers with PbB ≥56 µg/dL (Tuppurainen et al. 1988). Regression analysis found no

significant correlations between PbB and any of the thyroid measures. However, there were weak but statistically significant negative correlations between duration of exposure and levels of T_4 and FT_4, and these associations were stronger in the ≥56 µg/dL subgroup.

Several studies found alterations in serum thyroid hormone and TSH in the PbB range of 40–60 µg/dL (Gustafson et al. 1989; López et al. 2000; Singh et al. 2000a). Mean serum levels of T_4 and FT_4 were significantly higher in 75 male lead-battery factory workers with a mean PbB of 50.9 µg/dL (mean work duration 6.1 years) than in 62 unexposed referents (no workplace lead exposure) with a mean PbB of 19.1 µg/dL (López et al. 2000). There were no group differences in serum T_3 and TSH. Regression analyses showed significant positive correlations for serum T_4, FT_4, T_3, and TSH vs. PbB in the range 8–50 µg/dL, and significant negative correlations for T_4 and T_3 vs. PbB in the range 50–98 µg/dL, indicating a drop in circulating hormones at PbBs around 50 µg/dL that is consistent with the results of the Cullen et al. (1984) and Robins et al. (1983) studies cited above. There were no significant associations between PbB or hormone levels vs. time in workplace or age, and all hormone values were within normal reference ranges. Gustafson et al. (1989) measured serum levels of T_3, T_4, and TSH in 25 male lead smelter workers (mean PbB, 39 µg/dL) and 25 matched controls without occupational lead exposure (mean PbB, 4 µg/dL). There were no overall group differences in the three thyroid measures, although serum TSH was significantly increased in the most heavily exposed individuals (mean PbB, >41 µg/dL). Analysis of a subgroup that reported no intake of selenium pills showed that serum T_4 was significantly higher in the exposed workers. Additionally, serum T_4 was significantly increased in a subgroup of 14 workers under the age of 40 (mean PbB, 39 µg/dL). Serum T_4, T_3, and TSH were assessed in 58 male petrol pump workers or automobile mechanics who had a mean PbB of 51.9 µg/dL and mean lead exposure duration of 13 years (Singh et al. 2000a). Comparison with an unexposed control group of 35 men (mean PbB, 9.5 µg/dL) showed no significant differences in T_4 and T_3 levels, although T_3 was significantly lower in a subgroup of 17 workers with a longer mean exposure time (17.5 years) than in 41 workers with shorter exposure (2.4 years). Serum TSH was significantly higher in the exposed workers compared to controls, as well as in a subgroup of 50 workers with higher mean PbB (55.4 µg/dL) than in 8 workers with a lower mean PbB (31.5 µg/dL), although all TSH values remained within the normal laboratory range.

Workers with PbBs of approximately 20–30 µg/dL showed no clear indications of thyroid dysfunction (Dursun and Tutus 1999; Erfurth et al. 2001; Refowitz 1984; Schumacher et al. 1998). Serum T_4, EFT_4, and TSH were assessed in a cross-sectional study of 151 male lead smelter workers that examined dose-response relationships across specifically defined levels of lead exposure (Schumacher et al. 1998). The

mean duration of employment in lead-exposed areas was 4.3 years, the mean current PbB was 24 μg/dL (15% exceeded 40 μg/dL), and the mean PbB for the preceding 10 years was 31 μg/dL (26% exceeded 40 μg/dL). The thyroid hormones were evaluated in relation to four levels of current and 10-year cumulative lead exposure (<15, 14–24, 25–39, and ≥40 μg/dL). Mean levels of T_4, EFT_4, and TSH were similar in all exposure categories and within laboratory normal limits for both current and cumulative exposure. There was no evidence of an exposure response with increasing lead burden, and controlling for age and alcohol consumption did not significantly alter the findings. Erfurth et al. (2001) found that serum concentrations of FT_4, FT_3, and TSH were similar in groups of 62 secondary lead smelter workers (median PbB, 33.2 μg/dL, median exposure time, 8 years) and 26 matched referents with no known occupational exposure to lead (median PbB, 4.1 μg/dL). There were no significant associations between these hormones and PbB, plasma lead, and bone lead levels after adjustment for age. Additionally, there was no difference in TSH response to TRH stimulation in subgroups of 9 exposed workers (median PbB, 35.2 μg/dL) and 11 referents (median PbB, 4.1 μg/dL). There were no adverse changes in thyroid hormones in workers with a mean PbB of 17.1 μg/dL who were exposed to lead for an average of 16.70 years (range, 1–22 years) in a Turkish metal powder-producing factory (Dursun and Tutus 1999). Comparison with 30 subjects from the general population (mean PbB, 2.37 μg/dL) showed that serum levels of T_4, FT_4, and FT_3, but not T_3 or TSH, were statistically significantly increased in the workers. However, all five thyroid measures were within normal reference limits. Refowitz (1984) found no correlation between levels of T_4 or EFT_4 and PbB in 58 secondary copper smelter workers in which the preponderance of PbBs were below 40 μg/dL.

No significant effects of lead on thyroid function have been found in children, but the number and/or quality of the available studies do not allow drawing firm conclusions. 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). PbB, T_4, and T_4 uptake were determined, and sex, race, socioeconomic status, and hemoglobin were also assessed for each child. The PbBs ranged from 2.0 to 77 μg/dL, with a mean of 25 μg/dL. Forty-four percent of the children had moderately elevated lead levels (>24 μg/dL). Linear regression analysis revealed that there was no association between PbB and either T_4 or FT_4. The results of this study are consistent with the findings of a small study of 12 children (2–5 years old) from the Omaha Lead and Poison Prevention Program with PbBs in the range of 41–72 μg/dL (Huseman et al. 1992). The authors found that basal TSH, T_4, T_3, and prolactin were within normal ranges. Also, TSH and prolactin responses to TRH, and cortisol responses to insulin were not altered by lead. 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 (<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 was also associated with a lower mean insulin-like growth factor I. A study of male adolescents in Turkey reported that 42 subjects who worked at auto repair workshops and had a mean PbB of 7.3 µg/dL (SD±2.92 µg/dL) had a significantly lower ($p<0.05$) serum level of FT4 (1.12 ng/mL) compared to 55 control subjects (1.02 ng/mL) with a mean PbB of 2.1 µg/dL (SD±1.24 µg/dL) (Dundar et al. 2006). There were no significant effects on serum FT3 or TSH levels or in thyroid volume. Based on the small difference in FT4 values between exposed and unexposed subjects, the lack of increase in TSH, and the fact that many other chemicals normally present at auto repair workshops could have influenced the results, the significance of these findings is unknown.

Effects of occupational exposure to lead on pituitary gonadotrophins and testicular hormones were investigated in male workers (see also Section 3.2.5, Reproductive Effects). Changes in serum FSH, LH, and testosterone were found in several studies of highly exposed workers, but there are no clear patterns of response. The preponderance of evidence is consistent with an indirect effect(s) of lead on the hypothalamic-pituitary axis (i.e., a disruption of gonadotrophin secretions), although direct effects on testicular hormonal production are possible. Plasma concentrations of FSH, LH, testosterone, and prolactin were measured in a study of 122 male lead battery factory workers with a mean current PbB of 35.2 µg/dL and mean exposure duration of 6 years (Ng et al. 1991). Levels of FSH and LH were significantly increased compared to a control group of 49 nonexposed workers (8.3 µg/dL), and concentrations of these hormones increased with increasing PbB in the range of 10–40 µg/dL. Age was not a confounding factor, although duration of exposure affected the results. Workers exposed for <10 years had significantly increased LH and FSH and normal testosterone and prolactin levels, whereas those exposed for ≥10 years had increased testosterone and normal LH, FSH, and prolactin. Rodamilans et al. (1988) assessed serum levels of LH, FSH, testosterone, and steroid binding globulin (SBG) in 23 male lead smelter workers with PbB in the range of 60–80 µg/dL. Comparison with an unexposed group of 20 men (PbB 17 µg/dL) showed that serum LH was significantly increased in the workers and that the magnitude of the effect did not increase with duration of exposure. A significantly lower free testosterone index (testosterone/SBG ratio) in the workers exposed for 1–5 years and significant changes in serum testosterone (lower), SGB (higher), and free testosterone index (lower) in the workers exposed for >5 years indicated an exposure duration-related effect on serum testosterone.

Other studies of male workers have found different results. Erfurth et al. (2001) found no significant differences in basal serum levels of FSH, LH, prolactin, testosterone, sex hormone binding globulin, and cortisol in groups of 11 lead male workers (median PbB, 35.2 µg/dL) and 9 matched referents (median PbB, 4.1 µg/dL), although there was a tendency toward lower serum FSH concentrations in the exposed group. Additionally, measurements of serum FSH, LH, and prolactin after administration of gonadotrophin-releasing hormone (GRH) showed that the level of stimulated FSH was significantly lower in the workers. None of the basal or stimulated hormone levels correlated with lead exposure indices (blood lead, plasma lead, or bone lead) or age. Gustafson et al. (1989) found that plasma FSH, plasma LH, and serum cortisol levels were lower in male workers (mean PbB, 39 µg/dL) than in unexposed controls (mean PbB, 4 µg/dL); however, all hormone values were within normal reference limits. Serum FSH and LH values were similar in 98 male lead acid battery workers with a mean PbB of 51 of µg/dL and a group of 85 nonoccupationally exposed subjects (mean PbB, 20.9 µg/dL) (Gennart et al. 1992a), although the high PbB in the comparison group might have obscured detection of an effect. Cullen et al. (1984) found increased serum FSH and LH and borderline low serum testosterone levels in one of seven men with symptomatic occupational lead poisoning and a mean PbB of 87.4 µg/dL. Although serum testosterone concentration was normal in most of these patients, five had defects in spermatogenesis and six had subnormal glucocorticoid production. Serum testosterone levels were significantly lower in groups of male workers with lead poisoning (n=6, mean PbB, 38.7 µg/dL) and lead exposure (n=4, mean PbB, 29.0 µg/dL) than in an unexposed control group (n=9, mean PbB 16.1 µg/dL), but testosterone-estradiol-binding globulin capacity and serum levels of estradiol, LH, FSH, and prolactin were normal (Braunstein et al. 1978). Both lead groups had appropriate responses for serum testosterone and FSH to stimulation by human chorionic gonadotrophin (HCG) and clomiphene, and serum FSH to stimulation by gonadotrophin releasing hormone (GRH) and clomiphene citrate. The lead exposed group also had a normal LH response to challenge by GRH and clomiphene citrate, although the LH response was suppressed in the lead poisoned group. Both lead groups had reduced estradiol response to stimulation by clomiphene citrate, although there was no effect following stimulation by HCG. Testicular biopsies performed on the two most heavily exposed men showed oligospermia and testicular lesions. Further information regarding effects of lead on sex hormone levels in humans and animals can be found in Section 3.2.5.

Information is also available on the effects of lead exposure on serum erythropoietin (EPO) concentration. EPO is a glycoprotein hormone that regulates both steady-state and accelerated erythrocyte production. More than 90% of EPO is produced in the proximal renal tubules. Serum EPO was evaluated in a group of women from the Yugoslavia Prospective Study (see Section 3.2.4 for a detailed description of the Yugoslavia Prospective Study) in mid-pregnancy (n=5) and at time of delivery (n=48) (Graziano et al.

1991). Analysis of the variance showed that women with higher PbB had inappropriately low levels of EPO both at mid-pregnancy and at delivery. Graziano et al. (1991) speculated that lead may interfere with the mechanism of EPO biosynthesis, which appears to begin with increased calcium entry into the renal cells. In a study of lead workers, serum EPO levels from two groups of 28 exposed workers were significantly lower than in 113 control subjects (Romeo et al. 1996). Mean PbBs in the two exposed groups and in the controls were 38.3, 65.1, and 10.4 µg/dL, respectively. However, there was no correlation between PbB and EPO in any group. Hemoglobin levels were not affected by lead and were comparable among the three groups. In an additional study of male lead workers (n=20) with and without anemia, those with PbBs ≥60 µg/dL showed a significant reduction in erythroid progenitor cells and in granulocyte/macrophage progenitor cells (Osterode et al. 1999). However, EPO was in the normal range and did not increase in the presence of lead-induced anemia. Osterode et al. (1999) suggested that lead-induced kidney toxicity might be the reason why EPO was not adequately generated at higher PbB.

Ocular Effects. Lead is known to affect visual evoked potentials in adults and children (see Section 3.2.4 and review by Otto and Fox [1993]), but less is known regarding effects of lead on other eye structures. Recently, Schaumberg et al. (2004) examined the relationship of cumulative lead exposure with the development of cataracts in a group of 642 participants in the Normative Aging Study. Lead exposure was assessed by measuring PbB (mean, 5 µg/dL; range, 0–35 µg/dL) and lead in the tibia (mean, 20 ppm; range, 0–126 ppm) and patella (mean, 29 ppm; range, 0–165 ppm). The mean age of the subjects was 69 years (range, 60–93 years). A total of 122 cases of cataract were found. After controlling for age, tibia lead, but not patella lead, was a significant predictor of cataract. Also, PbB was not associated with increased risk of developing cataracts. Schaumberg et al. (2004) suggested that lead might be disrupting the lens redox status by inducing oxidative damage to lens epithelial cells. Changes consistent with lens opacity also were observed in Fisher 344 rats exposed to 2,000 ppm lead in the drinking water for 5 weeks, which produced a mean PbB of approximately 30 µg/dL (Neal et al. 2005). Examination of two-dimensional protein spot patterns of the rats' lenses showed significant alterations in the protein expression profile of both αA- and βA4-crystallins, alterations of which may decrease lens clarity through increased light scattering. The mechanism for this effect has not been elucidated.

In their review on lead effects on visual function, Otto and Fox (1993) mention that earlier studies reported alterations of the electroretinogram (ERG) in lead workers. Rothenberg et al. (2002a) reported alterations in scotopic (rod-mediated) retinal function in a group of 45 children (7–10 years old) participants in the Mexico City Lead Study (Rothenberg et al. 2002a). These alterations, consisting of increased a- and b-waves, appeared to be a new form of rod dysfunction and were associated with

maternal blood lead levels measured during the first trimester of pregnancy; the threshold for the effect was 10.5 µg/dL. Alterations in rod function, evidenced by the appearance of central scotoma, also had been reported earlier in lead workers with moderate PbB (mean, 47 µg/dL) (Cavalleri et al. 1982). Changes in ERG components also have been reported in rats (Fox and Chu 1988; Fox and Farber 1988; Fox and Katz 1992; Fox and Rubinstein 1989) and monkeys exposed during development (Bushnell et al. 1977; Kohler et al. 1997; Lilienthal et al. 1988, 1994). Tests conducted in monkeys >2 years after cessation of life exposure to lead revealed alterations in the ERG under scotopic conditions similar to those recorded during lead exposure, and at a time when PbB was below 10 µg/dL (Lilienthal et al. 1994). Since the alteration could be reproduced by treatment with dopamine antagonists, Lilienthal et al. (1994) suggested that the observed effects may be mediated by a permanent change of dopamine function. The series of studies from Fox and coworkers in the rat showed that low-level lead exposure during postnatal development has a detrimental effect on the rods of the retina, but not on cones. They also 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 (Fox et al. 1997). Using a preparation of rat retina *in vitro*, Fox and coworkers demonstrated that rod mitochondria are the target site for calcium and lead and that these ions bind to the internal metal binding site of the mitochondrial permeability transition pore, which initiates a cascade of apoptosis in rods (He et al. 2000).

Other Systemic Effects. 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 PbBs 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 was >62 µg/dL. In addition, children with PbB >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 ranging from 12 to 120 µg/dL, with no change in the slope of the line at levels <30 µg/dL (Mahaffey et al. 1982).

Results obtained by Koo et al. (1991) indicate that low to moderate lead exposure (average lifetime PbB between 4.9 and 23.6 µg/dL, geometric mean, 9.8 µg/dL) of young children (n=105) with adequate nutritional status, particularly with respect to calcium, phosphorus, and vitamin D, had no effect on vitamin D metabolism, calcium and phosphorus homeostasis, or bone mineral content. The authors attributed the difference in results from those other studies to the fact that the children in their study had lower PbB (only 5 children had PbB >60 µg/dL and all 105 children had average lifetime PbB <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 only be apparent in children with chronic nutritional deficiency and chronically elevated PbB. Similar conclusions were reached by IPCS (1995) after review of the epidemiological data.

In general, data in animals support the findings in humans. For example, 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 (≥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.

3.2.3 Immunological and Lymphoreticular Effects

Numerous studies have examined the effects of lead exposure on immunological parameters in lead workers and a smaller number of studies provide information on effects in members of the general population, including children. The results although mixed, give some indication that lead may have an effect on the cellular component of the immune system, while the humoral component is relatively unaffected. However, it should be noted that the clinical significance of these relationships is as yet unknown.

Workers exposed occupationally for 4–30 years, and whose PbB at the time of testing ranged from 25 to 53 µg/dL (mean, 38.4 µg/dL), had serum concentrations of IgG, IgA, and IgM not significantly different from unexposed controls whose PbB at the time of testing ranged from 8 to 17 µg/dL (mean, 11.8 µg/dL) (Kimber et al. 1986). Alomran and Shleamoon (1988) also reported nonsignificant alterations in serum IgG and IgA levels in 39 workers exposed to lead oxides with a mean PbB of 64 µg/dL compared to 19 unexposed subjects (PbB not provided). Another study found no alterations in serum IgA and IgM levels among 25 workers with a mean PbB of 74.8 µg/dL (range, 38–100 µg/dL) compared to 16.7 µg/dL (range, 11–30 µg/dL) among 25 controls; however, IgG was significantly reduced among the workers (Basaran and Ündeger 2000; Ündeger et al. 1996). A study of 145 lead-exposed male workers from a large secondary lead smelter in the United States with a median PbB of 39 µg/dL (range, 25–55 µg/dL) also found no significant differences in serum immunoglobulin levels between the workers and a group of 84 unexposed workers with a mean PbB of <2 µg/dL (range, 2–12 µg/dL) (Pinkerton et al. 1998). Ewers et al. (1982) reported that lead workers with PbB of 21–90 µg/dL (median, 59 µg/dL) had more colds and influenza infections per year and had a significant suppression of serum IgM levels relative to a comparison group (median PbB, 11.7 µg/dL); neither serum IgA or IgG levels in workers were significantly different than in the comparison group. However, salivary IgA levels were significantly lower in the workers than in the control group. Secretory IgA is a major factor in the defense against respiratory and gastrointestinal infections (Koller 1985). A study of 606 Korean workers found that mean serum IgE levels were positively related to PbB in the range of <10–≥30 µg/dL (Heo et al. 2004).

Alterations in response to T-cell mitogens also have been reported in lead workers. Mishra et al. (2003) studied three groups of workers (n=84) who had mean PbBs of 6.5, 17.8, and 128 µg/dL and found that lymphocyte proliferation to phytohemagglutinin (PHA) was inhibited relative to a control group; natural killer (NK) cell activity was unaffected. The lymphocytes from the workers studied by Alomran and Shleamoon (1988) (mean PbB, 64 µg/dL) also were significantly less responsive to stimulation by PHA and concanavalin A (con A) than those from the controls (PbB not provided), and the severity of the depression was related to the duration of exposure. Impaired response to T-cell mitogens was also reported among a group of 51 firearm instructors (Fischbein et al. 1993). Fifteen of the 51 firearm instructors had PbBs ≥25 µg/dL (mean 31.4 µg/dL), whereas the rest had a mean PbB of 14.6 µg/dL. In contrast, Kimber et al. (1986) reported that responses to PHA and NK cell activity were not altered in their study of workers whose mean PbB was 34.8 µg/dL, compared with an unexposed group with a mean PbB of 11.8 µg/dL. Pinkerton et al. (1998) found no alterations in lymphoproliferative responses to tetanus toxoid or in NK cell activity in workers with a median PbB of 39 µg/dL. It should be noted,

however, that firearm instructors are likely to be exposed to a number of metal haptens, such as nickel and antimony.

Changes in T-cell subpopulations also have been reported. Ündeger et al. (1996) and Basaran and Ündeger (2000) described a significant decrease in the number of $CD4^+$ cells and C3 and C4 complement levels in workers with a mean PbB of 74.8 µg/dL. A significant decrease in percentage and number of $CD3^+$ and $CD4^+$ cells also was observed in the study of firearm instructors, but other cell types including $CD8^+$, B-lymphocytes, or NK cells were not significantly altered relative to controls (Fischbein et al. 1993). Pinkerton et al. (1998) 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, but reported that the percentage and number of $CD4^+/CD45RA^+$ cells was positively associated with cumulative lead exposure. A study of 71 male workers engaged in the manufacturing of lead stearate who had a mean PbB of 19 µg/dL (range, 7–50 µg/dL) did not find significant differences in the number or percentages of $CD4^+$ or $CD3^+$ cells between the lead-exposed workers and a control group (PbB not measured) of 28 workers with no known occupational exposure to lead (Sata et al. 1998). 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 to controls. Also, there was a significant correlation between the percentage of $CD3^+CD45RA^+$ cells and PbBs in the exposed workers. At the time of the study, no subject had any signs or symptoms indicative of infection.

A small study of 10 occupationally-exposed workers whose mean PbB was 33 µg/dL reported that chemotaxis of polymorphonuclear leukocytes (PMN), stimulated through a specific membrane receptor, was impaired, compared to a group of 10 unexposed subjects with a mean PbB of 12.6 µg/dL (Valentino et al. 1991). The investigators suggested that the reduction of chemotaxis might be partially due to a lead-related modification of plasma membrane lipids, because PMN locomotion is influenced by fatty acids.

The data available on the immunologic effects of lead exposure on children are sparse. In a comparison of 12 preschool children having a mean PbB of 45.3 µg/dL (range, 41–51 µg/dL) and elevated FEP with 7 preschool children with a mean PbB of 22.6 µg/dL (range, 14–30 µg/dL), it was found that there were no differences between groups with respect to complement levels, immunoglobulin levels (IgM, IgG, IgA), or antitoxoid titers following booster immunization with tetanus toxoid (Reigart and Graher 1976). The small number of children and the relatively high PbB of the control group, as judged by current views, limit the conclusions that can be drawn from this report. Lutz et al. (1999) conducted a survey of the immune system's function in a cohort of 279 children aged 9 months to 6 years, with PbB ranging

from 1 to 45 µg/dL. Exposure was due primarily to lead-based paint. Of the comprehensive number of parameters of cellular and humoral immunity evaluated, only the serum IgE levels showed a statistically significant relationship with PbB, as PbB increased so did IgE levels. Variables controlled for in this study included age, race, gender, nutrition, and socioeconomic level. The assessment of IgE levels in this and other studies is important because IgE is the primary mediator for type-I hypersensitivity and is involved in various allergic diseases such as asthma. Some investigators have suggested that lead may be a risk factor for childhood asthma (Dietert et al. 2002), although recently, Joseph et al. (2005) conducted a study of 4,634 children screened for lead from 1995 to 1998 and found that PbB was less a predictor of asthma than was race and did not affect the relationship of race to prevalent or incident asthma. IgE levels were not monitored in the study.

A study of Chinese children (3–6 years old) also examined the association between PbB and serum IgG, IgM, and IgE levels (Sun et al. 2003). The cohort consisted of 38 children with PbB ≥10 µg/dL (high-lead group) and 35 children with PbB <10 µg/dL (controls). No significant association between immunoglobulins and PbB was found for the entire group (n=73). However, when the cohort was divided by sex, IgG and IgM were significantly lower and IgE was significantly higher in high-dose females (n=16) than in control females (n=17); no such relationship was seen among males. A study of 374 French mother-infant pairs reported a significant correlation ($p<0.001$) between infant hair level and cord blood IgE levels (Annesi-Maesano et al. 2003). In this cohort, mean PbB was relatively high, 96 µg/dL (SD, 58 µg/dL) in the mothers and 67 µg/dL (SD, 48 µg/dL) in cord blood. No significant association was found between placental lead level or cord PbB and IgE levels. Further suggestive evidence for an association between IgE and lead burden is provided by a study of 331 German children (7–8 years of age) with a geometric mean PbB of 2.7 µg/dL, which found a significant association ($p<0.05$) between PbB and increased serum IgE levels (Karmaus et al. 2005). Analysis of stratified data showed that the highest IgE levels were observed in the children with PbB in the range between 2.8–3.4 and >3.4 µg/dL. No significant associations were seen between PbB and serum levels of IgA, IgG, or IgM (Karmaus et al. 2005).

A small study of 70 Chinese children (3–6 years old) reported that 35 of them with a mean PbB of 14.1 µg/dL (SD, 4.0 µg/dL) had a significantly lower ($p<0.01$) serum levels of CD4+ cells than 35 children with a mean PbB of 6.4 µg/dL (SD, 1.3 µg/dL) (Li et al. 2005). There were no significant differences between the two groups regarding B, CD3+, CD8+, or NK cells. Sarasua et al. (2000) conducted a much bigger study of 2,041 children and adults who lived in areas with elevated soil levels of cadmium and lead (n=1,561) or in comparison communities (n=480) in the United States. Mean blood

lead levels were 7 µg/dL for participants aged 6–35 months; 6 µg/dL for participants aged 36–71 months; 4 µg/dL for participants aged 6–15 years, and 4.3 µg/dL for participants aged 16–75 years. Parameters monitored included IgA, IgG, and IgM, and peripheral blood lymphocyte phenotypes (T cells B cells, NK cells, and CD4/CD8 subsets). The results of the multivariate analyses showed no significant differences in any of the immune marker distributions attributed to lead for subjects over 3 years of age. However, in children under 3 years, there were small but significant associations between increased PbB, particularly in those over 15 µg/dL, and increases in IgA, IgG, IgM, and circulating B-lymphocytes.

Many studies have been published on the effects of lead on immune parameters in animals. Developing organisms appear to be more sensitive than adult animals and a number of studies have been designed to determine critical windows of vulnerability during development, including fetal development. Studies conducted in the late 1970s showed that prenatal and postnatal exposure of rats to lead leading to a PbB of approximately 29 µg/dL induced several alterations in the offspring tested at 35–45 days of age, including 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 DTH, and decreased thymus weights as compared with controls (Faith et al. 1979; Luster et al. 1978). In a later study, exposure of mice to lead through gestation and lactation resulted in reduced humoral immunity in the pups tested at 8 weeks of age (Talcott and Koller 1983). The DTH response was reduced but the difference with controls was not statistically significant. Blood lead levels were not available in this study. Miller et al. (1998) compared responses of the immune system between fetal and adult exposures. Exposure of pregnant rats to lead acetate in the drinking water during breeding and pregnancy resulted in PbBs of up to 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 was approximately 12 µg/dL in the dams and 0.68–2.63 µg/dL in offspring. Results from a comprehensive battery of tests showed no significant effects in lead-exposed dams. However, alterations were observed in the offspring and included decreased DTH response, altered cytokine production, and elevated serum IgE. Also, total leukocyte counts were significantly decreased, 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 when PbB had returned to the normal range. Similar results were reported in a study in mice in which immunotoxic changes were found at PbB <20 µg/dL (Snyder et al. 2000). Altered DTH responses were seen in adult mice at PbBs of 87 µg/dL but not 49 µg/dL (McCabe et al. 1999) providing further evidence of increased sensitivity in developing animals compared to adults. More recent studies by Dietert and coworkers have shown that gestational exposure to lead resulting in PbB of approximately 38 µg/dL has a greater immunotoxic effect

in female offspring than in male offspring (Bunn et al. 2001a) and that the embryo is more sensitive if exposure occurs late in gestation (gestation day [Gd] 15–21) than earlier during gestation (Gd 3–9) (Bunn et al. 2001b).

While many responses of the immune system observed in humans can be reproduced in experimental animals, recent observations from studies of perinatal exposure of animals suggest that caution should be exercised when extrapolating from animals to humans, since the immune functions depend on animal species, gender, and specially, developmental stage.

3.2.4 Neurological Effects

Neurological Effects 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.

Severe lead encephalopathy is generally not observed in adults except at extremely high PbBs (e.g., 460 µg/dL [Kehoe 1961]). 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 PbBs that range from approximately 50 to >300 µg/dL, but the data are somewhat ambiguous.

Neurobehavioral Effects in Adults. 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 PbBs that range from approximately 40 to 120 µg/dL following acute-, intermediate-, and chronic-duration occupational exposure (Awad El Karim et al. 1986; Baker et al. 1979, 1983; Campara et al. 1984; Haenninen et al. 1979; Holness and Nethercott 1988; Lucchini et al. 2000; Marino et al. 1989; Matte et al. 1989; Pagliuca et al. 1990; Pasternak et al. 1989; Pollock and Ibels 1986; Rosenman et al. 2003; Schneitzer et al. 1990; Zimmerman-Tanselia et al. 1983).

In addition to the findings mentioned above, numerous studies have reported neuropsychological effects in lead workers. PbB in these studies ranged between 40 and 80 µg/dL. For instance, Parkinson et al. (1986) reported that lead workers exhibited greater levels of conflict in interpersonal relationships compared with unexposed workers. In another study, lead workers (45–60 µg/dL) performed much worse than workers with lower PbB on neurobehavioral tests, with general performance on cognitive and visual-motor coordination tasks and verbal reasoning ability most markedly impaired (Campara et al. 1984). Disturbances in oculomotor function (saccadic eye movements) in lead workers with mean PbB of 57–61 µg/dL were reported in a study by Baloh et al. (1979) and a 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, 60.5 µg/dL) (NIOSH 1974). Most of the workers had been exposed between 5 and 20 years. A similar study, however, reported no differences in arousal, reaction time, or grip strength between a reference group (mean PbB, 28 µg/dL) and workers who had been exposed to lead for 12±9.5 years (mean PbB, 61 µg/dL) (Milburn et al. 1976); however, the relatively high mean PbB in the referents may have obscured the results. 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 PbBs 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). Baker et al. (1983) reported impaired verbal concept formation, memory, and visual/motor performance among workers with PbB >40 µg/dL. 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 of 42 µg/dL (Maizlish et al. 1995). The authors observed 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 study of 91 workers divided into three groups based on PbBs (<20, 21–40, and 41–80 µg/dL) noted that 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 (Stollery et al. 1989, 1991). In general, the magnitude of the impairment correlated with PbB. The impairment of serial reaction time was the best predictor of PbB. 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 of 70 workers 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 (Stollery 1996). A

study of 427 Canadian lead workers whose mean current PbB was 27.5 µg/dL, and mean duration of employment was 17.7 years examined the correlation between short- and long-term measures of exposure to lead and performance on neuropsychological tests (Lindgren et al. 1996). Tasks that tested primarily visuomotor skills were significantly associated with a cumulative dose-estimate. Lindgren et al. (1996) indicated that the lack of an association between current blood lead or a TWA and neuropsychological performance was not necessarily inconsistent with other studies that found such an association since in their study the current mean PbBs were lower than in other studies. Current PbB as well as a TWA may have lacked the sensitivity to detect the decrement in performance.

Ehle and McKee (1990) reviewed the methodology and conclusions of 14 published reports to determine if any consensus regarding neurobehavioral effects of low-level lead exposure in adults could be reached. A PbB of 60 µg/dL was set as the upper limit of exposure. The investigators concluded that "the methodologies in the studies reviewed were so varied and the cultures in which the studies were conducted so diverse that it is impossible to generalize across findings." However, Ehle and McKee (1990) found some evidence that increased irritability and fatigue may lead to interpersonal problems. They also found suggestive evidence for subtle changes in the ability to process information quickly and for impaired ability to input and integrate novel information and to store this information in short-term memory. Balbus-Kornfeld et al. (1995) reviewed 21 studies for evidence that cumulative exposure to lead is associated with decreased performance in neurobehavioral tests in adults. Only three studies used a measure of cumulative exposure and two others used duration of exposure as a surrogate for cumulative exposure. The conclusion of the analysis was that "the current (at the time of the Balbus-Kornfeld study) scientific literature provides inadequate evidence to conclude whether or not cumulative exposure to or absorption of lead adversely affects performance in neurobehavioral tests in adults."

More recent studies of lead workers have reported significant associations between longitudinal decrements in cognitive function and past high PbB (Bleecker et al. 2005; Chen et al. 2005; Hänninen et al. 1998; Lindgren et al. 2003) and past high tibial lead (Schwartz et al. 2000b; Stewart et al. 1999). In the Lindgren et al. (2003) study, results of five neuropsychological measures showed that verbal memory was significantly better in a group with past high exposure followed by lower exposure than in a group with continuous high exposure, suggesting that reversibility of function may occur when PbB is maintained below 40 µg/dL. A small study of 27 Chinese lead workers also reported improvement in neurobehavioral performance over a period of 4 years during which the mean PbB was reduced from 26 to 8 µg/dL (Chuang et al. 2005). From a battery of 10 neurobehavioral tests, finger tapping, pattern comparison reaction time, and memory (visual patterns) significantly improved during the study period.

Past high tibia lead (mean peak was 24 ppm), as a measure of cumulative lead dose, also was found significantly related to smaller total brain volume, frontal and total gray matter volume, and parietal white matter volume in 532 former organolead workers (Stewart et al. 2006). Of nine smaller regions of interest, higher tibia lead was associated with reduced volume of the cingulated gyrus and insula. Changes in brain morphology were assessed by brain MRI. Potential confounders assessed were age, systolic and diastolic blood pressure, smoking history, ApoE genotype, education, alcohol consumption, depression status, and race. Previous studies of this cohort had found tibia lead associated with a decline in cognitive function (Schwartz et al. 2000b; Stewart et al. 1999).

Lucchini et al. (2000) reported that in a group of 66 workers with a mean current PbB of 27 µg/dL (range, 6–61 µg/dL) and exposure of 11 years, current, but not cumulative, exposure was associated with impaired visual contrast sensitivity; results from neurobehavioral tests were unaffected. Barth et al. (2002) also found in a group of 47 workers a significant correlation between current exposure (mean PbB, 31 µg/dL, range, 11–62 µg/dL) and cognitive deficits, particularly visuo-spatial abilities and executive functions related to the prefrontal cortex; however, no correlation was found between cumulative exposure measures and cognitive parameters. Recently, Schwartz et al. (2005) reported on a longitudinal study of the effects of lead on neurobehavioral test scores using both PbB and tibia lead as measures of dose. The cohort comprised 576 former and current lead workers who were evaluated from 1997 to 2001. At baseline (Schwartz et al. 2001), mean PbB was 32 µg/dL (SD±15 µg/dL) and mean tibia lead was 37 ppm (SD±40 ppm). In the recent publication, the investigators developed regression models that separated recent from cumulative dose, acute from chronic effects, and cross-sectional from longitudinal relations. The results showed consistent associations of both PbB and tibia lead with current neurobehavioral test scores and also with declines in test scores over time; the associations with PbB were stronger than those with tibia lead. The stronger associations were mainly in executive abilities, manual dexterity, and peripheral vibration threshold; the magnitude across an interquartile range of exposure was equivalent to 1–5 years of aging. Schwartz et al. (2005) pointed out that: "the significant measurement error, especially for tibia lead and change measures, and the relatively short follow-up interval, could obscure the relations between lead dose and changes in test scores" and that this knowledge must be factored into their inferences about the likely health effects.

Meyer-Baron and Seeber (2000) did a meta-analysis to determine the size of performance effects caused by exposure to inorganic lead that translated into PbBs <70 µg/dL. A total of 22 studies that met some minimum requirements were considered, and of these, 12 studies provided data to analyze the results of 13 tests. The mean PbB in the lead workers ranged from 31 to 52 µg/dL and those of the controls ranged

from 6 to 20 µg/dL. Statistically significant effects were observed for the Block Design, Logical Memory, and Santa Ana (dominant hand) tests. The first two tests indicate impairments of central information processing, particularly for the functions visuo-spatial organization and short-term verbal memory; Santa Ana tests manual dexterity. Meyer-Baron and Seeber (2000) stated that the extent of decreased performance was comparable to changes of performance that can be expected during aging of up to 20 years. Goodman et al. (2002) conducted a meta-analysis of 22 studies that met inclusion criteria. The PbB among the study subjects ranged from 24 to 63 µg/dL for exposed and from 0 to 28 µg/dL for unexposed workers. Only 2 tests (Digit Symbol and D2) out of 22 neurobehavioral tests analyzed showed a significant effect between exposed and unexposed workers. Digit Symbol evaluated motor persistence, sustained attention, response-speed, and visuo-motor coordination, whereas D2 requires visual selectivity at a fast speed on a repetitive motor response task. The tests that were found altered in the Meyer-Baron and Seeber (2000) study were not significantly affected in the analysis of Goodman et al. (2002). The latter investigators concluded that the available data are inconclusive and unable to provide adequate information on the neurobehavioral effects of moderate PbB.

In summary, in studies where adults were exposed occupationally to lead, a number of neurobehavioral parameters were reportedly affected. Although as Goodman et al. (2002) pointed out, the lack of true measures of pre-morbid state, observer bias, and publication bias affect the overall assessment, the preponderance of the evidence indicates that lead is associated with neurobehavioral impairment in adult workers at PbBs below 70 µg/dL.

Krieg et al. (2005) used data from the NHANES III to assess the relationship between PbB in adults and performance on the three computerized neurobehavioral tests included in the survey: simple reaction time, symbol-digit substitution, and serial-digit learning. The age of the participants ranged from 20 to 59 years old and a total of 4,937 completed all three tests. The study also evaluated 26 previously published cross-sectional occupational studies conducted in various countries that used the same neurobehavioral tests included in the survey. Potential confounders evaluated in the analysis included sex, age, education, family income, race/ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase. In the NHANES III, the PbB of those taking the neurobehavioral tests ranged from 0.7 to 42 µg/dL and the geometric and arithmetic means were 2.5 and 3.3 µg/dL, respectively. The results showed no statistically significant relationships between PbB and neurobehavioral test performance after adjustment for confounders. In the occupational studies, the mean PbB in the controls was 11.4 µg/dL (range, 3.7–20.4 µg/dL), whereas the mean in the exposed groups was 41.1 µg/dL (range, 24.0–72 µg/dL). The groups exposed to lead in the occupational studies consistently

performed worse than control groups on the simple reaction time and digit-symbol substitution tests. Some possible explanations for the lack of association between PbB and neurobehavioral scores in the survey mentioned by Krieg et al. (2005) include lack of toxicity of lead in adults at the levels investigated, a sample size or study design that did not allow enough precision to detect a relationship, or neurobehavioral tests that are not sensitive to the toxicity of lead at the levels investigated.

The effects of lead exposure on neurobehavioral parameters in nonoccupational cohorts of older persons also have been evaluated. Muldoon et al. (1996) conducted a wide range of cognitive tests designed to assess memory, language, visuo-spatial 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 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. PbB showed a significant inverse association with performance only among the rural dwellers. After adjusting for age, education, and tobacco and alcohol consumption, women with PbB ≥8 µg/dL performed significantly worse in tests of psychomotor speed, manual dexterity, sustained attention, and mental flexibility than women with PbB ≤3 µg/dL. Similar results were found for reaction time tests after further adjusting for history of diabetes and/or arthritis. A similar study was conducted in a cohort of 141 men participants in the Normative Aging Study (Payton et al. 1998). In this study, in addition to PbBs, lead in bone (tibia and patella) was also measured. The mean PbB 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 PbB 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. 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.

A more recent study of 526 participants of the Normative Aging Study with a mean age of 67.1 years and mean PbB of 6.3 µg/dL reported that patellar lead was significantly associated with psychiatric symptoms such as anxiety, depression, and phobic anxiety (Rhodes et al. 2003). In an additional study of Normative Aging Study participants (mean PbB, 4.5 µg/dL; mean patella Pb, 29.5 ppm), it was found that both bone

and blood lead were associated with poor test performance (Weisskopf et al. 2004; Wright et al. 2003c). According to the investigators, these findings are consistent with the theory that bone lead chronically remobilizes into blood, thus accelerating cognitive decline. In yet an additional study, Shih et al. (2006) reported that in a group of 985 of sociodemographically diverse urban-dwelling adults in the United States (mean age, 59.4 years) higher tibia lead levels were consistently associated with worse performance in tests of cognitive function after adjusting for confounders; no such association was found with PbB. Mean tibia lead was 18.7 ppm (SD±11.2 ppm) and mean PbB was 3.5 µg/dL (SD±2.2 µg/dL). An increase in one interquantil range of tibia lead was equivalent to 2.2–6.1 more years of age across the tests conducted, the average tibia lead effects was 36% of the age effect. Shih et al. (2006) suggested that, in the population studied, a proportion of what was termed normal age-related decrements in cognitive function may be attributable to neurotoxicants such as lead.

Peripheral Physiological Effects 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. Representative studies are summarized below. A prospective occupational study found decreased nerve conduction velocities (NCVs) 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); PbBs ranged from 30 to 48 µg/dL. 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 and whose PbBs ranged from 60 to 80 µg/dL. 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). Ishida et al. (1996) found no significant association between PbBs of 2.1–69.5 µg/dL and median nerve conduction velocity among a group of 58 male and 70 female ceramic painters.

In cross-sectional occupational studies, significant decreases in NCVs were observed in fibular (motor) and sural (sensory) nerves as a function of PbB 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 PbBs >70 µg/dL (Triebig et al. 1984). Duration of exposure and number of lead-

exposed workers in these two 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 of 48.3 µg/dL were improved significantly when PbB was lowered through $CaNa_2EDTA$ chelation therapy. A study by Muijser et al. (1987) presented evidence of improvement of motor NCV after cessation of exposure. After a 5-month exposure, the PbB was 82.5 µg/dL and decreased to 29 µg/dL 15 months after the termination of exposure, at which time, NCVs were not different from a control group.

The results of these studies indicate that NCV effects occur in adults at PbBs <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 PbBs <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. 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 32 studies of effects of lead exposure on NCV (Davis and Svendsgaard 1990).

More recent studies also have 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 PbB were performed every 6 months over a 3-year period. The geometric mean PbB for the exposed workers at the beginning of the study was 36.9 µg/dL compared to 10.5 µg/dL for the referents. 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 28 workers who completed the 3-year period showed significant associations between PbB and five out

of the eight parameters measured. The same was observed when only workers with PbB ≥40 μg/dL were included in the analysis, but no significant association was found among workers with PbB <40 μg/dL.

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 was 63 μg/dL (range, 17–186 μg/dL); PbB was not measured in the control group. 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. Taken together, the data available suggest that in lead workers slowing of NCV starts at a mean PbB of 30–40 μg/dL.

Other Physiological Effects in Adults. Studies also have shown that exposure to lead affects postural balance. For example, Chia et al. (1996b) evaluated the possible association between postural sway parameters and current PbB, 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 mean PbB was 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. Although the postural sway parameters were not significantly correlated with current PbB or with total cumulative lead exposure, a significant correlation existed with exposure during the 2 years prior to testing. 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 (mean, 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 PbB 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. Changes in postural balance observed in a group of 29 female lead workers with a mean PbB of 55.7 µg/dL in a more recent study from the same group of investigators led them to suggest that lead affects the anterior cerebellar lobe, and the vestibulo-cerebellar and spinocerebellar afferent systems (Yokoyama et al. 2002). Other studies also have reported decreased postural stability in lead workers (Dick et al. 1999; Iwata et al. 2005; Ratzon et al. 2000), but whether the alterations are associated with current measures of exposure or measures of cumulative exposure remains to be elucidated.

The effect of lead exposure on somatosensory evoked potentials has been evaluated in numerous studies of lead workers. Comprehensive reviews on this topic are available (Araki et al. 2000; Otto and Fox 1993). For example, delayed latencies of visual evoked potentials have been reported in several studies of lead workers with PbB of approximately 40 µg/dL (Abbate et al. 1995; Araki et al. 1987; Hirata and Kosaka 1993). In contrast, 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 with a mean PbB of 56 µg/dL and mean exposure duration of 7.8 years (Murata et al. 1995). Also, in a similar study of 29 female lead workers with a mean PbB of 55.7 µg/dL (range, 26–79 µg/dL) and a mean employment duration of 7.9 years in a glass factory, Yokoyama et al. (2002) reported no significant differences in the latencies of brain auditory evoked potentials (BAEP) between the workers and 14 control workers (mean PbB, 6.1 µg/dL). Counter and Buchanan (2002) reported delayed wave latencies consistent with sensory-neural hearing impairment in adults with chronic exposure to lead through ceramic-glazing work and with mean PbB of 47 µg/dL, and suggested that this finding may be attributable to occupational noise exposure in combination with lead intoxication. Bleecker et al. (2003) found dose-dependent alterations in BAEP among lead workers with a mean PbB of 28 µg/dL and a mean-employment duration of 17 years. Analysis of the results led them to suggest that current lead exposure preferentially affected conduction in the distal auditory nerve while chronic lead exposure appeared to impair conduction in the auditory nerve and the auditory pathways in the lower brainstem.

An additional parameter that has been studied in lead-exposed workers is the electrocardiographic R-R interval variability, a measure of peripheral autonomic function. R-R interval variability was significantly depressed in a group of 36 female glass workers compared to a group of 17 referents with no known occupational exposure to lead (Murata et al. 1995). The mean PbB was 55.6 µg/dL and the mean exposure duration was 7.8 years. However, Gennart et al. (1992a) found no association between exposure

and R-R interval variations in the electrocardiogram. The study group consisted of 98 workers from a lead acid battery factory (exposure group) and 85 people who had no occupation exposure to lead (reference group). The mean duration of occupational exposure was 10.6 years. Mean PbB at the time of the examination was 51 µg/dL (range, 40–75 mg/dL) in the exposure group, and 20.9 µg/dL (range, 4.4–39 mg/dL) in the reference group. More studies are needed to establish whether this parameter is truly affected by lead exposure, and if so, to evaluate the shape of the dose-response relationship.

Neurological Effects 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 the National Academy of Sciences (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, associated with PbBs 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 of 60–300 µg/dL (mean, 105 µg/dL). Acute lead poisoning symptoms other than signs of encephalopathy were observed at PbB of approximately 60–450 µg/dL (mean, 178 µg/dL). Signs of encephalopathy such as hyperirritability, ataxia, convulsions, stupor, and coma were associated with PbB of approximately 90–800 µg/dL (mean, 330 µg/dL). The distribution of PbBs 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 PbBs in the range of 80–100 µg/dL. However, a study reported 19 cases of acute encephalopathy in infants of mean age 3.8 months and with mean PbB 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 ≤70 µg/dL. In this report, lead level at 2 months postchelation was a significant predictor of abnormal results in the Denver Developmental Screening Test carried out for a mean period of 20 months.

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, >80–100 μg/dL) also have an increased incidence of lasting neurological and behavioral damage.

Neurobehavioral Effects in Children. The literature on the neurobehavioral effects of lead in children is extensive. With the improvement in analytical methods to detect lead in the various biological media in recent years and in study design, the concentrations of lead, particularly in blood, associated with alterations in neurobehavioral outcomes keep decreasing. In fact, the results of some recent studies suggest that there may be no threshold for the effects of lead on intellectual function. Due to the enormous size of the database on neurobehavioral effects of lead in children, below are summaries of representative and/or major studies published on specific areas. For further information, the reader is referred to recent reviews on this topic (Bellinger 2004; Koller et al. 2004; Lidsky and Schneider 2003; Needleman 2004).

Many studies conducted decades ago reported negative associations between intellectual function, usually measured as IQ on various intelligence scales, and increased PbB, although other exposure indices were sometimes used. For example, de la Burde and Choate (1972) reported a mean Stanford-Binet IQ decrement of 5 points, fine motor dysfunction, and altered behavioral profiles in 70 preschool children exhibiting pica for paint and plaster and elevated PbBs (mean, 58 μg/dL), when compared with results for matched control subjects not engaged in pica for paint and plaster. A follow-up study on these children (ages 1–3 years) at 7–8 years of age 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 since the original study (de la Burde and Choate 1975). Rummo et al. (1979) 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 at the time of encephalopathy were 88 μg/dL (average PbB, 59–64 μg/dL). Asymptomatic children with long-term lead exposures and average maximum PbB 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. Children with short-term exposure and average maximum PbB of 61 μg/dL (average PbB, 46–50 μg/dL) did not differ from controls. PbB in the referent group averaged 21 μg/dL, which is high for so-called "controls." Fulton et al. (1987) provided evidence of changes in intellectual function at lower PbB in a study of 501 children, 6–9 years old from Edinburgh, Scotland, exposed to lead primarily

via drinking water. The geometric mean PbB of the study population was 11.5 µg/dL, with a range of 3.3–34 µg/dL and ten children had PbB >25 µg/dL. Multiple regression analyses revealed a significant relation between tests of cognitive ability and educational attainment (British Ability Scales [BAS]) and PbB after adjustment for confounding variables. The strongest relation was with the reading score. Stratification of the children into 10 groups of approximately 50 each based on PbB and plotting the group mean lead values against the group mean difference from the school mean score revealed a dose-effect relationship extending from the mean PbB of the highest lead groups (22.1 µg/dL) down through the mean PbB of the lowest-lead group (5.6 µg/dL), without an obvious threshold. It should be mentioned, however, that the size of the effect on the score was small compared with the effect of other factors. For the combined BAS score, only 0.9% of a total 45.5% variance explained by the covariates in the optimal regression model could be attributed to the effect of lead.

Needleman et al. (1979) examined the relationship between intellectual function and lead in dentin in a group of 158 first- and second-grade children. In comparison with children having dentin lead levels <10 ppm, children having 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 attention performance, and on a teachers' behavioral rating. A concentration of lead in dentin of 20 ppm corresponds to a PbB of approximately 30 µg/dL (EPA 1986a). Further analysis of Needleman's data showed that for children with elevated lead levels, the observed IQ was an average 3.94 points below the expected based on their mother's IQ scores, whereas for children with low lead levels, it was 1.97 points greater than the expected IQ (Bellinger and Needleman 1983). This meant that the children in the elevated lead group had a lower mean IQ than those in the low lead group when maternal IQ was partialled out. When 132 children from the initial study were reexamined 11 years later, impairment of neurobehavioral function was still related to the lead content of teeth shed at the ages of 6 and 7 years (Needleman et al. 1990). 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 studies of lead dentin and intellectual functions support Needleman's findings in that deficits have not been found below lead dentin concentrations of approximately 10 ppm (Damm et al. 1993; Hansen et al. 1989; Pocock et al. 1987). The association between bone lead and intellectual function also has been studied. A study of 156 male adolescents, 11–14 years of age, in the Pittsburgh school system reported

that increasing bone lead levels (10–53 ppm) was significantly associated with poorer performance on complex language processing tasks (e.g., 4-syllable Nonword Repetition Task, subset 8 of Revised Token Task, responding to spoken commands) (Campbell et al. 2000b). Covariates considered in the analysis included child age, race, SES, and maternal IQ.

Low Lead Level and Intellectual Function. Several studies have been published in recent years that support the view that there is no apparent threshold in the relationship between PbB and neurobehavioral functions. Most of these studies have been cross-sectional studies with the inherent limitation that such type of study of school-age children might reflect latent damage done by a higher PbB at an earlier age, which could only be reliably detected at school age. However, recent data from Chen et al. (2005) showed that the effect of concurrent PbB on IQ may be greater than currently believed. These investigators analyzed data from a clinical trial of 780 children who were treated for elevated PbB (20–44 μg/dL) at approximately 2 years of age and followed until 7 years of age with serial IQ tests and measurements of PbB. Mean PbB at 5 and 7 years of age was 12 and 8 μg/dL, respectively. The results showed that concurrent PbB always had the strongest association with IQ and, as the children aged, the relationship grew stronger. The peak PbB from baseline (approximately 2 years old) to 7 years of age was not associated with IQ at 7 years of age. Futhermore, in the model including both prior and concurrent PbB, concurrent PbB was always more predictive of later IQ scores. The results were interpreted as support for the idea that lead exposure continues to be toxic to children as they reach school age, and that not all of the damage is done by the time the child is 2 or 3 years old.

Lanphear et al. (2000a) analyzed data on blood lead concentrations and various assessments of cognitive abilities conducted on 4,853 U.S. children, ages 6–16 years, as part of the NHANES III, 1988–1994. Four cognitive measures were tested: arithmetic skills, reading skills, nonverbal reasoning (block design), and short-term memory (digit span). Potential confounders that were assessed included gender, racial/ethnic background, child's serum ferritin levels, serum cotinine level, region of the country, marital status and education level of primary caregiver, and poverty index ratio. Although no data were available on important potential confounding factors such as maternal IQ or direct observations of caretaking quality in the home, control for the poverty index ratio and education of the primary caregiver may have served as surrogate. The geometric mean PbB of the sample was 1.9 μg/dL and 2.1% exceeded 10 μg/dL. After adjustment for potential covariables, an inverse association between PbB and cognitive scores was evident, which was significant for all end points when PbBs of only <10 μg/dL were included in the analysis. When the PbB range was restricted to <7.5 μg/dL, the inverse relationship was significant for

arithmetic skills, reading skills, and nonverbal reasoning; when restricted to <5.0 µg/dL, the inverse relationship was significant for arithmetic skills and reading skills.

Canfield et al. (2003) reported the results of evaluations of 172 children from the Rochester Longitudinal Study. Fifty-eight percent of the children had PbBs below 10 µg/dL. PbB was measured at ages 6, 12, 24, 36, 48, and 60 months. IQ of children was assessed with the Stanford-Binet Intelligence Scale at the age of 3 and 5 years. The highest mean PbB was observed at age 2 years (9.7 µg/dL) and the lowest at the age of 6 months (3.4 µg/dL). The mean PbB at 5 years of age was 6.0 µg/dL. After adjustment for covariables, an increase in lifetime average PbB of 1 µg/dL was associated with a decrease in IQ of 0.46 IQ points (95% CI=-0.76–0.15). Similar findings were obtained when the children were tested at 3 and 5 years of age. When the analysis was limited to children whose highest observed PbB were <10 µg/dL, an increase in the lifetime average PbB of 1 µg/dL was associated with a decrease in IQ of 1.37 IQ points (95% CI=-2.56–0.17). The results also showed a nonlinear relationship between IQ and PbB (i.e., an increase from 1 to 10 µg/dL was associated with a decline of 8.0 points in IQ, whereas, an increase from 10 to 30 µg/dL was associated with a decline of approximately 2.5 points). At the age of 5.5 years, the children were given the Working Memory and Planning Battery of the Cambridge Neuropsychological Test Automated Battery to evaluate specific cognitive functions (Canfield et al. 2004). The results showed that children with the greatest exposure performed more poorly on tests of spatial working memory, spatial memory span, intradimensional and extradimensional shifts, and an analog of the Tower of London task.

Evidence for absence of a lower-bound threshold for postnatal lead exposure also was provided in a study of 237 African-American, inner-city children 7.5 years of age with a current mean PbB of 5.4 µg/dL (Chiodo et al. 2004). The children were assessed in areas of intelligence, reaction time, visual-motor integration, fine motor skills, attention (including executive function), off-task behaviors, and teacher-reported withdrawn behaviors. A total of 21 variables were considered as potential confounders. Multiple regression analysis showed negative association with lead exposure in the areas of overall IQ, performance IQ, reaction time, visual-motor integration, fine motor skills, and attention including executive function, off-task behaviors, and teacher-reported withdrawn behavior. Regression analyses in which lead exposure was dichotomized at 10 µg/dL were no more likely to be significant than analyses dichotomizing exposure at 5 µg/dL. Chiodo et al. (2004) indicated that data on maternal and child nutritional status, including iron deficiency, were not available so that their possible influence on the association between lead neurobehavioral outcomes could not be controlled.

Kordas et al. (2006) studied the association between lead and cognitive function in 594 first-grade children exposed to lead from a metal foundry in Torreón, Mexico. Their ages ranged from 6.2 to 8.5 years and their mean PbB was 11.4 μg/dL (SD±6.1 μg/dL). Fifty-one percent of the children had PbBs ≥10 μg/dL. Children were assessed on performance on 14 tests of global or specific cognitive function. Examiners were experienced testing children and were unaware the children's PbB. The nature of the lead-cognition relation was described using both linear and spline (segmented) regression methods. Covariates included in the analyses were age, gender, SES, maternal formal education, parental involvement in schooling family structure, birth order, arsenic exposure, and hemoglobin concentration. Also, all models were adjusted for the tester administering cognitive tasks and the school each child attended. After adjusting for covariates, PbB was significantly associated ($p<0.05$) with poorer scores measuring math abilities, vocabulary, and visual short-term memory. Using segmented regressions, the investigators observed that the slope describing the associations of PbB with the math and vocabulary test scores below a cutoff of 12 and 10 μg/dL, respectively, were steeper than slopes above those cutoff points. Examination of segmented lead coefficients using a stratified analysis at various levels of covariates showed that the pattern of steeper estimates at low PbBs vs. higher PbBs was generally conserved. Furthermore, the data showed that the nonlinear relationship was most pronounced for children who already tended to be at risk for poorer performance (fewer family resources, lower maternal education, and lower parental involvement in school work). Although some important covariates such as HOME inventory and maternal IQ were not controlled for in the study, control for other family background characteristics may have served as surrogates.

Using data from a prospective study conducted in Mexico City, Mexico, Téllez-Rojo et al. (2006) evaluated the relationship between PbB and neurodevelopment in 294 children at 12 and 24 months of age. Two cohorts comprised the sample: one recruited at the time of delivery and another recruited prenatally. To be included in the study, children needed to have a PbB <10 μg/dL at both 12 and 24 months of age, a gestation age of 37 weeks or longer, and a birth weight >2,000 g. MDI and PDI scores of a Spanish version of the Bayley Scales of Infant Development II (BSID II) were the primary dependent variables. Non-lead variables that were related to BDID II scores at $p<0.1$ in bivariate analysis were included in multivariate models. Also included in the multivariate models were maternal age and IQ and children's gender and birth weight. Adjusting for covariates, children's PbBs at 24 months were significantly inversely associated ($p<0.01$) with both MDI and PDI scores at 24 months. PbB at 12 months of age was not associated with concurrent MDI or PDI, or with MDI scores at 24 months of age, but was significantly associated ($p<0.01$) with PDI scores at 24 months. An increase of 1 logarithmic unit in 24-month PbB was associated with a reduction of 4.7 points in MDI score at

24 months. For both the MDI and PDI scores at 24 months of age, the coefficients that were associated with PbB were significantly larger ($p \leq 0.01$) among children with PbBs <10 µg/dL than in children with PbBs >10 µg/dL. Moreover, for MDI scores, the slope of the association was steeper over the range up to 5 µg/dL than between 5 and 10 µg/dL.

Perhaps the strongest evidence for an association between low PbB and intellectual impairment in children as well as for a nonlinear dose-response is provided by a pooled analysis of 1,333 children who participated in seven international prospective cohort studies and were followed from birth or infancy until 5–10 years of age (Lanphear et al. 2005). The participant sites included Boston, Massachusetts; Cincinnati, Ohio; Cleveland, Ohio; Rochester, New York; Mexico City; Port Pirie, Australia; and Kosovo, Yugoslavia. The full-scale IQ score was the primary outcome measured. The median lifetime PbB was 12.4 µg/dL (5^{th}–95^{th} percentiles, 4.1–34.8 µg/dL), while the concurrent mean PbB was 9.7 µg/dL (5^{th}–95^{th} percentiles, 2.5–33.2 µg/dL); 244 children (18%) had PbBs that never exceeded 10 µg/dL. Four measures of blood lead were examined: concurrent PbB (PbB closest to the IQ test), maximum PbB (peak PbB measured at any time before IQ test), average lifetime PbB (mean PbB from 6 months to concurrent PbB tests), and early childhood PbB (mean PbB from 6 to 24 months). In the subsequent analyses, concurrent PbB and average lifetime PbB were generally stronger predictors of lead-associated intellectual deficits than the other two indices. Potential confounding effects of other factors associated with IQ scores were examined by multiple regression analysis and included HOME inventory, child's sex, birth weight, birth order, maternal education, maternal IQ, maternal age, marital status, prenatal smoking status, and prenatal alcohol use. Using various models, including the linear model, cubic spline function, the log-linear model, and the piece-wise model, Lanphear et al. (2005) determined that the nonlinear model was a better fit for the data. Using a log-linear model, the investigators found a 6.9 IQ point decrement (95% CI, 4.2–9.4) for an increase in concurrent PbB from 2.4 to 30 µg/dL. However, the decrease in IQ points was greatest in the lowest ranges of PbB. The estimated IQ decrements associated with increases in PbB of 2.4–10, 10–20, and 20–30 µg/dL were 3.9 (95% CI, 2.4–5.3), 1.9 (95% CI, 1.2–2.6), and 1.1 (95% CI, 0.7–1.5), respectively. To further investigate whether the lead-associated decrement was greater at lower PbBs, the investigators divided the data at two cut-off points *a priori*, a maximal PbB of 7.5 and 10 µg/dL. They then fit separate linear models to the data in each of those ranges and compared the PbB coefficients for the concurrent PbB index. The coefficient for the 103 children with maximal PbB <7.5 µg/dL was significantly greater than the coefficient for the 1,230 children with maximal PbB ≥7.5 µg/dL (linear β=-2.94 [CI 95%, -5.16–-0.71]) vs. -0.16 (95% CI, -2.4–-0.08). The coefficient for the 244 children who had maximal PbB<10 µg/dL was not significantly greater than that for 1,089 children who had maximal PbB ≥10 µg/dL. Potential limitations

acknowledged by the authors included the fact that the HOME inventory and IQ tests had not been validated in all cultural or ethnic communities, lack of examination of other predictors of neurodevelopmental outcomes such as maternal depression, and the unique limitations of each individual study.

A nonlinear relationship between first trimester of pregnancy blood lead and the MDI at 24 months was recently reported by Hu et al. (2006). In the study, the investigators measured lead in maternal plasma and whole blood lead during each trimester in 146 pregnant women in Mexico City. Measurements were also conducted in cord blood at delivery and when the infants were 12 and 24 months old. The primary outcome was the MDI scores at 24 months of age. The criteria for inclusion in the study were: child born with at least 37 weeks of gestational age; at least one valid measurement of plasma lead during any of the three visits made during pregnancy; complete information on maternal age and IQ; and child's PbB at 24 months, sex, weight, and height. Potential confounders included in the analyses were child's sex, PbB at 24 months of age, height for age and weight, and maternal age and IQ. Mean maternal PbB during the first, second, third trimester, and delivery ranged from 6.1 μg/dL (SD±3.2 μg/dL) to 7.3 μg/dL (SD±4.3 μg/dL); plasma lead during pregnancy ranged between 0.014 and 0.016 μg/dL. Mean PbB in the cord, at 12 months, and 24 months were 6.2 μg/dL (SD±3.9 μg/dL), 5.2 μg/dL (SD±3.4 μg/dL), and 4.8 μg/dL (SD±3.8 μg/dL), respectively. The results of the analyses showed that both maternal plasma and whole blood lead during the first trimester (but not in the second or third trimester) were significant predictors ($p<0.05$) of poorer MDI scores. Also, in models combining all three trimester measures and using standardized coefficients, the effect of first-trimester maternal plasma was substantially greater than the effects of second- and third-trimester plasma lead. A one standard deviation change in first-trimester plasma lead was associated with a reduction in MDI scores of 3.5 points ($p=0.03$). Inspection of the relationship between first-trimester plasma lead and MDI at 24 months showed that the slope was steeper at plasma lead levels corresponding to whole blood lead levels <10 μg/dL than at higher plasma lead concentrations, as observed also in the studies summarized above. As a possible explanation, Hu et al. (2006) speculated that lead might be affecting the process of neuronal differentiation, which is primarily a first-trimester event. Limitations of the study acknowledged by the investigators include the relatively small sample size, the lack of control for a measure of home conditions, and the fact that infant PbB at 24 months did not significantly predict lower MDI score (as observed, for example, in Téllez-Rojo et al. [2006]). Another recent study that reported an association between prenatal lead exposure and intellectual function is that of Schnaas et al. (2006) who reported that IQ of 6–10-year-old children decreased significantly ($p<0.0029$; 95% CI, -6.45–-1.36) only with increasing natural-log third trimester PbB, but not with PbB at other times during pregnancy or postnatal PbB measurements. However,

because their observations began after the 12th week of pregnancy, the effects of the first trimester PbB could not be examined. As with other studies, the dose-response PbB-IQ function was log-linear, with a steeper slope at PbB <10 μg/dL.

Other studies that have reported cognitive impairments associated with low lead exposure include Al-Saleh et al. (2001), Bellinger and Needleman (2003), Carta et al. (2003), Emory et al. (2003), Gomaa et al. (2002), and Shen et al. (1998). Although individually all of these studies have limitations, collectively, they support the association between low blood lead and intellectual impairment in children.

Major Prospective Studies. The Port Pirie, Australia, prospective study examined cohorts of infants born to mothers living in the vicinity of a large lead smelting operation in Port Pirie and infants from outside the Port Pirie area. The study population consisted initially of 723 singleton infants. The children were followed from birth to age 11–13 years old; at this later age, 375 children remained in the cohort. Maternal blood and cord lead levels were slightly, but significantly, higher in the Port Pirie cohort than in the cohort from outside Port Pirie (e.g., mean cord blood lead was 10 vs. 6 μg/dL). The main outcome measures were the Bayley Mental Developmental Index (MDI) at age 2 years, the McCarthy GCI at age 4 years, and IQ from the Wechsler Intelligence Scale at ages 7 and 11–13 years (Baghurst et al. 1987, 1992, 1995; McMichael et al. 1988, 1994; Tong et al. 1996). Covariates in the models included: child gender, birth weight, siblings, infant feeding style and duration of breast feeding; maternal IQ, age at child's birth and marital status; parental tobacco use; SES, and HOME score. Analysis of the associations between blood lead concentrations (tertiles) in children of ages 2 or 11–13 years, and developmental status showed that the covariate-adjusted differences in development scores between the top and bottom tertiles were 4 points on the MDI at age 2; 4.8 points on the McCarthy GCI at age 4; and 4.9 and 4.5 IQ points at age 7 and 11–13 years, respectively. At age 7 years, both prenatal and postnatal PbB were inversely associated with visual motor performance (Baghurst et al. 1995). Analysis of the relationship between individual changes in PbB and individual changes in measures of cognitive development during the life of the cohort found that the mean PbB in the children decreased from 21.2 μg/dL at age 2 years to 7.9 μg/dL at age 11–13 years; however, cognitive scores in children whose blood lead concentration declined the most were generally not improved relative to the scores of children whose PbB declined least (Tong et al. 1998). Changes in IQ and declines in PbB that occurred between the ages of 7 and 11–13 years suggested better cognition among children whose PbB declined most. The overall conclusion was that the cognitive deficits associated with exposure to lead in early childhood appeared to be only partially reversed by a subsequent decline in PbB. Throughout the various assessments, it was noted that children from disadvantaged backgrounds were more sensitive to the effects of lead than those of a higher

socioeconomic status, and that girls were more sensitive to the effects of lead than boys (Tong et al. 2000).

The Mexico City, Mexico, Prospective Study evaluated children born to mothers residing in Mexico City (Rothenberg et al. 1989, 1994a; Schnaas et al. 2000). The study recruited 502 pregnant women; 436 ultimately were included in the study. An analysis of a subset of 112 children for whom complete data were available for evaluation of GCI (McCarthy scales) at 6-month intervals between ages 36 and 60 months revealed significant associations between PbB and GCI, after adjusting for covariates. Mean PbBs were 10.1 µg/dL at 6–18 months, 9.7 µg/dL at 24–36 months, and 8.4 µg/dL at 42–54 months of age. Increasing PbBs at 24–36 months, but not 6–18 months or prenatal, were associated with significant declines in GCI at 48 months; increasing PbBs at 42–54 months were associated with decreased GCI at 54 months. Covariates included in the models were child gender, 5-minute Apgar score, birth weight, and birth order; maternal education and IQ; and family SES. HOME scores were not included and were assumed to have been accounted for by maternal IQ because of the strong correlation between the latter and HOME score. The main finding of this series of studies was that postnatal, but not prenatal, PbBs were associated with intellectual function and that the strength of the association between mean PbB and GCI increases with age up to 4 years, after which, it becomes less strong and continues to decrease.

The Yugoslavia Prospective Study evaluated children born to women from two towns in Kosovo, Yugoslavia; Kosovska Mitrovica (K. Mitrovica), the site of a lead smelter, refinery, and battery plant; and Pristina, a town 25 miles to the south of K. Mitrovica, which was considered not to have been impacted by industrial lead emissions (Factor-Litvak et al. 1991, 1999; Wasserman et al. 1992). A total of 1,502 women were recruited at mid-pregnancy: 900 women from Pristina and 602 from K. Mitrovica. A sample of 392 infants was selected for follow-up based on umbilical cord lead, town of residence, and parental education. The infants from K. Mitrovica were assigned to one of three groups based on cord PbB: low (<15 µg/dL), middle (15–20 µg/dL), and high (>20 µg/dL). Outcomes examined in the follow-up included measures of intelligence at ages 2 (MDI of the Bayley Scales), 4 (McCarthy Scales of Children's Abilities), and 7 years (Wechsler Intelligence Scale for Children-III), and behavior problems at age 3 (Child Behavior Checklist) and 12 years (Wechsler Intelligence Scale for Children-III). Covariates included in the models were child gender, birth weight, iron status (blood hemoglobin), siblings and ethnicity (language spoken in home); maternal age, education and Raven's test score; and HOME score. The geometric mean PbB in children in K. Mitrovica increased from 22.4 µg/dL, at birth, to 39.9 µg/dL, at age 4; in children from Pristina, it increased from 5.4 to 9.6 µg/dL over this same age range (Wasserman et al. 1994). PbB was significantly associated with poorer intellectual function at ages

2 years (Wasserman et al. 1992), 4 years (Wasserman et al. 1994), and 7 years (Wasserman et al. 1997). An increase in PbB from 10 to 30 µg/dL was predicted to be associated with loss in intellectual function of 2.5 points at age 2 years, 4.5 points at age 4 years, and 4.3 points at age 7 years. In both towns combined, PbB measured concurrently with the Child Behavior Checklist was associated with small increases in behavioral problems, which the authors considered small compared with the effects of social factors (Wasserman et al. 1998). In a subsequent publication, Wasserman et al. (2000a) observed that while postnatal elevations that occurred before the age of 2 years and continued afterwards were associated with the largest decrements in IQ (50% increase in postnatal lead associated with 2.71 point IQ loss), elevations in PbB that occurred only after the age of 2 years were also associated with decrements. Thus, prenatal and postnatal exposures that occurred at any time during the first 7 years were independently associated with small decrements in later IQ scores (Wasserman et al. 2000a); identification of a particularly critical period of vulnerability during brain growth and maturation within this age range was not evident from this analysis.

In addition, evaluation of 283 children at the age of 54 months showed that PbB was significantly associated with poorer fine motor and visual motor function, but was unrelated to gross motor coordination. An estimated 2.6 and 5.8% of the variance in fine motor composite and visual motor integration was due to PbB, respectively. At age 12, the assessment of the children included measurements of tibial bone in addition to current PbB (Wasserman et al. 2003). At this age, mean PbB in the exposed children was approximately 31 µg/dL and mean tibial bone lead was 39 ppm, both measures significantly higher than those of a comparison group. Both bone lead and PbB were associated with intelligence decrements, but the bone lead-IQ associations were stronger than those for PbB. For each doubling of tibial bone, Full Scale, Performance, and Verbal IQ decreased by an estimated 5.5, 6.2, and 4.1 points, respectively. Analyses conducted in a subsample stratified by quartiles showed that the greatest decrements in intelligence appeared to occur at relatively low lead exposure, from quartile 1 to quartile 2. These transitions corresponded to tibial lead up to 1.85 ppm, mean serial PbB up to 7 µg/dL, and current PbB up to 5.6 µg/dL.

The Boston, Massachusetts, study examined the association between lead exposure and neurobehavioral parameters in 249 middle-class and upper-middle class Boston children (Bellinger et al. 1984, 1985a, 1985b, 1986a, 1986b, 1987a, 1987b, 1989a, 1989b, 1991, 1992). Cord PbBs were determined at delivery and MDI and PDI scores were measured every 6 months thereafter. Infants born at <34 weeks of gestation were excluded from the study. Cord PbBs were <16 µg/dL for 90% of the subjects, with the highest value being 25 µg/dL. On the basis of cord PbBs, 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. Multivariate regression analysis revealed an inverse correlation between cord PbB 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. Subsequent studies of this cohort showed that the younger the infants, the more vulnerable they are to lead-induced developmental toxicity (Bellinger et al. 1989a, 1989b). Infants in lower socioeconomic groups showed deficits at lower levels of prenatal exposure (mean PbB, 6–7 µg/dL) than children in higher socioeconomic groups. The early postnatal PbBs (range, 10–25 µg/dL) were also associated with lower MDI scores, but only among children in lower socioeconomic groups. Evaluation of the children at approximately 5 years of age showed that deficits in GCI scores correlated significantly with PbB at 24 months of age (mean 7 µg/dL), but not with prenatal PbB (Bellinger et al. 1991). These results suggest that prenatal PbB is 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. Evaluation of 148 of the Boston cohort children at age 10 years showed that all postnatal blood lead levels were inversely associated with Full Scale IQ measured at age 10; however, only the associations involving PbB at ages 10 years, 57 months, and 24 months were statistically significant (Bellinger et al. 1992). 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 of increase in 24-month PbB. PbB at 24 months was also significantly associated with Verbal IQ and five WISC-R subtest scores. Only PbBs at 24 months were significantly associated with adjusted K-TEA scores. For each 10 µg/dL of 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. Reanalyses of data, from 48 children whose PbB never exceeded 10 µg/dL at birth or at any of the evaluations throughout the study, showed that an inverse association between IQ and PbB persisted at PbBs below 5 µg/dL and that the inverse slope was greater at lower PbBs than at higher PbBs (Bellinger and Needleman 2003).

The Cincinnati, Ohio, study sample consisted of 305 mothers residing in predesignated lead-hazardous areas of the city (>80% black) (Dietrich et al. 1986, 1987a, 1987b). Maternal PbBs were measured at the

first prenatal visit; cord PbB was measured at delivery; infant PbB was measured at 10 days and at 3 months of age; and neurobehavioral tests were performed at 3 and 6 months of age. Mean PbBs 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 and performance on the MDI at 3 months, and between prenatal or 10-day neonatal PbB and performance on the MDI at 6 months. No significant correlation of PbB 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). Cognitive development of 258 children was assessed by the Kaufman Assessment Battery for Children (K-ABC) when the children were 4 years old (Dietrich et al. 1991). Higher neonatal PbBs were associated with poorer performance in all K-ABC subscales; however, there was a significant interaction between neonatal PbB and socioeconomic status, which suggested that children from less advantaged environments express cognitive deficits at lower PbBs than do children from families of relatively higher socioeconomic status. Prenatal (maternal) PbBs were not related to 4-year cognitive status. No statistically significant effects of postnatal PbB on any of the K-ABC subscales was found after covariate adjustment. Evaluation of 253 children at 6.5 years of age showed that 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 (Dietrich et al. 1993a). Also, 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. 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 average 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. At 72 months of age, 245 children were evaluated for motor development status (Dietrich et al. 1993b). The authors hypothesized that measures of motor development may be less confounded with socio-hereditary cofactors in lower socioeconomic status populations than cognitive or other language-based indices. After adjusting for HOME scores, maternal IQ, social class, and child sex and race, both neonatal and postnatal PbB were associated with poorer performance on a measure of upper-limb speed and dexterity and a composite index of fine motor coordination. Prenatal (maternal) PbB was not related to motor proficiency. 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. Information collected at approximately 6.5, 11, and 15 years of age showed that children with the highest PbB at age 15 years (mean, 2.8 µg/dL; range, 1–11.3 µg/dL) had lower verbal comprehension scores over time and greater decline in their rate of vocabulary development at age 15 than children with lower PbB (Coscia et al. 2003). The study also showed that socioeconomic status and maternal intelligence were statistically significantly associated with growth patterns in both tests scores, independent of the effects of lead. The most recent publication in this series provides the results of a neuropsychological evaluation of 195 adolescents age 15–17 years old from this cohort (Ris et al. 2004). The neuropsychological tests yielded five factors labeled Memory, Learning/IQ, Attention, Visual Construction, and Fine-Motor. The results showed a significant effect of PbB at 78 months on the Fine-Motor factor. The results also showed a stronger association between lead exposure and Attention and Visuoconstruction in males than in females. The study also confirmed that adolescents from disadvantaged homes had increased vulnerability toward the effects of lead.

The Cleveland, Ohio, study evaluated neurodevelopmental effects in a sample of urban, disadvantaged, mother-infant pairs (33% black) (Ernhart et al. 1985, 1986, 1987). The mean PbBs 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 with complete 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 and morphological anomalies was found. Using the complete set of data, abnormal reflexes and neurological soft signs scales were significantly related to cord PbB and the muscle tonicity scale was significantly related to maternal PbB. Using data from the mother-infant pairs, the only significant association that was found was between the Neurological Soft Signs score and cord PbB, which averaged 5.8 µg/dL and ranged up to only 14.7 µg/dL; no association with maternal PbBs was seen (Ernhart et al. 1985, 1986). A later analysis related PbBs 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 (Ernhart et al. 1987). After controlling for covariates and confounding risk factors, the only significant associations of PbB with concurrent or later development were an inverse association between maternal (but not cord) PbB 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 PbB and developmental test scores were "reasonably consistent with what might be expected on the basis of sampling variability," that any association of PbB 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.

Table 3-5 presents a summary of the major prospective studies.

While the majority of the available studies of neurobehavioral effects of lead in children have observed associations between increasing lead burden and measures of cognitive development, a smaller number of studies failed to detect such effects. Harvey et al. (1988) found no significant correlation between PbB (mean 13 µg/dL) and measures of IQ in a study of 201 children 5.5 years of age in England. Similar results were reported by McBride et al. (1982), Smith et al. (1983), Lansdown et al. (1986), Ernhart and Greene (1990), Wolf et al. (1994), Minder et al. (1998), and Prpić-Majić et al. (2000). In the former five studies, the mean PbB was between 10 and 16 µg/dL, whereas in the Minder et al. (1998) and Prpić-Majić et al. (2000) studies, the mean PbBs were 4.4 µg/dL (range, 0.8–16 µg/dL) and 7.1µg/dL (range, 2.4–14.2 µg/dL), respectively. Finding diverging results in the assessment of such complex parameters is not totally unexpected given the differences in methodology and the statistical issues involved (see Chapter 2 for further discussion).

Meta-analyses. Needleman and Gatsonis (1990) did a meta-analysis of 12 studies, 7 of which used blood lead as a measure of exposure and 5 used tooth lead. Covariates examined by the studies were 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 -0.03 in the tooth lead group. Their analysis also showed that no single study appeared to be responsible for the significance of the final finding. Somewhat unusual in this analysis is the fact that the evaluation is based on accumulated p values rather than accumulated effect sizes. Pocock et al. (1994) analyzed 5 prospective studies, 14 cross-sectional

Table 3-5. Major Prospective Studies of Intellectual Development in Children

Study cohort	Lead biomarker	Outcome measured	Results and main conclusions	Reference
592 Infants born to women living near a smelter in Port Pirie, Australia, followed from birth to age 11–13.	Mean cord PbB was 10 µg/dL; 21.2 µg/dL at age 2; 7.9 µg/dL at age 11–13	MDI, GCI, IQ	Four point difference in MDI score between top and bottom PbB tertiles at age 2; 4.8 point difference in GCI score at age 4; 4.5 IQ points difference at age 11–13. Deficits associated with lead were only partially reversed by decline in blood lead past infancy.	Baghurst et al. 1987, 1992, 1995; McMichael et al. 1988, 1994; Tong et al. 1996, 1998
112 Infants born to women in Mexico City, Mexico, followed at 6 months intervals between ages 6 and 60 months.	Mean PbB at 6–18 months was 10.1 µg/dL; 9.7 µg/dL at 24–63 months; 8.4 µg/dL at 42–54 months	GCI	Increasing PbB at 24–36 months associated with lowed GCI at 48 months; increasing PbB at 42–54 months associated with lower GCI at 54 months. Postnatal, but not prenatal PbB associated with intellectual function.	Rothenberg et al. 1989, 1994a; Schnaas et al. 2000
577 Infants born to women living near a lead smelter, refinery, and battery plant in K. Mitrovica, Yugoslavia, followed from birth to age 12.	Mean PbB at birth was 22.4 µg/dL; 39.9 µg/dL at age 4; 31 µg/dL at age 12; mean tibia lead was 39 ppm at age 12	MDI, GCI, WISC, IQ	PbB was associated with poorer MDI at age 2, GCI at age 4, WISC at age 7. Tibia lead showed stronger association with IQ decrements than PbB at age 12. Both prenatal and postnatal PbB independently associated with small decrements in IQ.	Factor-Litvak et al. 1991, 1999; Wasserman et al. 1992, 1994, 1998, 2000a, 2003
216 Middle- and upper-class Boston, Massachusetts, children followed from birth to age 10.	90% of cord PbB was <16 µg/dL; mean PbB of 7 µg/dL at 24 months	MDI, PDI, GCI, WISC, IQ	Inverse correlation between cord PbB and MDI scores at 6, 12, 18, and 24 months. No correlation between PDI scores and PbB. Lower GCI at age 5 correlated with PbB at age 2, but not prenatal PbB. Full scale IQ at age 10 associated with PbB at 24 months. Timing of exposure more important than magnitude alone.	Bellinger et al. 1984, 1985a, 1986b, 1987a, 1987b, 19889a, 1989b, 1991, 1992

Table 3-5. Major Prospective Studies of Intellectual Development in Children

Study cohort	Lead biomarker	Outcome measured	Results and main conclusions	Reference
305 Children born to women living in pre-designated lead-hazardous areas of Cincinnati, Ohio, followed to age 15–17.	Mean prenatal PbB was 8 µg/dL; cord PbB was 6.3 µg/dL; 5.9 µg/dL at 3 months; 2.8 µg/dL at age 15 years	K-ABC, MDI, PDI	Prenatal PbB inversely correlated with MDI at 3 and 6 months. Lower KABC scores at 4 years associated with higher neonatal PbB. Postnatal PbB associated with lower performance IQ at 6.5 years. Neonatal and postnatal PbB associated with altered motor development at age 6.	Coscia et al. 2003; Dietrich et al. 1986, 1987a, 1987b, 1991, 1993a, 1993b; Ris et al. 2004
389 Children born to urban disadvantaged women in Cleveland, Ohio followed from birth to 7 years old.	Mean PbB in cord was 5.8 µg/dL; mean prenatal PbB was 6.5 µg/dL	MDI, PDI, KID, NBAS, IQ	Neurological soft signs associated with cord PbB. Only maternal PbB at delivery (6.5 µg/dL) associated with MDI, PDI, and KID scores at 6 months. Dentine lead at 5 years associated with decreased verbal and full scale IQ.	Ernhart et al. 1985, 1986, 1987, 1988; Greene and Ernhart 1991

GCI = McCarthy General Cognitive Index; KABC = Kaufman Assessment Battery for Children; KID = Kent Infant Development Scale; MDI = Mental Developmental Index; NBAS = Brazelton Neonatal Behavioral Assessment Scale; PDI = Psychomotor Developmental Index; WISC = Weschler Intelligence Scale for Children

studies of blood lead, and 7 cross-sectional studies of tooth lead separately and 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 <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.

An 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 studies, the loss was 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 that 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 PbB. 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. When PbB 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 PbB and 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 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. IPCS (1995) concluded that their analysis revealed a consistency between studies which pointed towards a "collectively significant" inverse association between PbB and full-scale IQ. IPCS (1995) also noted that below the 10–20 µg/dL PbB range, "uncertainties increased, concerning firstly the existence of an association and secondly estimates of the magnitude of any putative association."

Thacker et al. (1992) reviewed 35 reports from five prospective studies that examined the relationship between PbB and mental development in children. However, efforts to pool the data with meta-analytic techniques were unsuccessful because the methods used in the studies to analyze and report data were inconsistent. Specific issues mentioned by Thacker et al. (1992) included (a) IQ and PbB were not always measured at comparable times in different studies, (b) there were differences among studies in independent variable, data transformations, and statistical parameters reported, (c) results conflicted when measurement intervals were comparable, (d) patterns of regression and correlation coefficients were inconsistent, and (e) data were insufficient to interconvert the parameters reported.

Lead and Delinquent Behavior. The possible association between lead and antisocial behavior has been examined in several studies. In 1996, Needleman and coworkers published the results of a study of 301 young males in the Pittsburgh School System. After adjustment for covariates, the investigators found that bone lead levels at 12 years of age were significantly related to parents and teacher's Child Behavior Checklist ratings of aggression, attention, and delinquency. A later study from the same group of investigators reported the results of a case-control study of 194 youths aged 12–18, arrested and adjudicated as delinquent by the Juvenile Court of Allegheny County, Pennsylvania, and 146 non-delinquent controls from high schools in the city of Pittsburgh (Needleman et al. 2002). The association between delinquent status and bone lead concentrations was modeled using logistic regression. Also, separate regression analyses were conducted after stratification by race. Care was taken to insure that unidentified delinquents did not populate the control group. Bone lead was significantly higher in cases than in controls (11.0 vs. 1.5 ppm) and this also applied to both racial categories, white and African American. After adjusting for covariates and interactions, and removal of noninfluential covariates, adjudicated delinquents were 4 times more likely to have bone lead concentrations higher than 25 ppm than controls. Covariates included in the models were child race; parental education and occupation; absence of two parental figures in the home; number of children in the home; and neighborhood crime rate. Limitations of the study include the lack of blood lead data and definition of dose-effect relationships. Also, explicit information on SES factors was not provided and there were large differences in social confounders between cases and controls.

Dietrich et al. (2001) examined the relationships between prenatal and postnatal exposure to lead and antisocial and delinquent behaviors in a cohort study of 195 urban, inner city adolescents recruited from the Cincinnati Prospective Lead Study between 1979 and 1985. At the time of the study, the subjects were between approximately 15 and 17 years of age; 92% were African-American and 53% were male. The mean prenatal (maternal) PbB concentration was 8.9 µg/dL. Blood was sampled shortly after birth and on a quarterly basis thereafter, until the children were 5 years old. From birth to 5 years of age, 35% of the cohort had PbBs in excess of 25 µg/dL, 79% >15 µg/dL, and 99% >10 µg/dL. As adolescents, the mean PbB was 2.8 µg/dL. After adjustment for covariables that were independently associated with delinquent behavior, prenatal blood lead concentration was significantly associated with an increase in the frequency of parent-reported delinquent and antisocial behaviors, while prenatal and postnatal blood lead concentrations (i.e., at 78 months or childhood average) were significantly associated with an increase in the frequency of self-reported delinquent and antisocial behaviors, including marijuana use. Limitations of the study are the inclusion of only four variables in the covariate analysis despite the fact that nine

were selected, only total scores were reported omitting the results for all delinquency variables, and maternal levels but not cord levels were used in the analysis.

Two ecological investigations correlated leaded gasoline sales or ambient lead levels with crime rates. Stretesky and Lynch (2001) examined the relationship between air lead concentrations and the incidence of homicides across 3,111 counties in the Unites States. The estimated air lead concentrations across all counties ranged from 0 to 0.17 μg/m^3. After adjusting for sociologic confounding and nine measures of air pollution, they reported a 4-fold increase in homicide rate in those counties with the highest air lead levels compared to controls. Nevin (2000) found a statistical association between sales of leaded gasoline and violent crime rates in the United States after adjusting for unemployment and percent of population in the high-crime age group. As with most ecological investigations, the results are difficult to interpret because there are no measurements of individual exposure levels or controls of confounders.

Many of the behavioral deficits observed in children exposed to lead have been reproduced in studies in animals, particularly monkeys, and at similar blood lead levels. Such studies have suggested that the impaired performance on a variety of tasks is the result, at least in part, of a combination of distractibility, inability to inhibit inappropriate responding, and perseveration in behavior that are no longer appropriate. Behavioral tests that have been proven useful in this area of research include discrimination reversal, spatial delayed alternation, delayed matching to sample, and intermittent schedules of reinforcement. Representative studies are summarized below. Additional information can be found in reviews about this topic and references therein (Cory-Slechta 1995, 1997, 2003; Rice 1993, 1996a).

Rhesus monkeys treated orally from birth with doses of lead that produced PbBs ≥32 μg/dL for 5 months to 1 year showed impairment in a series of discrimination reversal tasks early in life and when they were tested at 33 months of age and at 49–55 months of age (Bushnell and Bowman 1979a, 1979b). The monkeys tested at 49–55 months of age had mean PbBs of 4, 5, and 6 μg/dL, for controls, low-dose, and high-dose monkeys, respectively. The corresponding mean PbBs during the year of treatment were 4, 32, and 65 μg/dL. Additional experiments were conducted in monkeys exposed to lower levels of lead that peaked at approximately 15 or 25 μg/dL, and then decreased to steady state PbBs of about 11 and 13 μg/dL, respectively (Rice 1985). At 3 years of age, the monkeys were tested on a series of nonspatial discrimination reversal problems with irrelevant form cues, which provided the opportunity to study distractibility. The results showed that the treated monkeys attended to irrelevant cues in a systematic way. This suggested that the treated monkeys were being distracted by the irrelevant cues to a greater degree than the controls. Similar conclusions were reached when these same monkeys were tested again

at 9–10 years of age on a series of spatial discrimination reversal tasks without irrelevant cues. Studies in which the dosing periods varied in order to evaluate possible sensitive periods of exposure showed that spatial and nonspatial tasks were affected differentially depending on the developmental period of lead exposure (Rice 1990; Rice and Gilbert 1990a). These studies also suggested that while exposure beginning after infancy produces impairment, continuous exposure during and after infancy magnifies the effects.

Spatial delayed alternation testing has provided evidence of perseverative behavior and inability to inhibit inappropriate responding. For example, Levin and Bowman (1986) dosed monkeys from birth to 1 year of age, a regimen that produced PbBs of approximately 80 µg/dL during most of the treatment period, although peak PbB reached near 300 µg/dL during the initial phase of treatment. Tests conducted when the monkeys were 5–6 years of age, when mean PbB was about 5µg/dL, indicated that the treated monkeys perseverated on an alternation strategy even when it was not rewarded. Inappropriate responding also was observed in monkeys that had much lower (11–13 µg/dL) steady state PbBs and were tested at 7–8 years of age (Rice and Karpinski 1988). Further studies to determine possible sensitive periods of exposure showed no significant difference in the degree of impairment on a spatial delayed alternation task among three groups of monkeys exposed at different times during development (Rice and Gilbert 1990b). One group of monkeys was dosed with lead from birth onward; another group was dosed from birth to 400 days of age, and a third group began to receive lead at 300 days of age; testing was conducted at that 6–7 years of age. Perseverative behavior has also been put in evidence in studies in monkeys using the delayed matching to sample paradigm (Rice 1984).

Further evidence that lead induces behavior that can be characterized as failure to inhibit inappropriate responding has been obtained using intermittent schedules of reinforcement, particularly, the fixed interval (FI) schedule of reinforcement. For instance, monkeys with a steady-state PbB of approximately 30 µg/dL tended to respond excessively or inappropriately (e.g., with more responses than controls during time-outs) when responses were not rewarded (Rice and Willes 1979). In addition, lead-treated monkeys with a steady-state PbB of 11 or 13 µg/dL were also slower to learn reinforcement schedule, which required a low rate of responding (Rice and Gilbert 1985). Similar observations were made in adult monkeys dosed with lead from birth, having a peak PbB of 115 µg/dL by 100 days of age and a steady state PbB of 33 µg/dL at 270 days of age (Rice 1992). Increases in response rate on FI performance have been seen in rats at comparable PbB to those in monkeys. For example, Cory-Slechta et al. (1985) reported that postweaning exposure of rats having PbBs of 15–20 µg/dL had a significantly higher rate of response and significantly shorter interval bar-press responses on a FI operant schedule of food

reinforcement than control rats. 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). The same group of investigators also showed that rats exposed to lead after weaning and having a PbB of approximately 11 µg/dL showed inappropriate responding in a Fixed-Ratio (FR) waiting-for-reward paradigm (Brockel and Cory-Slechta 1998). Treated rats increased the response rates and decreased the mean longest waiting time than control rats.

Peripheral Neurological Effects in Children. Effects of lead on peripheral nerve function have been documented in children. Frank peripheral neuropathy has been observed in children at PbBs 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 that the authors suggested might indicate an increased susceptibility to lead neuropathy among children with sickle cell disease. Seto and Freeman (1964) reported signs of peripheral neuropathy in a child with a PbB of 30 µg/dL, but lead lines in the long bones suggested past exposures leading to peak PbB 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 over a PbB range of 13–97 µg/dL in children living near a smelter in Kellogg, Idaho (Landrigan et al. 1976). These data were reanalyzed to determine whether a threshold exists for this effect. Three different methods of analysis revealed evidence of a threshold for NCV at PbBs of 20–30 µg/dL (Schwartz et al. 1988). NCV in the sural and peroneal nerves from young adults exposed to lead during childhood (20 years prior to testing) while living near a lead smelter in the Silver Valley, Idaho, were not significantly different than in a control group. Current PbBs in the exposed and control groups were 2.9 and 1.6 µg/dL, respectively. Data from past blood lead surveillance indicated a mean childhood PbB of approximately 45 µg/dL.

Other Neurological Effects in Children. Several studies of associations between lead exposure and hearing thresholds in children have been reported, with mixed results. A study of 49 children aged 6–12 years revealed an increase in latencies of waves III and V of the BAEP associated with PbB measured 5 years prior to the tests (mean, 28 µg/dL) (Otto et al. 1985). The current mean PbB was 14 µg/dL (range, 6–59 µg/dL). Assessment of a group of children from the Mexico City prospective study revealed significant associations between maternal PbB at 20 weeks of pregnancy (geometric mean, 7.7 µg/dL; range, 1–31 µg/dL) and brainstem auditory evoked responses in 9–39-day-old infants, 3-month-old infants, and children at 67 months of age (Rothenberg et al. 1994b, 2000). In the most recent assessment, I–V and III–V interpeak intervals decreased as PbB increased from 1 to 8 µg/dL and then increased as PbB rose from 8 to 31 µg/dL. Rothenberg et al. (2000) hypothesized that the negative linear term was

related to lead effect on brainstem auditory pathway length, and that the positive term was related to neurotoxic lead effect on synaptic transmission or conduction velocity.

Robinson et al. (1985) and Schwartz and Otto (1987, 1991) provided suggestive evidence of a lead-related decrease in hearing acuity in 75 asymptomatic black children, 3–7 years old, with a mean PbB of 26.7 µg/dL (range, 6–59 µg/dL). Hearing thresholds at 2,000 Hertz increased linearly with maximum blood lead levels, indicating that lead adversely affects auditory function. 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). An increase in PbB from 6 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.

Osman et al. (1999) found a significant association between blood lead concentration (2–39 µg/dL) and hearing thresholds in a group of 155 children ages 4–14 years, after adjustment for covariates. The association remained significant when the analysis was confined to 107 children who had blood lead concentrations below 10 µg/dL. Osman et al. (1999) also reported increased latency of wave I of the BAEP in children with PbB above 10 µg/dL compared to children with PbB below 4.6 µg/dL. Covariates included in the regression models were child gender age, Apgar score, absence of ear and nasopharynx pathologies; history of ear diseases, frequent colds, mumps, gentamycin use, or exposure to environmental noise; and maternal smoking during pregnancy. Increased BAEP interpeak latencies was also described in a study of Chinese children with a mean PbB of 8.8 µg/dL (range, 3.2–38 µg/dL) after controlling for age and gender as confounding factors (Zou et al. 2003).

In contrast with results of the studies mentioned above, Counter et al. (1997a) found no difference in hearing threshold between groups of children who had relatively low or higher exposures to lead (mainly from local ceramics glazing and automobile battery disposal). PbBs were 6 µg/dL (range, 4–12 µg/dL, n=14) and 53 µg/dL (10–110 µg/dL, n=62), respectively. In a separate study of the same cohort, Counter et al. (1997b) found normal wave latencies and neural transmission times, and no correlation between PbB and interpeak latencies in children with a median PbB 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. Subsequent studies of these children showed no evidence that PbB affected the cochlea (Buchanan et al. 1999) or BAEP interpeak conduction (Counter 2002). It is worth noting that Counter and coworkers studied children in small villages in the Andes mountains who may not be very representative of the general population.

Studies in animals also have provided mixed results regarding exposure to lead and auditory function. Some monkeys dosed with lead from birth through 13 years of age had elevated thresholds for pure tones, particularly at higher frequencies (Rice 1997). These monkeys had a PbB of approximately 30 µg/dL until 10–11 years old and 50–70 µg/dL when they were tested at 13 years of age. Studies by Lasky et al. (1995) and Lilienthal and Winneke et al. (1996) in monkeys chronically exposed to lead and with moderate PbBs suggested that lead might be altering cochlear function. However, a more recent study by Lasky and coworkers showed that continuous exposure of monkeys beginning shortly after birth until 1–2 years old, resulting in PbB 35–40 µg/dL, had no significant effect on middle ear function, cochlear function, or auditory evoked potentials assessed at least 1 year after exposure to lead (Lasky et al. 2001c).

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. Alterations in scotopic (rod-mediated) retinal function were reported in a group of 45 children (7–10 years old) participants in the Mexico City Lead Study (Rothenberg et al. 2002a). The association was significant only with lead measures during the first trimester of pregnancy and not with other periods during pregnancy or throughout postnatal development. The threshold for the effect was 10.5 µg/dL. Results from studies in animals are in general agreement with the findings in humans. For example, studies in rats exposed to lead via the mother's milk, which produced PbBs of approximately 19 µg/dL in the pups, reported reductions in retinal sensitivity attributed to selective alterations of the rods (Fox et al. 1991, 1997). Impairment of scotopic visual function was reported in monkeys treated with lead during the first year of life to produce mean PbBs of 55 or 85 µg/dL and tested 18 months later when PbBs had returned near controls levels (14 µg/dL) (Bushnell et al. 1977). Lilienthal et al. (1988) reported alterations in visual evoked potentials and in the ERG in monkeys exposed to lead during gestation and then for life, and tested at approximately 7 years old; at this time, the PbBs in the two treated groups were approximately 40 and 60 µg/dL. Alterations of the ERG under scotopic conditions were still present when the monkeys were tested again more than 2 years after termination of exposure (Lilienthal et al. 1994). Rice (1998) reported that life-time exposure of monkeys to lead producing steady-state PbBs between 25 and 35 µg/dL altered temporal

visual function, in six out of nine animals; however, there was no evidence of impairment of spatial visual function.

Bhattacharya et al. (1993) examined the effect of lead exposure on postural balance in 109 children from the Cincinnati Lead Program Project. 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 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.

3.2.5 Reproductive Effects

A number of studies have examined the potential association between lead exposure and reproductive parameters in humans. The available evidence suggest that occupational and environmental exposure resulting in moderately high PbBs might result in abortion and pre-term delivery in women, and in alterations in sperm and decreased fertility in men.

Effects in Females. Female workers at a lead smelter in Sweden had an increased frequency of spontaneous miscarriage when employed during pregnancy (294 pregnancies, 13.9% ended in spontaneous abortion) or when employed at the smelter prior to pregnancy and still living within 10 km of the smelter (176 pregnancies, 17% ended in spontaneous abortion) (Nordstrom et al. 1979). The abortion rates in these two groups of pregnant women were significantly higher than in women who were pregnant before they became employed at the smelter and in women who became pregnant after employment but lived >10 km from the smelter. Although no environmental or biological monitoring for lead was available, women who worked in more highly contaminated areas of the smelter were more likely to have aborted than were other women. A nested control-case study of a cohort of 668 pregnant women in Mexico City showed that the risk of spontaneous abortion (defined as loss of pregnancy by gestation week 20) increased with increasing PbB (Borja-Aburto et al. 1999). Notably, there was a 1.13-fold increase in the risk of spontaneous abortion per μg/dL increase in PbB. Mean PbBs in cases and controls were 12.0 and 10.1 μg/dL, respectively.

Negative associations also have been reported. For instance, no association was found between PbBs and spontaneous abortions in a cohort of women living in Port Pirie, a lead smelter community in South Australia and the surrounding rural area and neighboring towns (Baghurst et al. 1987). Mean, midpregnancy PbBs in women living in Port Pirie or outside of the town were 10.6 µg/dL (n=531) and 7.6 µg/dL (n=171), respectively (Baghurst et al. 1987; McMichael et al. 1986). While no association was found between PbB and spontaneous abortions, 22 of 23 miscarriages and 10 of 11 stillbirths occurred among the Port Pirie residents, with only 1 miscarriage and 1 stillbirth occurring among residents outside Port Pirie. Maternal PbB was 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. Alexander and Delves (1981) showed a reduction in maternal PbB during the progression of pregnancy and concluded that the reduction could not be explained by dilution of PbB in an increasing plasma volume. The authors suggested that lead was being transferred to placental or fetal tissues or eliminated from maternal blood via other pathways. The rates of spontaneous abortions were also compared in a prospective study of females living close to a lead smelter (midpregnancy mean PbB, 15.9 µg/dL; n=304) and females living 25 miles away (midpregnancy mean PbB, 5.2 µg/dL; n=335) (Murphy et al. 1990). Women were recruited at midpregnancy 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 two groups. The spontaneous abortion rates in women living close to the smelter or 25 miles away were 16.4 and 14.0%, respectively, but the differences were not statistically significant.

In the study of Australian women mentioned above, the rate of preterm delivery (delivery before the 37th week) was significantly higher in women living in the smelter town (566 pregnancies, 5.3% preterm deliveries; mean PbB, 11.2 µg/dL at the time of delivery) than in women not living in the town (174 pregnancies, 2.9% preterm deliveries; mean PbB, 7.5 µg/dL at the time of delivery) (McMichael et al. 1986). Similarly, Torres-Sánchez et al. (1999) observed that preterm births were almost 3 times more frequent in women with umbilical PbB ≥5.1 µg/dL than in women with PbB <5.1 µg/dL. In a study of 121 women biologically monitored for exposure to lead at the Finnish Institute of Occupational Health from 1973 to 1983, there was no evidence of alterations in the time-to-pregnancy (TTP) or decreased fecundability (Sallmen et al. 1995). Women were categorized as having very low exposure (PbB, <10 µg/dL), low exposure (PbB, between 10 and 19 µg/dL), or moderate-to-high exposure (PbB, ≥20 µg/dL).

Stillbirths have been reported in rats exposed to doses of lead that resulted in PbBs much higher than those reported in the studies in women mentioned above. Treatment of Sprague-Dawley rats with lead 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). PbBs in the dams and offspring in this experiment were >200 µg/dL. In subsequent studies using a similar experimental protocol, the same group of investigators reported that treatment of rats with lead 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. In studies with female monkeys, exposure to lead in the drinking water for 75 months resulted in reduced circulating concentration of progesterone, suggesting impaired luteal function; however, treatment with lead did not prevent ovulation; the PbB was approximately 70 µg/dL (Franks et al. 1989). The monkeys also exhibited longer and more variable menstrual cycles and shorter menstrual flow. Female Cynomolgus treated daily for up to 10 years with gelatin capsules containing lead acetate had significantly suppressed circulating levels of LH, FSH, and estradiol although progesterone concentrations were not significantly affected (Foster 1992). PbB in these monkeys was approximately 35 µg/dL. Also, a study in rats showed that exposure to lead can enhance some parameters of estrogen stimulation, inhibit other estrogenic responses, and some responses remain unaltered (Tchernitchin et al. 2003). In that study, female rats were administered lead acetate every 3 days from age 7 days and until they were 19 days old; the PbB in these rats was approximately 47 µg/dL. Lead enhanced the estrogen-induced eosinophilia and reduced the estrogen-induced edema deep in the endometrial stroma of treated rats. In addition, lead altered the proportion of eosinophils in the different histological layers in the uterus. A recent study with human granulosa cell *in vitro* showed that incubation with lead reduced aromatase activity as well as P-450 aromatase and estrogen receptor β protein levels (Taupeau et al. 2003). P-450 aromatase converts C19 androgens to C18 estrogenic steroids and is essential for follicular maturation, oogenesis, ovulation, and normal luteal functions in females. Moreover, mice that lack the ability to synthesize endogenous estrogen suffer folliculogenic disruption and fail to ovulate and are thus infertile. Mice that lack the estrogen receptor β also have a poor reproductive capacity attributed to folliculogenesis blockade (Taupeau et al. 2003).

Effects in Males. A study of 2,111 Finnish workers occupationally exposed to inorganic lead showed a significant reduction in fertility relative to 681 unexposed men (Sállmen et al. 2000a). The risk ratio (RR) for infertility in exposed men appeared to increase with increasing PbB; thus, the RRs for the PbB categories 10–20, 21–30, 31–40, 41–50, and ≥51 µg/dL were 1.27, 1.35, 1.37, 1.50, and 1.90, respectively; however, there was no evidence of decreased fertility in couples who had achieved at least one pregnancy. Based on the latter finding, the authors suggested that lead exposure was not associated

with a delay in pregnancy. A significant reduction in fertility was observed in a group of 74 exposed workers (mean exposure period, 10.7 years; mean PbB, 46.3 µg/dL) relative to a control group of 138 men (mean PbB, 10.4 µg/dL) (Gennart et al. 1992b). Duration of exposure was associated with decreased fertility. A study of 4,256 male workers with PbB >40 µg/dL (sampled before 1986) or ≥25 µg/dL (sampled from 1981–1992) showed a reduction in the number of births relative to a control group of 5,148 subjects (Lin et al. 1996). Workers with the highest cumulative exposure to lead had the most marked reduction in fertility. A study of 163 Taiwanese male lead battery workers showed decreased fertility in men with PbB in the range of 30–39 and ≥40 µg/dL, but there was no significant reduction in fertility in men with PbB of ≤29 µg/dL (Shiau et al. 2004). There was no effect on fertility among men (n=229) employed in a French battery factory (Coste et al. 1991) or among Danish men (n=1,349) exposed to lead (mean PbB of a subset of 400 workers, 39.2 µg/dL) during the manufacture of batteries (Bonde and Kolstad 1997). There was weak evidence of increased time-to-pregnancy (TTP) in the wives of 251 occupationally-exposed men in Finland with PbB ranging from 10 to 40 µg/dL or higher (Sállmen et al. 2000b). The study included only couples who had at least one pregnancy and the association was limited to men whose wives were <30 years old. A study with similar exposure levels in 251 Italian men did not find an association between lead exposure in men and delayed TTP in their wives (Apostoli et al. 2000). There was no association between occupational exposure to lead and low fertility in a multi-country (Belgium, Finland, Italy, and England) study of 638 men exposed occupationally to lead (Joffe et al. 2003). Mean PbB in exposed men ranged from 29.3 to 37.5 µg/dL, but most were below 50 µg/dL. Although the evidence for reduced fertility is not conclusive, it appears that a threshold for fertility effects in men could be in the PbB range of 30–40 µg/dL.

Studies have shown that sperm quality is affected by occupational exposure to lead. Although there is some variation in the results, most of the available studies suggest that reductions in sperm concentration, indications of adverse effects on sperm chromatin, and evidence of sperm abnormalities may occur in men with mean PbB > 40 µg/dL but not in men with lower PbBs. A study of 81 lead smelter workers showed an association between PbB and sperm concentration (Alexander et al. 1998a). In addition, although PbB concentrations were not related to serum testosterone, a reduction in serum testosterone with increasing semen lead concentration was observed. In a study of 150 male workers with long-term lead exposure, men with a mean PbB of 52.8 µg/dL showed asthenospermia, hypospermia, and teratospermia (Lancranjan et al. 1975). These effects were not evident in two groups of men with mean PbBs of 41 or 23 µg/dL. 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. A cross-sectional study of 149 industrial workers in Zagreb, Croatia, found that 98 men who had

moderate occupational exposure to lead (mean PbB, 36.7 µg/dL) had significantly lower sperm density, and lower counts of total motile and viable sperm; lower percentage and count of progressively motile sperm; higher prevalence of morphologically abnormal sperm head; and lower level of indicators of prostate secretory function compared with 51 referents (mean PbB, 10.3 µg/dL) (Telisman et al. 2000). No significant differences were found for semen volume or percentages of motile, viable, and pathologic sperm. Workers also had significantly higher serum estradiol than the refernce group, but there were differences in serum FSH, LH, prolactin, and testosterone levels (Telisman et al. 2000). A study of workers in a Swedish battery factory showed decreased seminal plasma constituents, low semen volumes, and reduced functional maturity of sperm in men with mean PbB of approximately 45 µg/dL during the study period (Wildt et al. 1983). The unexposed (control) group of men had a mean PbB of about 21 µg/dL. A study of men employed in a lead smelter showed that workers with current PbB of ≥40 µg/dL had an increased risk of below normal sperm and total sperm count relative to those with PbBs <15 µg/dL (Alexander et al. 1996). A cross-sectional survey of 503 European workers showed a 49% reduction in the median sperm concentration in men with PbB ≥50 µg/dL, whereas there was no significant difference in sperm concentration between the reference group of men (mean PbB, ≤10 µg/dL) and men with mean PbB of 10–50 µg/dL (Bonde et al. 2002). Although there was no association between PbBs and abnormal sperm chromatin, there were indications of deterioration of the sperm chromatin in men with the highest lead concentrations in spermatozoa (Bonde et al. 2002). Changes in sperm chromatin also have been reported in monkeys exposed to lead for life and with a mean PbB of 56 µg/dL (Foster et al. 1996). In mammalian spermatozoa, DNA is tightly packaged with protamines in the nucleus. Since lead binds tightly to free thiols, it might compete or replace the zinc atoms that are normally bound with nuclear protamines. These changes could affect normal disulfide bond formation, alter DNA-protamine binding, or impair chromatin decondensation during fertilization (Quintanilla-Vega et al. 2000; Silbergeld et al. 2003). Sperm protamine plays an important role in the condensation-decondensation events that are critical to fertilization, and cases of male infertility have been associated with deficiencies in human protamine (Quintanilla-Vega et al. 2000). A recent study from the latter group supported their earlier hypothesis that lead affects sperm chromatin condensation (Hernández-Ochoa et al. 2005). In a group of 68 urban men with a geometric mean PbB of 9.3 µg/dL (range, 1.9–24.4 µg/dL) 54% of semen samples showed values for sperm chromatin condensation outside the normal range. In addition, evaluation of semen quality parameters and sperm chromatin showed that sperm concentration, motility, morphology, and viability were negatively associated with lead in spermatozoa, whereas semen volume was negatively associated with lead seminal fluid. PbB did not associate with either semen quality parameters or nuclear chromatin decondensation, and PbB did not correlate with lead levels in any semen compartment (Hernández-Ochoa et al. 2005). Smaller studies (<40 men/study) of men exposed to

lead have also shown detrimental changes in sperm quality (Assennato et al. 1987; Chowdhury et al. 1986; Lerda 1992).

Direct toxic effects of lead on the testicle might mediate the adverse reproductive effects of lead in occupationally exposed men. A study of 122 workers (mean PbB, 35.1 µg/dL; mean exposure duration, 6 years) employed in three lead battery factories in Singapore showed higher serum LH and FSH concentrations in the exposed workers than in 49 unexposed individuals (mean PbB, 8.3 µg/dL) (Ng et al. 1991). However, there was no difference in testosterone levels between these two groups. Raised LH and FSH levels are an indication of Leydig and Sertoli cell failure (Ng et al. 1991). These results are in general agreement with those of earlier studies of lead workers with high PbBs (≥66 µg/dL). These findings indicate that lead can act directly on the testes to cause depression of sperm count and peritubular testicular fibrosis, reduced testosterone synthesis, and disruption of regulation of LH (Braunstein et al. 1978; Cullen et al. 1984; Rodamilans et al. 1988).

The question of whether lead poisoning as a child can have adverse reproductive effects later in life was examined in a group of 35 survivors of childhood plumbism who had been admitted to the Boston Children's Hospital for treatment from 1930 to 1944 (Hu 1991b). Plumbism was diagnosed in children who showed repeated ingestion of lead-containing material or x-ray or clinical evidence of lead poisoning. Although the rates of spontaneous abortions or stillbirths in this group of survivors appeared to be higher than in unexposed matched subjects, the differences were not statistically significant (RR, 1.60; 95% CI, 0.6–4.0).

Sperm parameters also have been examined in animals exposed to lead. Evaluation of 15–20-year-old Cynomolgus monkeys administered lead acetate for their lifetime and having a mean PbB of 56 µg/dL showed no significant alterations in parameters of semen quality such as sperm count, viability, motility, and morphology, or in circulating levels of testosterone (Foster et al. 1996). Adverse sperm effects have been observed in rats, but at relatively high PbBs (Barratt et al. 1989; Hsu et al. 1998a, 1998b). A significant reduction in the number of spermatozoa within the epididymis was observed in mice administered lead acetate in drinking water for 6 weeks, but PbBs were not provided (Wadi and Ahmad 1999). In male rats exposed maternally to lead during gestation and lactation and administered lead for an additional 9 months after weaning, there were no significant effects on sperm count or sperm morphology (Fowler et al. 1980). The PbB in these animals ranged from 4.5 to 67 µg/dL.

Numerous studies in animals have reported testicular effects following exposure to lead. For example, Foster et al. (1998) evaluated changes in testis ultrastructure, semen characteristics, and hormone levels in monkeys exposed to lead from postnatal day 300 to 10 years of age (postinfancy), from postnatal day 0 to 400 (infancy), or for their lifetime. PbBs in lifetime and postinfancy exposed monkeys were approximately 35 µg/dL compared to <1.0 µg/dL in controls and infancy exposed animals. Electron microscopic analysis revealed disruption 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. Circulating concentrations of FSH, LH, and testosterone were not altered by treatment with lead, and semen characteristics were not affected by treatment with lead. Other effects reported in recent studies in rats following oral dosing with lead include disorganization and disruption of spermatogenesis and reduction in the activities of the enzymes alkaline phosphatase and Na^+-K^+-ATPase (Batra et al. 2001), and an increase in the percentage of seminiferous tubules showing apoptotic germ cells (Adhikari et al. 2001). No PbBs were reported in these two studies. Also, male rats administered lead acetate in water for 1 week (PbB, 12–28 µg/dL) showed a dose-related increase in gonadotropin-releasing hormone (GnRH) mRNA (Sokol et al. 2002). However, lead did not have an effect on the serum concentrations of hypothalamic gonadotropin-releasing hormone (GnRH) or LH, suggesting a compensatory mechanism in the hypothalamic-pituitary axis. In the only study of exposure by the inhalation route, CD-1 male mice exposed to 0.01 M lead acetate intermittently for 4 weeks showed a time-related increase in the fraction of damaged mitochondria in Sertoli cells, which according to the investigators could lead to a transformation process that may interfere with spermatogenesis (Bizarro et al. 2003).

3.2.6 Developmental Effects

This section summarizes studies of the effects of lead exposure on end points other than neurological in developing organisms exposed during the period from conception to maturity. Neurodevelopmental effects are summarized in Section 3.2.4.

No reports were found indicating low levels of lead as a cause of major congenital anomalies. However, in a study of 5,183 consecutive deliveries of at least 20 weeks of gestation, cord blood lead was associated with the incidence of minor anomalies (hemangiomas and lymphangiomas, hydrocele, skin anomalies, undescended testicles), but not with multiple or major malformations (Needleman et al. 1984). In

addition, no particular type of malformation was associated with lead. According to the investigators, the results suggested that lead may interact with other teratogenic risk factors to enhance the probability of abnormal outcome.

Anthropometric Indices. Since the report by Nye (1929) of runting in overtly lead-poisoned children, a number of epidemiological studies have reported an association between PbB and anthropometric dimensions. For example, a study of 1-month-old Mexican infants found that infant PbB (measured at birth in umbilical cord and at 1 month of age) was inversely associated with weight gain, with an estimated decline of 15.1 grams per μg/dL of blood lead (Sanín et al. 2001). The mean infant (at 1 month) and maternal PbBs (1 month postpartum) were 5.6 and 9.7 μg/dL, respectively; mean umbilical cord lead was 6.8 μg/dL. They also found that children who were exclusively breastfed had significantly higher weight gains, but this gain decreased significantly with increasing levels of maternal patella lead. An additional study from the same groups of investigators reported that birth length of newborns decreased as maternal patella lead increased, and also that patella lead was significantly related to the risk of a low head circumference score (Hernandez-Avila et al. 2002). In the Mexico City Prospective Study, an increase in PbB at 12 months of age from 6 to 12.5 μg/dL was associated with a decrease in head circumference of 0.34 cm (Rothenberg et al. 1999c). Also, a study by Stanek et al. (1998) reported that in children aged 18–36 months, with a mean PbB of 6.4 μg/dL, PbB was inversely related with head circumference.

In the Cincinnati Prospective Study, higher prenatal PbB was associated with reduced birth weight and reduced gestational age (Dietrich et al. 1987a). Analyses of the data 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 (Bornschein et al. 1989). The investigators 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 cm per natural log unit of maternal PbB was seen, but only in white infants. In a later report, the prenatal PbB (mean, 8.2 μg/dL; range, 1–27 μg/dL) was related to lower birth weight (Dietrich et al. 1989). PbBs ≥10 μg/dL also were significantly associated ($p<0.05$) with a decrease in total days of gestation and an increase risk of preterm and small-for-gestational-age birth in a sample of 262 mother-infant pairs from the general population in California (Jelliffe-Pawlowski et al. 2006). Lower mean birth weight and In a study of 705 women from Camden, New Jersey, with PbBs throughout pregnancy below 1.5 μg/dL, PbB showed no significant association with low birth weight, preterm delivery, Apgar scores, or small-for-gestational age (Sowers et al. 2002a). In contrast, in a study of 148 Russian mothers and 114 Norwegian mothers with maternal and cord PbBs as low as 1.2 μg/dL, PbBs had a negative impact on birth weight

and child's body mass index (BMI, weight in kg divided by the square of the height in meters) with or without adjusting for gestational age (Odland et al. 1999). In a study of 89 mother-infant pairs from Spain, higher placental lead levels were unrelated to smaller birth weight, head and abdominal circumference, or shorter length at birth (Falcón et al. 2003).

Analyses of data for 2,695 children ≤7 years old from the NHANES II study indicated that PbB (range, 4–35 µg/dL) was a statistically significant predictor of children's height, weight, and chest circumference, after controlling for age, race, sex, and nutritional covariates (Schwartz et al. 1986). The mean PbB 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 had been zero. An analysis of data on PbB for 4,391 U.S. children, ages 1–7 years, recorded in the NHANES III (1988–1994) showed that increasing PbB (1–72 µg/dL) was significantly associated with decreasing body stature (length or height) and head circumference, after adjusting for covariates (Ballew et al. 1999). An increase in PbB of 10 µg/dL was associated with a 1.57 cm decrease in stature and a 0.52 cm decrease in head circumference. A study of 1,454 Mexican-American children aged 5–12 who were participants in the Hispanic Health and Nutrition Examination Survey (HHANES) conducted in 1982–1984 found that PbBs in the range of 2.8–40 µg/dL were related with decreased stature (Frisancho and Ryan 1991). The mean PbB 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 by hematocrit and PbB; in females, the same 82% was accounted by age, poverty index, and PbB. After adjusting for these covariates, children whose PbB was above the median for their age and sex (9–10 µg/dL range) were 1.2 cm shorter than children with PbBs below the median. Angle and Kuntzelman (1989) also reported reduced rates of height and weight from birth to 36 months in children with PbB of ≥30 µg/dL.

Evaluation of 260 infants from the Cincinnati Prospective Study revealed that postnatal growth rate (stature) from 3 to 15 months of age was inversely correlated with increases in PbB during the same period, but this effect was significant only for infants whose mothers had prenatal PbB >7.7 µg/dL (Shukla et al. 1989). Reevaluation of 235 infants during the second and third years of life revealed that mean PbB during the second and third years was negatively associated ($p=0.002$) with attained height at 33 months of age (Shukla et al. 1991). However, this association was observed only among children who had mean PbBs greater than the cohort median (10.8 µg/dL) during the 3–15-month 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.

An absence of significant associations between lead exposure and anthropomorphic measures has also been reported. Evaluation of 359 mother-infant pairs from the Cleveland Prospective Study found no statistically significant effect of PbBs on growth from birth through age 4 years 10 months after controlling for a variety of possible confounding factors (Greene and Ernhart 1991). Also, a study of 104 children who suffered lead poisoning (PbB up to 470 µg/dL) between the ages of 16 and 55 months and underwent chelation therapy showed normal height when they were evaluated at 8 and 18 years of age (Sachs and Moel 1989). At age 18, all patients had PbBs <27 µg/dL. A study by Kim et al. (1995) found that bone lead was not associated with physical growth in a cohort of children followed longitudinally for 13 years. The children were first assessed in 1975–1978 and then in 1989–1990. However, the study found that dentin lead was positively associated with BMI as of 1975–1978 and increased BMI between 1975–1978 and 1989–1990. Confounders controlled for included age, sex, baseline body size, and mother's socioeconomic status. According to the investigators, the results suggested that chronic lead exposure during childhood may result in obesity that persists into adulthood.

As previously mentioned under *Musculoskeletal Effects*, studies in animals, mostly 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 (Escribano et al. 1997; Gonzalez-Riola et al. 1997; Gruber et al. 1997; Hamilton and O'Flaherty 1994, 1995; Ronis et al. 2001). Ronis et al. (2001) showed that in rats, exposure to lead reduced somatic longitudinal bone growth and bone strength during the pubertal period. These effects could not be reversed by a growth hormone axis stimulator or by sex appropriate hormone, suggesting that the lead effects are not secondary to growth hormone axis disruption. It should be mentioned that the blood lead levels achieved in the pups were in the range of 67–192 µg/dL.

Sexual Maturation. Two studies provide information on the effect of lead exposure on sexual maturation in girls. Selevan et al. (2003) performed an analysis of data on blood lead concentrations and various indices of sexual maturation in a group of 2,741 U.S. female children and adolescents, ages 8–18 years, recorded in the NHANES III (1988–1994). Increasing PbB was significantly associated with decreasing stature (height) and delayed sexual development (lower Tanner stage, a numerical categorization of female sexual maturity based on breast and pubic hair development), after adjusting for covariates. The geometric mean PbB among the three major race/ethnicity categories recorded in the NHANES III was 1.4 µg/dL (95% CI, 1.2–1.5) in non-Hispanic whites, 2.1 µg/dL (95% CI, 1.9–2.3) in African Americans, and 1.7 µg/dL (95% CI, 1.6–1.9) in Mexican Americans. ORs for differences in breast and pubic hair development, and age at menarche were significant in comparisons made at PbBs of 1 and 3 µg/dL in the

African American group. Delays in sexual development, estimated for Tanner stages 2–5, ranged from 4 to 6 months. ORs were significant for breast and pubic hair development, but not for age at menarche in the Mexican American group. Covariates included in the models were age, height, body mass index; history of tobacco smoking or anemia; dietary intakes of iron, vitamin C and calcium; and family income. Selevan et al. (2003) acknowledged that other factors associated with body lead burden and pubertal development that they did not assess may be responsible for the observed associations. In addition, they noted that reporting of past events, such as age at menarche and dietary history, could have been subject to errors in recall. Finally, potential confounders that were measured at the time of the study may have differed during periods critical for pubertal development or other unmeasured confounders may have affected the results.

An additional study of the same cohort also found a significant and negative association between PbB and delayed sexual maturation (Wu et al. 2003a). The study included 1,706 girls 8–16 years old with PbB ranging from 0.7 to 21.7 µg/dL. PbBs were categorized in three levels: 0.7–2, 2.1–4.9, and 5.0–21.7 µg/dL. Covariates included in the models were race/ethnicity, age, family size, residence in a metropolitan area, poverty income ratio, and body mass index. Girls who had not reached menarche or stage 2 pubic hair had higher PbBs than did girls who had. Among girls in the three levels of PbB mentioned above, the unweighted percentages of 10-year-old girls who had attained Tanner stage 2 pubic hair were 60, 51, and 44%, respectively, and for 12-year-old girls who reported reaching menarche, the values were 68, 44, and 39%, respectively. These negative relationships remained significant in logistic regression even after adjustment for the covariates mentioned above. Interestingly, no significant association was found between PbB and breast development, in contrast to the findings of Selevan et al. (2003) who used the same database. Wu et al. (2003b) concluded that although they found a significant negative association between low PbB and some markers of sexual maturation, judicious interpretation of the results is needed given the cross-sectional study sample and limited attention to other nutritional or genetic factors that may impact the findings.

Some studies have reported delays in sexual maturation in animals exposed to lead, although associated with PbBs much higher than those measured in girls in the Selevan et al. (2003) and Wu et al. (2003b) studies. For example, Grant et al. (1980) reported delayed vaginal opening in female rats exposed *in utero* and via lactation and then directly. PbBs in these female offspring ranged between 20 and 40 µg/dL. Exposure of male and female Sprague-Dawley rats prepubertally (age 24–74 days) to lead acetate in the drinking water 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 PbBs in rats exposed prepubertally and postpubertally were 57 and 31 µg/dL, respectively. In the same study, an additional group of rats was exposed 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 PbB achieved in the offspring, approximately 316 µg/dL. In follow-up studies, it was found that prenatal lead exposure that continued until adulthood (85 days old) delayed sexual maturation in male and female pups in a dose-related manner (Ronis et al. 1998a, 1998b, 1998c). PbBs in the pups between the ages of 21 and 85 days were >100 µg/dL and reached up to 388 µg/dL. Effects at much lower PbBs were reported by Dearth et al. (2002), who treated Fisher 344 rats with lead by gavage from 30 days before mating until weaning the pups at 21 days of age. A cross-fostering design allowed the female pups to be exposed during gestation and lactation or during only one of those periods. PbB in the dams was about 38 µg/dL at breeding, peaked at about 46 µg/dL on lactation day 1, and decreased thereafter. Pups exposed during gestation and lactation had the highest PbB of 38.5 µg/dL on day 10; at this time, the PbBs in pups exposed during gestation only and lactation only were 13.7 and 27.6 µg/dL, respectively. By day 30, all three groups had PbBs ≤3 µg/dL. Vaginal opening as well as first diestrus was significantly delayed to similar extents in all treated groups. This delay was associated with decreased serum levels of insulin-like growth factor-1 (IGF-1), LH, and estradiol. Since liver IGF-1 mRNA was not affected, it appeared that lead altered translation and/or secretion of IGF-1, which in turn decreased LH-releasing hormone at the hypothalamic level. A subsequent study in both Sprague-Dawley and Fisher 344 rats (Dearth et al. 2004) showed that the latter strain is more sensitive to maternal lead exposure than Sprague-Dawley rats regarding puberty-related effects, which could, in part, explain the discrepancy with the effect levels reported by Ronis and coworkers. Results similar to those of Dearth et al. (2002) were reported in Swiss mice by Iavicoli et al. (2004). Female offspring of mice treated with various levels of lead in the diet during pregnancy, lactation, and then directly showed dose-related delay in sexual maturation. Blood lead levels of the dams were not determined; blood lead levels of the female offspring determined once at estrus (day 24–44) ranged from 0.7 to 13.2 µg/dL. Removing lead from the control diet (0.2 ppm Pb) reduced PbB in the offspring from 2–3 to 0.7 µg/dL and accelerated puberty from age 33–37 days to age 21 days.

Hematological Effects. The hypothesis that PbB might be associated with depressed erythropoietin (EPO) in children was examined in subjects from the Yugoslavia Prospective Study (Factor-Litvak et al. 1998; Graziano et al. 2004) (see Section 3.2.4 for a detailed description of the Yugoslavia Prospective Study). EPO is a glycoprotein hormone that regulates both steady-state and accelerated erythrocyte

production. Nearly all of the EPO is produced in the proximal tubule of the kidney. PbB, EPO, and hemoglobin were measured at ages 4.5, 6.5, 9.5, and 12. In addition, tibial lead concentration was measured at age 12. Mean PbBs in the exposed children at the age of 4.5 and 9 years were 39 and 28 µg/dL, respectively, and mean hemoglobin concentration throughout the study period was within normal limits. The results of the analyses, after adjusting for hemoglobin, showed that serum EPO was positively associated with PbB at ages 4.5 and 6.5 years, but the magnitude of the association gradually declined from 4.5 to 12 years. This suggested that in children with moderate PbB, hyperproduction of EPO is necessary to maintain normal hemoglobin concentrations. The decline in slope with age suggested that the compensatory mechanism gradually begins to fail due to lead-induced loss of renal endocrine function. No association was found between tibia lead and EPO. Different results were reported by Liebelt et al. (1999) in a pilot study of 86 children between 1 and 6 years of age with a median PbB of 18 µg/dL (range, 2–84 µg/dL) recruited from a university-based lead clinic and primary care clinic. The investigators in that study found an inverse relationship between PbB and serum EPO concentration. Confounding by age in the Liebelt et al. (1999) study may have contributed to the discrepancy in results. A study of 88 children (2–15 years old) living in a highly lead-contaminated area in the Equatorian Andes reported a significant inverse correlation between PbB and hemoglobin concentration (Counter et al. 2000). The mean PbB was 43.2 µg/dL and the range was 6.2–128.2 µg/dL.

3.2.7 Genotoxic Effects

The potential genotoxic effects of lead have been studied in lead workers and members of the general population, as well as in *in vitro* cultures of mammalian cells and microorganisms. Although not always consistent, the results suggest that lead is a clastogenic agent, as judged by the induction of chromosomal aberrations, micronuclei, and sister chromatid exchanges (SCE) in peripheral blood cells (Table 3-6).

Nordenson et al. (1978) reported a significant increase in chromosomal aberrations in peripheral lymphocytes from a group of 26 lead workers with a mean PbB of approximately 65 µg/dL, and so did Schwanitz et al. (1970), Forni et al. (1976), Al-Hakkak et al. (1986), and Huang et al. (1988b) in workers with mean PbBs of 60–80 µg/dL (n=8), 40–50 µg/dL (n=11), 64 µg/dL (n=19), and 50 µg/dL (n=21), respectively. Schwanitz et al. (1975) reported a small, but not statistically significant increase in chromosomal aberrations in lead workers with a mean PbB of 38 µg/dL. Negative results were reported by Mäki-Paakkanen et al. (1981) among a group of 13 workers with a mean PbB of 49 µg/dL, by Bulsma and De France (1976) in 11 volunteers who ingested lead acetate for 49 days and had a PbB of 40 µg/dL, and by O'Riordan and Evans (1974) in 70 workers with PbBs ranging from <40 µg/dL to 120 µg/dL. A

Table 3-6. 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
Lead workers, peripheral lymphocytes	Micronuclei	+	Vaglenov et al. 2001
		+	Vaglenov et al. 1998
Lead workers, peripheral lymphocytes	DNA damage	+	Danadevi et al. 2003
		+	Fracasso et al. 2002
Lead workers, peripheral lymphocytes	Chromosomal aberration	+	Al-Hakkak et al. 1986
		+	Forni et al. 1976
		–	Mäki-Paakkanen et al. 1981
		+	Nordenson et al. 1978
		–	O'Riordan and Evans 1974
		+	Schwanitz et al. 1975
		+	Huang et al. 1988b
Children, general population	Chromosomal aberration	–	Bauchinger et al. 1977
Adults, general population	Chromosomal aberration	–	Bulsma and De France 1976
Lead workers, peripheral lymphocytes	Sister chromatid exchange	±	Grandjean et al. 1983
		–	Mäki-Paakkanen et al. 1981
		+	Huang et al. 1988b
		+	Duydu et al. 2001
		+	Wu et al. 2002
Children, general population	Sister chromatid exchange	–	Dalpra et al. 1983
Adults, general population	Altered cell division	+	Bulsma and De France 1976
Lead workers, peripheral lymphocytes	Altered cell division	+	Sarto et al. 1978
		+	Schwanitz et al. 1970

– = negative result; + = positive result; ± = inconclusive result; DNA = deoxyribonucleic acid

study of 30 children living in a town with a lead plant also found no evidence for lead-induced chromosomal aberrations; PbBs among the children ranged from 12 to 33 µg/dL (Bauchinger et al. 1977). Exposure concentrations were not reported in any of the studies mentioned above.

A significant increase in sister chromatid exchanges was reported in 23 lead workers whose mean PbB was approximately 32 µg/dL (Wu et al. 2002). In this study, the TWA exposure concentration, measured for 11 lead workers, ranged from 0.19 to 10.32 mg/m^3. Similar results were obtained in a study of 31 workers with a mean PbB of 36 µg/dL (Duydu et al. 2001). In the latter study, the urinary concentration of ALA exhibited a stronger correlation with SCE frequencies than PbB, which led the authors to suggest a possible ALA-mediated mechanism in the genotoxic effects of lead. An increase in SCE frequencies also was reported in workers with a PbB ≥80 µg/dL, but not less (Huang et al. 1988b). In contrast, in a group of 18 workers with a mean PbB of 49 µg/dL, there was no detectable increase in SCE frequency relative to controls (PbB <10µg/dL) (Mäki-Paakkanen et al. 1981); the concentration of lead in air ranged from 0.05 to 0.5 mg/m^3. Grandjean et al. (1983) observed that PbB and SCE rates decreased in lead workers after summer vacation. They also noticed that newly employed workers failed to show any increase in SCE rates during the first 4 months of employment despite increases in both ZPP and PbB, suggesting that genotoxic effects may occur after long exposure to lead. This could also suggest that current PbB is not a good biomarker of genotoxic effects. A study of 19 children living in a widely contaminated area reported no significant differences in SCE rates between the exposed children (PbB, 30–60 µg/dL) and 12 controls (PbB, 10–21 µg/dL) (Dalpra et al. 1983).

An increased incidence of micronuclei in peripheral lymphocytes was observed in a group of 22 lead workers whose mean PbB was 61 µg/dL relative to control groups with mean PbBs of 18 or 28 µg/dL (Vaglenov et al. 1998). The concentration of lead in the air ranged from 0.13 to 0.71 mg/m^3 (mean, 0.45 mg/m^3). After the workers consumed a polyvitamin-rich diet for 4 months, the micronuclei frequency showed a significant reduction, which led the authors to suggest that oxidative damage might be involved in the genotoxicity of lead. However, since concurrent controls were not administered vitamins, and the exposed workers were not divided into vitamin-treated and untreated groups, the possibility that the reduction in micronuclei was unrelated to the treatment with vitamins could not be ruled out. In a subsequent study from the same investigators in which lead workers were stratified into four exposure levels, PbBs >25 µg/dL were associated with significant increases in micronuclei frequency (Vaglenov et al. 2001).

Lead exposure also has been shown to be associated with DNA damage. For example, battery plant workers (n=37) had significantly elevated levels of DNA breaks in lymphocytes compared to unexposed subjects (n=29) (Fracasso et al. 2002). Moreover, the authors found significant correlations between DNA breaks and increased production of reactive oxygen species (ROS) and decreased glutathione levels in the lymphocytes, pointing to oxidative stress as a possible cause for the specific responses. Similar results were reported in a study in which workers were exposed to an air lead concentration of 0.004 mg/m^3 and had a mean PbB of 25 µg/dL (Danadevi et al. 2003). DNA damage also was observed in a mice model of lead inhalation (Valverde et al. 2002). A single 60-minute exposure to 6.8 µg/m^3 lead acetate induced DNA damage in the liver and lung, but subsequent inhalation induced DNA damage also in the nasal epithelium, whole blood, kidney, bone marrow, and brain; no DNA damage was seen in the testicles. In general, DNA damage in the lung, liver, and kidney was correlated with length of exposure and lead concentration in the tissue.

For the most part, mutagenicity tests in microorganisms have yielded negative results (Table 3-7).

3.2.8 Cancer

Almost all of the information regarding lead exposure and cancer in humans is derived from studies of lead workers and involves exposure to inorganic lead. Several reviews on this topic have been published recently (Landrigan et al. 2000; Silbergeld 2003; Silbergeld et al. 2000; Steenland and Boffetta 2000).

Malcolm and Barnett (1982) studied the causes of death of 754 subjects from a cohort of 1,898 retired lead acid battery workers during the period 1925–1976 in the United Kingdom. The only significant finding regarding cancer was a small but significant excess of malignant neoplasms of the digestive tract (observed/expected, 21/12.6) among men dying in service and who were classified as having the highest lead exposure; the excess was confined to the period 1963–1966, when lead levels were presumably higher than in later years. A subsequent study of workers from the same manufacturing facilities found no association between lead exposure and deaths from malignant neoplasms, either in general or for specific sites (Fanning 1988). Cooper et al. (1985) followed mortality rates among cohorts of 4,519 battery-plant workers and 2,300 lead production workers during 34 years. An increased SMR was found 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 or duration of exposure. In addition, no adjustments could be made for other concomitant industrial exposures or for smoking. Smoking could easily explain the small increase in

Table 3-7. Genotoxicity of Lead *In Vitro*

End point	Species (test system)	Results[a] With activation	Results[a] Without activation	Reference
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	+	Ariza et al. 1998; Bauchinger and Schmid 1972; Costa et al. 1982; Robison et al. 1984; Zelikoff et al. 1988
Chinese hamster fibroblasts	Micronuclei	NA	+	Thier et al. 2003
Human melanoma cells	Micronuclei	NA	+	Poma et al. 2003
Human lymphocytes	Structural chromosomal aberration	NA	+ – – –	Beek and Obe 1974 Deknudt and Deminatti 1978 Gasiorek and Bauchinger 1981 Schmid et al. 1972
Human lymphocytes	DNA double-strand breaks, DNA-protein cross-links	NA	+	Woźniak and Blasiak 2003
Human lymphocytes	Sister chromatid exchange	NA	– +	Beek and Obe 1975 Niebuhr and Wulf 1984
Human melanoma cells	Sister chromatid exchange	NA	+	Poma et al. 2003

C = negative result; + = positive result; DNA = deoxyribonucleic acid; NA = not applicable; RNA = ribonucleic acid

respiratory cancer in an industrial cohort that contained an excess of heavy smokers. Cocco et al. (1998b) found a 60% increased risk of cancer of the gastric cardia for subjects with high-level exposure to lead. However, cross-tabulation of gastric cardiac cancer risk by probability and levels of exposure to lead did not show consistent trends. No association was found between lead exposure and stomach cancer in a nested case-control study at a battery plant that had 30 stomach cancer deaths (Wong and Harris 2000); the 30 cases represented half of 60 stomach cancers in the total cohort of about 6,800 workers. No dose-response was found using a variety of exposure indices.

A study of 437 Swedish smelter workers with verified high lead exposure for at least 3 years from 1950 to 1974 reported an increased SMR only for lung cancer, which did not achieve statistical significance when compared with national and county mortality rates specified for cause, sex, and calendar periods (Gerhardsson et al. 1986b). Environmental lead levels and PbBs were available for all workers since 1950. Mean PbB for the workers was 58 µg/dL in 1950 and 34 µg/dL in 1974. A follow-up study of 1,992 workers at this smelter found an increased SMR (1.5, 95% CI, 0.8–2.4) for all malignancies among a group with the highest exposure, and a considerably higher SMR (4.1, 95% CI, 1.5–9.0) for lung cancer (Lundstrom et al. 1997). However, since the workers may have been exposed to other carcinogens, including arsenic, the specific role of lead cannot be ascertained. A third study of 664 Swedish workers found an increase in deaths due to malignant neoplasms, but no dose-response pattern could be discerned, and the risk estimates did not increase when a latency period of 15 years was applied (Gerhardsson et al. 1995a). The study also found an increased incidence of gastrointestinal malignancies among the workers exposed to lead, a tendency that was related to employment before 1970 and not to lead dose or to latency time. Data regarding dietary and smoking habits were not available.

A study of 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 PbB ≥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 a subsequent study of this same cohort, an excess risk of nervous system cancer, specifically gliomas, was found in workers with a PbB ≥29 µg/dL compared with those whose PbB 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. Data from Cocco et al. (1998a) also suggested that exposure to lead may be associated with an increase in brain cancer risk. The authors analyzed 27,060 cases of brain cancer and 108,240 controls that died of nonmalignant diseases in

24 U.S. states in 1984–1992. The risk was observed mainly among men likely to have been heavily exposed to lead, which comprised 0.3–1.9% of the study population.

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. Compared with the national mortality rates, stomach cancer and lung cancer were significantly decreased, while deaths from cancer of the liver and biliary tract, bladder cancer, and kidney cancer were increased nonsignificantly above expectation. Compared to regional mortality rates, bladder cancer, kidney cancer, and brain cancer were increased. 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. Selevan et al. (1985) and a follow-up by Steenland et al. (1992) also reported an excess in kidney cancer among workers employed at a lead smelter in Kellogg, Idaho.

Finally, 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 (OR, 3.7; 90% CI, 1.3–10.2) (Fayerweather et al. 1997). The OR increased 4 times at the high-to-very high cumulative exposure level, demonstrating a dose-response relationship. When a latency period of 10 years 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.

Fu and Boffetta (1995) conducted a meta-analysis of lead-worker studies focusing on overall cancer, stomach cancer, lung cancer, kidney cancer, and bladder cancer. They found a significant excess risk of overall cancer, stomach cancer, lung cancer, and bladder cancer. More recently, Steenland and Boffetta (2000) did a meta-analysis of eight major occupational studies on cancer mortality or incidence in workers with high lead exposure. The results provided some limited evidence of increased risk of lung cancer and stomach cancer, although there might have been confounding with arsenic exposure in the study with highest relative risk of lung cancer. The results also showed a weak evidence for an association with kidney cancer and gliomas.

In the only available study of the general population, Jemal et al. (2002) examined the relationship of PbB and all cancer mortality using data from the NHANES II Mortality Study. The study consisted of 203 deaths (117 men, 86 women) among 3,992 whites (1,702 men, 1,890 women) with an average of 13.3 years of follow-up. Log-transformed PbB was either categorized into quartiles or treated as a

continuous variable in a cubic regression spline. After adjusting for confounding covariates, the analyses of the association of quartiles of PbB with all cancer mortality revealed that the risk of cancer mortality was not significantly associated with PbB among men and women combined and among separate analyses of men and women. In addition, none of the site-specific cancer relative risks were significant. Spline analyses found no dose-response for men and women combined or for men alone. However, for women, there appeared to be a threshold at about the 94th percentile of lead, corresponding to a PbB of 24 µg/dL. The authors noted that the results of the spline analysis in women need to be replicated before they can be considered believable and concluded that individuals with PbB in the range of the NHANES II (weighted median, 13 µg/dL) do not appear to have increased risk of cancer mortality.

The available data on the carcinogenicity of lead following ingestion by laboratory animals indicate that lead is carcinogenic, and that the most common tumors that 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. Subcutaneous administration of lead phosphate to rats was associated with high incidence of renal tumors (Balo et al. 1965; Zollinger 1953). A study in mice provided suggestive evidence of carcinogenicity of lead following perinatal exposure (Waalkes et al. 1995). In that study, mice were exposed to one of three doses of lead acetate in the drinking water from gestation day 12 until 4 weeks postpartum, such that offspring were exposed *in utero* and via lactation. Offspring were not exposed directly and were sacrificed at 112 weeks postpartum. Renal tubular cell adenomas occurred in high-dose male offspring at a rate of 20% (5/25), whereas renal tubular cell carcinomas occurred in low-dose males (1/25) and in mid-dose males (1/25); no carcinomas were seen in low- or mid-dose males. In exposed male offspring, the incidence of renal tubular cell atypical hyperplasia was increased in a dose-related manner. In female offspring, lesions occurred at a lower rate.

The mechanism of lead-induced carcinogenicity in animals is not known, but some nongenotoxic mechanisms that have been proposed include inhibition of DNA synthesis and repair, alterations in cell-to-cell communication, and oxidative damage (Silbergeld et al. 2000). Based on inadequate evidence in humans and sufficient evidence in animals, EPA has classified inorganic lead in Group B2, probable human carcinogen (IRIS 2005). The Department of Health and Human Services has determined that lead and lead compounds are reasonably anticipated to be human carcinogens (NTP 2005). The International Agency for Research on Cancer has determined that inorganic lead is probably carcinogenic to humans and that organic lead compounds are not classifiable as to their carcinogenicity to humans (IARC 2004).

3.3 TOXICOKINETICS

Overview. Inorganic lead can be absorbed following inhalation, oral, and dermal exposure, but the latter route is much less efficient than the former two. Studies in animals have shown that organic lead is well absorbed through the skin. Inorganic lead in submicron size particles can be almost completely absorbed through the respiratory tract, whereas larger particles may be swallowed. The extent and rate of absorption of lead through the gastrointestinal tract depend on characteristics of the individual and on physicochemical characteristics of the medium ingested. Children can absorb 40–50% of an oral dose of water-soluble lead compared to 3–10% for adults. Gastrointestinal absorption of inorganic lead occurs primarily in the duodenum by saturable mechanisms. The distribution of lead in the body is route-independent and, in adults, approximately 94% of the total body burden of lead is in the bones compared to approximately 73% in children. Lead in blood is primarily in red blood cells. Conditions such as pregnancy, lactation, menopause, and osteoporosis increase bone resorption and consequently also increase lead in blood. Lead can be transferred from the mother to the fetus and also from the mother to infants via maternal milk. Metabolism of inorganic lead consists of formation of complexes with a variety of protein and nonprotein ligands. Organic lead compounds are actively metabolized in the liver by oxidative dealkylation by P-450 enzymes. Lead is excreted primarily in urine and feces regardless of the route of exposure. Minor routes of excretion include sweat, saliva, hair, nails, and breast milk. The elimination half-lives for inorganic lead in blood and bone are approximately 30 days and 27 years, respectively. Several models of lead pharmacokinetics have been proposed to characterize such parameters as intercompartmental lead exchange rates, retention of lead in various tissues, and relative rates of distribution among the tissue groups. Some models are currently being used or are being considered for broad application in lead risk assessment.

3.3.1 Absorption

3.3.1.1 Inhalation Exposure

Inorganic Lead. Inorganic lead in ambient air consists of aerosols of particulates that 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 air-stream velocity within the respiratory tract (James et al. 1994). 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. Smaller particles (<1 μm), which can be deposited in the alveolar region, can be absorbed after extracellular dissolution or ingestion by phagocytic cells (see Section 3.4.1 for further discussion).

The respiratory tract deposition and clearance from the respiratory tract have been measured in adult humans (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). In these studies, exposures were to lead-bearing particles having mass median aerodynamic diameters (MMAD) below 1 μm and, therefore, deposition of the inhaled lead particles can be assumed to have been primarily in the bronchiolar and alveolar regions of the respiratory tract (James et al. 1994) where transport of deposited lead to the gastrointestinal tract is likely to have been only a minor component of particle clearance (Hursh et al. 1969). Approximately 25% of inhaled lead chloride or lead hydroxide (MMAD 0.26 and 0.24 μm, respectively) was deposited in the respiratory tract in adult subjects who inhaled an inorganic lead aerosol through a standard respiratory mouthpiece for 5 minutes (Morrow et al. 1980). Approximately 95% of deposited inorganic lead that is inhaled as submicron particles is absorbed (Hursh et al. 1969; Wells et al. 1975). Rates of clearance from the respiratory tract of inorganic lead inhaled as submicron particles of lead oxide, or lead nitrate, were described with half-times of 0.8 hours (22%), 2.5 hours (34%), 9 hours (33%), and 44 hours (12%) (Chamberlain et al. 1978). These rates are thought to represent, primarily, absorption from the bronchiolar and alveolar regions of the respiratory tract.

Rates and amounts of absorption of inhaled lead particles >2.5 μm will be determined, primarily, by rates of transport to and absorption from the gastrointestinal tract. Absorption of lead from the gastrointestinal tract varies with the chemical form ingested, age, meal status (e.g., fed vs. fasted), and a variety of nutritional factors (see Section 3.3.1.2 for further discussion).

Organic Lead. Following a single exposure to vapors of radioactive (^{203}Pb) tetraethyl lead (approximately 1 mg/m^3 breathed through a mouthpiece for 1–2 minutes) in four male subjects, 37% of inhaled ^{203}Pb was initially deposited in the respiratory tract, of which approximately 20% was exhaled in the subsequent 48 hours (Heard et al. 1979). One hour after the exposure, approximately 50% of the ^{203}Pb burden was associated with liver, 5% with kidney, and the remaining burden widely distributed throughout the body (determined by external gamma counting), suggesting near complete absorption of the lead that was not exhaled. In a similar experiment conducted with (^{203}Pb) tetramethyl lead, 51% of the inhaled ^{203}Pb dose was initially deposited in the respiratory tract, of which approximately 40% was

exhaled in 48 hours. The distribution of ^{203}Pb 1 hour after the exposure was similar to that observed following exposure to tetraethyl lead.

The relatively rapid and near complete absorption of tetraalkyl lead that is inhaled and deposited in the respiratory tract is also supported by studies conducted in animal models (Boudene et al. 1977; Morgan and Holmes 1978).

3.3.1.2 Oral Exposure

Inorganic Lead. The extent and rate of gastrointestinal absorption of ingested inorganic lead are influenced by physiological states of the exposed individual (e.g., age, fasting, nutritional calcium and iron status, pregnancy) and physicochemical characteristics of the medium ingested (e.g., particle size, mineralogy, solubility, and lead species). Lead absorption may also vary with the amount of lead ingested.

Effect of Age. Gastrointestinal absorption of water-soluble 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 that approximately 40–50% of ingested lead is absorbed (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) ranged from 3 to 10% in fed subjects (Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1980; Watson et al. 1986). 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. 1997b).

Studies in experimental animals provide additional evidence for an age-dependency of gastrointestinal absorption of lead. Absorption of lead, administered as lead acetate (6.37 mg lead /kg, oral gavage), was higher in juvenile Rhesus monkeys (38% of dose) compared to adult female monkeys (26% of the dose) (Pounds et al. 1978). Rat pups absorb approximately 40–50 times more lead via the diet than do adult rats (Aungst et al. 1981; Forbes and Reina 1972; Kostial et al. 1978). This age difference in absorption may be due, in part, to the shift from the neonatal to adult diet, and to postnatal physiological development of intestine (Weis and LaVelle 1991).

Effect of Fasting. The presence of food in the gastrointestinal tract decreases absorption of water-soluble lead (Blake and Mann 1983; Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Maddaloni et al. 1998; Rabinowitz et al. 1980). In adults, absorption of a tracer dose of lead acetate in water was approximately 63% when ingested by fasted subjects and 3% when ingested with a meal (James et al. 1985). Heard and Chamberlain (1982) reported nearly identical results. The arithmetic mean of reported estimates of absorption in fasted adults was 57% (calculated by ATSDR based on Blake et al. 1983; Heard and Chamberlain 1982; James et al. 1985; Rabinowitz et al. 1980). Reported fed/fasted ratios for absorption in adults 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 and Mann 1983; Blake et al. 1983; Heard and Chamberlain 1982).

Effect of Nutrition. 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 PbB (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 (Bannon et al. 2003; Barton et al. 1978b; Morrison and Quaterman 1987) (see Section 3.4.1 for further discussion).

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. 1978a). 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) (see Section 3.4.1 for further discussion).

Effect of Pregnancy. Absorption of lead may increase during pregnancy. Although there is no direct evidence for this in humans, an increase in lead absorption may contribute, along with other mechanisms (e.g., increased mobilization of bone lead), to the increase in PbB that has been observed during the later half of pregnancy (Gulson et al. 1997b, 1998b, 2004; Lagerkvist et al. 1996; Rothenberg et al. 1994b; Schuhmacher et al. 1996).

Effect of Dose. 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 limited by dose. Numerous observations of nonlinear relationships between blood lead concentration and lead intake in humans provide 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 and Quinn 1986; Sherlock et al. 1984) (see Section 3.4.1 for discussion of saturable uptake of lead in red blood cells). However, in immature swine that received oral doses of lead in soil, lead dose-blood lead relationships were curvilinear, whereas dose-tissue lead relationships for bone, kidney, and liver were linear. The same pattern (nonlinearity for blood lead concentration and linearity for tissues) was observed in swine administered lead acetate intravenously (Casteel et al. 1997). These results suggest that the nonlinearity in the lead dose-blood lead concentration relationship may derive from an effect of lead dose on some aspect of the biokinetics of lead other than absorption. 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, suggesting a limitation on absorption imposed by dose (Aungst et al. 1981). Evidence 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 nonlinear (see Section 3.4.1 for further discussion); however, the dose at which absorption becomes appreciably limited in humans is not known.

Effect of Particle Size. Particle size influences the degree of gastrointestinal absorption (Ruby et al. 1999). In rats, an inverse relationship was found between absorption and particle size of lead in diets containing metallic lead particles that were ≤250 μm in diameter (Barltrop and Meek 1979). Tissue lead concentration was a 2.3-fold higher when rats ingested an acute dose (37.5 mg Pb/kg) of lead particles that were <38 μm in diameter, than when rats ingested particles having diameters in the range 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

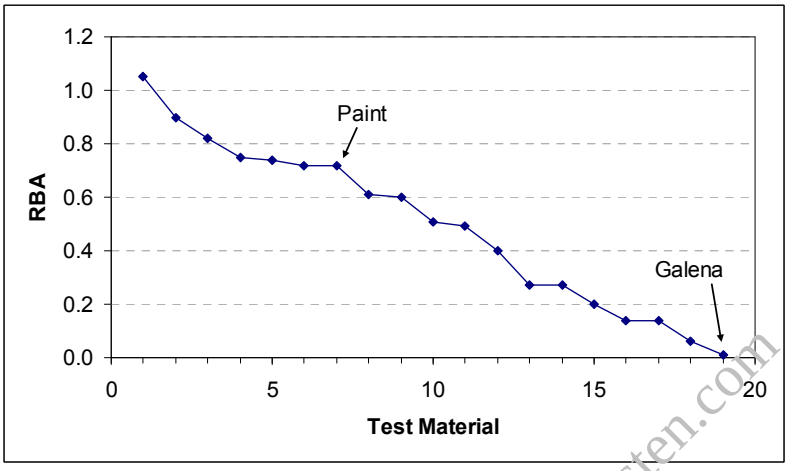
(Davis et al. 1994). Similarly, Healy et al. (1982) found that the solubility of lead sulfide in gastric acid *in vitro* was much greater for particles that were 30 μm in diameter than for particles that were 100 μm in diameter.

Absorption from Soil. 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 <250 μm) collected 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). The value reported for fasted subjects (26%) was approximately half that reported for soluble lead ingested by fasting adults, approximately 60% (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980). Measurements of the absorption of soil lead in infants or children have not been reported.

Additional evidence for a lower absorption of soil lead compared to dissolved lead is provided from studies in laboratory animal models. In immature swine that received oral doses of soil-like materials from various mine waste sites (75 or 225 μg Pb/kg body weight), relative bioavailability of soil-borne lead ranged from 6 to 100%, compared to that of a similar dose of highly water-soluble lead acetate (Casteel et al. 1997; EPA 2004b; Figure 3-4). Electron microprobe analyses of lead-bearing grains in the various test materials revealed that the grains ranged from as small as 1–2 μm up to a maximum of 250 μm (the sieve size used in preparation of the samples), and that the lead was present in a wide range of different mineral associations (phases), including various oxides, sulfides, sulfates, and phosphates (Table 3-8). These variations in size and mineral content of the lead-bearing grains are the suspected cause of variations in the rate and extent of gastrointestinal absorption of lead from different samples of soil. Based on these very limited data, the relative bioavailability of lead mineral phases were rank-ordered (Table 3-9).

Studies conducted in rats provide additional evidence for a lower absorption of soil-borne lead compared to water-soluble lead. 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 PbB (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

Figure 3-4. Relative Bioavailability (RBA) of Ingested Lead from Soil and Soil-like Test Materials as Assessed in an Immature Swine Model*



Test Material
1 California Gulch Fe/Mn PbO
2 Jasper Co Low Lead Yard
3 Jasper Co High Lead Mill
4 Aspen Residential
5 Aspen Berm
6 California Gulch Phase 1 Residential Soil
7 NIST Paint
8 Jasper Co High Lead Smelter
9 Palmerton Location 2
10 Murray Smelter Soil
11 Palmerton Location 4
12 Murray Smelter Slag
13 Bingham Creek Residential
14 Bingham Creek Channel
15 Califonria Gulch AV Slag
16 Midvale Slag
17 Butte Soil
18 California Gulch Oregon Gulch Tailings
19 Galena-enriched Soil

*RBA is the bioavailability (BA) of the lead in the test material compared to that of lead acetate relative to lead acetate ($BA_{test}/BA_{acetate}$). See Table 3-8 for mineral composition of test materials.

Source: EPA 2004c

Table 3-8. Percent Relative Lead Mass of Mineral Phases Observed in Test Materials Assessed for Relative Bioavailability in Immature Swine[a]

Test material	1 Cal. Gulch Fe/Mn PbO	2 Jasper County low lead yard	3 Jasper County high lead mill	4 Aspen residential	5 Aspen Berm	6 Cal. Gulch Phase I residential soil	7 NIST paint	8 Jasper County high lead smelter	9 Palmerton location 2	10 Murray smelter soil	11 Palmerton location 4	12 Murray smelter slag	13 Bingham Creek residential	14 Bingham Creek channel soil	15 Cal. Gulch AV slag	16 Midvale slag	17 Butte soil	18 Cal. Gulch Oregon Gulch tailings	19 Galena-enriched soil
Mineral phase																			
Anglesite		0.5	2	1	7	10	1	1	6		4	1.0		28	2		36		
As(M)O										0.003									
Calcite			0.1					0.2											
Cerussite		81	57	64	62	20	55	32		14		1.1	2	0.3	1	4	0.3		
Clay	0.01	0.003	0.017		0.1			0.018	0.03		0.13						0.1		
Fe-Pb oxide	8	2	10	7	9	6		14	2	0.13	2	2	6	3	51	0.3	7		
Fe-Pb sulfate	3	1	1	5	5	6		3	1	0.6		0.3	22	30	0.3	0.1	20		
Galena		8	3	17	12	2				20		9		9	3	6	12	100	100
Lead barite	0.14		0.01		0.06	0.15			1		0.1			0.04			0.007		
Lead organic	0.11			0.03	0.03	0.11								0.3	1				
Lead oxide			7				44	0.09		27		69							
Lead phos-phate	15	6	7	1	1	30		21	24		1		50	26			3.6		
Lead silicate	0.8	0.04	0.5			1.9					1.4								
Lead vanidate	0.4					0.1					18								
Mn-Pb oxide	72	2	9	5	4	22		2	66		66	0.8	18	2			20.2		
Native lead			2					22				0.7				15			
Pb(M)O										3	7	4				26			
Pb-As oxide		0.15				0.1				29		6	2	1	31	33			

Table 3-8. Percent Relative Lead Mass of Mineral Phases Observed in Test Materials Assessed for Relative Bioavailability in Immature Swine[a]

Test material	1 Cal. Gulch Fe/Mn PbO	2 Jasper County low lead yard	3 Jasper County high lead mill	4 Aspen residential	5 Aspen Berm	6 Cal. Gulch Phase I residential soil	7 NIST paint	8 Jasper County high lead smelter	9 Palmerton location 2	10 Murray smelter soil	11 Palmerton location 4	12 Murray smelter slag	13 Bingham Creek residential	14 Bingham Creek channel soil	15 Cal. Gulch AV slag	16 Midvale slag	17 Butte soil	18 Cal. Gulch Oregon Gulch tailings	19 Galena-enriched soil
PbO-cerussite						1													
Slag			1			1		+		6		7			10	16			
Sulfosalts																0.4			
Zn-Pb silicate											2	0.03							

[a]Test material numbers refer to Figure 3-4.

Source: EPA 2004c

Table 3-9. Ranking of Relative Bioavailability of Lead Mineral Phases in Soil[a]

Low bioavailability (RBA<0.25)	Medium bioavailability (RBA=0.25–0.75)	High bioavailability (RBA>0.75)
Angelsite	Lead oxide	Cerussite
Fe(M) oxide	Lead phosphate	Mn(M) oxide
Fe(m) sulfate		
Galena		
Pb(m) oxide		

[a]Estimates are based on studies of immature swine (see Figure 3-4, Table 3-8).

M = metal; RBA = relative bioavailability (compared to lead acetate)

Source: EPA 2004c

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 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%.

3.3.1.3 Dermal Exposure

Inorganic Lead. Dermal absorption of inorganic lead compounds is generally considered to be much less than absorption by inhalation or oral routes of exposure; however, few studies have provided quantitative estimates of dermal absorption of inorganic lead in humans, and the quantitative significance of the dermal absorption pathway as a contributor to lead body burden in humans remains an uncertainty. Lead was detected in the upper layers of the stratum corneum of lead-battery workers, prior to their shifts and after cleaning of the skin surface (Sun et al. 2002), suggesting adherence and/or possible dermal penetration of lead. Following skin application of ^{203}Pb-labeled lead acetate in cosmetic preparations (0.12 mg Pb in 0.1 mL or 0.18 mg Pb in 0.1 g of a cream) to eight male volunteers for 12 hours, absorption was ≤0.3%, based on whole-body, urine and blood ^{203}Pb measurements, and was predicted to be 0.06% during normal use of such preparations (Moore et al. 1980). Most of the absorption took place within 12 hours of exposure. Lead also appears to be absorbed across human skin when applied to the skin as lead nitrate; however, quantitative estimates of absorption have not been reported. Lead (4.4 mg, as lead nitrate) was applied (vehicle or solvent not reported) to an occluded filter placed on the forearm of an adult subject for 24 hours, after which, the patch was removed, the site cover and the forearm were rinsed with water, and total lead was quantified in the cover material and rinse (Stauber et al. 1994). The amount of lead recovered from the cover material and rinse was 3.1 mg (70% of the applied dose). Based

on this recovery measurement, 1.3 mg (30%) of the applied dose remained either in the skin or had been absorbed in 24 hours; the amount that remained in or on the skin and the fate of this lead (e.g., exfoliation) was not determined. Exfoliation has been implicated as an important pathway of elimination of other metals from skin (e.g., inorganic mercury; Hursh et al. 1989). Lead concentrations in sweat collected from the right arm increased 4-fold following the application of lead to the left arm, indicating that some lead had been absorbed (amounts of sweat collected or total lead recovered in sweat were not reported). In similar experiments with three subjects, measurements of ^{203}Pb in blood, sweat and urine, made over a 24-hour period following dermal exposures to 5 mg Pb as ^{203}Pb nitrate or acetate, accounted for <1% of the applied (or adsorbed) dose. This study also reported that absorption of lead could not be detected from measurements of lead in sweat following dermal exposure to lead as lead carbonate.

Information on relative dermal permeability of inorganic and organic lead salts of lead comes from studies of *in vitro* preparations of excised skin; the rank ordering of penetration rates through excised human skin were: lead nuolate (lead linoleic and oleic acid complex) > lead naphthanate > lead acetate > lead oxide (nondetectable) (Bress and Bidanset 1991).

Studies conducted in animals provide additional evidence that dermal absorption of inorganic lead is substantially lower than absorption from the inhalation or oral route. In a comparative study of dermal absorption of inorganic and organic salts of lead conducted in rats, approximately 100 mg of lead was applied in an occluded patch to the shaved backs of rats. Based on urinary lead measurements made prior to and for 12 days following exposure, lead compounds could be ranked according to the relative amounts absorbed (i.e., percent of dose recovered in urine; calculated by ATSDR): lead naphthalene (0.17%), lead nitrate (0.03%), lead stearate (0.006%), lead sulfate (0.006%), lead oxide (0.005%), and metal lead powder (0.002%). This rank order (i.e., lead naphthalene>lead oxide) is consistent with a rank ordering of penetration rates of inorganic and organic lead salts through excised skin from humans and guinea pigs: lead nuolate (lead linoleic and oleic acid complex) > lead naphthanate > lead acetate > lead oxide (nondetectable) (Bress and Bidanset 1991).

Following application of lead acetate to the shaved clipped skin of rats, the concentration of lead in the kidneys was found to be higher relative to controls, suggesting that absorption of lead had occurred (Laug and Kunze 1948). This study also observed that dermal absorption of lead from lead arsenate was significantly less than from lead acetate, and that mechanical injury to the skin significantly increased the dermal penetration of lead.

Organic Lead. Relative to inorganic lead and organic lead salts, 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). Evidence for higher dermal permeability of organic lead compounds compared to inorganic organic salts of lead also comes from *in vitro* studies conduced with excised skin. The rank order of absorption rates through excised skin from humans and guinea pigs was as follows: tetrabutyl lead > lead nuolate (lead linoleic and oleic acid complex) > lead naphthanate > lead acetate > lead oxide (nondetectable) (Bress and Bidanset 1991).

3.3.2 Distribution

Inorganic Lead. Absorbed inorganic lead appears to be distributed in essentially the same manner regardless of the route of absorption (Chamberlain et al. 1978; Kehoe 1987); therefore, the distribution of absorbed lead (i.e., by any route) is discussed in this section, rather than in separate sections devoted to specific routes of exposure. The expression, body burden is used here to refer to the total amount of lead in the body. Most of the available information about the distribution of lead to major organ systems (e.g., bone, soft tissues) derives from autopsy studies conducted in the 1960s and 1970s and reflect body burdens accrued during periods when ambient and occupational exposure levels were much higher than current levels (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). In general, these studies indicate that 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 3.3.3 for further discussion). Several models of lead pharmacokinetics have been proposed to characterize such parameters as intercompartmental lead exchange rates, retention of lead in various tissues, and relative rates of distribution among the tissue groups (see Section 3.3.5 for further discussion of the classical compartmental models and physiologically based pharmacokinetic (PBPK) models developed for lead risk assessments).

Lead in Blood. Concentrations of lead in blood vary considerably with age, physiological state (e.g., pregnancy, lactation, menopause) and numerous factors that affect exposure to lead. The NHANES provide estimates for average blood lead concentrations in various demographic strata of the U.S. population. Samples for the most recent NHANES III were collected during the period 1999–2002. Geometric mean PbB of U.S. adults, ages 20–59 years, estimated from the NHANES III 1999–2002, were

1.5 µg/dL (95% CI, 1.5–1.6) (CDC 2005a). Among adults, blood lead concentrations were highest in the strata that included ages 60 years and older (2.2 µg/dL; 95% CI, 2.1–2.3). Geometric mean PbB of children, ages 1-5 years, was 1.9 (95% CI, 1.8–2.1) for the 1999–2002 survey period; however, the geometric mean PbB for non-Hispanic black children is higher than that for Mexican-American and non-Hispanic white children, showing that differences in risk for exposure still exist (CDC 2005a). Central estimates from NHANES 1999–2002 when compared to those from NHANES III Phase 2 (1991–1994), and from Phase 1 of the NHANES III (1988–1991) and NHANES II (1976–1980), indicate a downward temporal trend in blood lead concentrations in the United States, over this period.

The excretory half-life of lead in blood, in adult humans, is approximately 30 days (Chamberlain et al. 1978; Griffin et al. 1975; Rabinowitz et al. 1976). Lead in blood is primarily in the red blood cells (99%) (Bergdahl et al. 1997a, 1998, 1999; Hernandez-Avila et al. 1998; Manton et al. 2001; Schutz et al. 1996; Smith et al. 2002). Most of the lead found in red blood cells is bound to proteins within the cell rather than the erythrocyte membrane. Approximately 40–75% of lead in the plasma is bound to plasma proteins, of which albumin appears to be the dominant ligand (Al-Modhefer et al. 1991; Ong and Lee 1980a). Lead may also bind to γ-globulins (Ong and Lee 1980a). Lead in serum that is not bound to protein exists largely as complexes with low molecular weight sulfhydryl compounds (e.g., cysteine, homocysteine) and other ligands (Al-Modhefer et al. 1991).

Lead in 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). Lead concentrations in bone increase with age throughout the lifetime, indicative of a relatively slow turnover of lead in adult bone (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). This large pool of lead in adult bone can serve to maintain blood lead levels long after exposure has ended (Fleming 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 maternal bone is resorbed for the production of the fetal skeleton (Franklin et al. 1997; Gulson et al. 1997b, 1999b, 2003).

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 suggests that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 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). 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 (Barry 1975; Gross et al. 1975; Schroeder and Tipton 1968). 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 <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 and release of lead from resorbed bone to blood (Gulson et al. 2002). 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 came into equilibrium with a novel environmental lead isotope signature indicated that 10–88% of the lead in blood may derive from the mobilization of bone lead stores and approximately 80% of cord blood may be contributed from maternal bone lead (Gulson 2000; Gulson et al. 1997b, 1999c, 2003). The mobilization of bone lead during pregnancy may contribute, along with other mechanisms (e.g., increased absorption), to the increase in lead concentration that has been observed during the later stages of pregnancy (Gulson et al. 1997b; Lagerkvist et al. 1996; Schuhmacher et al. 1996). Bone resorption during pregnancy can be reduced by ingestion of calcium supplements (Janakiraman et al. 2003). Additional evidence for increased mobilization of bone lead into blood during pregnancy is provided from studies in nonhuman 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 was transferred to the fetus appeared to have been derived from the maternal skeleton (Franklin et al. 1997).

In addition to pregnancy, other states of increased bone resorption appear to result in release of bone lead to blood; these include lactation and osteoporosis. Analysis for kinetics of changes in the stable isotope signatures of blood lead in postpartum women as they came into equilibrium with a novel environmental lead isotope signature indicated that the release of maternal bone lead to blood appears to accelerate during lactation (Gulson et al. 2003, 2004). Similar approaches have detected increased release of bone lead to blood in women, in association with menopause (Gulson et al. 2002). These observations are consistent with epidemiological studies that have shown increases in PbB after menopause and in association with decreasing bone density in postmenopausal women (Berkowitz et al. 2004; Hernandez-Avila et al. 2000; Nash et al. 2004; Symanski and Hertz-Picciotto 1995).

Lead in Soft Tissues. Several studies have compared soft tissue concentrations of lead in autopsy samples of soft tissues (Barry 1975, 1981; Gross et al. 1975; Schroeder and Tipton 1968). These studies were conducted in the 1960s and 1970s and, therefore, reflect burdens accrued during periods when ambient and occupational exposure levels were much higher than current levels. Average PbBs reported in the adult subjects were approximately 20 µg/dL in the Barry (1975) and Gross et al. (1975) studies, whereas more current estimates of the average for adults in the United States are below 5 µg/dL (Pirkle et al. 1998). Levels in other soft tissues also appear to have decreased substantially since these studies were reported. For example, average lead concentrations in kidney cortex of male adults were 0.78 µg/g wet tissue and 0.79 µg/g, as reported by Barry (1975) and Gross et al. (1975), respectively (samples in the Barry study were from subjects who had no known occupational exposures). In a more recent analysis of kidney biopsy samples collected in Sweden, the mean level of lead in kidney cortex among subjects not occupationally exposed to lead was 0.18 µg/g (maximum, 0.56µg/g) (Barregård et al. 1999). In spite of the downward trends in soft tissue lead levels, the autopsy studies provide a basis for describing the relative soft tissue distribution of lead in adults and children. Most of the lead in soft tissue is in liver. Relative amounts of lead in soft tissues as reported by Schroeder and Tipton (1968), expressed as percent of total soft tissue lead, were: liver, 33%; skeletal muscle, 18%; skin, 16%; dense connective tissue, 11%; fat, 6.4%; kidney, 4%; lung, 4%; aorta, 2%; and brain, 2% (other tissues were <1%). The highest soft tissue concentrations in adults also occur in liver and kidney cortex (Barry 1975; Gerhardsson et al. 1986a, 1995b; Gross et al. 1975; Oldereid et al. 1993). The relative distribution of lead in soft tissues, in males and females, expressed in terms of tissue:liver concentration ratios, were: liver, 1.0 (approximately 1 µg/g wet weight); kidney cortex, 0.8; kidney medulla, 0.5; pancreas, 0.4; ovary, 0.4; spleen, 0.3;

prostate, 0.2; adrenal gland, 0.2; brain, 0.1; fat, 0.1; testis, 0.08; heart, 0.07; and skeletal muscle, 0.05 (Barry 1975; Gross et al. 1975). In contrast to lead in bone, which accumulates lead with continued exposure in adulthood, concentrations in soft tissues (e.g., liver and kidney) are relatively constant in adults (Barry 1975; Treble and Thompson 1997), reflecting a faster turnover of lead in soft tissue, relative to bone.

Maternal-Fetal-Infant Transfer. The maternal/fetal blood lead concentration ratio, indicated from cord blood lead measurements, is approximately 0.9 (Carbone et al. 1998; Goyer 1990; Graziano et al. 1990). In one of the larger studies of fetal blood lead concentration, maternal and cord blood lead concentration were measured at delivery in 888 mother-infant pairs; the cord/maternal ratio was relatively constant, 0.93, over a PbB range of approximately 3–40 µg/dL (Graziano et al. 1990). A study of 159 mother-infant pairs also found a relatively constant cord/maternal ratio (0.84) over a maternal blood lead range of approximately 1–12 µg/dL (Carbone et al. 1998). As noted in the discussion of the distribution of lead in bone, measurements of stable lead isotope ratios in pregnant women and cord blood, as they came into equilibrium with a novel environmental lead isotope signature, indicated that approximately 80% of lead in fetal cord blood appears to derive from maternal bone stores (Gulson et al. 2003). A recent study looked at factors that might influence the amount of lead that infants receive (Harville et al. 2005). The analysis, conducted on 159 mother-infant pairs, revealed that higher blood pressure and alcohol consumption late in pregnancy were associated with more lead in cord blood relative to maternal PbB. In addition, higher hemoglobin and sickle cell trait were associated with reduced cord blood lead relative to maternal PbB. No associations were found for calcium intake, physical activity, or smoking.

Maternal lead can also be transferred to infants during breastfeeding. Numerous studies have reported lead concentrations in maternal blood and breast milk. In general, these studies indicate that breast milk/maternal blood concentration ratios are <0.1, although values of 0.9 have been reported (Ettinger et al. 2006; Gulson et al. 1998a). Ettinger et al. (2006) assessed factors influencing breast milk lead concentration in a group of 367 women and found that PbB (mean, 8–9 µg/dL; range, 2–30) was a stronger predictor of breast milk lead (mean, 0.9–1.4 µg/L; range, 0.2–8 µg/dL) than bone lead, and that tibia lead (mean, 9.5 µg/g; range, <1–76.5 µg/dL) was a stronger predictor of breast milk lead than patella bone lead (mean, 14.6 µg/dL; range, <1–67.2 µg/dL). Stable lead isotope dilution measurements in infant-mother pairs, measured as they came into equilibrium with a novel environmental lead isotope signature, suggested that lead in breast milk can contribute substantially to isotope profile of infant blood (approximately 40–80%; Gulson et al. 1998b).

Organic Lead. Information on the distribution of lead in humans following exposures to organic lead is extremely limited. One hour following 1–2-minute inhalation exposures to ^{203}Pb tetraethyl or tetramethyl lead (1 mg/m^3), approximately 50% of the ^{203}Pb body burden was associated with liver and 5% with kidney; the remaining ^{203}Pb was widely distributed throughout the body (Heard et al. 1979). The kinetics of ^{203}Pb in blood of these subjects showed an initial declining phase during the first 4 hours (tetramethyl lead) or 10 hours (tetraethyl lead) after the exposure, followed by a phase of gradual increase in PbB that lasted for up to 500 hours after the exposure. Radioactive lead in blood was highly volatile immediately after the exposure and transitioned to a nonvolatile state thereafter. These observations may reflect an early distribution of organic lead from the respiratory tract, followed by a redistribution of de-alkylated lead compounds (see Section 3.3.3 for further discussion of alkyl lead metabolism).

In a man and woman who accidentally inhaled a solvent containing 31% tetraethyl lead (17.6% lead by weight), lead concentrations in the tissues, from highest to lowest, were liver, kidney, brain, pancreas, muscle, and heart (Bolanowska et al. 1967). 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).

3.3.3 Metabolism

Inorganic Lead. Metabolism of inorganic lead consists of formation of complexes with a variety of protein and nonprotein ligands. Major extracellular ligands include albumen and nonprotein sulfhydryls (see Section 3.3.2 for further discussion). The major intracellular ligand in red blood cells is ALAD (see Section 3.3.2 for further discussion). Lead also forms complexes with proteins in the cell nucleus and cytosol (see Section 3.4.2 for further discussion).

Organic Lead. Alkyl lead compounds are actively metabolized in the liver by oxidative dealkylation catalyzed by cytochrome P-450. Relatively few studies that address the metabolism of alkyl lead compounds in humans have been reported. Occupational monitoring studies of workers who were exposed to tetraethyl lead have shown that tetraethyl lead is excreted in the urine as diethyl lead, ethyl lead, and inorganic lead (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994). 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 re-appearance 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 lead compounds that were formed from the metabolic conversion of the volatile parent compounds (Heard et al. 1979).

3.3.4 Excretion

Independent of the route of exposure, absorbed lead is excreted primarily in urine and feces; sweat, saliva, hair and nails, and breast milk are minor routes of excretion (Chamberlain et al. 1978; Griffin et al. 1975; Hursh and Suomela 1968; Hursh et al. 1969; Kehoe 1987; Rabinowitz et al. 1976; Stauber et al. 1994). Fecal excretion accounts for approximately one-third of total excretion of absorbed lead (fecal/urinary excretion ratio of approximately 0.5), based on intravenous injection studies conducted in humans (Chamberlain et al. 1978). A similar value for fecal/urinary excretion ratio, approximately 0.5, has been observed following inhalation of submicron lead particles (Chamberlain et al. 1978; Hursh et al. 1969).

3.3.4.1 Inhalation Exposure

Inorganic Lead. Inorganic lead inhaled as submicron particles is deposited primarily in the bronchiolar and alveolar regions of the respiratory tract, from where it is absorbed and excreted primarily in urine and feces (Chamberlain et al. 1978; Hursh et al. 1969; Kehoe 1987). Fecal/urinary excretion ratios were approximately 0.5 following inhalation of submicron lead-bearing particles (Chamberlain et al. 1978; Hursh et al. 1969). Higher fecal-urinary ratios would be expected following inhalation of larger particle sizes (e.g., >1 μm) as these particles would be cleared to the gastrointestinal tract from where a smaller percentage would be absorbed (Kehoe 1987; see Section 3.3.1.2).

Organic Lead. Lead derived from inhaled tetraethyl and tetramethyl lead is excreted in exhaled air, urine, and feces (Heard et al. 1979). Following 1–2-minute inhalation exposures to ^{203}Pb tetraethyl (1 mg/m^3), in four male subjects, 37% of inhaled ^{203}Pb was initially deposited in the respiratory tract, of which approximately 20% was exhaled in the subsequent 48 hours (Heard et al. 1979). In a similar experiment conducted with (^{203}Pb) tetramethyl lead, 51% of the inhaled ^{203}Pb dose was initially deposited in the respiratory tract, of which approximately 40% was exhaled in 48 hours. Lead that was not exhaled was excreted in urine and feces. Fecal/urinary excretion ratios were 1.8 following exposure to tetraethyl lead and 1.0 following exposure to tetramethyl lead (Heard et al. 1979). Occupational monitoring studies of workers who were exposed to tetraethyl lead have shown that tetraethyl lead is excreted in the urine as

diethyl lead, ethyl lead, and inorganic lead (Turlakiewicz and Chmielnicka 1985; Vural and Duydu 1995; Zhang et al. 1994).

3.3.4.2 Oral Exposure

Inorganic Lead. Much of the available information on the excretion of ingested lead in adults derives from studies conducted on five male adults who received daily doses of ^{207}Pb nitrate for periods up to 210 days (Rabinowitz et al. 1976). The dietary intakes of the subjects were reduced to accommodate the tracer doses of ^{207}Pb without increasing daily intake, thus preserving a steady state with respect to total lead intake and excretion. Total lead intakes (diet plus tracer) ranged from approximately 210 to 360 µg/day. Urinary excretion accounted for approximately 12% of the daily intake (range for five subjects: 7–17%) and fecal excretion, approximately 90% of the daily intake (range, 87–94%). Based on measurements of tracer and total lead in saliva, gastric secretions, bile, and pancreatic secretions (samples collected from three subjects by intubation), gastrointestinal secretion of lead was estimated to be approximately 2.4% of intake (range, 1.9–3.3%). In studies conducted at higher ingestion intakes, 1–3 mg/day for up to 208 weeks, urinary lead excretion accounted for approximately 5% of the ingested dose (Kehoe 1987).

3.3.4.3 Dermal Exposure

Inorganic lead is excreted in sweat and urine following dermal exposure to lead nitrate or lead acetate (Moore et al. 1980; Stauber et al. 1994).

3.3.5 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 pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

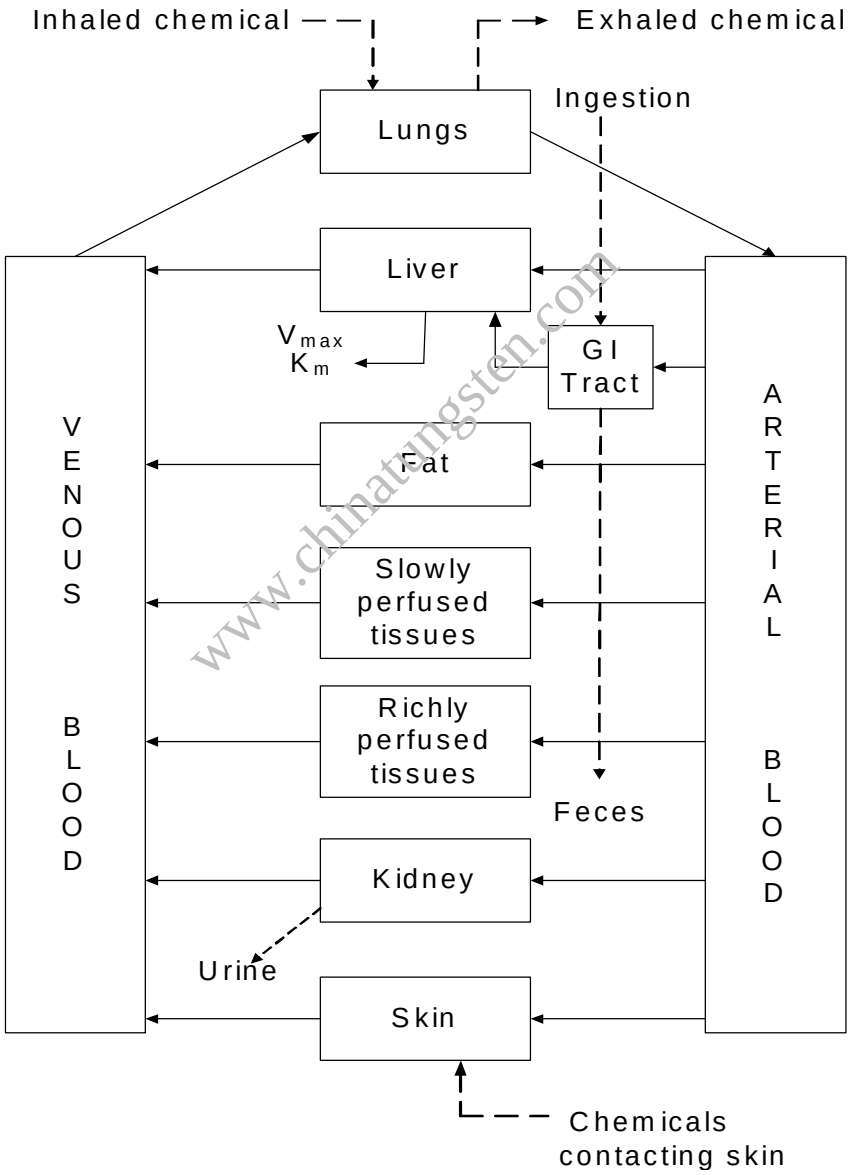
PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen and Krishnan 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) are 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 3-5 shows a conceptualized representation of a PBPK model.

Figure 3-5. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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.

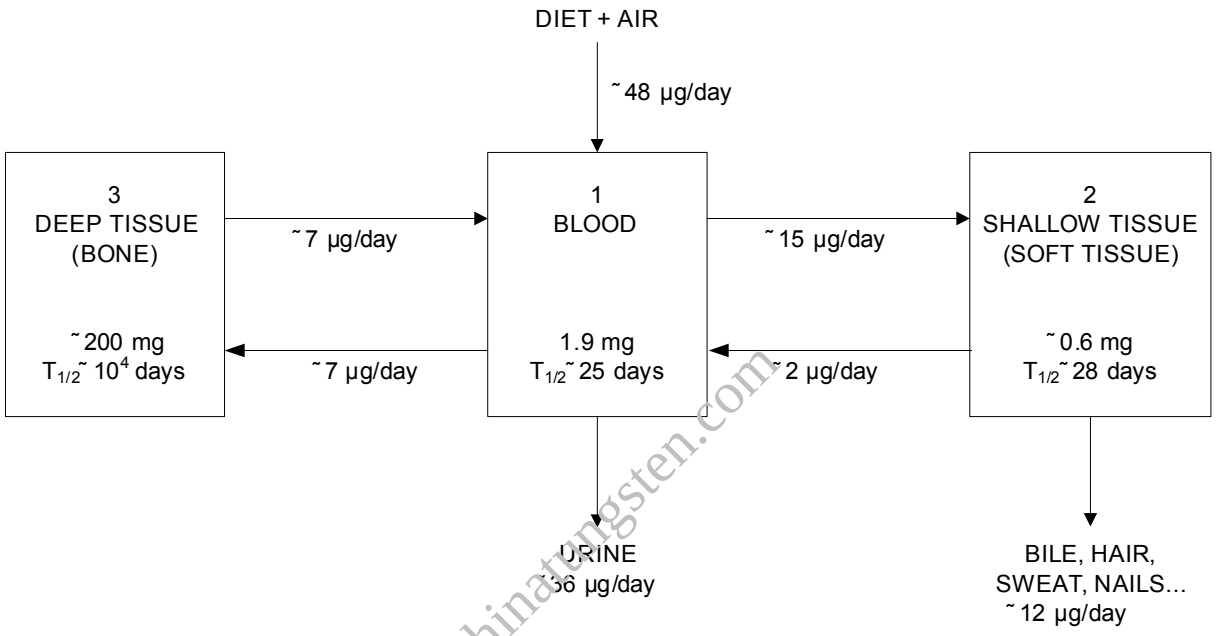
Source: adapted from Krishnan et al. 1994

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

Early lead modeling applications relied on classical pharmacokinetics. Compartments representing individual organs or groups of organs that share a common characteristic were defined as 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 might be "shallow" or "deep" (i.e., they may exchange relatively rapidly or relatively slowly with blood plasma) (O'Flaherty 1987). One of the first of such models was proposed by Rabinowitz et al. (1976) based on a study of the kinetics of ingested stable lead isotope tracers and lead balance data in five healthy adult males. The Rabinowitz model includes three compartments: a central compartment representing blood and other tissues and spaces in rapid equilibrium with blood (e.g., interstitial fluid); a shallow tissue compartment, representing soft tissues and rapidly exchanging pools within the skeleton; and a deep tissue compartment, representing, primarily, slowly exchanging pools of lead within bone. Excretion pathways represented in the model included urinary, from the central compartment, and bile, sweat, hair, and nails, from the shallow tissue compartment. A diagram of the model is shown in Figure 3-6, along with the lead content and reported mean residence times and the rates of lead movement between compartments (residence times are the reciprocal of the sum of the individual elimination rate constants). The model predicts pseudo-first order half-times for lead of approximately 25, 28, and 10^4 days in the central, shallow tissue, and deep compartments, respectively. The slow kinetics of the deep tissue compartment leads to the prediction that it would contain most of the lead burden after lengthy exposures (e.g., years), consistent with lead measurements made in human autopsy samples (see Section 3.3.2 Distribution). Note that this model did not simulate the distribution of lead within blood (e.g., erythrocytes and plasma), nor did it simulate subcompartments within bone or physiological processes of bone turnover that might affect kinetics of the deep tissue compartment.

Marcus (1985b) reanalyzed the data from stable isotope tracer studies of Rabinowitz et al. (1976) and derived an expanded multicompartment kinetic model for lead (Figure 3-7). The model included separate compartments for cortical (slow, $t_{1/2}$ $1.2x10^4$–$3.5x10^4$ days) and trabecular (fast, $t_{1/2}$ 100–700 days), an approach subsequently adopted in several models (Bert et al. 1989; EPA 1994a, 1994b; Leggett 1993; O'Flaherty 1993, 1995a). A more complex representation of the lead disposition in bone included explicit simulation of diffusion of lead within the bone volume of the osteon and exchange with blood at the canaliculus (Marcus 1985a; Figure 3-8). The bone diffusion model was based on lead kinetics data from studies conducted in dogs. Marcus (1985c) also introduced nonlinear kinetics of exchange of lead

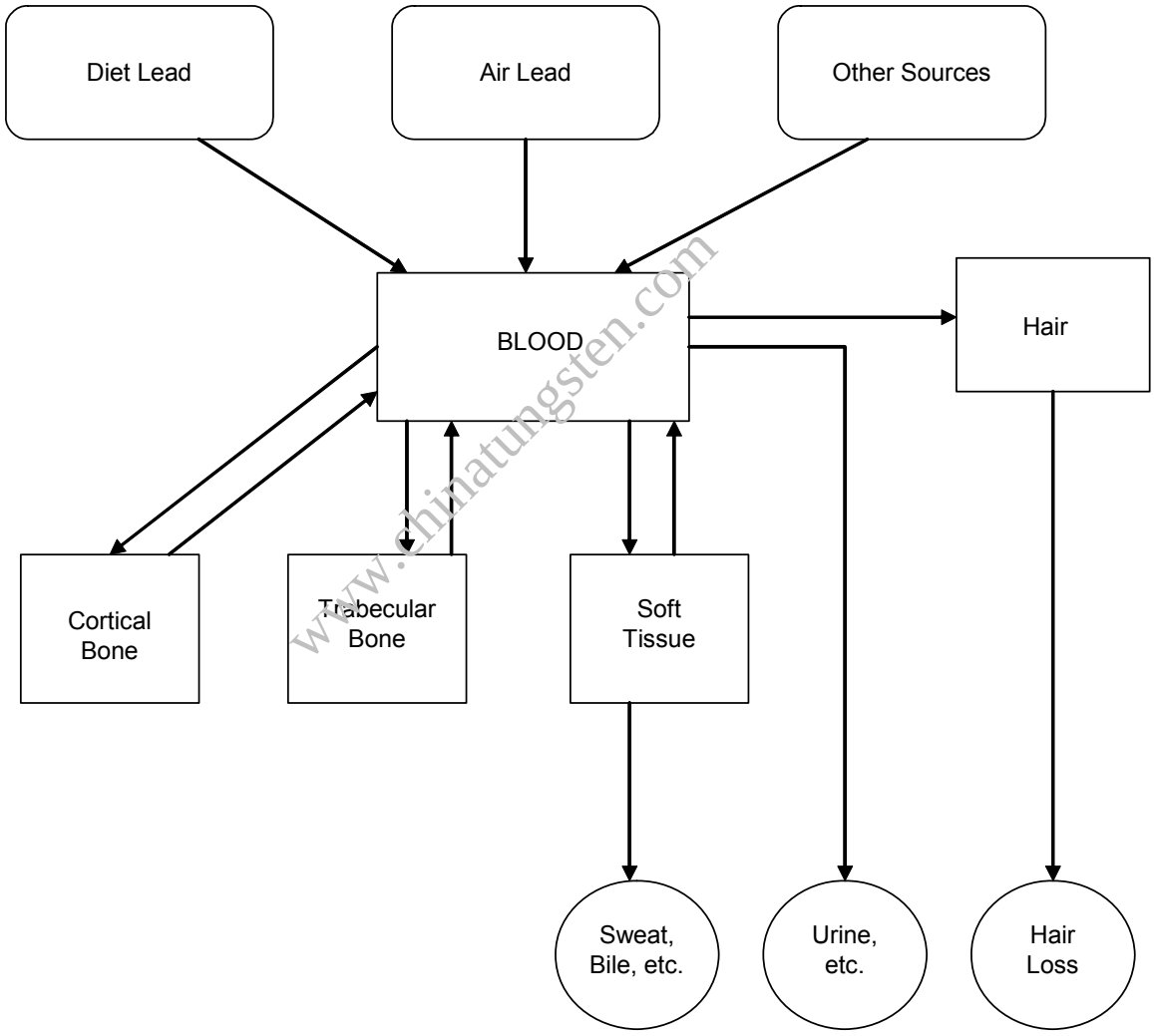
Figure 3-6. Lead Metabolism Model*



*Schematic model for lead kinetics, in which distribution is represented as a central (blood) compartment and peripheral soft-tissue (fast = $t_{1/2}$ 28 days) and deep tissue (slow = $t_{1/2}$ 10,000 days) compartments.

Source: Rabinowitz et al. 1976

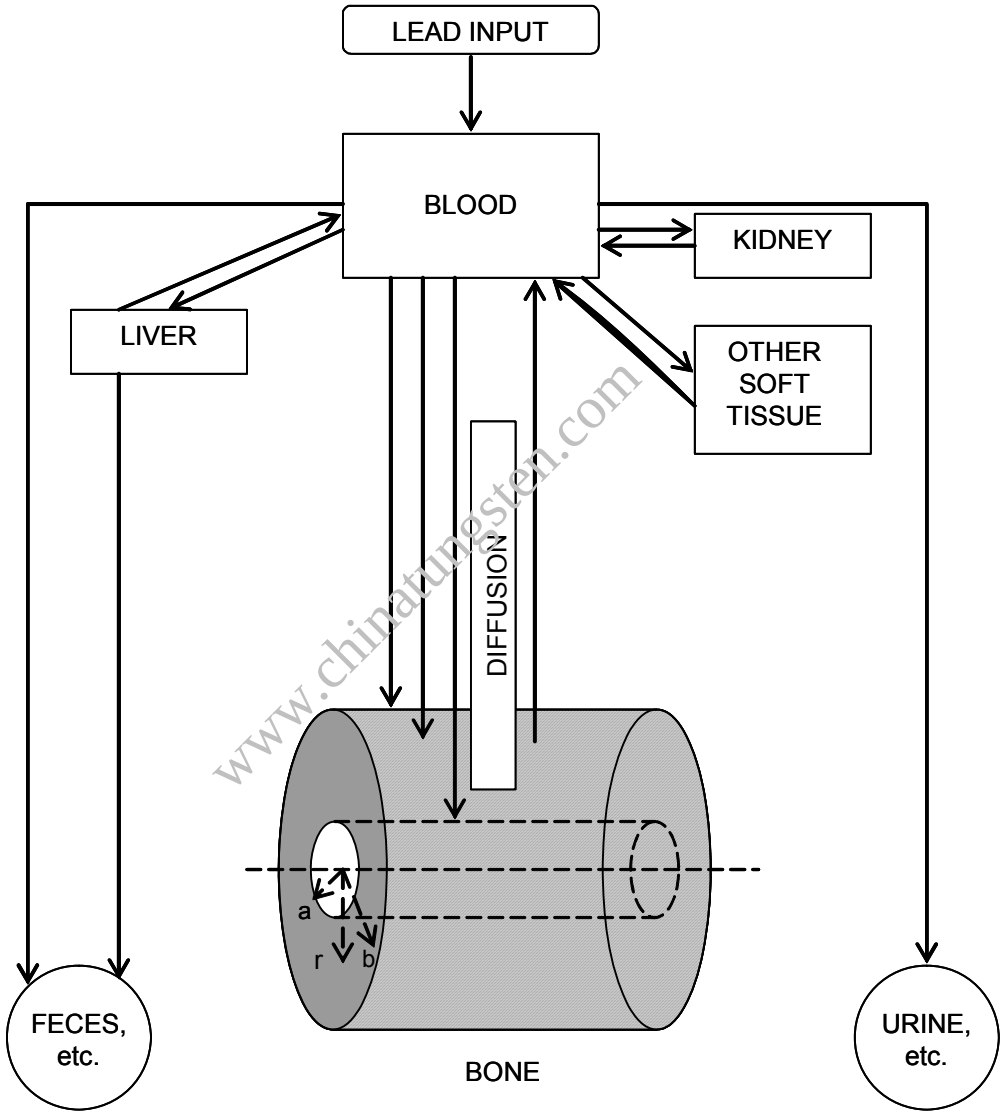
Figure 3-7. Compartments and Pathways of Lead Exchange in the Marcus (1985b) Model*



*Schematic model for lead kinetics, in which bone is represented as a cortical (slow=$t_{1/2}$ $1.2x10^4$–$3.5x10^4$ days) and trabecular (fast=$t_{1/2}$ 100–700 days) compartments.

Source: Marcus 1985b

Figure 3-8. Schematic Model for Lead Kinetics in Marcus (1985a) Bone Model*



*Schematic model for lead kinetics, in which bone is represented as an extended cylindrical *canalicular territory*. The canalicular territory has a radius b, and surrounds the canaliculus of radius a. Lead diffuses across radius r, between the fluid in the canaliculus (which is in communication with blood in the Haversian canal, not shown) and the bone volume of the canalicular territory.

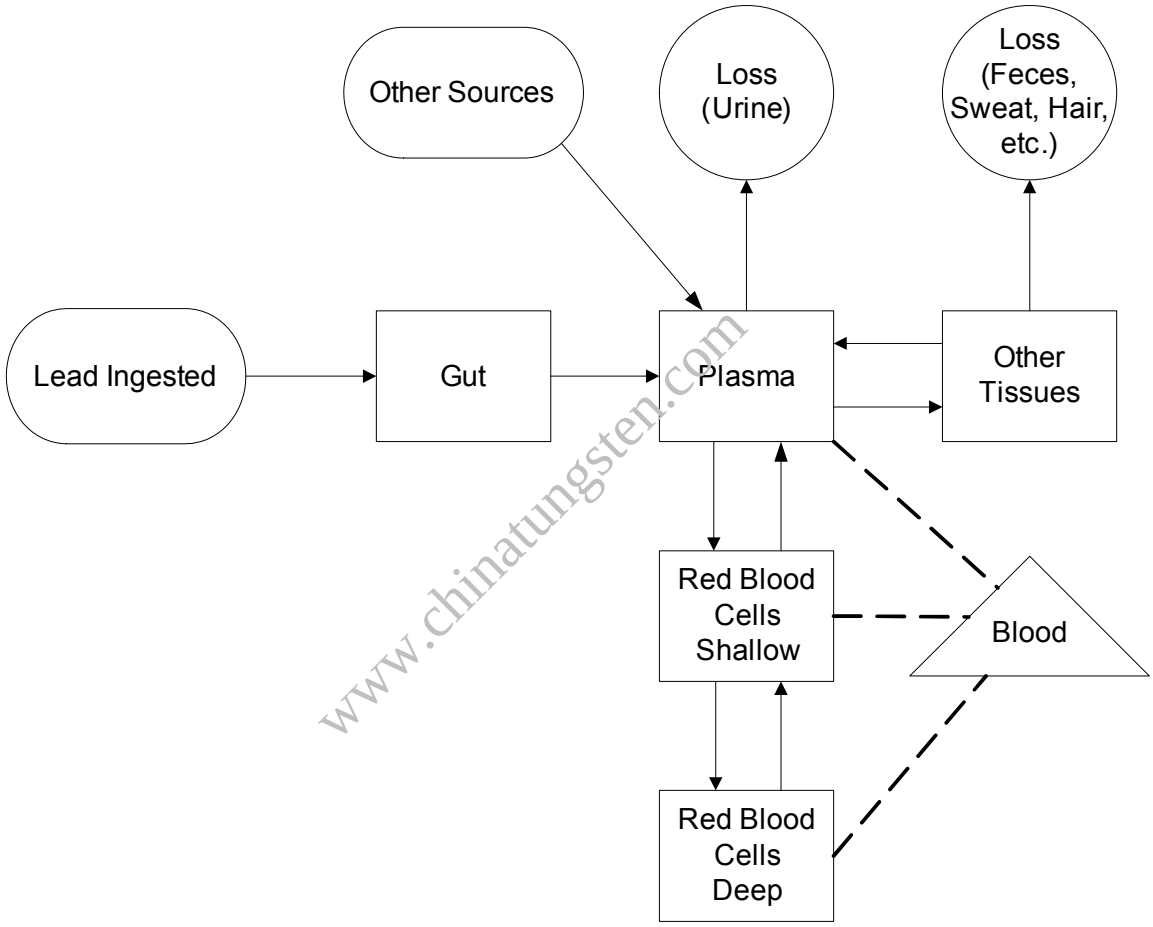
Source: Marcus 1985a

between plasma and erythrocytes. The blood model included four blood subcompartments: diffusible lead in plasma, protein-bound lead in plasma, a "shallow" erythrocyte pool, and a "deep" erythrocyte pool (see Figure 3-9). This model predicted the curvilinear relationship between plasma and blood lead concentrations observed in humans (see Section 3.3.2 Distribution for further discussion of plasma-erythrocyte lead concentrations).

Additional information on lead biokinetics, bone mineral metabolism, and lead exposures has led to further refinements and expansions of these earlier modeling efforts. Three pharmacokinetic models, in particular, are currently being used or are being considered for broad application in lead risk assessment: (1) the O'Flaherty Model, which simulates lead kinetics from birth through adulthood (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, which simulates lead kinetics from birth through adulthood (Leggett 1993). Of the three approaches, the O'Flaherty Model has the fewest lead-specific parameters and relies more extensively on physiologically based parameters to describe volumes, flows, composition, and metabolic activity of blood and bone 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 for lead are based on kinetics data obtained from studies conducted 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. All three models represent the rate of uptake of lead (i.e., amount of lead absorbed per unit of time) as relatively simple functions (f) 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 simulates multimedia exposures, uptake, and kinetics of lead in children ages 0–7 years; the model is not intended for use in predicting lead pharmacokinetics in adults. The O'Flaherty and Leggett models are lifetime models, and include parameters that simulate uptake and kinetics of lead during infancy, childhood, adolescence, and adulthood. Lead 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 includes parameters for simulating exposures and uptake to estimate average daily uptake of lead (µg/day) among populations of children potentially

Figure 3-9. Compartmental Model for Lead in Plasma and Red Blood Cells in the Marcus (1985c) Model*



*Schematic model for lead kinetics in which blood is represented as plasma (central exchange compartment) and red blood cells, the latter having shallow and deep pools.

Source: Marcus 1985c

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) (Beck et al. 2001; Griffin et al. 1999). In evaluating models for use in risk assessment, exposure data collected at hazardous waste sites have been used to drive model simulations (Bowers and Mattuck 2001; Hogan et al. 1998). The exposure module in the IEUBK Model makes this type of evaluation feasible.

The focus on relying on blood lead concentrations for model evaluation and calibration derives from several concerns. 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 blood lead concentration (see Section 3.2.2). In this context, blood lead 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 blood lead concentrations. Also, the most available data with which to calibrate and validate the models has been data relating exposure and/or lead intake to blood concentration. Thus, there is greater confidence in the validity of the models for estimating blood concentrations, rather than lead levels in other physiologic compartments. Although the principal adverse health effects of lead have been related to concentrations of lead in blood, other biomarkers of lead exposure, such as bone lead concentrations, are also of value in assessing associations between lead exposure and health; hence, there is a need for models that predict concentrations of lead in tissues other than blood (see Section 3.2.2).

The following three pharmacokinetic models are discussed in great detail 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).

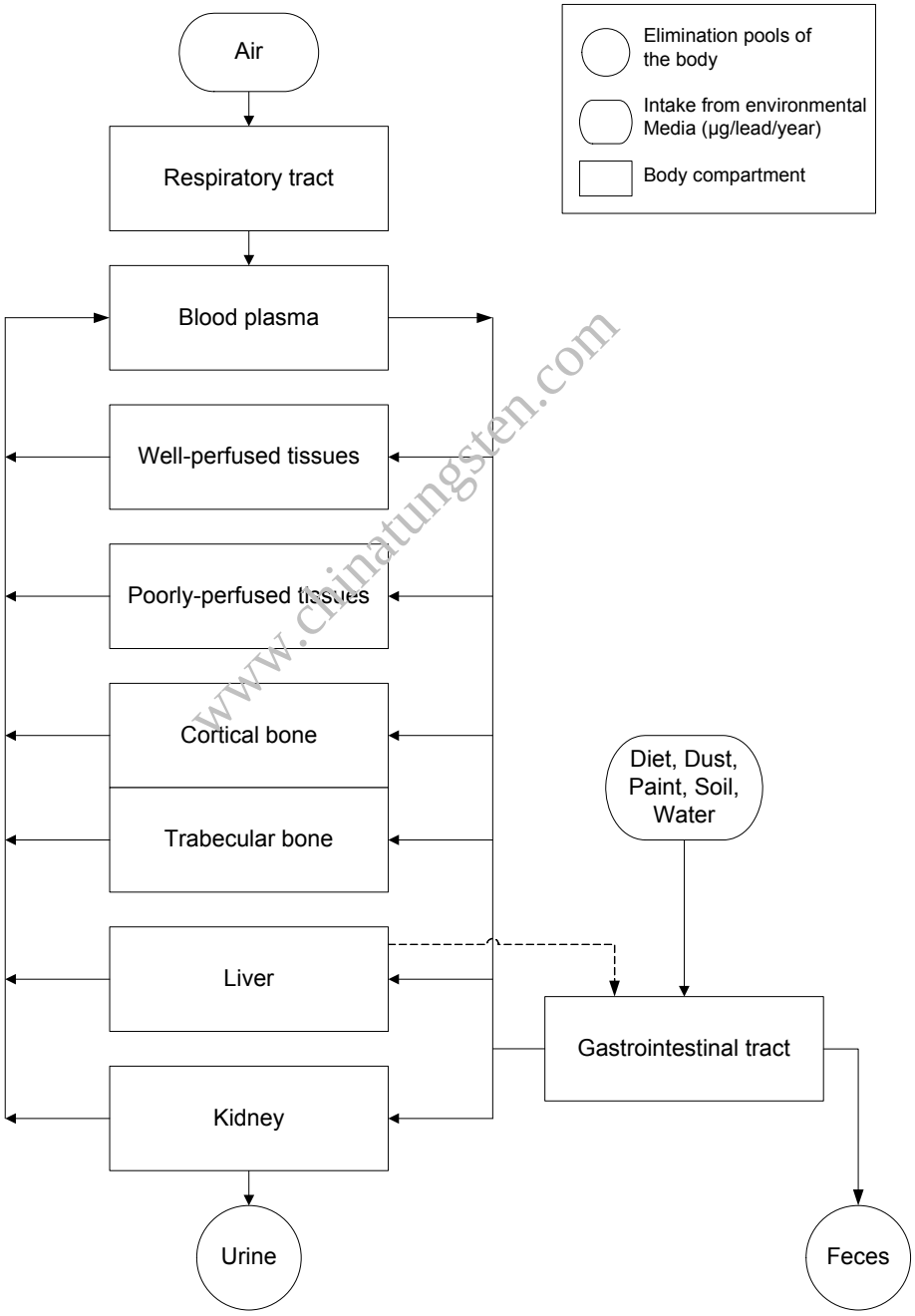
3.3.5.1 O'Flaherty Model

The O'Flaherty Model simulates lead exposure, uptake, and disposition in humans, from birth through adulthood (O'Flaherty 1993, 1995a). Figure 3-10 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. The model 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 blood lead 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 from birth through adulthood. 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. Tissue growth and volumes are linked to body weight; this provides explicit modeling of concentrations of lead in tissues. Other physiologic functions (e.g., bone formation) are linked to body weight, to age, or to both.

Lead exchange between blood plasma and bone is simulated as parallel processes occurring in cortical (80% of bone volume) and trabecular bone (20% of bone volume). Uptake and release of lead from trabecular bone and metabolically active cortical bone are functions of bone formation and resorption rates, respectively. Rates of bone formation and resorption are simulated as age-dependent functions, which gives rise to an age-dependence of lead kinetics in bone. The model simulates an age-related transition from immature bone, in which bone turn-over (formation and resorption) rates are relatively high, to mature bone, in which turn-over is relatively slow. Changes in bone mineral turnover associated with senescence (e.g., postmenopausal osteoporosis) are not represented in the model. In addition to metabolically active regions of bone, in which lead uptake and loss is dominated by bone formation and loss, a region of slow kinetics in mature cortical bone is also simulated, in which lead uptake and release to blood occur by heteroionic exchange with other minerals (e.g., calcium). Heteroionic exchange is simulated as a radial diffusion in bone volume of the osteon. All three processes are linked to body weight, or the rate of change of weight with age. This approach allows for explicit simulation of the effects of bone formation (e.g., growth) and loss, changes in bone volume, and bone maturation on lead

Figure 3-10. Compartments and Pathways of Lead Exchange in the O'Flaherty Model*



*Schematic model for lead kinetics in which lead distribution is represented by flows from blood plasma to liver, kidney, richly-perfused tissues, poorly-perfused tissues, and cortical and trabecular bone. The model simulates tissue growth with age, including growth and resorption of bone mineral.

Sources: O'Flaherty 1991b, 1993, 1995a

uptake and release from bone. Exchanges of lead between blood plasma and soft tissues (e.g., kidney and liver) are represented as flow-limited processes. The model simulates saturable binding of lead in erythrocytes; this replicates the curvilinear relationship between plasma and erythrocyte lead concentrations observed in humans (see Sections 3.3.2 and 3.4.1). Excretory routes include kidney to urine and liver to bile. Total excretion (clearance from plasma attributable to bile and urine) is simulated as a function of glomerular filtration rate. Biliary and urinary excretory rates are proportioned as 70 and 30% of the total plasma clearance, respectively.

The O'Flaherty Model simulates lead intake from inhalation and ingestion. Inhalation rates are age-dependent. Absorption of inhaled lead is simulated as a fraction (0.5) of the amount inhaled, and is independent of age. The model simulates ingestion exposures from infant formula, soil and dust ingestion, and drinking water ingestion. Rates of soil and dust ingestion are age-dependent, increasing to approximately 130 mg/day at age 2 years, and declining to <1 mg/day after age 10 years. Gastrointestinal absorption of lead in diet and drinking water is simulated as an age-dependent fraction, declining from 0.58 of the ingestion rate at birth to 0.08 after age 8 years. These values can be factored to account for relative bioavailability when applied to absorption of lead ingested in dust or soil.

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 blood lead 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 blood lead concentrations (O'Flaherty 1993, 1995a).

The O'Flaherty Model, as described in O'Flaherty (1993, 1995a), utilizes point estimates for parameter values and yields point estimates as output; however, a subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability in exposure, absorption, and erythrocyte lead binding capacity (Beck et al. 2001). This extension of the model can be used to predict the probability that children exposed to lead in environmental media will have blood lead concentrations exceeding a health-based level of concern (e.g., 10 µg/dL).

The model was designed to operate with an exposure time step on 1 year (the smallest time interval for a single exposure event). However, the implementation code allows constructions of simulations with an exposure time step as small as 1 day, which would allow simulation of rapidly changing intermittent exposures (e.g., an acute exposure event).

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 (*M. 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. 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). Although the model has been 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 has been successfully extrapolated, with modification, to nonhuman primates (O'Flaherty et al. 1998). Crucial to the extrapolation of the model across species are the parameters describing bone formation, resorptions, and volume. Certain parameter values describing bone physiology and metabolism are likely to be relatively 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). 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). These factors would have to be evaluated in extrapolating the model to other species.

Interroute extrapolation. The O'Flaherty Model simulates intakes and uptake of ingested and inhaled lead and includes media-specific estimates of absorption from the gastrointestinal tract.

3.3.5.2 IEUBK Model

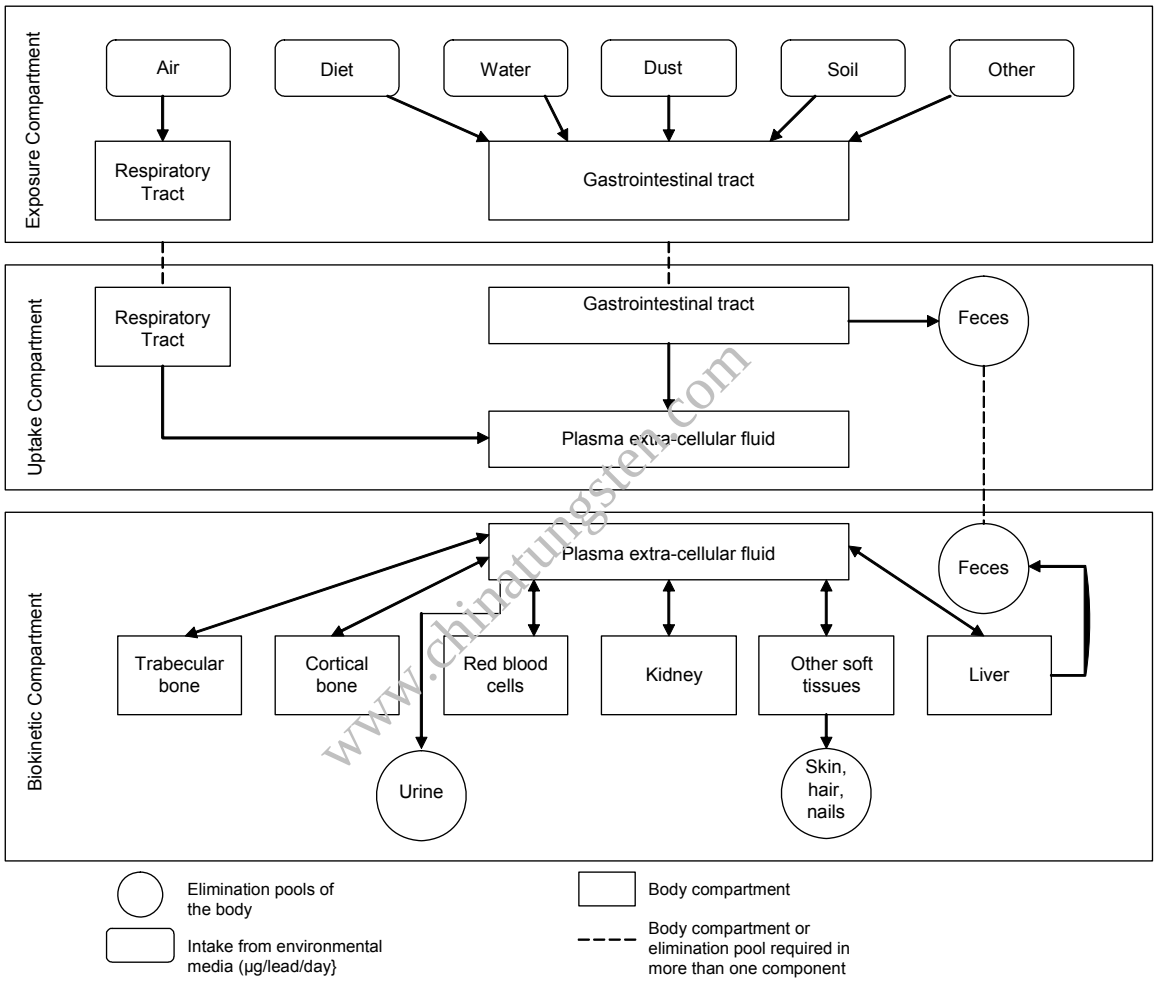
The IEUBK Model for Lead in Children is a classical multicompartmental pharmacokinetics model linked to an exposure and probabilistic model of blood lead concentration distributions in populations of children ages 0–7 years (EPA 1994a, 1994b; White et al. 1998). Figure 3-11 shows a conceptualized representation of the IEUBK Model. The model has four major submodels: (1) exposure model, in which average daily intakes of lead (μg/day) are calculated for each inputted exposure concentration (or rates) of lead in air, diet, dust, soil, and water; (2) uptake model, which converts environmental media-specific lead intake rates calculated from the exposure model into a media-specific time-averaged uptake rate (μg/day) of lead to the central compartment (blood plasma); (3) biokinetic model, which simulates the transfer of absorbed lead between blood and other body tissues, elimination of lead from the body (via urine, feces, skin, hair, and nails), and predicts an average blood lead concentration for the exposure time period of interest; and (4) blood lead probability model, which applies a log-normal distribution (with parameters geometric mean and geometric standard deviation) to predict probabilities for the occurrence of a specified given blood lead concentration in a population of similarly exposed children.

Description of the Model

Exposure Model. The exposure model simulates intake of lead (μg/day) for inputted exposures to lead in air (μg/m^3), drinking water (μg/L), soil-derived dust (μg/g), or diet (μg/day). The exposure model operates on a 1-year time step, the smallest time interval for a single exposure event. The model accepts inputs for media intake rates (e.g., air volumes breathing rates, drinking water consumption rate, soil and dust ingestion rate). The air exposure pathway is partitioned in exposures to outdoor air and indoor air; with age-dependent values for time spent outdoors and indoors (hours/day). Exposure to lead to soil-derived dust is also partitioned into outdoor and indoor contributions. The intakes from all ingested exposure media (diet, drinking water, soil-derived dust) are summed to calculate a total intake to the gastrointestinal tract, for estimating capacity-limited absorption (see description of the uptake model).

Uptake Model. The uptake model simulates lead absorption for the gastrointestinal tract as the sum of a capacity-limited (represented by a Michaelis-Menten type relationship) and unlimited processes (represented by a first-order, linear, 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 that suggest a capacity limitation to lead absorption (see Sections 3.3.2 and 3.4.1). One of the parameters for the capacity-limited absorption process (that represents that maximum rate of absorption)

Figure 3-11. Structure of the IEUBK Model for Lead in Children*



*Schematic for integrated lead exposure-kinetics model in which simulated multi-media exposures are linked to simulations of lead uptake (i.e., absorption into the plasma-ECF) tissue distribution, and excretion.

Sources: EPA 1994a, 1994b

is age-dependent. The above representation gives rise to a decrease in the fractional absorption of ingested lead as a function of total lead intake as well as an age-dependence of fractional lead absorption. Absorption fractions are also medium-specific. At 30 months of age, at low intakes (<200 μg/day), below the rates at which capacity-limitation has a significant impact on absorption, the fraction of ingested lead in food or drinking water that is absorbed is 0.5 and decreases to approximately 0.11 (intake, >5,000 μg/day). For lead ingested in soil or dust, fractional absorption is 0.35 at low intakes (<200 μg/day) and decreases to 0.09 (intake, >5,000 μg/day).

The uptake model assumes that 32% of inhaled lead is absorbed. This value was originally assigned based on a scenario of exposure to active smelter emissions, which assumed the particle size distribution in the vicinity of an active lead smelter (<1 μm, 12.5%; 1–2.5 μm, 12.5%; 2–15 μm, 20%; 15–30 μm, 40%; >30 μm, 15%); size-specific deposition fractions for the nasopharyngeal, tracheobronchial, and alveolar regions of the respiratory tract; and region-specific absorption fractions. Lead deposited in the alveolar region is assumed to be completely absorbed from the respiratory tract, whereas lead deposited in the nasopharyngeal and tracheobronchial regions (30–80% of the lead particles in the size range 1–15 μm) is assumed to be transported to the gastrointestinal tract.

Biokinetics Model. The biokinetics model includes a central compartment, six peripheral body compartments, and three elimination pools. The body compartments include plasma and extra cellular fluid (central compartment), kidney, liver, trabecular bone, cortical bone, and other soft tissue (EPA 1994a). The model simulates growth of the body and tissues, compartment volumes, and lead masses and concentrations in each compartment. Blood lead concentration at birth (neonatal) is assumed to be 0.85 of the maternal blood lead. Neonatal lead masses and concentrations are assigned to other compartments based on a weighted distribution of the neonatal blood lead concentration. Exchanges between the central compartment and tissue compartments are simulated as first-order processes, which are parameterized with unidirectional, first-order rate constants. Bone is simulated as two compartments: a relatively fast trabecular bone compartment (representing 20% of bone volume) and a relatively slow cortical bone compartment (representing 80% of the bone volume). Saturable uptake of lead into erythrocytes is simulated, with a maximum erythrocyte lead concentration of 120 μg/L. Excretory routes simulated include urine, from the central compartment; bile-feces, from the liver; and a lumped excretory pathway represented losses from skin, hair and nail, from the other soft tissue compartment.

Blood Lead Probability Model. Inputs to the IEUBK Model are exposure point estimates that are intended to represent time-averaged central tendency exposures. The output of the model is a central

tendency estimate of blood lead concentration for children who might experience the inputted exposures. However, within a group of similarly exposed children, blood lead concentrations would be expected to vary among children as a result of inter-individual variability in media intakes, absorption, and biokinetics. The model simulates the combined impact of these sources of variability as a lognormal distribution of blood lead concentration for which the geometric mean (GM) is given by the central tendency blood lead concentration outputted from the biokinetics model and the GSD is an input parameter. The resulting lognormal distribution also provides the basis for predicting the probability of occurrence of given blood lead concentration within a population of similarly exposed children. The model can be iterated for varying exposure concentrations (e.g., a series of increasing soil lead concentration) to predict the media concentration that would be associated with a probability of 0.05 for the occurrence of a blood lead concentration exceeding 10 µg/dL. A subsequent elaboration of the model has been developed that utilizes a Monte Carlo approach to simulate variability and uncertainty in exposure and absorption (Goodrum et al. 1996; Griffin et al. 1999). This extension of the model provides an alterative to the blood lead probability model for incorporating, explicitly, estimates of variability (and uncertainty in variability) in exposure and absorption into predictions of an expected probability distribution of blood lead concentrations.

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. Thus, the IEUBK Model can be used to predict the probability that children of ages up to 7 years who are exposed to lead in multiple environmental media would have blood lead concentrations exceeding a given 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 IEUBK Model was not developed to assess lead risks for age groups older than 7 years. The model operates with an exposure time step on 1 year (the smallest time interval for a single exposure event) and, therefore, is more suited to applications in which long-term (i.e., >1 year) average exposures and blood lead concentrations are to be simulated (Lorenzana et al. 2005).

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 inputs 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. The 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/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. Similar empirical comparisons of the IEUBK Model have shown that agreement between model predictions and observed blood lead concentrations at specific locations is influenced by numerous factors, including the extent to which the exposure and blood lead measurements are adequately matched, and site-specific factors (e.g., soil characteristics, behavior patterns, bioavailability) that may affect lead intake or uptake in children (Bowers and Mattuck 2001; EPA 2001c). In addition to the above empirical comparisons, the computer code used to implement the IEUBK Model (IEUBK version 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.

3.3.5.3 Leggett Model

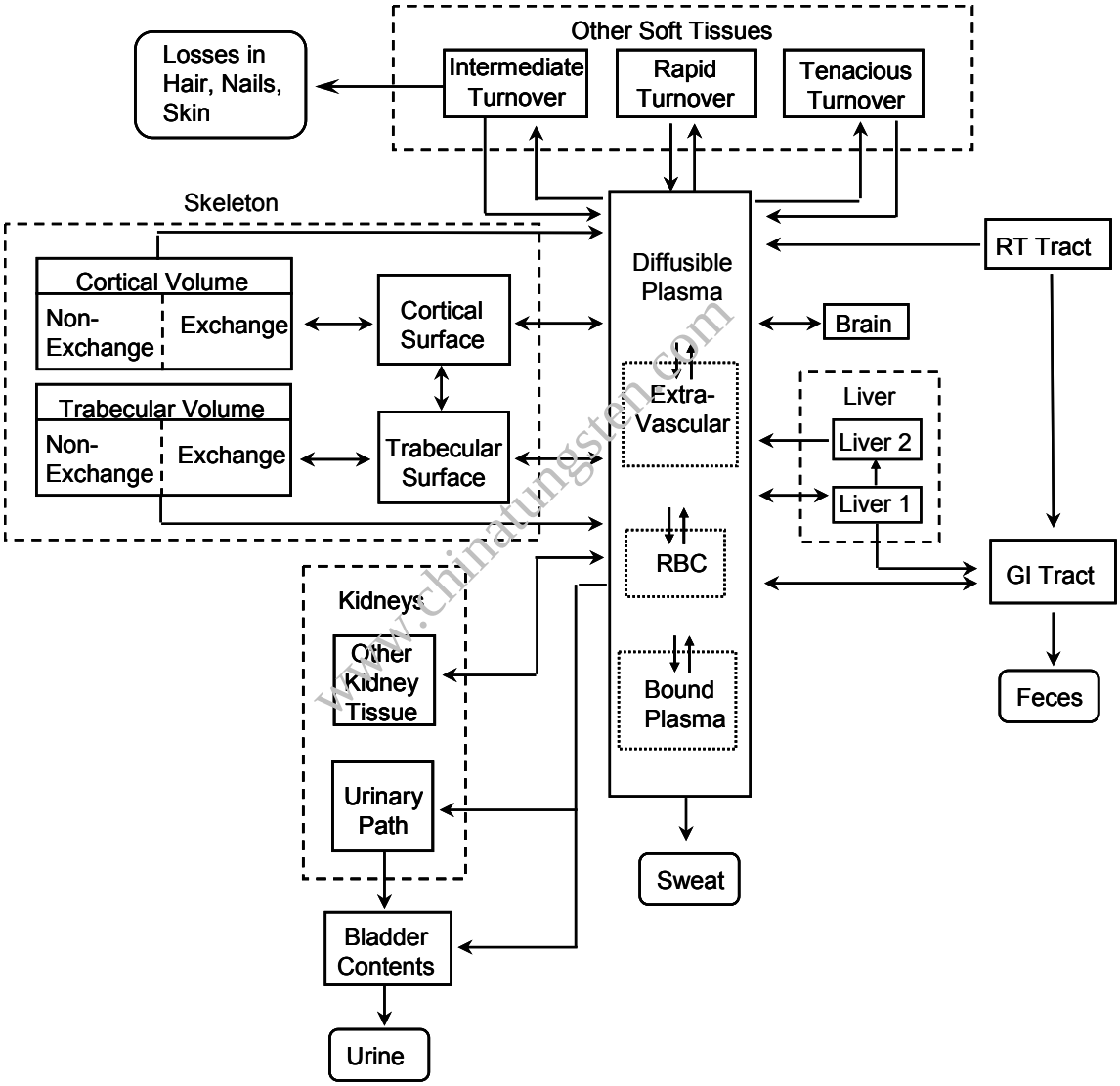
The Leggett Model is a classical multicompartmental pharmacokinetic model of lead uptake and disposition in children and adults (Leggett 1993). Figure 3-12 shows a conceptualized representation of the model, including the movement of lead from exposure media (i.e., intake via inhalation or ingestion) 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. 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 3-12. Transport of lead from blood plasma to tissues is assumed to follow first-order kinetics. Transfer rate constants vary with age and blood lead concentration. Above a nonlinear threshold concentration in red blood cells (assumed to be 60 μg/dL), the rate constant for transfer to red blood cells declines and constants to all other tissues increase proportionally (Leggett 1993). This replicates the nonlinear relationship between plasma and red blood observed in humans (see Section 3.4.1). The model simulates blood volume as an age-dependent function, which allows simulation of plasma and blood lead concentrations. Lead masses are simulated in all other tissues (tissue volumes are not simulated).

Unidirectional, first-order transfer rates (day^{-1}) between compartments were developed for six age groups, and intermediate age-specific values are obtained by linear interpolation. 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-dependent bone physiology using a model structure developed for application to the alkaline earth elements, but parameterized using data specific to lead where possible. The model simulates both rapid

Figure 3-12. Compartments and Pathways of Lead Exchange in the Leggett Model*



*Schematic model for lead kinetics in which lead distribution is represented by exchanges between the central plasma-ECF and tissue compartments. Bone is represented as having surface (which rapidly exchanges with plasma-ECF), and volume compartments; the latter simulates slow exchange with the surface and slow return of lead to the plasma-ECF from bone resorption.

Source: Leggett 1993

exchange of lead with plasma via bone surface and slow loss by bone resorption. Cortical bone volume (80% of bone volume) and trabecular bone volume (20% of bone volume) are simulated as bone surface compartments, which rapidly exchange with lead the blood plasma, and bone volume, within which are *exchangeable* and *nonexchangeable* pools. Lead enters the exchangeable pool of bone volume via the bone surface and can return to the bone surface, or move to the nonexchangeable pool, from where it can return to the blood only when bone is resorbed. Rate constants for transfer of lead from the nonexchangeable pools and blood plasma vary with age to reflect the age-dependence of bone turnover.

The liver is simulated as two compartments; one compartment has a relatively 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. The kidney is simulated as two compartments, one that exchanges slowly with blood plasma and accounts for lead accumulation in kidney tissue and a second compartment that receives lead from blood plasma and rapidly transfers lead to urine, with essentially no accumulation (urinary pathway). Other soft tissues are simulated as three compartments representing rapid, intermediate, and slow turnover rates (without specific physiologic correlates). Other excretory pathways (hair nails and skin) are represented as a lumped pathway from the intermediate turnover rate soft tissue compartment.

The Leggett Model simulates lead intakes from inhalation, ingestion, or intravenous injection. The latter was included to accommodate model evaluations based on intravenous injection studies in humans and animal models. The respiratory tract is simulated as four compartments into which inhaled lead is deposited and absorbed with half-times of 1, 3, 10, and 48 hours. Four percent of the inhaled lead is assumed to be transferred to the gastrointestinal tract. These parameter values reflect the data on which the model was based, which were derived from studies in which human subjects inhaled submicron lead-bearing particles (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). These assumptions would not necessarily apply to exposures to large airborne particles (see Section 3.3.1.1). Absorption of ingested lead simulated as an age-dependent fraction of the ingestion rate, declining from 0.45 at birth to 0.3 at age 1 year (to age 15 years), and to 0.15 after age 25 years.

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 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 operates with an exposure time step on 1 day (the smallest time interval for a single exposure event), which allows simulation of rapidly changing intermittent exposures (Khoury and Diamond 2003; Lorenzana et al. 2005). The model does not contain a detailed exposure module and, therefore, requires assumptions regarding total lead intake from multiple exposure media. In addition, the model utilizes point estimates for intakes and yields point estimates as output (e.g., blood lead concentration) and predicted 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.

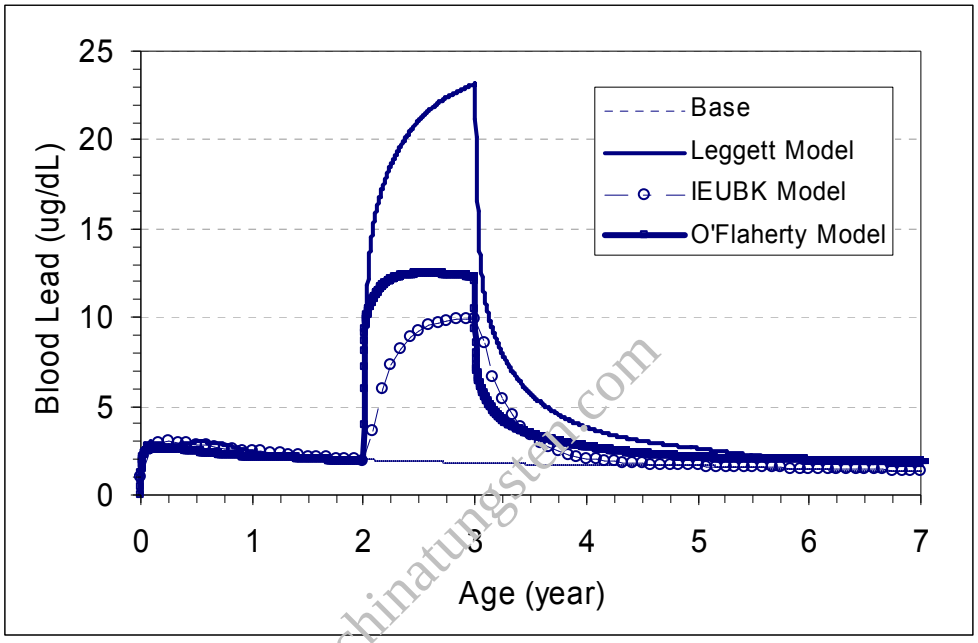
Species extrapolation. Data on both animals and humans (children and adults) describing the absorption, distribution, metabolism, and excretion of lead provide the biological basis of the biokinetic model and parameter values used in the Leggett Model. The model is calibrated to predict compartmental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

3.3.5.4 Model Comparisons

The O'Flaherty, IEUBK, and Leggett Models differ considerably in the way each represents tissues, exchanges of lead between tissues, and lead exposure. Figure 3-13 compares the PbBs predicted by each model for a hypothetical child who ingests 100 µg lead/day in soil for a period of 1 year beginning at the

Figure 3-13. Blood Lead Concentrations in Children Predicted by the O'Flaherty, IEUBK, and Leggett Models*



*The simulations are of a hypothetical child who has a PbB of 2 ⏭g/dL at age 2 years, and then experiences a 1-year exposure to 100 ⏭g Pb/day. The 100 ⏭g/day exposure was simulated as an exposure to lead in soil in the IEUBK Model. Default bioavailability assumptions were applied in all three models.

age of 2 years (e.g., equivalent to ingestion of 100 µg soil/day at a soil lead concentration of 1,000 mg lead/g soil). The 100-µg/day exposure is superimposed on a baseline exposure that yields a PbB of approximately 2 µg/dL at 2 years of age. All three models predict an increase in PbB towards a quasi-steady state during the exposure period, followed by a decline towards the pre-exposure baseline PbB with a half-time of approximately 1 month. Predicted PbBs at the end of the 12-month soil exposure period were 6, 10, and 23 µg/dL for the IEUBK, O'Flaherty, and Leggett Models, respectively. Differences in the magnitude of the predicted impact of the soil exposure on PbB reflect differences in assumptions about lead biokinetics and cannot be attributed solely to different assumptions about lead bioavailability. Bioavailability assumptions in the three models for the age range 2–3 years are: O'Flaherty Model, 45% (50% at age 2 years, decreasing to 40% at age 3 years); IEUBK Model, 30% (soil lead at low intakes); and Leggett Model, 30%. A comparison of model predictions for a similar exposure during adulthood (100 µg Pb/day for 1 year, beginning at age 25) is shown in Figure 3-14. Predicted PbBs at the end of the12-month soil exposure period were: 3 and 8 µg/dL for the O'Flaherty and Leggett Models, respectively. Both the O'Flaherty and Leggett Models predict a smaller change in PbB in adults, compared to children, for a similar increment in exposure. This is attributed, in part, to assumptions of lower lead bioavailability in adults (i.e., O'Flaherty, 8%; Leggett, 15%).

3.3.5.5 Slope Factor Models

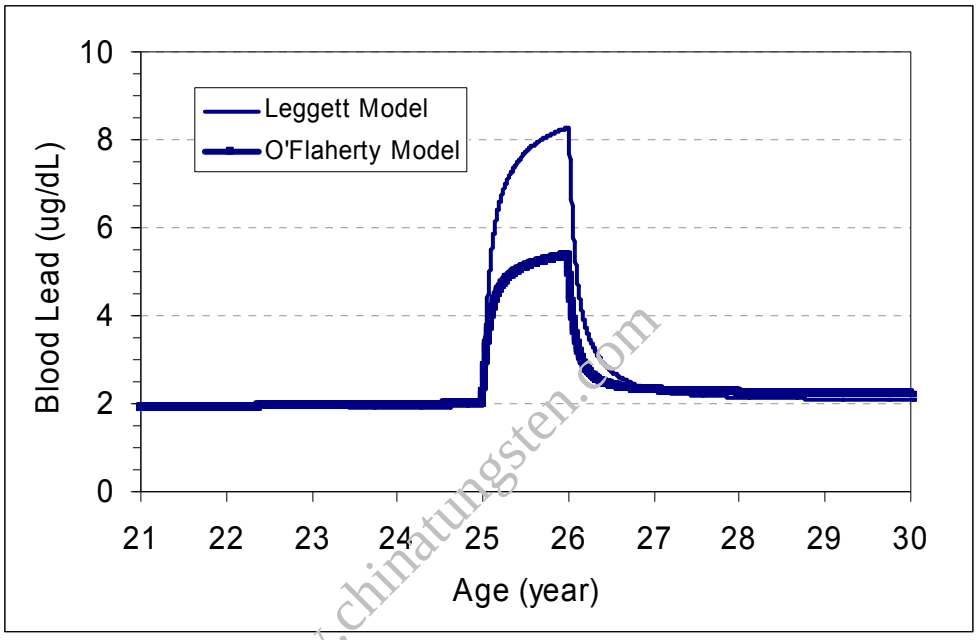
Slope factor models have been used as simpler alternatives to compartmental models for predicting PbBs, or the change in PbB, associated with a given exposure (Abadin et al. 1997a; Bowers et al. 1994; Carlisle and Wade 1992; EPA 2003b, Stern 1994, 1996). In slope factor models, lead biokinetics is represented with a simple linear relationship between the PbB and either lead uptake (biokinetic slope factor, BSF) or lead intake (intake slope factor, ISF). The models take the general mathematical forms:

$$PbB = E \cdot ISF$$

$$PbB = E \cdot AF \cdot BSF$$

where E is a expression for exposure (e.g., soil intake x soil lead concentration) and AF is the absorption fraction for lead in the specific exposure medium of interest. Intake slope factors are based on ingested rather than absorbed lead and, therefore, integrate both absorption and biokinetics into a single slope factor, whereas models that utilize a biokinetic slope factor to account for absorption in the relationship include an absorption parameter. Slope factors used in various models are presented in Table 3-10. Of

Figure 3-14. Blood Lead Concentrations in Adults Predicted by the O'Flaherty and Leggett Models*



*The simulations are of a hypothetical adult who has a PbB of 2 ⏭g/dL at age 25 years, and then experiences a 1-year exposure to 100 ⏭g Pb/day. Default bioavailability assumptions were applied in all three models.

Table 3-10. Comparison of Slope Factors in Selected Slope Factor Models

Model	Receptor	Slope factor		Absorption fraction
		Intake	Biokinetics	
Bowers et al. 1994	Adult	ND	0.375	0.08
Carisle and Wade 1992	Child	Soil/dust: 0.07 Water: 0.04	ND	ND
Carisle and Wade 1992	Adult	Soil/dust: 0.018 Water: 0.04	ND	ND
EPA 1996	Adult	ND	0.4	0.12
Stern 1994	Child	Residential: T (0.056, 0.16, 0.18)	ND	ND
Stern 1996	Adult	Non-residential: U (0.014, 0.034)	ND	ND

ND = No data; T = triangular probability distribution function (PDF); U = uniform PDF

the various models presented in Table 3-9, two Bowers et al. (1994) and EPA (2003b) models implement BSFs. The slope factors used in both models (approximately 0.4 µg/dL per µg Pb/day) are similar to biokinetic slope factors predicted from the O'Flaherty Model (0.65 µg/dL per µg Pb uptake/day) and Legget Model (0.43 µg/dL per µg Pb uptake/day) for simulations of adult exposures (Maddaloni et al. 2005). In general, intake slope factors are derived from epidemiologic observations. A review of slope factors relating medium-specific exposures and blood lead concentrations derived from epidemiologic studies is provided in Appendix D (Abadin et al. 1997a).

3.4 MECHANISMS OF ACTION

3.4.1 Pharmacokinetic Mechanisms

Absorption

Gastrointestinal Absorption of Inorganic Lead. Gastrointestinal absorption of inorganic 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. *In vitro* studies of lead speciation in simulated human intestinal chyme indicate that the concentration of ionized lead is negligible at lead concentrations below 10^{-3} M (207 mg/L) and that lead phosphate and bile acid complexes are the dominant forms when inorganic lead salts (e.g., lead nitrate) are added to chyme (Oomen et al. 2003a). However, these complexes may be sufficiently labile to provide ionized lead for transport across cell membranes (Oomen et al. 2003b). Saturable mechanisms of absorption 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 and iron, these are thought to represent membrane carriers (e.g., Ca^{2+}-Mg^{2+}-ATPase, Ca^{2+}/Na^{+} exchange, DMT1) or facilitated diffusion pathways (e.g., Ca^{2+} channel) and intracellular binding proteins for Ca^{2+} (Bronner et al. 1986; Fleming et al. 1998b; Gross and Kumar 1990; Teichmann and Stremmel 1990). Numerous observations of nonlinear relationships between blood lead 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 nonlinear; however, dose-tissue lead

relationships for bone, kidney, and liver were linear. The same pattern (nonlinearity for blood lead 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 blood lead 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 also associated with increased blood lead 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 Quaterman 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. When mRNA for DMT1, a mucosal membrane carrier for iron, was suppressed in Caco 2 cells (a human gastrointestinal cell line) the rate of iron and cadmium uptake decreased by 50% compared to cells in which DMT1 mRNA was not suppressed; however, DMT1 mRNA suppression did not alter the rate of lead uptake by Caco 2 cells, indicating that lead may enter Caco 2 cells through a mechanism that is independent of DMT1 (Bannon et al. 2003). 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.

Distribution

Red Blood Cells. Lead in blood is rapidly taken by red blood cells, where it binds to several intracellular proteins. Although the mechanisms by which lead crosses cell membranes have not been fully elucidated, results of studies in intact red blood cells and red blood cell ghosts indicate that there are two, and possibly three, pathways for facilitated transfer of lead across the red cell membrane. The major proposed pathway is an anion exchanger that is dependent upon HCO_3^- and is blocked by anion exchange inhibitors (Bannon et al. 2000, Simons 1985, 1986a, 1986b, 1993). A second minor pathway, which does not exhibit HCO_3^- dependence and is not sensitive to anion exchange inhibitors, may also exist (Simons 1986b). Lead and calcium may also share a permeability pathway, which may be a Ca^{2+}-channel (Calderon-Salinas et al. 1999). Lead is extruded from the erythrocyte by an active transport pathway, most likely a (Ca^{2+}, Mg^{2+})-ATPase (Simons 1988).

ALAD is the primary binding ligand for lead in erythrocytes (Bergdahl et al. 1997a, 1998; Sakai et al. 1982; Xie et al. 1998). Lead binding to ALAD is saturable; the binding capacity has been estimated to be approximately 850 µg/dL red blood cells (or approximately 40 µg/dL whole blood) and the apparent dissociation constant has been estimated to be approximately 1.5 µg/L (Bergdahl et al. 1998). Two other lead-binding proteins have been identified in the red cell, a 45 kDa protein (Kd 5.5 µg/L) and a smaller protein(s) having a molecular weight <10 kDa (Bergdahl et al. 1996, 1997a, 1998). Of the three principal lead-binding proteins identified in red blood cells, ALAD has the strongest affinity for lead (Bergdahl et al. 1998) and appears to dominate the ligand distribution of lead (35–84% of total erythrocyte lead) at blood lead levels below 40 µg/dL (Bergdahl et al. 1996, 1998; Sakai et al. 1982).

Lead binds to and inhibits the activity of ALAD (Gercken and Barnes 1991; Gibbs et al. 1985; Sakai et al. 1982, 1983). Synthesis of ALAD appears to be induced in response to inhibition of ALAD and, therefore, in response to lead exposure and binding of lead to ALAD (Boudene et al. 1984; Fujita et al. 1982). Several mechanisms may participate in the induction of ALAD, including (1) inhibition of ALAD directly by lead; (2) inhibition by protoporphyrin, secondary to accumulation of protoporphyrin as a result of lead inhibition of ferrochelatase; and (3) accumulation of ALA, secondary to inhibition of ALAD, which may stimulate ALAD synthesis in bone marrow cells (Boudene et al. 1984; Fujita et al. 1982).

ALAD is a polymorphic enzyme with two alleles (ALAD 1 and ALAD 2) and three genotypes: ALAD 1,1, ALAD 1,2, and ALAD 2,2 (Battistuzzi et al. 1981). Higher PbBs were observed in individuals with the ALAD 1,2 and ALAD 2,2 genotypes compared to similarly exposed individuals with

the ALAD 1,1 genotype (Astrin et al. 1987; Hsieh et al. 2000, Schwartz et al. 2000b; Wetmur et al. 1991). This observation has prompted the suggestion that the ALAD-2 allele may have a higher binding affinity for lead than the ALAD 1 allele (Bergdahl et al. 1997b), a difference that could alter lead-mediated outcomes. Several studies have been conducted to specifically evaluate whether ALAD genotypes are associated with differences in partitioning of lead between red blood cells and plasma, differences in distribution of lead to other tissue compartments, and altered susceptibility to lead toxicity. Further details on ALAD and other polymorphisms involved in lead toxicity are presented in Section 3.8, Populations that are Unusually Susceptible.

Lead in Blood Plasma. Lead binds to several constituents in plasma and it has been proposed that lead in plasma exists in four states: loosely bound to serum albumin or other proteins with relatively low affinity for lead, complexed to low molecular weight ligands such as amino acids and carboxylic acids, tightly bound to a circulating metalloprotein, and as free Pb^{2+} (Al-Modhefer et al. 1991). Free ionized lead (i.e., Pb^{2+}) in plasma represents an extremely small percentage of total plasma lead. The concentration of Pb^{2+} in fresh serum, as measured by an ion-selective lead electrode, was reported to be 1/5,000 of the total serum lead (Al-Modhefer et al. 1991). Approximately 40–75% of lead in the plasma is bound to plasma proteins, of which albumin appears to be the dominant ligand (Al-Modhefer et al. 1991; Ong and Lee 1980a). Lead may also bind to γ-globulins (Ong and Lee 1980a). Lead in serum that is not bound to protein exists largely as complexes with low molecular weight sulfhydryl compounds (e.g., cysteine, homocysteine). Other potential low molecular weight lead-binding ligands in serum may include citrate, cysteamine, ergothioneine, glutathione, histidine, and oxylate (Al-Modhefer et al. 1991).

Lead in Bone. 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 (Aufderheide and Wittmers 1992). This also gives rise to an age-dependence in bone lead distribution. 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 suggests that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Bone lead burdens in adults are slowly lost by diffusion (heteroionic exchange) as well as by resorption (O'Flaherty 1995a, 1995b). 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 (Berkowtiz et al. 2004; Bonithon-Kopp et al. 1986c; Hernandez-Avila et al. 2000; Markowitz and Weinberger 1990; Nash et al. 2004; Silbergeld et al. 1988; Symanski and Hertz-Picciotto 1995; Thompson et al. 1985).

Soft Tissues. Mechanisms by which lead enters soft tissues have not been fully characterized (Bressler et al. 2005). Studies conducted in preparations of mammalian small intestine support the existence of saturable and nonsaturable pathways of lead transfer and suggest that lead can interact with transport mechanisms for calcium and iron (see Section 3.4.2, Absorption). Lead can enter cells through voltage-gated L-type Ca^{2+} channels in bovine adrenal medullary cells (Legare et al. 1998; Simons and Pocock 1987; Tomsig and Suszkiw 1991) and through store-operated Ca^{2+} channels in pituitary GH3, glial C3, human embryonic kidney, and bovine brain capillary endothelial cells (Kerper and Hinkle 1997a, 1997b). Anion exchangers may also participate in lead transport in astrocytes (Bressler et al. 2005). In addition to the small intestine, DMT1 is expressed in the kidney (Canonne-Hergaux et al. 1999); however, little information is available regarding the transport of lead across the renal tubular epithelium. In Madin-Darby canine kidney cells (MDCK), lead has been shown to undergo transepithelial transport by a mechanism distinct from the anion exchanger that has been identified in red blood cells (Bannon et al. 2000). The uptake of lead into MDCK cells was both time and temperature dependent. Overexpression of DMT1 in the human embryonic kidney fibroblast cells (HEK293) resulted in increased lead uptake compared to HEK293 cells in which DMT1 was not overexpressed (Bannon et al. 2002). Based on this limited information, it appears that DMT1 may play a role in the renal transport of lead.

Lead in other soft tissues such as kidney, liver, and brain exists predominantly bound to protein. High affinity cytosolic lead binding proteins (PbBPs) have been identified in rat kidney and brain (DuVal and Fowler 1989; Fowler 1989). The PbBPs of rat are cleavage products of α2μ globulin, a member of the protein superfamily known as retinol-binding proteins (Fowler and DuVal 1991). α2μ-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). Other high-affinity lead binding proteins (Kd approximately 14 nM) have been isolated in human kidney, two of which have been identified as a 5 kD peptide, thymosin 4 and a 9 kD peptide, acyl-CoA binding protein (Smith et al. 1998b). Lead also binds to metallothionein, but does not appear to be a significant inducer of the protein in comparison with the inducers of cadmium and zinc (Eaton et al. 1980; Waalkes and Klaassen 1985). *In vivo*, only a small fraction of the lead in the kidney is bound to metallothionein, and appears to have a binding affinity that is less than Cd^{2+}, but higher than Zn^{2+} (Ulmer and Vallee 1969); thus, lead will more readily displace zinc from metallothionein than cadmium (Goering and Fowler 1987; Nielson et al. 1985; Waalkes et al. 1984).

Metabolism. Metabolism of inorganic lead consists primarily of reversible ligand reactions, including the formation of complexes with amino acids and nonprotein 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 undego oxidative dealkylation to the highly neurotoxic metabolites, triethyl and trimethyl lead, respectively (Bolanowska 1968; Kehoe and Thamann 1931). 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

Urinary Excretion. Mechanisms by which inorganic lead is excreted in urine have not been fully characterized. 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. Renal plasma clearance was approximately 20–30 mL/minute in a subject who received a single intravenous injection of a ^{203}Pb chloride tracer (Chamberlain et al. 1978). 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.

Mechanisms of secretory and absorptive transfer of lead in the kidney have not been characterized. Studies conducted in preparations of mammalian small intestine support the existence of saturable and nonsaturable pathways of lead transfer and suggest that lead can interact with transport mechanisms for calcium and iron. Although these observations may be applicable to the kidney, empirical evidence for specific transport mechanisms in the renal tubule are lacking (Diamond 2005).

Fecal Excretion. In humans, absorbed inorganic lead is excreted in feces (Chamberlain et al. 1978; Rabinowitz et al. 1976). The mechanisms for fecal excretion of absorbed lead have not been elucidated; however, pathways of excretion may include secretion into the bile, gastric fluid and saliva (Rabinowitz et al. 1976). Biliary excretion of lead has also been observed in the dog, rat, and rabbit (Klaassen and Shoeman 1974; O'Flaherty 1993).

3.4.2 Mechanisms of Toxicity

Target Organ Toxicity. This section focuses on mechanisms for sensitive health effects of major concern for lead—cardiovascular/renal effects, hematological effects, and neurological effects, particularly in children.

Cardiovascular Effects. A variety of diverse mechanisms may contribute to the increased blood pressure that is observed with chronic exposure to lead. Lead affects important hormonal and neural systems that contribute to the regulation of peripheral vascular resistance, heart rate and cardiac output (Carmignani et al. 2000; Khalil-Manesh et al. 1993; Ni et al. 2004; Vaziri and Sica 2004). Lead-induced hypertension in rats is accompanied by depletion of nitric oxide (NO), which plays an important role in regulating blood pressure, through peripheral (i.e., vasodilation, naturesis) and central (anti-sympathetic) mechanisms (Gonick et al. 1997; Vaziri et al. 1997). NO depletion induced by lead is thought to derive, at least in part, from oxidative stress and associated increased activity of reactive oxygen species (ROS) and reactivity with NO (Ding et al. 2001; Vaziri et al. 1999a, 199b). Lead may also disrupt the vasodilatory actions of NO by altering cell-signaling mechanisms in endothelial cells. Lead exposure in rats is

associated with a down regulation of the expression of soluble guanylate cyclase, the enzyme that produces cyclic GMP, which mediates NO-induced vasodilation (Marques et al. 2001). Lead-induced hypertension is also associated with abnormalities in the adrenergic system, including increased central sympathetic nervous system activity, elevated plasma norepinephrine, and decreased vascular β-adrenergic receptor density (Carmignani et al. 2000; Chang et al. 1996; Tsao et al. 2000). Chronic lead exposure also activates the renin-angiotensin-aldosterone system, either directly or indirectly, through stimulation of the sympathetic nervous system. Chronic exposure to lead elevates plasma renin activity, plasma angiotensin-converting-enzyme (ACE), and plasma aldosterone concentrations (Boscolo and Carmignani 1988; Carmignani et al. 1988). Lead-induced hypertension is also associated with alterations in the regulation of kallikrein-kinin system and the production of associated vasodilatory hormones (Carmignani et al. 1999) and alterations in production of renal prostaglandins (Gonick et al. 1998; Hotter et al. 1995). Lead exerts direct constrictive effects on vascular smooth muscle, which are thought to be mediated by inhibition or Na-K-ATPase activity and associated elevation of intracellular Ca^{2+} levels, and possibly through activation of protein kinase C (Hwang et al. 2001; Kramer et al. 1986; Piccinini et al. 1977; Watts et al. 1995).

Renal Effects. Lead in cells binds to a variety of proteins, some of which have been implicated in lead toxicity (see Section 3.4.1 for further discussion). A characteristic histologic feature of lead nephrotoxicity is the formation of intranuclear inclusion bodies in the renal proximal tubule (Choie and Richter 1972; Goyer et al. 1970a, 1970b). Inclusion bodies contain lead complexed with protein (Moore et al. 1973). Appearance of nuclear inclusion bodies is associated with a shift in compartmentalization of lead from the cytosol to the nuclear fraction (Oskarsson and Fowler 1985). Sequestration of lead in nuclear inclusion bodies can achieve a lead concentration that is 100 times higher (μg Pb/mg protein) than that in kidney cytosol (Goyer et al. 1970a, 1970b; Horn 1970); thus, the bodies can have a profound effect on the intracellular disposition of lead in the kidney.

The sequestration of lead in intranuclear inclusion bodies may limit or prevent toxic interactions with other molecular targets of lead. In rats exposed to nephrotoxic doses of lead acetate, few intranuclear inclusion bodies occurred in the S3 segment of the proximal tubule, where acute injury was most severe, whereas, intranuclear inclusion bodies were more numerous in the S2 segment, where the injury was less severe (Murakami et al. 1983).

The exact identity of the lead-protein complex in inclusion bodies remains unknown, as is the mechanism of formation of the inclusion body itself. Although proteins that appear to be unique to lead-induced

inclusion bodies have been isolated, their role in the lead sequestration has not been elucidated (Shelton and Egle 1982). Cytosolic proteins may serve as carriers of lead or intermediary ligands for uptake of lead into the nucleus. Two cytosolic proteins, which appear to be cleavage products of 2-microglobulin (Fowler and DuVal 1991), have been isolated from rat kidney cytosol that have high affinity binding sites for lead (Kd=13 and 40 nM, respectively) and can mediate uptake of lead into isolated nuclei (Mistry et al. 1985, 1986). These proteins can also participate in ligand exchange reactions with other cytosolic binding sites, including δ-aminolevulinic dehydratase, which binds and is inhibited by lead (Goering and Fowler 1984, 1985). Other high-affinity lead binding proteins (Kd approximately 14 nM) have been isolated in human kidney, two of which have been identified as a 5 kD peptide, thymosin 4 and a 9 kD peptide, acyl-CoA binding protein (Smith et al. 1998b). Lead also binds to metallothionein, but does not appear to be a significant inducer of the protein in comparison with the inducers of cadmium and zinc (Eaton et al. 1980; Waalkes and Klaassen 1985). *In vivo*, only a small fraction of the lead in the kidney is bound to metallothionein, and appears to have a binding affinity that is less than Cd^{2+}, but higher than Zn^{2+} (Ulmer and Vallee 1969); thus, lead will more readily displace zinc from metallothionein than cadmium (Goering and Fowler 1987; Nielson et al. 1985; Waalkes et al. 1984). The precise role of cytosolic lead binding proteins in inclusion body formation has not been determined, although it has been hypothesized that aggregations of 2-microglobulin may contribute to the lead-protein complex observed in nuclear inclusion bodies (Fowler and DuVal 1991).

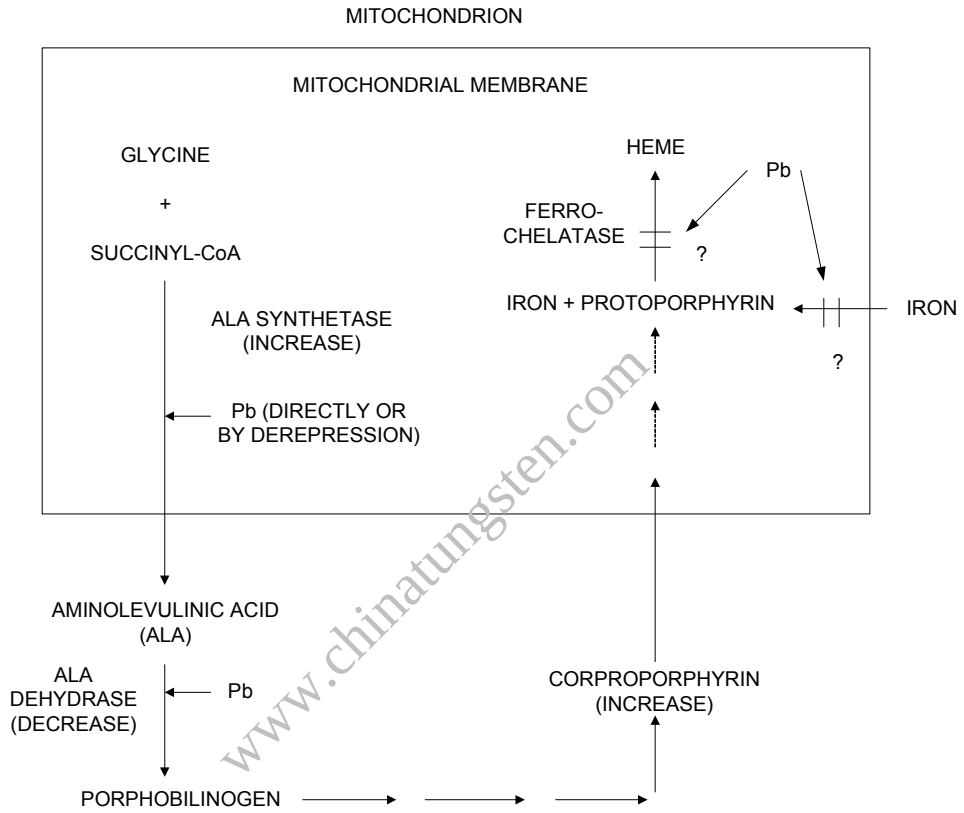
A consistent feature of lead-induced nephropathy is the finding of structural abnormalities of mitochondria of renal proximal tubule cells (Fowler et al. 1980; Goyer 1968; Goyer and Krall 1969). Mitochondria isolated from intoxicated rats contain lead, principally associated with the intramembrane space or bound to the inner and outer membranes, and show abnormal respiratory function, including decreased respiratory control ratio during pyruvate/malate- or succinate-mediated respiration (Fowler et al. 1980; Oskarsson and Fowler 1985). Lead inhibits uptake of calcium into isolated renal mitochondria and may enter mitochondria as a substrate for a calcium transporter (Kapoor et al. 1985). This would be consistent with evidence that lead can interact with calcium binding proteins and thereby affect calcium-mediated or regulated events in a variety of tissues (Fullmer et al. 1985; Goldstein 1993; Goldstein and Ar 1983; Habermann et al. 1983; Platt and Busselberg 1994; Pounds 1984; Richardt et al. 1986; Rosen and Pounds 1989; Simons and Pocock 1987; Sun and Suszkiw 1995; Tomsig and Suszkiw 1995; Watts et al. 1995). Impairments of oxidative metabolism could conceivably contribute to transport deficits and cellular degeneration; however, the exact role this plays in lead-induced nephrotoxicity has not been elucidated.

Lead exposure also appears to produce an oxidative stress of unknown, and possibly multi-pathway, origin (Daggett et al. 1998; Ding et al. 2001; Hermes-Lima et al. 1991; Lawton and Donaldson 1991; Monteiro et al. 1991; Nakagawa 1991; Sandhir et al. 1994; Sugawara et al. 1991). Secondary responses to lead-induced oxidative stress include induction of nitric oxide synthase, glutathione S-transferase and transketolase in the kidney (Daggett et al. 1998; Moser et al. 1995; Vaziri et al. 2001; Witzmann et al. 1999; Wright et al. 1998). Depletion of nitric oxide has been implicated as a contributor to lead-induced hypertension in the rat (Carmignani et al. 2000; Gonick et al. 1997; Vaziri et al. 1997, 1999a, 1999b) and thereby may contribute to impairments in glomerular filtration and possibly in the production of glomerular lesions; however, a direct role of this mechanism in lead-induced proximal tubular injury has not be elucidated. Both lead and L-N-(G)-nitro arginine methyl ester (L-NAME), an inhibitor of nitric oxide synthetase, increased the release of N-acetyl-D-glucosaminidase (NAG) from isolated rat kidneys perfused with an albumin-free perfusate (Dehpour et al. 1999). The addition of L-arginine decreased the effect of lead on NAG release. This observation is consistent with an oxidative stress mechanism possibly contributing to lead-induced enzymuria and increased urinary excretion of NAG (see Section 3.2.2, Renal Effects).

Experimental studies in laboratory animals have shown that lead can depress glomerular filtration rate and renal blood flow (Aviv et al. 1980; Khalil-Manesh et al. 1992a, 1992b). In rats, depressed glomerular filtration rate appears to be proceeded with a period of increased filtration (Khalil-Manesh et al. 1992a; O'Flaherty et al. 1986). The mechanism by which lead alters glomerular filtration rate is unknown and, its mechanistic connection to lead-induced hypertension has not been fully elucidated. Glomerular sclerosis or proximal tubule injury and impairment could directly affect renin release (Boscolo and Carmignani 1988) and/or renal insufficiency could secondarily contribute to hypertension.

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 3-15. 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 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,

Figure 3-15. Effects of Lead on Heme Biosynthesis



Source: EPA 1986a

which is normally found at the active site, binds to only one of these sulfhydryls. Inhibition of ALAD and feedback derepression of ALAS results in accumulation of ALA. Lead decreases, in a noncompetitive 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. In the past, assays used in studies of protoporphyrin accumulation measured ZPP or FEP, because ZPP is converted to FEP during extraction and older technology could not differentiate FEP from ZPP. However, contemporary technology permits the direct quantification of ZPP, a far more clinically useful parameter. 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 PbBs than those noted as threshold levels for inhibition or stimulation of enzyme activities involved in heme synthesis (EPA 1986a). Inappropriate renal production of erythropoietin due to renal damage, leading to inadequate maturation of erythoid progenitor cells, also has been suggested as a contributing mechanism for lead-induced anemia (Osterode et al. 1999).

The increase in erythrocyte destruction may be due in part to inhibition by lead of pyrimidine-5'-nucleotidase, 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 energetics (Angle et al. 1982; EPA

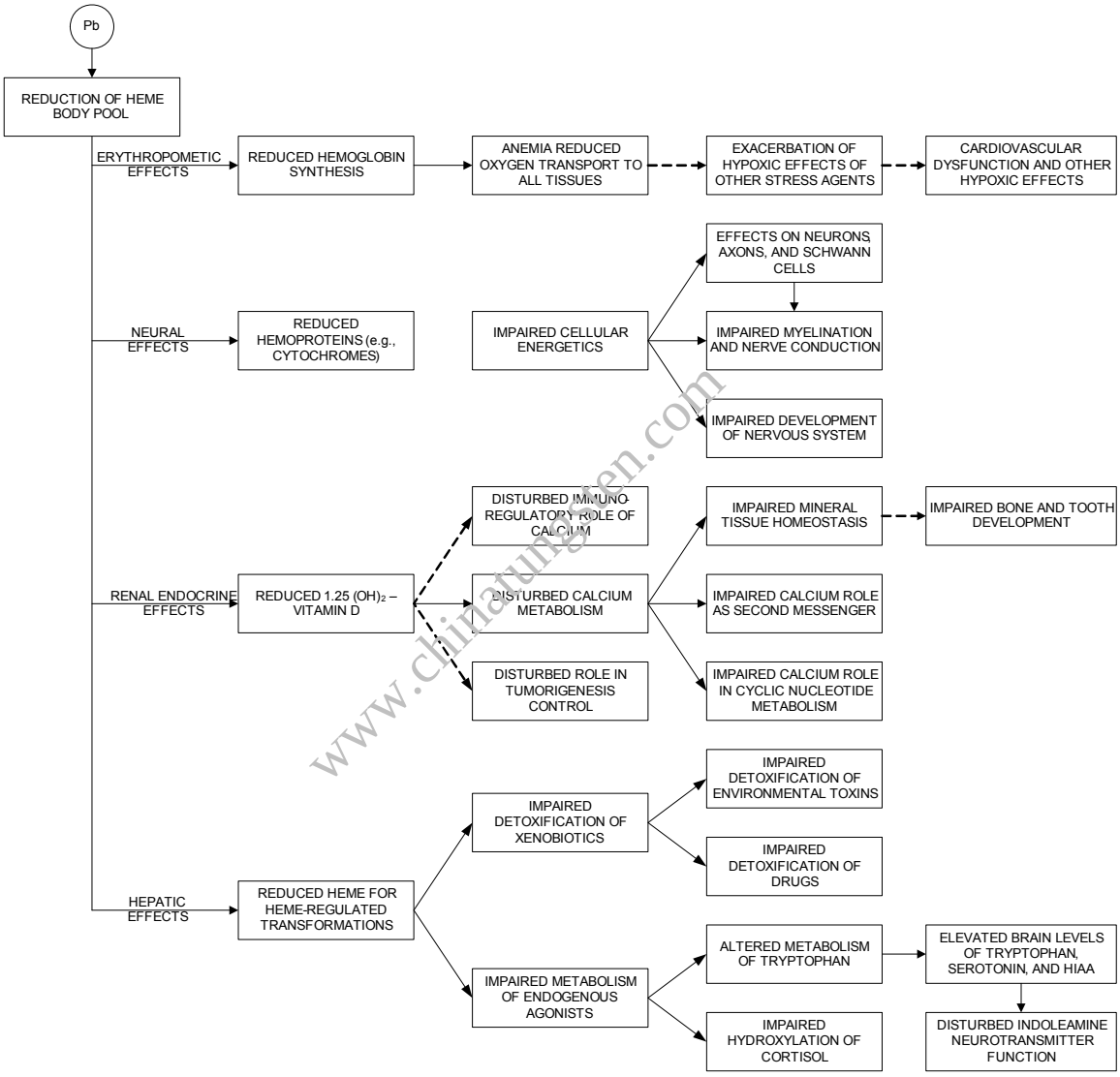
1986a). Formation of the heme-containing cytochromes is inhibited in animals treated intraperitoneally or orally with lead compounds. An inverse dose-effect relationship between lead exposure and P-450 content of hepatic microsomes and also activity of microsomal mixed-function oxygenases has been observed (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 may have 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 3-16. Solid arrows indicate well-documented effects, whereas dashed arrows indicate effects considered to be plausible further consequences of the impairment of heme synthesis. More detailed information on the exposure levels or blood lead levels at which these impacts may be experienced was provided in Section 3.2.

Neurotoxicity. The literature on mechanisms of neurotoxicity of lead is enormous. Most studies conducted in recent years have focused on trying to determine the biochemical or molecular basis of the intellectual deficits observed in exposed children using animal models. Trying to cite all of the studies that have contributed to our current knowledge is an almost impossible task. Therefore, the major topics summarized below have been extracted from experts' reviews and the reader is referred to references cited therein for more detailed information (Bouton and Pevsner 2000; Bressler et al. 1999; Cory-Slechta 1995, 2003; Gilbert and Lasley 2002; Lasley and Gilbert 2000; Nihei and Guilarte 2002; Suszkiw 2004; Toscano and Guilarte 2005; Zawia et al. 2000).

Lead can affect the nervous system by multiple mechanisms, one of the most important of which is by mimicking calcium action and/or disruption of calcium homeostasis. Because calcium is involved as a cofactor in many cellular processes, it is not surprising that many cell-signaling pathways are affected by lead. One pathway that has been studied with more detail is the activation of protein kinase C (PKC). PKC is a serine/threonine protein kinase involved in many processes important for synaptic transmission such as the synthesis of neurotransmitters, ligand-receptor interactions, conductance of ionic channels, and dendritic branching. The PKC family is made up of 12 isozymes, each with different enzymatic cofactor requirements, tissue expression, and cellular distributions. The γ-isoform is one of several calcium-dependent forms of PKC and is a likely target for lead neurotoxicity; it is neuron-specific and is

Figure 3-16. Multiorgan Impact of Reduction of Heme Body Pool by Lead



Source: EPA 1986a

involved in long-term potentiation (see below), spatial learning, and memory processes. PKC has the capacity to both activate and inhibit PKCs. Studies have shown that micromolar concentrations of lead can activate PKC-dependent phosphorylation in cultured brain microvessels, whereas picomolar concentrations of lead activate preparations of PKC *in vitro*. Interestingly, studies in rats exposed to low lead levels have shown few significant changes in PKC activity or expression, suggesting that the whole animal may be able to compensate for lead PKC-mediated effects compared to a system *in vitro*. PKC induces the formation of the AP-1 transcriptional regulatory complex, which regulates the expression of a large number of target genes via AP-1 promoter elements. A gene regulated by lead via AP-1 promoters is the glial fibrillary acidic protein (GFAP), an astrocytic intermediate filament protein that is induced during periods of reactive astrocytic gliosis. Astrocytes along with endothelial cells make up the blood brain barrier (BBB). Studies in rats exposed chronically to low lead levels have reported alterations in the normal pattern of GFAP gene expression in the brain, and the most marked long-lasting effects occurred when the rats were exposed during the developmental period. 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 PKC. Thus, it appears that premature activation of PKC 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. 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 sequester lead.

Another enzyme altered by lead is calmodulin, a major intracellular receptor for calcium in eukaryotes. Normally, calcium induces a conformational change in calmodulin that converts the protein to an active form; lead improperly activates the enzyme. Some studies suggest that activation of calmodulin by lead results in protein phosphorylation in the rat brain and brain membrane preparations and can alter proper functioning of cAMP messenger pathways. It has been shown that calmodulin can mediate gene expression via calmodulin-dependent kinases. The effects of lead on gene expression via activation of

calmodulin are not as marked as those via PKC because activation of calmodulin requires 100-fold more lead than activation of PKC.

Lead also can substitute for zinc in some enzymes and in zinc-finger proteins, which coordinate one or more zinc cations as cofactors. The substitution of lead for zinc in zinc-finger proteins can have significant effects on *de novo* expression of the bound proteins and in any genes transcriptionally-regulated by a particular protein. Lead has been found to alter the binding of zinc-finger transcriptional regulator Sp1 to its specific DNA sequences. This is accompanied by aberrant expression of Sp1 target genes such as myelin basic protein and proteolipid protein. Another gene regulated by Sp1 is the β-amyloid precursor protein (APP) gene. Recently, it was shown that lead exposure in neonatal rats transiently induces APP mRNA, which is overexpressed with a delay of 20 months after exposure to lead ceased. In contrast, APP expression, Sp1 activity, as well as APP ans β-amyloid protein levels, were unresponsive to lead during old age, suggesting that exposures occurring during brain development may predetermine the expression and regulation of APP later in life. It has been suggested that the multiple responses to lead exposure are due to lead specifically targeting zinc-finger proteins found in enzymes, channels, and receptors.

Lead affects virtually every neurotransmitter system in the brain, but most information on changes is available on the glutamatergic, dopaminergic, and cholinergic systems. Of these, special attention has been paid to the glutamatergic system and its role in hippocampal long-term potentiation (LTP). Hippocampal LTP is a cellular model of learning and memory characterized by a persistent increase in synaptic efficacy following delivery of brief tetanic stimulation (high-frequency stimulation). LTP provides a neurophysiological substrate for learning and storing information and is thought to utilize the same synaptic mechanisms as the learning process. LTP is established only with complex patterns of stimulation but not with single pulse stimulation. While it has been studied primarily in the hippocampal subregions CA1 and dentate gyrus, it can also be evoked in cortical areas. Exposure of intact animals or tissue slices to lead diminishes LTP by a combination of three actions: increasing the threshold for induction, reducing the magnitude of potentiation, and shortening its duration by accelerating its rate of decay. This effect on LTP involves actions of lead on glutamate release (presynaptic effects) and on the N-methyl-D-aspartate (NMDA) receptor function. Studies have shown that the effects of lead vary as a function of the developmental exposure period and that lead exposure early in life is critical for production of impaired LTP in adult animals. LTP is more readily affected by lead during early development, but exposure initiated after weaning also affects synaptic plasticity. Studies also have shown that both LTP magnitude and threshold exhibit a U-shape type response with increasing lead

doses. While LTP is primarily a glutamatergic phenomenon, it can be modulated through input from extrahippocampal sources including noradrenergic, dopaminergic, and cholinergic sources.

Studies in animals treated with lead (PbB 30–40 μg/dL) have shown that induction of pair-pulse facilitation in dentate gyrus is impaired. Since the phenomenon is mediated primarily by increased glutamate release, the reasonable assumption is that lead reduces glutamate release. Support for this assumption is also derived from studies in which depolarization-induced hippocampal glutamate release was reduced in awake animals with similar PbBs. This inhibition of glutamate release was shown to be due to lead-related decrements in a calcium-dependent component. The exact mechanism for the inhibition of glutamate release by lead is not known, but is consistent with lead at nanomolar concentrations preventing maximal activation of PKC, rather than lead blocking calcium influx into the presynaptic terminal through voltage-gated calcium channels. Reduced glutamate release can be observed in rats exposed from conception through weaning and tested as adults, when lead was no longer present, suggesting that a direct action of lead is not necessary and that other mechanisms, such as reductions in synaptogenesis, also may be involved. As with LTP, depolarization-evoked hippocampal glutamate release in rats treated chronically with several dose levels of lead exhibited a U-shaped response. That is, glutamate release was inhibited in rats treated with the lower lead doses, but not in those exposed to the higher concentrations of lead. Although speculative, this was interpreted as lead at the higher doses mimicking calcium in promoting transmitter release and overriding the inhibitory effects of lead that occur at lower lead levels.

The findings regarding the effects of lead on postsynaptic glutamatergic function have been inconsistent across laboratories, but a direct inhibitory action of lead on the NMDA receptor is unlikely at environmentally relevant exposure levels. Some studies have shown that continuous exposure of rats from gestation to adulthood results in a significant increase in NMDA receptor numbers in cortical areas, hippocampus, and forebrain. This was observed in the forebrain at PbB of 14 μg/dL. Other studies, however, have reported changes in the opposite direction and the reason for the discrepancy in results may be due to the different exposure protocols used. From a functional point of view, it seems plausible that a lead-induced reduction in presynaptic transmitter release be compensated by a postsynaptic increase in number or density of receptors in order to maintain a viable function.

The dopaminergic system also has a role in aspects of cognitive function since lesions of dopaminergic neurons impair behavior in various types of learning and cognitive tasks. Also, individuals who suffer from Parkinson's disease, a disease associated with dopamine depletion in the striatum, sometimes show

difficulties in cognitive functions. Most of the evidence available suggests that lead may impair regulation of dopamine synthesis and release, indicating a presynaptic site of action. Studies in animals often report opposing effects of lead on nigrostriatal and mesolimbic dopamine systems regarding receptor binding, dopamine synthesis, turnover, and uptake. Postweaning exposure of rats to lead resulted in supersensitivity of D1 and D2 dopamine receptors, which can be interpreted as a compensatory response to decreased synthesis and/or release of dopamine. Lesions to the nucleus acumbens (a terminal dopamine projection area) and the frontal cortex result in perseverative deficits, suggesting that the mesolimbic system is preferentially involved in the effects of lead. Results of studies using dopaminergic compounds seem to indicate that changes in dopamine systems do not play a role in the effects of lead on learning. Instead, it has been suggested that changes in dopaminergic systems may play a role in the altered response rates on Fixed-Interval (FI) schedules of reinforcement that have been observed in animals exposed to lead. This type of changes has been thought to represent a failure to inhibit inappropriate responding.

It is widely accepted that the cholinergic system plays a role in learning and memory processes. Some cognitive deficits observed in patients with Alzheimer's disease have been attributed to impaired cholinergic function in the cortex and hippocampus. Exposure to lead induces numerous changes in cholinergic system function, but the results, in general, have been inconsistently detected, or are of opposite direction in different studies, which may be attributed to the different exposure protocols used in the different studies. However, it is clear that lead blocks evoked release of acetylcholine and diminishes cholinergic function. This has been demonstrated in central and peripheral synapses. Studies with the neuromuscular junction showed that lead reduces acetylcholine release by blocking calcium entry into the terminal. At the same time, lead prevents sequestration of intracellular calcium by organelles, which results in increased spontaneous release of the neurotransmitter. Studies *in vitro* show that lead can block nicotinic cholinergic receptors, but it is unclear whether such effects occur *in vivo* or whether lead alters the expression of nicotinic cholinergic receptors in developing brain. Evidence for an involvement in lead-induced behavioral deficits has been presented based on the observation that intrahippocampal transplants of cholinergic-rich septal and nucleus basalis tissue improve the deficits and that treatment with nicotinic agonists can improve learning and memory impairments following perinatal lead treatment of rats. Chronic exposure of rats to lead has resulted in decreased muscarinic-receptor expression in the hippocampus. Whether or not lead exposure during development alters muscarinic receptor sensitivity is unclear as there are reports with opposite results. The preponderance of the binding data suggests that lead does not directly affect muscarinic receptors with the exception of visual cortex, where lead may have a direct inhibitory effect on muscarinic receptors from rods and bipolar of the retina.

3.4.3 Animal-to-Human Extrapolations

Studies in rodents, dogs, and nonhuman primates have demonstrated all of the major types of health effects of lead that have been observed in humans, including cardiovascular, hematological, neuro-developmental, 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 cognitive function in mammals and for providing insights into possible mechanisms for these effects. Studies in rats and nonhuman primates have demonstrated deficits in learning associated with blood lead concentrations between 10 and 15 µg/dL, a range that is comparable to those reported in epidemiological studies, which found learning deficits in children (Cory-Slechta 2003; Rice 1996b).

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 3.2.2). 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.

3.5 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 resulting from 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 6.6, 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 prenatal and postnatal 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. 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 et al. 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 newborns who all have a low glomerular filtration rate and have 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 remaining 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, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar 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, 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 PbBs ≥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, low birth weight, and low gestational age, growth retardation, and delayed sexual maturation in girls (Bellinger et al. 1992; Canfield et al. 2004; Coscia et al. 2003; Lanphear et al. 2000a; Ris et al. 2004; Schnaas et al. 2000; Selevan et al. 2003; Tong et al. 1998; Wu et al. 2003a). These effects, which are discussed in Section 3.2, 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, although Needleman et al. (1984) reported an association between cord blood lead and the incidence of minor anomalies (hemangiomas and lymphangiomas, hydrocele, skin anomalies, undescended testicles) in a study of 5,183 women who delivered neonates of at least 20 weeks of gestational age. Exposure to lead during childhood may result in neurobehavioral effects that persist into adulthood (e.g., Byers and Lord 1943; Stokes et al. 1998; White et al. 1993).

Children and developing organisms in general, 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 Section 3.2 for more detailed discussion). This suggests that children are more vulnerable to absorbed lead than adults. The mechanism for this increased vulnerability is not completely understood. Lead affects processes such as cell migration and synaptogenesis, as well as pruning of unnecessary connections between neurons, all key processes during brain development. Lead also affects glial cells and the blood brain barrier. Alterations in any of these parameters can produce permanent improper connections that will lead to altered specific brain functions. 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 3.3.1.2 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 3.4.2). Infants are born with a lead body burden that reflects the burden of the mother (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 2000; Gulson et al. 1997b, 1999b, 2003). Additional lead exposure may occur during breast feeding (Gulson et al. 1998b) (see Section 3.3.2 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, 1997a; 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 6.6 for more detailed discussion). Some children engage in pica, or the ingestion of nonfood 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 3.3.2 for details). Limited information suggests that organic lead compounds undergo enzymatic (cytochrome P-450) biotransformation and that inorganic lead is complexed (nonenzymatically) with proteins and nonprotein 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 3.3.5.

The important biomarkers of exposure that have been explored in children include PbB concentration (CDC 1991), bone lead levels (as measured from noninvasive 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 1996; Gulson and Wilson 1994; 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 3.6.1. The most sensitive biomarkers of effects of lead in children relate to the effects of lead on heme metabolism, they include ALAD activity, EP, FEP, and 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 3.6.2.

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, dimercaptosuccinic acid [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 3.9. Several studies (described in Section 3.9) have examined whether lead-lowering interventions, such as with chelators, are paralleled by improvement in health outcomes reportedly altered by lead (Dietrich et al. 2004; Liu et al. 2002; Rogan et al. 2001; Ruff et al. 1993). The conclusion of these studies was that chelation therapy is not indicated in children with moderate PbB (≤40 µg/dL).

3.6 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).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. 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 molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), 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 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 3.6.1.

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 not often 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 3.6.2.

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, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.8, Populations That Are Unusually Susceptible.

3.6.1 Biomarkers Used to Identify or Quantify Exposure to Lead

The ideal biomarker of lead exposure would be a measurement of total lead body burden. Biomarkers of exposure in practical use today are measurements of total lead levels in tissues or body fluids, such as blood, bone, urine, or hair; or measurement of certain biological responses to lead (e.g., zinc protoporphyrin). Tetraalkyl lead compounds may also be measured in the breath. Of these, blood lead concentration (PbB) is the most widely used and considered to be the most reliable biomarker for general clinical use and public health surveillance. Currently, blood lead measurement is the screening test of choice to identify children with elevated PbBs (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, PbBs between 10 and 14 µg/dL should trigger community-wide childhood lead poisoning prevention activities (CDC 1991). Since the elimination half-time of lead in blood is approximately 30 days, PbBs generally reflect relatively recent exposure and cannot be used to distinguish between low-level intermediate or chronic exposure and high-level acute exposure. In 1997, 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.

Blood Lead Concentration. Measurement of PbB is the most widely used biomarker of lead exposure. Elevated blood lead concentration (e.g., >10 µg/dL) is an indication of excessive exposure in infants and children (CDC 1991) and is considered to be excessive for women of child-bearing age (ACGIH 1998). The biological exposure index (BEI) for lead in blood of exposed workers is 30 µg/dL (ACGIH 2004). The NIOSH recommended exposure limit (REL) for workers (50 µg/m^3 air, 8-hour TWA) is established to ensure that the blood lead concentration does not exceed 60 µg/dL (NIOSH 2005).

The extensive use of blood lead as a dose metric reflects mainly the greater feasibility of incorporating blood lead measurements into clinical or epidemiological studies, compared to other potential dose indicators, such as lead in kidney, plasma, urine, or bone (Skerfving 1988). PbB measurements have several limitations as measures of lead body burden. Blood comprises <2% of the total lead burden; most of the lead burden resides in bone (Barry 1975). The elimination half-time of lead in blood is approximately 30 days (Chamberlain et al. 1978; Griffin et al. 1975; Rabinowitz et al. 1976); therefore, the lead concentration in blood relatively reflects, mainly, the exposure history of the previous few

months and does not necessarily reflect the larger burden and much slower elimination kinetics of lead in bone (Graziano 1994; Lyngbye et al. 1990b). The relationship between lead intake and PbB is curvilinear; the increment in PbB per unit of intake decreases with increasing PbB (Ryu et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1982, 1984). Lead intake-blood lead relationships also vary with age as a result of age-dependency of gastrointestinal absorption of lead, and vary with diet and nutritional status (Mushak 1991). A practical outcome of the above characteristics of PbB is that PbB can change relatively rapidly (e.g., weeks) in response to changes in exposure; thus, PbB can be influenced by short-term variability in exposure that may have only minor effects on lead body burden. A single blood lead determination cannot distinguish between lower-level intermediate or chronic exposure and higher-level acute exposure. Similarly, a single measurement may fail to detect a higher exposure that occurred (or ended) several months earlier. Time-integrated measurements of PbB may provide a means for accounting for some of these factors and thereby provide a better measure of long-term exposure (Roels et al. 1995).

Bone and Tooth Lead Measurements. The development of noninvasive 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 1991b; Hu et al. 1989, 1990, 1995; Rosen et al. 1993; Wedeen 1988, 1990, 1992). Lead in bone is considered 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 suggests that lead accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Patella, calcaneus, and sternum XRF measurements primarily reflect lead in trabecular bone, whereas XRF measurements of midtibia, 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; Brito et al. 2005; Nilsson et al. 1991; Schutz et al. 1987). Longitudinal measures of bone lead over a 3-year period showed no significant decline in cortical bone lead, whereas trabecular bone lead declined by approximately 15% (Kim et al. 1997). Estimates of cortical bone lead elimination half-times (5–50 years) show a dependence on lead burden, with longer half-times in people who have higher bone lead burdens (Brito et al. 2005). Further 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 PbB. Lead levels in trabecular bone (in adults) correlate more highly with contemporary PbB 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 epidemiology studies, but not as extensively as have other biomarkers of exposure such as PbB. These studies suggest that bone lead levels may be predictors of certain health outcomes, including neurodevelopmental and behavioral outcomes in children and adolescents (Campbell et al. 2000a; Needleman et al. 1996, 2002; Payton et al. 1998); and hypertension and declines in renal function in adults (Cheng et al. 2001; Gerr et al. 2002; Hu et al. 1996a, 1998; Korrick et al. 1999; Rothenberg et al. 2002a; Tsaih et al. 2004).

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 (Ericson 2001; Gomes et al. 2004; Omar et al. 2001; 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 1996; Gulson and Wilson 1994). 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 1996; Gulson and Wilson 1994; 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 Fergusson 1986).

An analysis of eight cross-sectional and/or prospective studies that reported tooth lead and PbBs of the same children found considerable consistency among the studies (Rabinowitz 1995). The mean tooth lead levels ranged from <3 to >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.

Plasma Lead Concentration. The concentration of lead in plasma is extremely difficult to measure accurately because levels in plasma are near the quantitation limits of most analytical techniques (e.g., approximately 0.4 µg/L at blood lead concentration of 100 µg/L (Bergdahl and Skerfving 1997; Bergdahl et al. 1997a) and because hemolysis that occurs with typical analytical practices can contribute substantial measurement error (Bergdahl et al. 1998, 2006; Cavalieri et al. 1978; Smith et al. 1998a). Recent advances in inductively-coupled plasma mass spectrometry (ICP-MS) offer sensitivity sufficient for measurements of lead in plasma (Schütz et al. 1996). The technique has been applied to assessing lead exposures in adults (Cake et al. 1996; Hernandez-Avila et al. 1998; Manton et al. 2001; Smith et al. 2002; Tellez-Rojo et al. 2004). A direct comparison of lead concentrations in plasma and serum yielded similar results (Bergdahl et al. 2006); however, the interchangeability of plasma and serum lead measurements for biomonitoring of lead exposure or body burden had not been thoroughly evaluated in large numbers of subjects (Bergdahl et al. 2006; Manton et al. 2001; Smith et al. 2002).

Urinary Lead. Measurements of urinary lead levels have been used to assess lead exposure (e.g., Fels et al. 1998; Gerhardsson et al. 1992; Lilis et al. 1968; Lin et al. 2001; Mortada et al. 2001; Roels et al. 1994). However, like PbB, urinary lead excretion reflects, mainly, recent exposure and, thus, shares many of the same limitations for assessing lead body burden or long-term exposure (Sakai 2000; Skerfving 1988). The measurement is further complicated by variability in urine volume, which can affect concentrations independent of excretion rate (Diamond 1988) and the potential effects of decrements in kidney function on excretion, in association with high, nephrotoxic lead exposures or kidney disease (Lilis et al. 1968; Wedeen et al. 1975). Urinary lead concentration increases exponentially with PbB and can exhibit relatively high intra-individual variability, even at similar PbBs (Gulson et al. 1998a; Skerfving et al. 1985). 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).

The measurement of lead excreted in urine following an injection (intravenous or intramuscular) of the chelating agent, calcium disodium EDTA (*EDTA provocation*) has been used to detect elevated body burden of lead in adults (Biagini et al. 1977; Lilis et al. 1968; Wedeen 1992; Wedeen et al. 1975) and children (Chisolm et al. 1976; Markowitz and Rosen 1981), and is considered to be a reliable measure of the potentially toxic fraction of the lead body burden (WHO 1995). The assay is not a substitute for blood lead measurements in the clinical setting. Children whose PbBs are ≥45 µg/dL should not receive a provocative chelation test; they should be immediately referred for appropriate chelation therapy (CDC 1991). Further limitations for routine use of the test are that EDTA must be given parenterally and requires timed urine collections. A study conducted in rats found that intraperitoneal administration of a single dose of EDTA following 3–4-month exposures to lead in drinking water increased levels of lead in the liver and brain (Cory-Slechta et al. 1987) raising concern for similar effects in humans who undergo the EDTA provocation test. The use of EDTA to assess bone stores of lead (Wedeen 1992) are largely being supplanted by more direct, noninvasive procedures for measuring lead in bone.

Lead in Saliva and Sweat. Lead is excreted in human saliva and sweat (Lilley et al. 1988; Rabinowitz et al. 1976; Stauber and Florence 1988; Stauber et al. 1994). However, sweat has not been widely adopted for monitoring lead exposures. Lilley et al. (1988) found that lead concentrations in sweat were elevated in lead workers; however, sweat and blood lead concentrations were poorly correlated. This may reflect excretion of lead in or on the skin that had not been absorbed into blood. Studies conducted in rats have found relatively strong correlations between lead concentrations in plasma and saliva (e.g., $r^2>0.9$), compared to blood lead and saliva; therefore, saliva may serve as a better predictor of plasma lead than blood lead concentration (Timchalk et al. 2006).

Hair and Nail Lead. Lead is incorporated into human hair and hair roots (Bos et al. 1985; Rabinowitz et al. 1976) and has been explored as a possibly noninvasive approach for estimating lead body burden (Gerhardsson et al. 1995b; Wilhelm et al. 1989). The method is subject to error from contamination of the surface with environmental lead and contaminants in artificial hair treatments (i.e., dyeing, bleaching, permanents) and is a relatively poor predictor of PbB, particularly at low concentrations (<12 µg/dL) (Campbell and Toribara 2001; Drasch et al. 1997; Esteban et al. 1999). Nevertheless, levels of lead in hair were positively correlated with children's classroom attention deficit behavior in a study (Tuthill 1996). 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).

Semen Lead. Correlations between concentrations of lead in semen and blood have been reported and vary in strength across studies (Alexander et al. 1998a, 1998b; Farias et al. 2005; Telisman et al. 2000). This variation may relate, in part, to analytical challenges in the measurement of the relatively low concentrations of lead in semen. Using ICP-MS and rigorous collection methods to avoid contamination, Farias et al. (2005) reported a detection limit of 0.2 µg/L semen. Mean semen lead concentration in a group of 160 adults (age range: 19–48 years) who were not exposed to lead occupationally was 2.66 µg/L (range: 0.08–19.42) and significantly correlated with blood lead concentration (mean: 10.8 µg/dL, range: 4.5–40.2) and tibia bone lead (mean: 14.51 µg/g, range: non-detect–44.71 µg/g).

Stable Lead Isotopes. Analysis of the relative abundance of stable isotopes of lead in blood and other accessible body fluids (e.g., breast milk, urine) has been used to differentiate exposures from multiple sources (Flegal and Smith 1995). Relative abundances of stable isotopes of lead (^{204}Pb, ^{206}Pb, ^{207}Pb, and ^{208}Pb) in lead ores vary with the age of the ore (which determines the extent to which the parent isotopes have undergone radioactive decay to stable lead). Humans have lead isotope abundance profiles that reflect the profiles of lead deposits to which they have been exposed. Conversely, if exposure is to lead from a predominant deposit, that source can be identified by the relative abundance profile in blood (or other biological sample). Similarly, if exposure abruptly changes to a lead source having a different isotope abundance profile, the kinetics of the change in profile in the person can be measured, reflecting the kinetics of uptake and distribution of lead from the new source (Gulson et al. 2003; Maddaloni et al. 1998; Manton et al. 2003). Numerous examples of the application of stable isotope abundance measurements for studying sources of lead exposures have been reported (Angle et al. 1995; Graziano et al. 1996; Gulson and Wilson 1994; Gulson et al. 1996; Manton 1977, 1998).

Effect Biomarkers Used to Assess Exposure to Lead. Certain physiological changes that are associated with lead exposure have been used as biomarkers of exposure (see Section 3.6.2). These include measurement of biomarkers of impaired heme biosynthesis (blood zinc protoporphyrin, urinary coproporphyrin, erythrocyte ALAD activity). These types of measurements have largely been supplanted with measurement of blood lead concentration for the purpose of assessing lead exposure.

3.6.2 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 not specific for lead (Bernard and Becker 1988). However,

inhibition of ferrochelatase in the heme pathway causes accumulation of protoporphyrin in erythrocytes (CDC 1985). Most protoporphyrin in erythrocytes (about 90%) exists as ZPP. This fraction is preferentially measured by hematofluorometers. Extraction methods measure all of the protoporphyrin present, but strip the zinc from the ZPP during the extraction process. For this reason, extraction results are sometimes referred to as (zinc) 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, ZPP, or FEP all reflect essentially the same analyte. 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). The concentration of EP rises above background at PbBs of 25–30 µg/dL, above which, there is a positive correlation between PbB and EP (CDC 1985; Gennart et al. 1992a; Roels and Lauwerys 1987; Soldin et al. 2003; Wildt et al. 1987). Lead toxicity is generally considered to be present when a PbB ≥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). Similarly, 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). Conversely, since EP does not go up until the PbB exceeds 25 µg/dL, and the level of concern is 10 µg/dL, relying on EP measures would result in many false negative cases. Some have estimated that relying only on ZPP screening to predict future lead toxicity would miss approximately 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. 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).

ALAD, an enzyme occurring early in the heme pathway, is also considered a sensitive indicator of lead effect (Graziano 1994; Hernberg et al. 1970; Morris et al. 1988; Somashekaraiah et al. 1990; Tola et al. 1973). ALAD activity is negatively correlated with PbBs of 5–95 µg/dL, with >50% inhibition occurring at PbBs >20 µg/dL (Hernberg et al. 1970; Morita et al. 1997; Roels and Lauwerys 1987). However, ALAD activity may also be decreased with other diseases or conditions such as porphyria, liver cirrhosis, and alcoholism (Somashekaraiah et al. 1990). ALAD was found to be a more sensitive biomarker than urinary ALA and ZPP at PbBs between 21 and 30 µg/dL (Schuhmacher et al. 1997). A marked increase in urinary excretion of ALA, the intermediate that accumulates from decreased ALAD, can be detected

when PbB exceeds 35 µg/dL in adults and 25–75 µg/dL in children (NAS 1972; Roels and Lauwerys 1987; Sakai and Morita 1996; Schuhmacher et al. 1997).

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). The activity of adenine dinucleotide synthetase (NADS) in erythrocytes has also been explored as a biomarker for predicting PbBs >40 µg/dL; NADS activity is negatively correlated with PbB over the range 5–80 µg/dL (Morita et al. 1997).

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 (Agency for Toxic Substances and Disease Registry 1995). The geometric mean PbB 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, the target and comparison values were 3.06 and 3.63 µg/dL, respectively. Ninety percent of target and 93% of comparison area participants had PbBs <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 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.

Reduction in the serum 1,25-dihydroxyvitamin D concentration has been reported as an indicator of increased lead absorption or lead concentrations 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 PbBs of 12–120 µg/dL showed decreased serum 1,25-dihydroxyvita-

min 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.

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 PbBs as low as 70 µg/dL (CDC 1985). An early sign of peripheral manifestations of neurotoxicity is gastrointestinal colic, which can occur with PbBs above 50 µg/dL. The most sensitive peripheral index of neurotoxicity of lead is reported to be slowed conduction velocity in small motor fibers of the ulnar nerve in workers with PbBs of 30–40 µg/dL (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.

Functional deficits associated with lead-induced nephrotoxicity increase in severity with increasing PbB. Effects on glomerular filtration evident at PbBs below 20 µg/dL, enzymuria and proteinuria occurs above 30 µg/dL, and severe deficits in function and pathological changes occur in association with PbBs exceeding 50 µg/dL (see Table 3-3 and Figure 3-3). Biomarkers for these changes include elevation of serum creatinine, urinary enzymes (e.g., NAG), or protein (albumin, β2µ-globulin, α1µ-globulin, retinol binding protein). However, none of these markers are specific for lead-induced nephrotoxicity. A characteristic histologic feature of lead nephrotoxicity is the formation of intranuclear inclusion bodies in the renal proximal tubule (Choie and Richter 1972; Goyer et al. 1970a, 1970b).

3.7 INTERACTIONS WITH OTHER CHEMICALS

The toxicokinetics 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 PbBs >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 Petering 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 PbBs (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 PbBs ranging from 45 to 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 was observed in 66 children with elevated PbB (Chisolm 1981). Another study reported that the lead absorption rate was 2–3 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 PbB 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 PbB 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 PbBs, suggesting that dietary iron may inhibit lead absorption. A study of 319 children ages 1–5 from Sacramento, California found that iron-deficient children had an unadjusted geometric mean PbB 1 µg/dL higher than iron-replete children (Bradman et al. 2001). The difference persisted after adjusting for potential confounders by multivariate regression; the largest difference in PbB was approximately 3µg/dL and was present among those living in the most contaminated areas. While the studies mentioned above point to a link between iron deficiency and lead poisoning, it is unclear whether there is a causal link or whether iron deficiency is just a marker of high environmental lead. Also considered should be the possibility that children who do not get adequate nutrition (including iron) may be more prone to ingestion of paint chips and this may confound the type of study that attempts to associate iron deficiency with lead poisoning. A longitudinal analysis of 1,275 children whose blood was screened for lead and complete blood count on two consecutive visits to a clinic suggested that the risk of subsequent lead poisoning associated with iron deficiency is 4–5 times greater than the baseline risk of lead poisoning (Wright et al. 2003c). The subject of lead/iron interactions was recently reviewed by Kwong et al. (2004).

The relationship between nutritional factors, other than those mentioned above, and PbB 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 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 3-11.

People who live near waste sites may be simultaneously exposed to more than one chemical, and there is concern that chemicals in a mixture may interact with each other in such a manner that the toxicity of chemical A may be increased in the presence of chemical B. Studies have shown that both the toxicity and toxicokinetics of lead can be influenced by the presence of other chemicals that are commonly found together with lead at hazardous waste sites, particularly other metals. The studies available indicate that the outcome of the interaction of lead with other metals depends on many factors such as exposure levels, timing of exposure, and end point examined, to name a few. As a result, global statements cannot be made. However, it appears that, in general, zinc and copper are protective of the effects of lead. For details on the interactive effects of lead with other metals, the reader is referred to the *Interaction Profile for Arsenic, Cadmium, Chromium, and Lead* (Agency for Toxic Substances and Disease Registry 2004a), *Interaction Profile for Lead, Manganese, Zinc, and Copper* (Agency for Toxic Substances and Disease Registry 2004b), and *Interaction Profile for Chlorpyrifos, Lead, Mercury, and Methylmercury* (Agency for Toxic Substances and Disease Registry 2006).

3.8 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

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.

Table 3-11. 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	Mahaffey et al. 1973; Six and Goyer 1970
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

Table 3-11. Effects of Nutritional Factors on Lead Uptake in Animals

Factor	Species	Index of effect	Interactive effect	References
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
Copper	Rat	Lead absorption	Low copper in diet increases lead absorption	Klauder and Petering 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

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. 1989a; 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; Ettinger et al. 2006; Gulson et al. 1998a). Calcium supplementation during lactation has been shown to decrease both maternal PbB and lead concentration in breast milk (Ettinger et al. 2006; Hernandez-Avila et al. 2003).

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. 1989; 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 increase the risk of lead poisoning (Bradman et al. 2001; Johnson and Tenuta 1979; Wright et al. 2003c; 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 3.5.

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 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. Bone resorption during pregnancy can be reduced by ingestion of calcium supplements (Janakiraman et al. 2003). 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* (Section 3.2.4).

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. An increased release of bone lead to blood occurs in women, in association with menopause (Gulson et al. 2002). These observations are consistent with epidemiological studies that have shown increases in PbB after menopause and in association with decreasing bone density in postmenopausal women (Berkowtiz et al. 2004; Bonithon-Kopp et al. 1986c; Ewers et al. 1990; Hernandez-Avila et al. 2000; Korrick et al. 2002; Markowitz and Weinberger 1990; Nash et al. 2004; Silbergeld et al. 1988; Symanski and Hertz-Picciotto 1995). Long-term effects of lead exposure were also reported by Hu (1991b) 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 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). A more recent study of 526 participants of the Normative Aging Study with a mean age of 67.1 years and mean PbB of 6.3 µg/dL reported that patellar lead was significantly associated with psychiatric symptoms such as anxiety, depression, and phobic anxiety (Rhodes et al. 2003). In yet an additional study of Normative Aging Study participants (mean PbB, 4.5 µg/dL), it was found that both bone and blood lead were associated with poor test performance (Wright et al. 2003c). According to the investigators, these findings are consistent with the theory that bone lead chronically remobilizes into blood, thus accelerating cognitive decline.

People with Genetic Diseases and Gene Polymorphisms. 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 G6PD-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 B12), 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).

ALAD is a polymorphic enzyme with two alleles (ALAD-1 and ALAD-2) and three genotypes: ALAD 1,1;, ALAD 1,2; and ALAD 2,2 (Battistuzzi et al. 1981). Various single nucleotide polymorphisms of the ALAD gene have been reported (Chia et al. 2005). Approximately 80% of Caucasians have the ALAD 1,1 genotype, 19% have the ALAD 1,2 genotype, and only 1% have the ALAD 2,2 genotype (Astrin et al. 1987; Battistuzzi et al. 1981). Studies of the relationship between ALAD genotype and blood lead levels have yielded conflicting results. Higher blood lead levels were observed in individuals with the ALAD 1,2 and ALAD 2,2 genotypes compared to similarly exposed individuals with the ALAD 1,1 genotype (Astrin et al. 1987; Hsieh et al. 2000; Schwartz et al. 2000b; Wetmur et al. 1991). There are also reports of children with the ALAD 2,2 having higher PbB than noncarriers (Pérez-Bravo et al. 2004; Shen et al. 2001). However, results of several other studies have found no association between blood lead levels and ALAD genotype in lead-exposed workers (Alexander et al. 1998b; Bergdahl et al. 1997b; Schwartz 1995; Schwartz et al. 1997a, 1997b; Smith et al. 1995; Süzen et al. 2003), although ALAD-2 carriers were 2.3 times more likely to have blood levels ≥40 µg/dL (Schwartz et al. 1997a). The observations of higher blood level levels in ALAD 2 carriers has prompted

the suggestion that the ALAD-2 allele may have a higher binding affinity for lead than the ALAD-1 allele (Bergdahl et al. 1997b), a difference that could alter lead-mediated outcomes. Several studies have been conducted to specifically evaluate whether ALAD genotypes are associated with differences in partitioning of lead between red blood cells and plasma, differences in distribution of lead to other tissue compartments, and altered susceptibility to lead toxicity.

Studies investigating the effects of ALAD polymorphism on the distribution of lead in the blood have also yielded conflicting results. In lead-exposed workers, a higher percentage of erythrocyte lead was bound to ALAD in carriers of the ALAD-2 allele (84%) compared to carriers of the ALAD-1 allele (81%) (Bergdahl et al. 1997b). Although this difference is small, it did reach statistical significance ($p<0.03$), supporting the hypothesis that the ALAD-2 allele has a higher binding affinity for lead than the ALAD-1 allele. However, higher whole blood levels were not observed for ALAD-2 carriers compared to ALAD-1 homozygotes. Furthermore, no ALAD allele-specific differences were detected for the ratio of blood lead to plasma lead. Results of studies by Fleming et al. (1998a) substantiate earlier reports of higher blood lead levels for carriers of the ALAD-2 allele and indicate that ALAD polymorphism has an effect on the distribution of lead in the blood and, ultimately, to other tissue compartments. Serum lead levels for carriers of the ALAD-2 allele were higher than for ALAD-1 homozygotes (ALAD-2 carriers = 0.335±0.025 µg/dL; ALAD-1 homozygotes = 0.285±0.009 µg/dL), an 18% difference that approached statistical significance ($p<0.06$) (Fleming et al. 1998a).

Based on the higher plasma lead levels observed for ALAD-2 carriers, it is reasonable to project that distribution of lead to other tissue compartments could be higher for ALAD-2 carriers, in which case, the ALAD genotype could exert effects on the dose-response relationship for lead. In lead-exposed workers, urinary excretion of lead following oral administration of DMSA was less in ALAD-2 carriers than in ALAD-1 homozygotes ($p=0.07$), suggesting that carriers of the ALAD-2 allele may have lower levels of lead, or, at least, lower amounts of lead accessible to complexation with DMSA (Schwartz et al. 1997b). Studies investigating the effects of ALAD polymorphism on the distribution of lead to bone have also yielded conflicting results. No ALAD allele-specific differences were observed for the net accumulation of lead in bone (Bergdahl et al. 1997b, Fleming et al. 1998a; Lee et al. 2001) or for patellar bone (Lee et al. 2001; Theppeang et al. 2004). However, ALAD-2 carriers accumulated slightly more lead in bone than ALAD-1 homozygotes ($p=0.06$) (Fleming et al. 1998a). Higher bone lead levels were reported in lead-exposed workers carrying the ALAD-2 gene compared to ALAD-1 homozygotes (Smith et al. 1995). The cortical-trabecular bone lead differential (patellar minus tibial lead concentration) in ALAD-1 homozygotes was lower than in ALAD-2 carriers ($p=0.06$). In these same workers, blood urea

nitrogen (BUN) and uric acid (UA) were elevated in ALAD-2 carriers (BUN, p=0.03; UA, p=0.07), indicating that ALAD-2 carriers could be more susceptible to the renal toxicity of lead. However, in a multivariate logistic regression model that included PbB and ALAD genotype (along with age and alcohol consumption), increases in BUN and serum uric acid concentration were significantly associated with increases in PbB (regression coefficient, 0.13 mg/dL per μg Pb/dL; p=0.005), but not ALAD genotype (p=0.06). Wu et al. (2003a) also found apparent effects of ALAD genotype on the relationship between bone lead levels and serum uric acid levels in a study conducted as part of the Normative Aging Study. Increasing patella bone lead levels above a threshold of 15 μg/g was positively associated with serum uric acid levels among ALAD 1-1/2-2 heterozygotes; however, among ALAD 1-1 homozygotes, the threshold for the association was 101 μg/g. In contrast, young adults with ALAD 1-2 genotype did better on cognitive tests given the same amount of lead exposure (Bellinger et al. 1994), suggesting possible age-specific interactions. Chia et al. (2005) examined interactions between PbB and the presence of various single nucleotide polymorphisms (SNP) in the ALAD gene on various kidney outcomes among a group of lead workers in Vietnam (n=323). This study found significant interactions between increasing PbB and the HpyCH4 SNP on increasing urinary retinal binding protein, α1μ-globulin, β2μ-globulin, and albumin. Lee et al. (2001) examined the possible influence of ALAD genotype on systolic and diastolic blood pressure in a cohort of Korean lead workers (789 workers, 135 controls). Lead body burden measures (i.e., PbB, tibia blood lead, DMSA-chelatable lead) and blood pressures were not significantly different between ALAD 1-1 and ALAD 1-2 genotypes.

The finding of associations between ALAD-2 and bone lead concentrations and ALAD-2 and markers of renal toxicity suggest that differential binding of lead to ALAD-2 may influence both the toxicokinetics and certain aspects of the toxicodynamics of lead. No information is available on the distribution of lead to other tissue compartments relative to ALAD genotype. Thus, based on the limited data available, it appears that ALAD polymorphism may be a genetic factor in the kinetic behavior of lead in the body. However, the exact nature and significance of ALAD polymorphism remains to be elucidated. A recent meta-analysis of 24 studies that included lead workers, the general population, and children found a statistically significant association beween ALAD-2 carriers and higher PbB in lead-exposed workers (Scinicariello et al. 2007). However, the ALAD-2 genotype did not appear to be a significant determinant of PbB among adults with PbBs <10 μg/dL. The study also found that ALAD-2 carriers appeared to be protected against adverse hematopoietic effects of lead as measured by hemoglobin levels, possibly because of decreased lead bioavailability to enzymes of the heme pathway.

The role of the vitamin D receptor (VDR) polymorphism in lead intoxication also has been studied. The VDR gene regulates the production of calcium-binding proteins and is reported to account for up to 75% of the total genetic effect on bone density (Onalaja and Claudio 2000). The VDR exists in several polymorphic forms in humans (Morrison et al. 1992). Restriction enzyme digestion of the VDR results in three genotypes commonly termed bb, when the restriction site is present, BB when the site is absent, and Bb when the two alleles are present. Schwartz et al. (2000a) studied the association of tibial lead and VDR genotype in 504 former organolead manufacturing workers in the United States. Tibial and blood lead concentrations were relatively low, with means of 14.4 ppm, and 4.6 µg/dL, respectively. Analyses of unadjusted data showed that there were only small differences in tibial lead concentrations by VDR genotype. However, in a multiple linear regression model of tibial lead concentrations, subjects with the B allele had larger increases in tibial lead concentrations with increasing age. In addition, whereas in subjects with the bb genotype, tibial lead declined since their last exposure to lead, subjects with Bb and BB showed increases in tibial lead. A study of 798 Korean lead workers whose mean tibial lead concentration and mean PbB were 37.2 ppm and 32 µg/dL, respectively, reported that lead workers with the VDR B allele had significantly higher PbB, chelatable lead level, and tibial lead than did workers with the VDR bb genotype (Schwartz et al. 2000b). A more recent study of this cohort reported that workers with the VDR B allele had significantly higher patellar lead than lead workers with the VDR bb genotype (Theppeang et al. 2004).

Two other genetic polymorphisms have been studied in the context of potential influence on lead associations with blood pressure. The endothelial nitric oxide synthase (eNOS) converts L-arginine into nitric oxide in the endothelium, resulting in the relaxation of vascular smooth muscle and contributes to the regulation of peripheral vascular resistance and blood pressure. Theppeang et al. (2004) reported that, in a cohort of Korean lead workers, there was no association of the endothelial nitric oxide synthase (eNOS) gene with patella lead. Polymorphisms in the α2 subunit of Na+-K+ ATPase (ATP1A2) have also been shown to influence associations between lead exposure and blood pressure (Glenn et al. 2001).

Another genetic susceptibility that has been studied in relation to lead toxicity is that of the hemochromatosis gene. Results published so far provided seemingly conflicting results. Hemochromatosis is a disease in which the absorption of iron is increased, resulting in excess iron depositing in many internal organs, particularly the liver, and leading to progressive damage (Onalaja and Claudio 2000). The gene codes for a protein designated HFE and has two variants: C282Y and H63D. Wright et al. (2004) studied 730 men from the Normative Aging Study and found that the presence of a hemochromatosis variant, either C282Y or H63D, predicted lower bone and blood lead concentration. Based on the fact that iron

status is inversely related to lead absorption, Wright et al. (2004) hypothesized that the results may be secondary to increased iron stores among HFE variant carriers leading to decreased lead absorption in the gastrointestinal tract. Previously, Barton et al. (1994) found that homozygous individuals who suffered from hemochromatosis had higher PbB than individuals who did not have the gene. An additional study found no difference in PbB between subjects with hemochromatosis and controls (Åkesson et al. 2000). Wright et al. (2004) speculated that the different results could be due to the different characteristics of the participants studied in terms of age, health status, and sex.

Finally, the possible association between Apolipoprotein E (APOE) genotype and susceptibility to lead toxicity also has been studied. APOE is an intracellular transporter of cholesterol and fatty acids that is synthesized by astrocytes in the brain and that plays a key role in the structure of cell membranes and myelin. There are three alleles of the APOE gene: E2, E3, and E4. Wright et al. (2003b) evaluated the relationship between the APOE gene and infant neurodevelopment in a sample of 311 mother-infant pairs living in and around Mexico City. The primary outcome assessed in the study was the 24-month MDI of the Bayley Scale. The authors also evaluated the modifying effect of APOE genotype on the association between PbB in umbilical cord and MDI score. After adjustment for potential confounders, infants carrying at least one copy of the APOE4 allele scored 4.4 points higher in the MDI than E3/E2 carriers. Furthermore, APOE genotype modified the dose–response relationship between umbilical PbB and MDI score in a manner that suggested that those with APOE4 were more protected against lead exposure than E3/E2 carriers. The APOE genotype also was reported to influence the relation between tibia lead and neurobehavioral test scores in a group of 529 former organolead workers (Stewart et al. 2002). The authors used linear regression to model the relations between each of 20 neurobehavioral test scores and tibia lead, a binary variable for APOE genotype. In 19 of the 20 regression models, the coefficients for the APOE and tibia lead interaction were negative. This meant that the slope for the relation between tibia lead and each neurobehavioral test was more negative for individuals with at least one APOE4 allele than for those who did not have an APOE4 allele. Stewart et al. (2002) concluded that some persistent effects of lead may be more toxic in individuals who have at least one APOE4 allele. The apparent contrast between the results of Stewart et al. (2002) and Wright et al. (2003b) may reflect age-specific gene-lead interactions.

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-hydroxy-

tryptamine 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).

3.9 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. The following texts provide specific information about treatment following exposures to lead:

Ellenhorn MJ. 1997. Medical toxicology: Diagnosis and treatment of human poisoning. Metals and related compounds. 2nd ed. Baltimore, MD: Williams and Wilkins, 1563-1579.

Homan CS, Brogan GX, Orava RS. 1998. Emergency toxicology: Lead toxicity. Philadelphia, PA: Lippincott-Raven, 363-378.

Leikin JB, Paloucek FP. 2002. Poisoning and toxicology handbook. 3rd ed. Hudson, OH: Lexi-Comp, Inc., 725-731.

3.9.1 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 3.3, Toxicokinetics). 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 adults absorb approximately

10% of an administered dose, whereas children absorb 4–50% of ingested lead (see Section 3.3, Toxicokinetics). 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 and that children eat regular meals since more lead is absorbed on an empty stomach (CDC 1991). Good sources of iron include liver, fortified cereal, cooked legumes, and spinach, whereas milk, yogurt, cheese, and cooked greens are good sources of calcium (CDC 1991).

General recommendations to reduce absorption of lead following acute exposure 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 (Kosnett 2004; 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) (Kosnett 2004). The blood lead level can be monitored and used as an indication for surgical removal of the projectile.

3.9.2 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 3.3.2).

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), $CaNa_2$-EDTA (or EDTA), penicillamine, and 2,3-dimercaptosuccinic acid (DMSA; Succimer®). Most of the information below regarding chelators has been extracted from Homan et al. (1998).

Dimercaprol (BAL) is the chelator of choice in the presence of renal compromise. Sulfhydryl ligands in BAL form stable chelate-metal compounds intra- and extracellularly. The onset of action for BAL is 30 minutes. BAL increases fecal excretion of lead as chelated lead is excreted predominantly in bile within 4–6 hours; BAL also increases urinary excretion of chelated lead. The use of BAL is indicated in cases of high lead levels without symptoms, in acute encephalopathy, and in symptomatic plumbism characterized by abdominal pain, anemia, headache, peripheral neuropathy, ataxia, memory loss, lethargy, anorexia, dysarthria, and encephalopathy. BAL is administered intramuscularly as a 10% solution in oil and the recommended dosage is 50–75 mg/m^2 every 4 hours. The full course is 3–5 days. Contra-indications for the use of BAL include liver failure, since BAL chelates are excreted primarily in bile. Also, patients with glucose-6-phosphate dehydrogenase deficiency develop hemolysis if BAL is administered. Concurrent administration of iron is contraindicated due to the high toxicity of the BAL-iron chelate. BAL also is contraindicated in subjects with a history of peanut oil allergy and in pregnancy. A number of adverse reactions have been described in BAL user including nausea, vomiting, hypertension, tachycardia, headache, increased secretions, anxiety, abdominal pain, and fever. Premedication with diphenylhydramine may mitigate these effects. Elevated liver function tests and sterile abscesses may also occur.

$CaNa_2$-EDTA (or EDTA) works by forming a stable metal-chelate complex that is excreted by the kidney. It increases renal excretion of lead 20–50 times. Numerous adverse effects have been described due to treatment with EDTA including rash, fever, fatigue, thirst, myalgias, chills, and cardiac dysrhythmias. EDTA should be used together with BAL (4 hours after the first dose of BAL) because acute lead encephalopathy may progress if EDTA given alone secondary to lead from soft tissue lead mobilization resulting in increased PbB. Since EDTA chelates zinc, patients with low zinc stores may be adversely affected by EDTA. Since EDTA also chelates other metals, administration of EDTA (or BAL) to persons occupationally exposed to cadmium may result in increased renal excretion of cadmium and renal damage. The dosage recommended for children is 1,000–1,500 mg/m^2/24 hours in 0.5% procaine i.m. to avoid fluid overload, although the preferred route of administration of EDTA is intravenously. This dose

may be given in up to six divided daily doses. For adults, the recommended dose is 1.5 g/24 hours in two divided doses. The full course for EDTA therapy is 5 days, but the course may be repeated if the patient is still symptomatic or when PbB is >50µg/dL.

D-Penicillamine is an orally-administered lead chelator whose mechanism of action is unknown, and that increased urinary excretion of lead. The FDA has not approved the use of d-penicillamine during pregnancy. Administration of d-penicillamine is contraindicated in subjects allergic to penicillin because of cross-reactivity with the latter. Among the adverse effects are rash, fever, anorexia, nausea, vomiting, leucopenia, thrombocytopenis, eosinophilia, hemolytic anemia, Stevens-Johnson syndrome (severe erythema multiforme), nephrotoxicity, and proteinuria. Furthermore, continued exposure to lead will result in continued absorption of lead at a higher rate. The recommended dose is 10 mg/kg/24 hours for 7 days, but may be increased to 10–15 mg/kg every 12 hours over 2–4 weeks. One way to minimize toxicity is to start medication at ¼ the dosage and gradually increase it to full dosage over 3–4 weeks. The CDC recommends giving children an entire dose on an empty stomach 2 hours before breakfast and to give adults an entire dose in two or three divided doses on an empty stomach 2 hours before meals.

2,3-Dimercaptosuccinic acid (DMSA; Succimer®) has a mechanism of action similar to BAL, but is far less toxic than BAL. DMSA is currently approved for asymptomatic children with PbB <45 µg/dL and an experimental protocol is available for mild encephalopathy and use in the adult. DMSA can be used with concurrent administration of iron. DMSA has been shown to be as effective as EDTA in increasing the urinary excretion of lead. Minimal adverse effects that have been reported include anorexia, nausea, vomiting, and rashes. DMSA increases the excretion of zinc, but to a much lesser extent than other chelators, and has minimal effects on Ca, Fe, Mg, and Cu. The recommended dosage is 10 mg/kg 3 times/day for 5 days, then 10 mg/kg 3 times/day for 14 days.

The following are treatment guidelines for lead exposure in children developed by the American Academy of Pediatrics (Berlin et al. 1995).

1. *Chelation treatment is not indicated in patients with blood lead levels of less than 25 µg/dL, although environmental intervention should occur.*

2. *Patients with blood levels of 25 to 45 µg/dL need aggressive environmental intervention but should not routinely receive chelation therapy, because no evidence exists that chelation avoids or reverses neurotoxicity. If blood lead levels persist in this range despite repeated environmental study and abatement, some patients may benefit from (oral) chelation therapy by enhanced lead excretion.*

3. *Chelation therapy is indicated in patients with blood lead levels between 45 and 70 µg/dL. In the absence of clinical symptoms suggesting encephalopathy (e.g., obtundation, headache, and persisting vomiting), patients may be treated with succimer at 30 mg/kg per day for 5 days, followed by 20 mg/day for 14 days. Children may need to be hospitalized for the initiation of therapy to monitor for adverse effects and institute environmental abatement. Discharge should be considered only if the safety of the environment after hospitalization can be guaranteed. An alternate regimen would be to use $CaNa_2EDTA$ as inpatient therapy at 25 mg/kg for 5 days. Before chelation with either agent is begun, if an abdominal radiograph shows that enteral lead is present, bowel decontamination may be considered as an adjunct to treatment.*

4. *Patients with blood lead levels of greater than 70 µg/dL or with clinical symptoms suggesting encephalopathy require inpatient chelation therapy using the most efficacious parenteral agents available. Lead encephalopathy is a life-threatening emergency that should be treated using contemporary standards or intensive care treatment of increased intracranial pressure, including appropriate pressure monitoring, osmotic therapy, and drug therapy in addition to chelation therapy. Therapy is initiated with intramuscular dimercaprol (BAL) at 25 mg/kg per day divided into six doses. The second dose of BAL is given 4 hours later, followed immediately by intravenous $CaNa_2EDTA$ at 50 mg/day as a single dose infused during several hours or as a continuous infusion. Current labeling of $CaNa_2EDTA$ does not support the intravenous route of administration, but clinical experience suggests that it is safe and more appropriate in the pediatric population. The hemodynamic stability of these patients, as well as changes in neurologic status that may herald encephalopathy, needs to be closely monitored.*

5. *Therapy needs to be continued for a minimum of 72 hours. After this initial treatment, two alternatives are possible: (1) the parenteral therapy with two drugs ($CaNa_2EDTA$ and BAL) may be continued for a total of 5 days; or (2) therapy with $CaNa_2EDTA$ alone may be continued for a total of 5 days. If BAL and $CaNa_2EDTA$ are used for the full 5 days, a minimum of 2 days with no treatment should elapse before considering another 5-day course of treatment. In patients with lead encephalopathy, parenteral chelation should be continued with both drugs until they are clinically stable before therapy is changed.*

6. *After chelation therapy, a period of reequilibration of 10 to 14 days should be allowed, and another blood lead concentration should be obtained. Subsequent treatment should be based on this determination, following the categories presented above.*

3.9.3 Interfering with the Mechanism of Action for Toxic Effects

Lead has multiple mechanisms of action at many different levels that affect many enzyme systems and cellular processes throughout the body. Thus, while it seems plausible that specific effects could be prevented or at least minimized, it is unlikely that one could prevent all of the physiological alterations that have been attributed to exposure to lead. However, several studies have examined whether lead-lowering interventions, such as with chelators, are paralleled by improvement in health outcomes

reportedly altered by lead. For example, Ruff et al. (1993) studied a group of 154 children with PbB between 25 and 55 µg/dL who were treated with $CaNa_2EDTA$ if eligible and/or with orally administered iron supplement if iron deficient. The outcome measured was a global index of cognitive functioning. It was found that within a period of 6 months, improvement in performance was significantly related to decreases in PbB, but there was no effect of chelation treatment. Ruff et al. (1993) speculated that a reduction or elimination of exposure may have led to decreases in PbB, and this may have occurred for chelated and nonchelated children.

Rogan et al. (2001) studied a group of 780 children enrolled in a randomized, placebo-controlled, double-blind trial of up to three 26-day courses of treatment with succimer. The PbB for the group ranged from 20 to 44 µg/dL. Although treatment with succimer lowered PbB by a mean of 4.5 µg/dL during the 6 months after initiation of treatment, it did not improve scores on tests of cognition, behavior, or neuropsychological function in children with PbB below 45 µg/dL. Rogan et al. (2001) noted that the failure to demonstrate a significant difference in test scores could have been due to the small difference in PbB between the two groups. Re-analysis of these data using change in PbB as the independent variable showed that improvement in test scores was associated with greater falls in PbB only in the placebo group and suggested that factors other than declining PbB were responsible for cognitive improvement (Liu et al. 2002). A further evaluation of this cohort at the age of 7 years showed that chelation therapy with succimer, although lowering mean PbB for approximately 6 months, produced no benefit in cognitive, behavioral, and neuromotor end points (Dietrich et al. 2004). Also in this cohort, treatment with succimer did not have a beneficial effect on blood pressure (Chen et al. 2006) or growth during or after treatment (Peterson et al. 2004). In fact, from baseline to 9 months, children receiving succimer were on the average 0.27 cm shorter than children receiving placebo, and 0.43 cm shorter during 34 months of follow-up. The conclusion of this series of studies reached by the investigators was that chelation therapy is not indicated in children with moderate PbB (≤40 µg/dL). Additional information regarding the safety and efficacy of succimer in children can be found in O'Connor and Rich (1999) and Chisolm (2000).

In a study similar to those described above, Kordas et al. (2005) tested the hypothesis that iron and zinc supplementation could improve behavior ratings in a population of first-grade children who attended a school near a metal foundry in Torreón, Mexico. The mean PbB for the whole sample was 11.5 µg/dL (SD, ±6.1 µg/dL). The overall prevalency of iron and zinc deficiency was 21.7 and 28.9%, respectively. During the trial, which lasted 6 months, parents and teachers provided ratings of child behavior using the Conners Rating Scales. Neither iron nor zinc (combined or separately) induced a marked reduction in PbB. Although all parent ratings and some teacher ratings improved with time, the change was unrelated

to treatment and the clinical significance was unclear. The only beneficial change was that children receiving any zinc had a higher likelihood of no longer receiving clinically-significant teacher ratings of oppositional behaviors.

A series of studies in monkeys provide relevant information regarding lead exposure and succimer. In adult Rhesus monkeys treated chronically with lead to maintain a target PbB of 35–40 μg/dL, treatment with succimer was ineffective in reducing brain lead levels (Cremin et al. 1999). However, cessation of exposure reduced brain lead levels by 34% both in succimer- and placebo-treated monkeys. In addition, the concentration of lead in the prefrontal cortex prior to treatment with succimer was significantly correlated with the integrated PbB (AUC) over the period of exposure to lead, but not with the single pretreatment PbB sample collected concurrently with the brain biopsy. These results indicated that succimer treatment did not reduce brain lead levels beyond the cessation of lead exposure alone. A subsequent study in this series showed that treatment with succimer did not reduce skeletal levels of lead and that the efficacy of succimer in reducing PbB did not persist beyond the completion of treatment due to posttreatment rebounds in PbB from endogenous sources (Smith et al. 2000).

3.10 ADEQUACY OF THE DATABASE

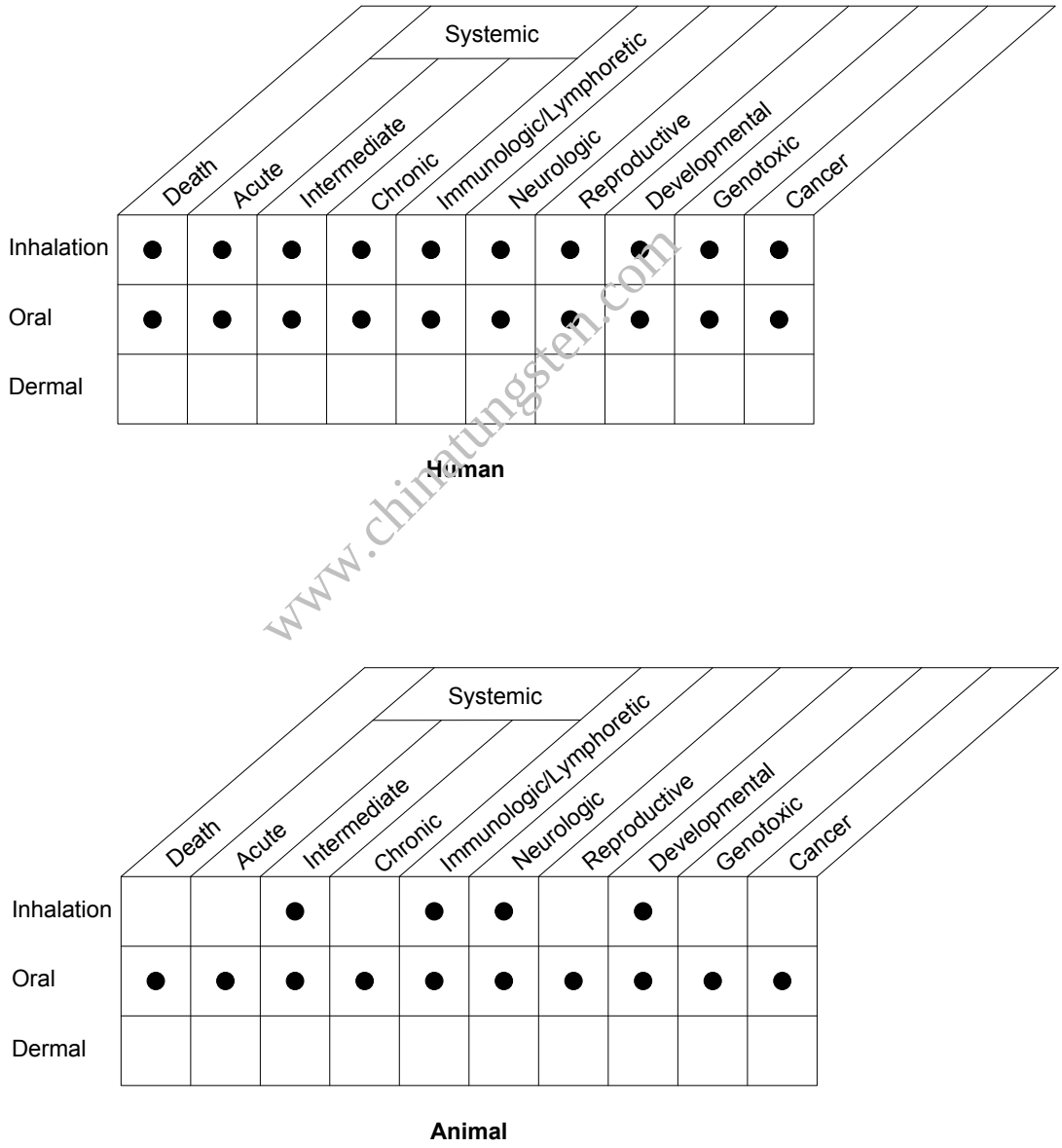
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of lead is available. Where adequate information is not available, ATSDR, in conjunction with 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 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.

3.10.1 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 3-17. The purpose of this figure is to illustrate the existing information

Figure 3-17. Existing Information on Health Effects of Lead



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* (Agency for Toxic Substances and Disease Registry 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.

There is a wealth of information regarding the health effects of lead in humans and in animals. In fact, lead may be a chemical for which there is as much information in humans as there is in animals. Human data consist of studies of children and adults, occupational exposures, and exposures of the general population. A number of studies of children are studies of cohorts that have been followed for years, and these have provided the most valuable information. Children and developing organisms, in general, are more vulnerable to the toxic effects of lead than adults, and therefore, much of the lead research in the past decades has focused on these populations. The most sensitive end points for lead toxicity are the developing nervous system, and the cardiovascular, renal, and hematological systems, but lead can affect any system or organ in the body. The most significant routes of exposure to lead for humans are the inhalation and oral routes; the latter is the main route of exposure for young children mainly due to their hand-to-mouth activities. The toxicity of lead is not route-specific. Studies in animals support the findings in humans and have been of great utility in elucidating the underlying mechanisms of lead toxicity.

3.10.2 Identification of Data Needs

Acute-Duration Exposure. There are relatively few data available for acute exposures in humans and most are derived from cases of accidental or intentional ingestion of lead-containing dirt or lead-based paint in adults and children. Exposure to high amounts of lead can induce encephalopathy, a general term that describes various diseases that affect brain function. Symptoms develop following prolonged exposure and include dullness, irritability, poor attention span, epigastric pain, constipation, vomiting, convulsions, coma, and death (Chisolm 1962, 1965; Chisolm and Harrison 1956; Kehoe 1961; Kumar et al. 1987). The utility of further acute-duration exposure studies in animals for the sole purpose of obtaining dose-response relationships is questionable. However, further short-term studies or studies

in vitro designed to elucidate mechanisms of action for the various toxicities discussed below might be useful.

Intermediate-Duration Exposure. Intermediate and chronic exposures in humans should be considered together because the duration of exposure is not usually known. Specific studies that have evaluated a variety of end points are presented below under *Chronic-Duration Exposure and Cancer.* As with acute-duration exposure, additional standard 90-day toxicity studies in animals are unlikely to produce new key information about the toxicity of lead, but studies could be designed to elucidate mechanisms of action involved in the specific toxicities described below. For example, exposures during different developmental periods can help identify critical periods of vulnerability for immunocompetence, development of sex organs, or neurobehavioral parameters.

Chronic-Duration Exposure and Cancer. The effects of chronic-duration exposure to lead in humans and in animals have been relatively well studied. In humans, exposure to lead has been associated with (only representative citations are included) cardiovascular effects (Nawrot et al. 2002; Schwartz 1995; Staessen et al. 1994), hematological effects (Chisolm et al. 1985; Hernberg and Nikkanen 1970; Roels and Lauwerys 1987; Roels et al. 1976), musculoskeletal effects (Holness and Nethercott 1988; Marino et al. 1989; Pagliuca et al. 1990), effects on teeth in children (Gemmel et al. 2002; Moss et al. 1999), renal effects (Kim et al. 1996a; Muntner et al. 2003), alterations in serum hormone levels (Gustafson et al. 1989; López et al. 2000; Singh et al. 2000a), cataracts (Schaumberg et al. 2004), alterations in electroretinograms (Cavalleri et al. 1982; Otto and Fox 1993; Rothenberg et al. 2002a), altered vitamin D metabolism (Rosen et al. 1980), alterations in immunological parameters (Fischbein et al. 1993; Karmaus et al. 2005; Lutz et al. 1999; Pinkerton et al. 1998; Sata et al. 1998; Sun et al. 2003; Ündeger et al. 1996), neurobehavioral effects in adults (Awad El Karim et al. 1986; Baker et al. 1979, 1983; Haenninen et al. 1979; Holness and Nethercott 1988; Lucchini et al. 2000; Matte et al. 1989; Pagliuca et al. 1990; Pollock and Ibels 1986; Schwartz et al. 2005; Stollery 1996; Stollery et al. 1991) and children (Bellinger et al. 1992; Canfield et al. 2003; Chiodo et al. 2004; Kordas et al. 2006; Lanphear et al. 2000a; Ris et al. 2004; Schnaas et al. 2000; Téllez-Rojo et al. 2006; Tong et al. 1998; Wasserman et al. 2003), reproductive effects in females (Borja-Aburto et al. 1999; Nordstrom et al. 1979; Torres-Sánchez et al. 1999) and males (Gennart et al. 1992b; Hernández-Ochoa et al. 2005; Lancranjan et al. 1975; Sállmen et al. 2000a), altered children's growth (Dietrich et al. 1987a; Hernández-Avila et al. 2002; Schwartz et al. 1986), delayed sexual maturation in girls (Selevan et al. 2003; Wu et al. 2003a), decreased erythropoietin in children (Graziano et al. 2004), genotoxic effects in workers (Forni et al. 1976; Fracasso et al. 2002; Nordenson et al. 1978; Vaglenov et al. 2001; Wu et al. 2002), and possibly increased risk of

lung cancer and stomach cancer in lead workers (Steenland and Boffetta 2000). It is unlikely that additional standard chronic-duration exposure studies in animals would provide new key information on the toxicity of lead, but special studies that examine biochemical and morphological effects of lead may provide new information on mechanisms of action of lead, particularly for the effects of greatest concern such as neurobehavioral alterations in children. However, as indicated below under *Epidemiological Studies*, the children and adolescents from the prospective studies should continue to undergo periodic comprehensive evaluations.

There are several studies of cancer on lead-exposed workers (Anttila et al. 1995; Cocco et al. 1997, 1998a, 1998b; Cooper et al. 1985; Fanning 1988; Gerhardsson et al. 1986b; Lundstrom et al. 1997; Malcolm and Barnett 1982; Wong and Harris 2000), which provided inconclusive evidence of carcinogenicity. A meta-analysis of eight major occupational studies on cancer mortality or incidence in workers with high lead exposure concluded that there is some limited evidence of increased risk of lung cancer and stomach cancer, although there might have been confounding with arsenic exposure in the study with highest relative risk of lung cancer (Steenland and Boffetta 2000). The results also showed weak evidence for an association with kidney cancer and gliomas. Follow-up of the cohorts from the prospective lead studies may provide information on possible shifts in age-related cancer incidence and on associations between perinatal exposure to lead and increased cancer risk.

Exposure of rodents to lead has produced mainly renal tumors (Azar et al. 1973; Koller et al. 1985; Van Esch and Kroes 1969). In a study in mice exposed to lead during pregnancy, the offspring developed renal proliferative lesions and renal tumors; no renal tumors occurred in controls (Waalkes et al. 1995). Replication of these findings would be useful. In addition, studies could be conducted in which animals are exposed at different times during pregnancy to determine the existence of potential windows of vulnerability. Silbergeld et al. (2000) suggest that the hypothesis that lead-induced cancer is secondary to cytotoxicity and target organ damage needs further testing. Silbergeld et al. (2000) also identified the need for studies examining the potential role of lead-zinc interactions in transcription regulation and DNA protection using reporter gene systems and combined exposures to lead and other mutagens. Other types of studies suggested include evaluation of the effects of lead on the expression of specific genes, such as oncogenes and suppressor genes, and evaluation of the potential role of lead-induced inhibition of DNA repair on systems where the fidelity of DNA replication can be directly studied.

Genotoxicity. Lead is a clastogenic agent, as shown by the induction of chromosomal aberrations, micronuclei, and sister chromatid exchanges in peripheral blood cells from lead workers (i.e., Duydu et al.

2001; Forni et al. 1976; Nordenson et al. 1978; Vaglenov et al. 1998, 2001). *In vitro* mutagenicity studies in microorganisms have yielded mostly negative results for lead, and additional studies of this type are unlikely to provide new key information. The lines of research suggested previously with regard to cancer also apply for genotoxicity. In addition, studies of chromosomal changes in germ cells involved in gametogenesis would provide valuable information on potential transgenerational effects of lead.

Reproductive Toxicity. Some studies of humans occupationally or environmentally exposed to lead have reported associations between PbB and abortion and pre-term delivery in women (Borja-Aburto et al. 1999; Nordstrom et al. 1979) and alterations in sperm and decreased fertility in men (Gennart et al. 1992b; Sállmen et al. 2000a; Shiau et al. 2004). For the effects in males, the threshold PbB appears to be in the range of 30–40 µg/dL. Additional research might be warranted to study the effects of lead on the gonado-hypothalamic-pituitary axis. An earlier study by Cullen et al. (1984) found increased serum FSH and LH and borderline low serum testosterone levels in one of seven men with symptomatic occupational lead poisoning and a mean PbB of 87.4 µg/dL. Although serum testosterone concentration was normal in most of these patients, five had defects in spermatogenesis. Studies in monkeys using protocols designed to evaluate age of exposure on lead-induced effects have reported structural alterations in the testis at PbBs relevant to the human population (Foster et al. 1996, 1998). Studies in rats exposed to lead concentrations that produced relatively high PbB 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). Replication of these studies in primates would be useful. Also, further research on the interaction of lead and protamines could provide valuable information on lead-induced effects in sperm. Protamines specifically are bound to sperm DNA and their interaction with lead has been suggested to possibly decrease the protection of DNA to mutagens (Quintanilla-Vega et al. 2000).

Developmental Toxicity. In addition to inducing neurobehavioral alterations in developing organisms (see below under Neurotoxicity), exposure to lead has been associated in some studies with reduced birth weight and gestational age (Dietrich et al. 1987a; Jelliffe-Pawlowski et al. 2006), reduced stature in children (Hernández-Avila et al. 2002; Sanín et al. 2001; Schwartz et al. 1986), and delayed sexual maturation in girls (Selevan et al. 2003; Wu et al. 2003a). These findings are supported by results from studies in animals (Dearth et al. 2002; Grant et al. 1980; Ronis et al. 1996, 1998a, 1998b, 1998c, 2001). It would be useful to collect data on growth of children from the ongoing lead prospective studies, although some information is available from the Cincinnati Prospective Study (Shukla et al. 1989, 1991), the Cleveland Prospective Study (Greene and Ernhart 1991), and a study of children from Boston (Kim et al. 1995). Because of the enormous influence of nutrition on growth and on lead toxicity, it would be

advantageous to conduct studies of populations of children as homogeneous as possible with respect to nutrition, even if the cohort size is less than optimal. A study in rats reported that lead reduced somatic longitudinal bone growth and bone strength during the pubertal period by a mechanism that appeared not to involve disruption of the growth hormone axis (Ronis et al. 2001). Further studies in animals as well as in bone cells *in vitro* should help elucidate the mechanism(s) of lead on growth.

Studies have shown that exposure of rats and mice to lead during various developmental periods alters sexual maturation of both male and female animals (Dearth et al. 2002; Iavicoli et al. 2004; Ronis et al. 1996, 1998a, 1998b, 1998c). Therefore, it would be desirable to evaluate adolescents of both sexes who are participating in the ongoing prospective lead studies to determine possible delays in sexual maturation, and if found, determine which lead biomarker best predicts the outcome. Follow-up of the children studied by Selevan et al. (2003) and Wu et al. (2003a) or the cohorts studied longitudinally could provide information on whether lead exposure during infancy has long-term effects on parameters such as fertility in males and females or on female's ability to maintain pregnancy. Dearth et al. (2004) recently reported that Fisher 344 rats are more sensitive than Sprague-Dawley rats regarding puberty-related effects. Researchers should be aware of this strain difference when comparing results between these two strains of rats. As with other lead-induced toxicities, the role of some polymorphisms (i.e., ALAD genotype) on growth and sexual maturation could be evaluated.

Immunotoxicity. Altered immune parameters have been described in lead workers. Reported effects have included changes in some T-cell subpopulations (Fischbein et al. 1993; Pinkerton et al. 1998; Sata et al. 1998; Ündeger et al. 1996), altered response to T-cell mitogens (Mishra et al. 2003), and reduced chemotaxis of polymorphonuclear leukocytes (Valentino et al. 1991). Three studies of children reported significant associations between PbB and increases in serum IgE levels (Karmaus et al. 2005; Lutz et al. 1999; Sun et al. 2003). IgE is the primary mediator for type-I hypersensitivity and is involved in various allergic diseases such as asthma; therefore, the suggestion has been raised that *in utero* exposure to lead may be a risk factor for childhood asthma (Dietert et al. 2002). Perinatal exposure of rodents to lead also has induced increased IgE levels in the offspring (Miller et al. 1998; Snyder et al. 2000). Additional studies in which animals are exposed at different developmental periods are necessary to identify vulnerable periods during development and to determine potential long-term consequences of exposures during discrete periods of development (Dietert et al. 2002, 2004). Also, studies that compare the effects of lead on immunological end points in different species, different strains, and animals of both sexes would provide valuable information, as there is some evidence that the immune response may depend on the species, strain, and/or gender (Bunn et al. 2001a, 2001b, 2001c). In addition, further information on

how lead-induced changes in immune balance (Heo et al. 1998; McCabe et al. 1999) affect the immune response profile and the host's defense capabilities would be valuable. This is important because there is evidence that suggests that lead or other chemicals during development may cause inappropriate Th1 development and a potentially serious imbalance toward Th2-associated capacity resulting in elevated IgE production and increased risk for atopy and asthma (Peden 2000).

Neurotoxicity. The nervous system is a sensitive target for lead toxicity in humans (for representative references, see Chronic-Duration Exposure and Cancer, above) and in animals. Of special concern are the results of recent studies that have reported neurobehavioral deficits in children associated with PbBs <10 µg/dL and an apparent lack of threshold down to even the lowest PbBs recorded in these studies (Bellinger and Needleman 2003; Canfield et al. 2003; Chiodo et al. 2004; Kordas et al. 2006; Lanphear et al. 2000a, 2005; Téllez-Rojo et al. 2006). Some of these studies found that the slope of the dose-response is steeper at lower PbBs than at higher PbBs; that is, the effects of lead on cognitive function is greater in children with lower PbB than in children with higher PbB. However, a mechanism that could produce this result has not yet been identified, and this represents a data need. The neurotoxicity of lead is the result of multiple modes of action and research needs can be identified at almost any level of action, from studies of basic biochemical and physiological mechanisms (i.e., transport of lead across biological barriers in general and nerve membranes in particular) to studies of populations. There are several ongoing prospective studies of lead in children (i.e., Bellinger et al. 1992; Ris et al. 2004; Schnaas et al. 2000; Tong et al. 1998; Wasserman et al. 2003) and it is assumed that follow-up of some of these cohorts will continue. With regard to these and other studies in humans, researchers have identified some specific needs. For example, there is a need to develop new and more sensitive tests of specific neuropsychological functions (Bellinger 1995). Also, not enough research has been conducted in adults using measures of cumulative exposure to lead. Another area where additional research would be valuable is to determine the extent to which lead contributes as a risk factor to disease and dysfunction. There is a limited number of studies that have linked lead to amyotrophic lateral sclerosis (Kamel et al. 2002), essential tremor (Louis et al. 2003), schizophrenia (Opler et al. 2004), and Parkinson's disease (Gorell et al. 1997, 1999). Also, the possibility that lead contributes to attention deficit disorder has never been adequately addressed, despite the increased levels of diagnosis of this disorder in children over the past 20 years. Studies in animal models of these diseases can provide valuable information to answer such questions. With regard to the interpretation of studies with seemingly differing results, it would be important to identify the basis of individual differences in sensitivity to neurotoxicants (Bellinger 2000). In addition, epidemiological studies should be designed in a manner that permits more rigorous assessments of effect modification. In order to minimize confounding and effect modification,

researchers should make greater use of more focused sampling frames that ensure adequate representation of specific subgroups of interest (Bellinger 2000). Additional information is needed to characterize the nature of the relationships between lead and nutritional factors, as well as determining what dietary modifications might be particularly beneficial in alleviating lead uptake and or effects. Banks et al. (1997) suggest that further studies using electrophysiological methods in infancy and early childhood can add to knowledge about the effects of lead on specific sensory systems such as vision and audition, as well as on higher, more cortically-controlled cognitive processes.

With regard to studies in animals, further studies of the specific behavioral nature of lead-induced learning impairments and of the behavioral mechanisms contributing to such effects would be valuable (Cory-Slechta 1995). Such studies in conjunction with microdialysis and microinjection techniques could provide critical information related to the roles of various neurotransmitter systems and different brain regions in behavioral manifestations (Cory-Slechta 1995). Such research may also shed light on possible interactions between neurotransmitter systems that might contribute to lead effects and allow researchers to examine the efficacy of potential behavioral or chemical therapeutic approaches for reversing behavioral impairments (Cory-Slechta 2003). Additional studies of the roles of developmental periods of lead exposure and the levels of lead exposure should be conducted to resolve the possibility of differential mechanisms at different stages of the life cycle (Cory-Slechta 1997). Further development of molecular techniques to study the action of lead on the function of specific components of proteins associated with synaptic transmission also would be helpful (Atchison 2004; Suszkiw 2004). Additional research on lead-gene interactions is critical to further the understanding of these issues.

Epidemiological and Human Dosimetry Studies. There are dozens of epidemiological studies that investigated the health effects of lead in both adults and children. The studies listed above under *Chronic-Duration Exposure and Cancer* and others cited throughout Section 3.2, *Discussion of Health Effects*, provide information on lead-induced effects on multiple systems and organs, but the most sensitive targets for lead toxicity are the nervous system, heme synthesis, and kidney function. Children are more sensitive than adults to lead toxicity and a great number of studies conducted in the last decades have focused on the evaluation of neurobehavioral effects of lead in children that have been associated with relative low blood lead levels (i.e., <10 µg/dL) (Bellinger and Needleman 2003; Canfield et al. 2003; Chiodo et al. 2004; Kordas et al. 2006; Lanphear et al. 2000a, 2005; Téllez-Rojo et al. 2006). Although the preponderance of the evidence suggests that lead exposure in children is associated with small decrements in intelligence, there are studies that have not found such an association. In this regard, a major information need regarding epidemiological studies of lead is identifying the basis of individual

differences in sensitivity to lead toxicity. Another important issue that future studies need to consider is the presence of modifying factors. Bellinger (2000) states that effect modification is a property of a true association and should be distinguished from confounding. Effect modification can explain inconsistencies in findings, and if it exists, failure to address it will lead to an error in inference. Maternal stress and environmental enrichment have recently been identified as modifying factors of lead-induced behavioral effects in studies in animals (Cory-Slechta 2006; Cory-Slechta et al. 2004; Guilarte et al. 2003; Schneider et al. 2001) and continued research in these areas may provide valuable information for understanding effects in humans. Effects of lead through alterations in corticoids may have enormous implications since changes in the hypothalamic-pituitary-adrenal axis could be a mechanism for multiple effects of lead, including those on the immune system as well as on the brain.

Most of the research gaps identified in the preceding sections could also be listed in this section. For example, it is expected that children from some of the prospective studies of lead will continue to be evaluated periodically with appropriate neurobehavioral tests. As children in these cohorts (or in newly identified cohorts) go through adolescence and eventually into adulthood, it would be desirable also to evaluate other end points for potential late-appearing effects. Such evaluations may include, but not be limited to, immunocompetence, sexual development, fertility, kidney and cardiovascular functions, or cancer incidence. The usefulness of studies involving adult populations exposed to lead as adults (i.e., lead workers) in understanding neurotoxicity of lead in children is questionable. This is because the impact of a brain lesion experienced as an adult can be dramatically different than that of a lesion incurred during periods in which the brain is still undergoing substantial changes (Bellinger 2004). However, studies regarding other end points of interest would be useful. For example, associations between lead exposure and decreases in glomerular filtration rate have been observed, but not fully characterized (Kim et al. 1996a; Muntner et al. 2003; Payton et al. 1994; Staessen et al. 1990, 1992; Weaver et al. 2003a). Major uncertainties in the dose-response relationship include: (1) the appropriate exposure biomarker (i.e., PbB or bone lead concentration); and (2) the strength of the interactions between glomerular filtration rate, blood pressure, and certain diseases such as diabetes. Regarding cardiovascular effects, meta-analyses of the association between blood pressure and PbB have found an average effect size of approximately 1 mmHg increase in blood pressure per doubling of PbB (Nawrot et al. 2002; Schwartz 1995; Staessen et al. 1994); however, more recent studies have observed a larger effect in older populations and associations between blood pressure and bone lead concentrations that is stronger than the association with PbB (Cheng et al. 2001; Korrick et al. 1999; Nash et al. 2003). Major uncertainties in the dose-response relationship for blood pressure effects include: (1) the appropriate exposure

biomarker (i.e., PbB or bone lead concentration); and (2) the strength of the association in older males and post-menopausal women.

Biomarkers of Exposure and Effect.

Exposure. Inorganic lead can be measured in blood, serum, urine, sweat, cerebrospinal fluid, tissues, bone, teeth, and hair and nails (see Section 3.6.1). While measurements of lead in any of the above tissues can be useful as an indicator of excessive exposure to lead, quantitative associations with exposure levels and health effects have been most rigorously explored for blood lead concentration (PbB). Currently, PbB is the most widely used biomarker of lead exposure in humans. However, because of the relatively rapid elimination of lead from blood (elimination half-time <30 days), PbB reflects exposures that occurred within a few months previous to the measurement. The need exists for the development of a biomarker that would accurately reflect the total body burden from both acute and chronic durations at both low- and high-level exposures. Bone lead concentration may serve as a more reliable biomarker of long-term exposure because lead is eliminated slowly from bone (elimination half-time of decades). It may also provide a better reflection of long-term time-integrated plasma lead concentration (Cake et al. 1996; Chuang et al. 2001; Tellez-Rojo et al. 2004). This may explain why bone lead concentration has been observed to be a better predictor of cardiovascular/renal effects in older populations than is PbB (Cheng et al. 1998, 2001; Korrick et al. 1999; Tsaih et al. 2004). Further characterization of bone lead concentration as a biomarker of exposure for various effect end points in adults may improve lead dose-response assessment and characterization of health risks from exposure to lead in humans.

The development of inductively-coupled plasma mass spectrometry (ICP-MS) (see Chapter 7) has provided adequate analytical sensitivity to measure plasma lead concentrations with greater confidence than in the past (Schutz et al. 1996). Recent studies using this technique have shown that plasma lead concentrations in adults correlate more strongly with bone lead levels than do PbB (Cake et al. 1996; Chuang et al. 2001; Hernandez-Avila et al. 1998; Tellez-Rojo et al. 2004). 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 measurements of PbB. 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.

Effect. No clinical disease state is pathognomonic for lead exposure. The neurotoxic 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 (see Section 3.6.1). Biomarkers for the nephrotoxic effects of lead in humans include elevation of serum creatinine, urinary enzymes (e.g., NAG), or protein (albumin, β2μ-globulin, α1μ-globulin, retinol binding protein; see Table 3-3 and Figure 3-3). However, none of these markers are specific for lead-induced nephrotoxicity. More specific biomarkers of effects for lead may improve the assessment of health risks derived from exposure to lead.

Absorption, Distribution, Metabolism, and Excretion. Inhalation of airborne lead-bearing surface dusts can be an important exposure pathway for human. However, available studies of the deposition and absorption of inhaled lead in humans are of exposures of adults to submicron lead-bearing particles (Chamberlain et al. 1978; Hursh and Mercer 1970; Hursh et al. 1969; Morrow et al. 1980; Wells et al. 1975). No studies are available on deposition and absorption of larger particles that might be encountered from inhalation of airborne surface dusts. No data are available 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).

Ingestion of lead can occur as a result of 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 nonfood materials through their normal mouthing activity and pica (abnormal ingestion of nonfood items). Fractional absorption of ingested lead appears to vary in magnitude with age, being as much as 5–10 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. 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. 1997b).

Ingested soil lead is less readily absorbed than ingested water-soluble lead acetate (Casteel et al. 1997; EPA 2004b; 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 and studies aimed at elucidating such mechanisms are needed. 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.

Few studies are available on the 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; Sun et al. 2002). 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.

Several models of the toxicokinetics of lead in humans have been developed (Bert et al. 1989; EPA 1994a, 1994c; Leggett 1993; Marcus 1986a, 1986b, 1986c; O'Flaherty 1993; Rabinowitz et al. 1976). Major uncertainties in these models include: (1) absence of calibration data for the kinetics of lead in blood and bone in children in association with exposures that have been quantified with high certainty; (2) absence of calibration data on bone lead concentrations in adolescents and adults in association with

exposures that have been quantified with high certainty; (3) absence of data on the absolute bioavailability of ingested lead in older children and adolescents; (4) incomplete understanding of lead kinetics during periods of changing bone metabolism, including adolescence, pregnancy, and menopause; and (5) incomplete understanding of inter- and intra-individual variability in model parameters values in humans. In addition, there is a need for models that predict concentrations of lead in tissues other than blood.

Comparative Toxicokinetics. The immature swine has been used extensively as a model for assessing relative bioavailability of lead in ingested soil in humans (Casteel et al. 1997; EPA 2004c) and for evaluating *in vitro* approaches to assessing bioaccessibility of lead (EPA 2004c; Ruby et al. 1999). However, no studies are available in which the absolute or relative bioavailability of ingested lead has been quantitatively compared in swine and humans. Such studies would be useful for validating both the *in vivo* swine model and the *in vitro* bioaccessibility model.

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 that interact with lead (Kwong et al. 2004; Mahaffey and Annest 1986; Mahaffey et al. 1986; Ziegler et al. 1978). 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 (Berlin et al. 1995; Homan et al. 1998). 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 questionable, as shown in a series of recent studies (Dietrich et al. 2004; Liu et al. 2002; Rogan et al. 2001). Clinical studies of oral chelation should monitor not only PbB, but also the possibility of ongoing lead exposure, the child's age, sources of lead exposure, length of exposure, and general health status. Also, the potential benefits of chelation in reducing chronic impairments in adults are completely unknown. Lead inhibits heme synthesis by inhibiting the enzyme ALAD, and this results in a diffuse effect that involves many systems and 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 is unlikely that one could prevent all of the physiological alterations that have been attributed to exposure to lead.

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

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 postnatal 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. An additional important issue that needs to be studied is the potential prevalence of elevated bone lead stores in women of reproductive age and the associated risk that this poses to fetal development by mobilization of maternal bone stores during pregnancy.

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. 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, 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 et al. 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 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 ICP-MS (see Chapter 7) has provided adequate analytical sensitivity to measure plasma lead concentrations with greater confidence than in the past. Studies using this technique have shown that plasma lead concentrations in adults correlate more strongly with bone lead levels than does PbB (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. 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 1995, 2003; Rice 1993, 1996a). 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 (Ballew et al. 1999; Frisancho and Ryan 1991; Shukla et al. 1989, 1991). 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.

Dermal absorption of inorganic lead compounds occurs, but the quantitative significance of the dermal absorption pathway as a contributor to lead body burden remains an uncertainty, although it is generally considered to be much lower than absorption by the inhalation or oral routes of exposure. 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 (Franklin et al. 1997; Gulson et al. 1997b, 1999b, 2003). Thus, changes in maternal bone metabolism (e.g., formation and remodeling) are likely to have a significant impact on *in utero* exposure of the fetus. Approximately 80% of lead in cord blood appears to derive from maternal bone stores (Gulson et al. 2003). Further information about the kinetics of the mobilization of maternal bone lead, or its incorporation into the fetal skeleton 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 6.8.1, Identification of Data Needs: Exposures of Children.

3.10.3 Ongoing Studies

Ongoing studies pertaining to lead have been identified and are shown in Table 3-12.

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Audesirk GJ	University of Colorado at Denver/Health Science Center, Denver, Colorado	Differential lead toxicity in neurons and astrocytes	National Institute of Environmental Health Sciences
Benoff SH	Jewish Research Institute, Manhasset, New York	Developing an understanding of toxic metal action in the human testis	National Institute of Environmental Health Sciences
Berkowitz GS	Mount Sinai School of Medicine, New York, New York	Lead mobilization during pregnancy and lactation in urban women	National Center for Research Resources
Blum CB	Columbia University Health Sciences, New York, New York	Bioavailability of soil lead and arsenic in humans	National Institute of Environmental Health Sciences
Bornschein RL	University of Cincinnati, Cincinnati, Ohio	Treatment of lead exposed children follow up	National Institutes of Health
Brain JD	Harvard School of Public Health, Boston, Massachusetts	Transport of lead, manganese, iron, and cadmium from the environment to critical organs	National Institutes of Health
Burchiel SW	University of New Mexico School of Medicine, Albuquerque, New Mexico	Effects of immunotoxic xenobiotics on human peripheral blood	National Center for Research Resources
Burt BA	University of Michigan Dental School, Ann Arbor, Michigan	Lead exposure/dietary factors in children's oral health	National Institute of Dental and Craniofacial Research
Cecil KM	Children's Hospital Medical Center, Cincinnati, Ohio	MR assessment of brain function altered by lead exposure	National Institute of Environmental Health Sciences
Cohen MD	New York University School of Medicine, Tuxedo, New York	Investigation of how properties of metals may govern toxicities in the lungs	National Institute of General Medical Sciences
Cory-Slechta DA	University of Rochester, Rochester, New York	Behavioral toxicity of lead--a pharmacological analysis	National Institute of Environmental Health Sciences
Ehrich M, Meldrum JB, Parran D, Magnin-Bissel G, and Inzana KD	Virginia Polytechnic Institute, College of Veterinary Medicine, Blacksburg, Virginia	Insecticide exposure and the permeability of the blood-brain barrier to lead	Department of Agriculture
Ercal N	University of Missouri, Rolla, Missouri	Role of selenocystine in lead toxicity	National Institute of Environmental Health Sciences

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Evanylo GK, Daniels WL, and Zelazny LW	Virginia Polytechnic Institute, Crop and Soil Environmental Sciences, Blacksburg, Virginia	Chemistry and bioavailability of waste constituents in soils	Department of Agriculture
Fox DA	University of Houston, Houston, Texas	Low-level prenatal lead exposure and retinal toxicity	National Institute of Environmental Health Sciences
Gao F-B	J David Gladstone Institutes, San Francisco, California	Genetic analysis of heavy metals neurotoxicity	National Institute of Neurological Disorders and Stroke
Garshick E	Department of Veterans Affairs, Medical Center, Brockton, Massachusetts	Lead intoxication-prevalence and its relation to anemia in India	Department of Veterans Affairs
Gonick H	Department of Veterans Affairs, Medical Center, West Los Angeles, California	Influence of lead on blood vessel contraction	Department of Veterans Affairs
Godwin HA	Northwestern University, Evanston, Illinois	Mechanisms of lead toxicity	National Institute of General Medical Sciences
Gray LC	University of Texas, Health Science Center, Houston, Texas	Effects of lead on deficits in hearing rapid changes in sound	National Institute on Deafness and Other Communication Disorders
Graziano JH	Columbia University Health Sciences, New York, New York	Health effects and geochemistry of arsenic and lead	National Institute of Environmental Health Sciences
Guilarte TR	Johns Hopkins University, Baltimore, Maryland	NMDA receptor function in lead neurotoxicity	National Institute of Environmental Health Sciences
Harry GJ	Not specified	Environmental effects and development of neuron and glia	National Institute of Environmental Health Sciences
Hassett JJ	University of Illinois, Natural Resources and Environmental Sciences, Urbana, Illinois	Continued studies on bioavailability of lead in soil	Department of Agriculture
Henkens RW	Alderon Biosciences, Inc., Durham, North Carolina	One-step rapid screening for childhood lead poisoning	National Institute of Environmental Health Sciences
Hu H	Harvard University School of Public Health, Boston, Massachusetts	Dietary supplements and suppression of bone resorption and lead mobilization	National Institute of Environmental Health Sciences

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Hu H	Brigham and Women's Hospital, Boston, Massachusetts	Lead, blood pressure, neurologic and renal function in two study populations	National Center for Research Resources
Hu H	Brigham and Women's Hospital, Boston, Massachusetts	Lead-gene interactions and cognition	National Institute of Environmental Health Sciences
Hu H	Brigham and Women's Hospital, Boston, Massachusetts	Development of Parkinson's disease and the exposure to lead	National Institute of Environmental Health Sciences
Ike JO	Fisk University, Nashville, Tennessee	Lead toxicity and serotonergic system in developing rat brain	National Institute of General Medical Sciences
Kamel F	Not specified	Lead and other neurotoxins as risk factors for amyotrophic lateral sclerosis	National Institute of Environmental Health Sciences
Knight JQ	Safer Pest Control Project, Chicago, Illinois	Asthma and lead prevention in Chicago public housing	National Institute of Environmental Health Sciences
Korrick SA	Harvard University School of Public Health, Boston, Massachusetts	*In utero* PCB, pesticide and metal exposure and childhood cognition	National Institute of Environmental Health Sciences
Korrick SA	Brigham and Women's Hospital, Boston, Massachusetts	Lead exposure, genetics and osteoporosis epidemiology	National Center for Research Resources
Lanphear BP	Children's Hospital Medical Center, Cincinnati, Ohio	Neurobehavioral effects of prevalent toxicants in children	National Institute of Environmental Health Sciences
Lawrence DA	Wadsworth Center, Rensselaer, New York	Immunotoxic effects of lead on cytokine expression	National Institute of Environmental Health Sciences
Lubin BH	University of California San Francisco, California	Erythrocyte isozyme biomarkers of low lead overburden	National Center for Research Resources
Lurie D	University of Montana, Center of Environmental Health Sciences, Missoula, Montana	Lead on development of auditory temporal process	National Center for Research Resources
Lutz PM	University of Missouri Rolla, Rolla, Michigan	Immunity in children with exposure to environmental lead	National Institute of Environmental Health Sciences
Mori S	Johns Hopkins University, Baltimore, Maryland	MR-based study of hypomyelination by lead poisoning	National Institute of Environmental Health Sciences

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Neary JT	Department of Veterans Affairs, Medical Center, Miami, Florida	Molecular mechanisms of lead neurotoxicity	Department of Veterans Affairs
Oteiza P	University of California, Davis, California	Exposure during gestation and infancy and its impact on neurobehavioral and learning capacities	Not specified
Pettit DL	Albert Einstein College of Medicine, Yeshiva University, New York, New York	Micromapping of lead induced changes to NMDA receptors	National Institute of Environmental Health Sciences
Pevsner JA	Kennedy Krieger Research Institute, Inc., Baltimore, Maryland	Effects of lead on calcium-binding proteins in rats	National Institute of Environmental Health Sciences
Pitts DK	Wayne State University, College of Pharmacy and ANP, Wayne State University, Detroit, Michigan	Lead toxicity—midbrain dopaminergic system	National Institute of Environmental Health Sciences
Pollitt E	University of California, Independent, Davis, California	The relationship between lead and iron and behavioral development in infants and young children	Department of Agriculture
Poretz RD	Rutgers University, Biochemistry and Microbiology, New Brunswick, New Jersey	A mechanism for lead-induced neurotoxicity	Department of Agriculture
Puzas JE	University of Rochester, Rochester, New York	Lead toxicity in the skeleton and its role in osteoporosis	National Institute of Environmental Health Sciences
Rajanna B	Alcorn State University, Lorman, Mississippi	Mechanism of lead neurotoxicity	National Institute of General Medical Sciences
Ris MD	Children's Hospital Medical Center, Cincinnati, Ohio	Early exposure to lead and adult antisocial outcome	National Institute of Environmental Health Sciences
Rogan W	Not specified	Toxicity of lead in children—clinical trial	National Institute of Environmental Health Sciences
Rosen HN	Beth Israel Deaconess Medical Center, Boston, Massachusetts	Lead and skeletal health in Boston area women	National Center for Research Resources
Ruden DM	University of Alabama at Birmingham, Birmingham, Alabama	QTL and microarray mapping lead sensitivity genes	National Institute of Environmental Health Sciences

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Schwab AP and Joern BC	Purdue University, Agronomy, West Lafayette, Indiana	Bioavailability and chemical lability of lead in agricultural soils amended with metal-containing biosolids	Department of Agriculture
Schwartz BS	Johns Hopkins University, Baltimore, Maryland	Role of lead in the decline in cognitive function in older adults	National Institute of Aging
Schwarz D	Children's Hospital of Philadelphia, Philadelphia, Pennsylvania	Treatment of lead in children	National Center for Research Resources
Shine JP	Harvard University, School of public Health, Boston, Massachusetts	Transport and fate of metals from mine wastes	National Institute of Environmental Health Sciences
Soliman KFA	Florida Agricultural and Mechanical University, Tallahassee, Florida	Neonatal lead exposure effects on the adrenal cortex function	National Institute of General Medical Sciences
Sparrow D	Department of Veterans Affairs, Medical Center, Boston, Massachusetts	Neurochemical and genetic markers of lead toxicity	Department of Veterans Affairs
Sparrow D	Department of Veterans Affairs, Medical Center, Boston, Massachusetts	Lead biomarkers, aging, and chronic disease	Department of Veterans Affairs
Timchalk C	Battelle Memorial Institute, Pacific Northwest Laboratories, Richland, Washington	Innovative biomonitoring for lead in saliva	National Institute of Environmental Health Sciences
Todd AC	Mount Sinai, School of Medicine, New York, New York	African-Americans, hypertension and lead exposure	National Institute of Diabetes and Digestive and Kidney Diseases
Watson GE, II	Department of Dentistry, University of Rochester, Rochester, New York	A longitudinal study of lead exposure and dental caries	National Institute of Dental and Craniofacial Research
Weisskopf MG	Harvard University, School of Public Health, Boston, Massachusetts	New biomarkers of neurotoxicity	National Institute of Environmental Health Sciences
White RF	Department of Veterans Affairs, Medical Center, Boston, Massachusetts	Functional neuroimaging in lead exposed adults	Department of Veterans Affairs, Research And Development

Table 3-12. Ongoing Studies on Lead

Investigator	Affiliation	Research Description	Sponsor
Worobey J	Rutgers University, Nutritional Sciences, New Brunswick, New Jersey	Behavioral outcomes in children screened for lead burden and nutritional risk	Department of Agriculture
Wright RO	Harvard School of Public Health, Boston, Massachusetts	Metals, nutrition, and stress in child development	National Institute of Environmental Health Sciences
Wright RO	Brigham And Women's Hospital, Boston, Massachusetts	Neurochemical and genetic markers of lead toxicity	National Institute of Environmental Health Sciences

MR = magnetic resonance; NMDA = N-methyl-D-aspartate; PCBs = polychlorinated biphenyls; QTL = quantitative trait loci

Source: FEDRIP 2005

4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

Lead is a naturally occurring element and is a member of Group 14 (IVA) of the periodic table. Natural lead is a mixture of four stable isotopes, ^{208}Pb (51–53%), ^{206}Pb (23.5– -27%), ^{207}Pb (20.5–23%), and ^{204}Pb (1.35–1.5%). Lead isotopes are the stable decay product of three naturally radioactive elements: ^{206}Pb from uranium, ^{207}Pb from actinium, and ^{208}Pb from thorium.

Lead is not a particularly abundant element, but its ore deposits are readily accessible and widely distributed throughout the world. Its properties, such as corrosion resistance, density, and low melting point, make it a familiar metal in pipes, solder, weights, and storage batteries. The chemical identities of lead and several of its compounds are given in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

Lead exists in three oxidation states: Pb(0), the metal; Pb(II); and Pb(IV). In the environment, lead primarily exists as Pb(II). Pb(IV) is only formed under extremely oxidizing conditions and inorganic Pb(IV) compounds are not found under ordinary environmental conditions. While organolead(II) compounds are known, organolead chemistry is dominated by the tetravalent (+4) oxidation state. Metallic lead, Pb(0) exists in nature, but its occurrence is rare.

Lead's extensive use is largely due to its low melting point and excellent corrosion resistance in the environment. When exposed to air and water, films of lead sulfate, lead oxides, and lead carbonates are formed; these films act as a protective barrier that slows or halts corrosion of the underlying metal. Lead is amphoteric, forming plumbous and plumbic salts in acid and plumbites and plumbates in alkali. Lead is positioned slightly above hydrogen in the electromotive series and therefore should theoretically replace hydrogen in acids. However, the potential difference is small and the high hydrogen overvoltage prevents replacement (King and Ramachandran 1995; Sutherland and Milner 1990).

Data on the physical and chemical properties of lead and several of its compounds are given in Table 4-2.

Table 4-1. Chemical Identity of Lead and Compounds

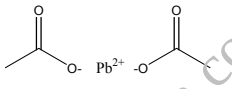
Characteristic	Lead[a]	Lead acetate[a]	Lead azide[b]	Lead bromide[c]
Synonyms	Lead metal; plumbum; pigment metal	Lead(2+) acetic acid; plumbous acetate	Lead (2+) azide; Lead diazinde	Lead (II) bromide[d]
Trade name	CI77575	Salt of Saturn; sugar of lead; Unichem PBA	RD 1333	No data
Chemical formula	Pb	$C_4H_6O_4Pb$	N_6Pb	Br_2Pb
Chemical structure[e]	Pb		$Pb(N_3)_2$	$PbBr_2$
Identification numbers:				
CAS registry	7439-92-1	301-04-2	13424-46-9	10031-22-8
NIOSH RTECS	OF7525000[b]	AI5250000[b]	OF8650000	No data
EPA hazardous waste	D008	U144, D008	No data	No data
OHM/TADS	7216776	7217255	No data	No data
DOT/UN/NA/IMCO 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 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead chloride[a]	Lead chromate[a]	Lead fluoroborate[a]	Lead iodide[a]
Synonyms	Lead(2+) chloride; lead (II) chloride; plumbous chloride	Chromic acid (H_2CrO_4) lead(2+) salt; lead chromate (VI); Yellow 34	Borate(1-), tetrafluoro, lead(2+); lead borofluoride; lead boron fluoride; lead tetrafluoroborate	Lead diiodide; lead(II) iodide; plumbous iodide
Trade name	No data	Canary Chrome Yellow 40-2250; Cologne Yellow; King's Yellow	No data	No data
Chemical formula	Cl_2Pb	CrO_4Pb	$B_{24}F_8Pb$	I_2Pb
Chemical structure[e]	$PbCl_2$	$PbCrO_4$	$Pb(BF_4)_2$	PbI_2
Identification numbers:				
CAS registry	7758-95-4	7758-97-6	13814-96-5	10101-63-0
NIOSH RTECS	OF9450000[b]	GB2975000[b]	ED2700000[b]	OG1515000[b]
EPA hazardous waste	No data	D007, D008	D008	D008
OHM/TADS	7217256	No data	7217378	No data
DOT/UN/NA/IMCO 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 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead molybdenum chromate[b]	Lead nitrate[a]	Lead oxide[a]
Synonyms	Chromic acid, lead and molybdenum salt; molybdenum-lead chromate; molybdenum orange; Scarlet chrome; Red 104	Lead dinitrate; nitric acid lead(2+) salt; lead (II) nitrate; plumbous nitrate	Lead(2+) oxide; lead oxide, yellow lead monoxide; litharge; massicot
Trade name	C.I. Pigment Red 104	No data	CI 77577; CI Pigment Yellow 46
Chemical formula	CRMoOPb	N_2O_6Pb	OPb
Chemical structure[e]	No data	$Pb(NO_3)_2$	PbO
Identification numbers:			
CAS registry	12709-98-7	10099-74-8	1317-36-8
NIOSH RTECS	OG1625000	OG2100000[b]	OG1750000[b]
EPA hazardous waste	No data	D008	D008
OHM/TADS	No data	7217257	No data
DOT/UN/NA/IMCO shipping	No data	UN 1469, IMO 5.1	No data
HSDB	No data	637	638
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Lead and Compounds

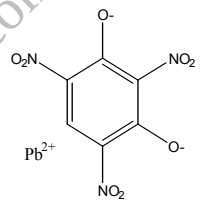
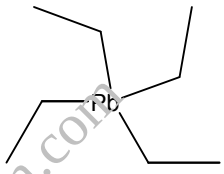
Characteristic	Lead phosphate[a]	Lead styphnate[f]	Lead sulfate[a]
Synonyms	Lead(2+) phosphate; phosphoric acid lead(2+) salt	1,3-benzenediol, 2,4,6-trinitro, lead (2+) salt (1:1); resorcinol, 2,4,6-trinitro; lead (2+) salt (1:1); lead (II) styphnate	Sulfuric acid lead(2+) salt; lead (II) sulfate
Trade name	Perlex Paste 500; Perlex Paste 600A; CI 77622	No data	CI 77630; Fast White; Lead Bottoms; Mulhouse White
Chemical formula	$O_8P_2Pb_3$	$C_6H_3N_3O_8Pb$	O_4PbS
Chemical structure[e]	$Pb_3(PO_4)_2$		$PbSO_4$
Identification numbers:			
CAS registry	7446-27-7	15245-44-0	7446-14-2
NIOSH RTECS	OG3675000[b]	No data	OG4375000[b]
EPA hazardous waste	D008, U145	No data	No data
OHM/TADS	No data	No data	No data
DOT/UN/NA/IMCO shipping	No data	No data	UN 1794; NA 1794; IMO 8.0
HSDB	2637	No data	6308
NCI	No data	No data	No data

Table 4-1. Chemical Identity of Lead and Compounds

Characteristic	Lead sulfide[a]	Tetraethyl lead[a]	Lead carbonate[a]
Synonyms	Lead monosulfide; lead(2+) sulfide; Lead (II) sulfide; plumbous sulfide; natural galena	Lead, tetraethyl; TEL; tetraethyllead; tetraethyl-plumbane	Carbonic acid lead salt; cerussite
Trade name	No data	No data	No data
Chemical formula	PbS	$C_8H_{20}Pb$	$PbCO_3$
Chemical structure[e]	PbS		$PbCO_3$
Identification numbers:			
CAS registry	1314-87-0	78-00-2	598-63-0
NIOSH RTECS	OG4550000	TP4550000	OF9275000
EPA hazardous waste	D008	P110; D008	D008
OHM/TADS	7800071	7216922	No data
DOT/UN/NA/IMCO shipping	NA 2291; IMO 6.1	NA 1649; IMO 6.1	No data
HSDB	639	841	1649
NCI	No data	C54988	No data

[a]HSDB 2007
[b]RTECS 2007
[c]Lewis 1993
[d]Lenga 1988
[e]ChemIDplus 2005
[f]EPA 2006

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 4-2. 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
Density at 20 °C	11.34 g/cm^3	3.25 g/cm^3	No data	6.66 g/cm^3 [d]
Odor	None	Slightly acetic	No data	No data
Odor threshold:				
Water	No data	No data	No data	No data
Air	No data	No data	No data	No data
Solubility:				
Water at 25 °C	Insoluble	443,000 mg/L at 520 °C	230 mg/L at 18 °C	8,441 mg/L at 20 °C
Nitric acid	Soluble	No data	No data	No data
Hot conc. sulfuric acid	Soluble	No data	No data	No data
Organic solvents	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 mmHg at 1,000 °C	No data	No data	1 mm Hg at 513 °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[j]	Not relevant[e]	Not relevant[e]	Not relevant[e]	Not relevant[e]
Explosive limits	No data	Lead acetate-lead bromate double salt is explosive	No data	No data
Valence state	0[f]	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead chloride[a]	Lead chromate[a]	Lead fluoroborate[b]	Lead iodide[a]
Molecular weight	278.11	323.19	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	Decomposes at 872 °C
Density at 20 °C	5.85 g/cm^3	6.12 g/cm^3 at 15 °C	1.75 g/cm^3	6.16 g/cm^3
Odor	No data	Faint odor (solution)	Odorless	No data
Odor threshold	No data	No data	No data	No data
Solubility:				
Water at 25 °C	9,900 mg/L at 20 °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 conc. sulfuric acid	No data	No data	No data	No data
Organic solvents	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 mm Hg at 547 °C	No data	No data	1 mm Hg 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	Not relevant[e]	Not relevant[e]	Not relevant[e]	Not relevant[e]
Explosive limits	No data	No data	No data	No data
Valence state	+2	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead molybdenum chromate[a]	Lead nitrate[a]	Lead oxide[a]
Molecular weight	886.26[g]	331.21	223.20
Color	No data	Colorless or white	Reddish-yellow; yellow (above 489 °C)
Physical state	No data	Solid	Solid
Melting point	No data	Decomposes at 470 °C	888 °C
Boiling point	No data	No data	Decomposes at 1,472 °C
Density at 20 °C	No data	4.53 g/cm^3	9.3 g/cm^3 (Litharge); 8.0 g/cm^3 (Massicot)[d]
Odor	No data	Odorless	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water at 25 °C	No data	376,500 mg/L at 0 °C 565,000 mg/L at 20 °C	17 mg/L at 20 °C
Nitric acid	No data	Insoluble	Soluble (Litharge)
Hot conc. sulfuric acid	No data	No data	No data
Organic solvents	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
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	Fire risk with organics	Not readily ignited
Conversion factors	Not relevant[e]	Not relevant[e]	Not relevant[e]
Explosive limits	No data	Explosive with easily oxidizable substances, and lead nitrate-lead hypophosphite double salt	2B3 drops 90% peroxyformic acid causes violent explosion
Valence state	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead phosphate[a]	Lead styphnate[h]	Lead sulfate[a]
Molecular weight	811.54	450.29[g]	303.26
Color	White	Orange-yellow (monohydrate)	White
Physical state	Solid	Monoclinic crystals	Solid
Melting point	1,014 °C	No data	1,170 °C
Boiling point	No data	No data	No data
Density at 20 °C	6.9B7.3 g/cm^3 [d]	No data	6.2 g/cm^3[c]
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water at 25 °C	0.14 mg/L at 20 °C	Insoluble	42.5 mg/L
Nitric acid	Soluble	No data	More than in water
Hot conc. sulfuric acid	No data	No data	Slightly soluble
Organic solvents	Soluble in fixed alkali hydroxides; insoluble in alcohol	No data	Insoluble in alcohol
Partition coefficients:			
Log K_{ow}	No data	No data	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	No data	No data	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	No data	No data
Flammability limits	No data	Detonates at 260 °C	Not flammable
Conversion factors	Not relevant[e]	Not relevant[e]	Not relevant
Explosive limits	No data	No data	No data
Valence state	+2	+2	+2

Table 4-2. Physical and Chemical Properties of Lead and Compounds

Property	Lead sulfide[a]	Tetraethyl lead[a]	Lead carbonate[a]
Molecular weight	239.27	323.45	267.2
Color	Black, blue, or silvery	Colorless	Colorless rhombic crystals
Physical state	Cubic or metallic crystals; powder	Oily liquid	Solid
Melting point	1,114 °C	No data	315 °C (decomposes)
Boiling point	Sublimes at 1,281 °C	200 °C; 227.7 °C (with decomposition)	No data
Density at 20 °C	7.57–7.59 g/cm^3	1.653 g/cm^3	6.6 g/cm
Odor	No data	No data	No data
Odor threshold:	No data	No data	No data
Solubility:			
Water at 25 °C	0.86 mg/L at 13 °C	0.29 mg/L	1.1 mg/L
Nitric acid	Soluble	No data	Soluble
Hot conc. sulfuric acid	Soluble (in acid)	No data	Soluble
Organic solvents	Nitric acid, hot diluted hydrochloric acid[b]; insoluble in alcohol	Benzene, ethanol, diethyl ether, gasoline petroleum ether	Insoluble in ammonia and alcohol
Partition coefficients:			
Log K_{ow}	No data	4.15	No data
Log K_{oc}	No data	No data	No data
Vapor pressure	10 mmHg at 975 °C	0.26 mm Hg at 25 °C	No data
Henry's law constant	No data	No data	No data
Autoignition temperature	No data	No data	No data
Flashpoint	No data	93 °C (closed cup); 85 °C (open cup)	No data
Flammability limits	Noncombustible	1.8%	Not flammable
Conversion factors	Not relevant	Not relevant	Not relevant
Explosive limits	No data	Potentially, above 80 °C	No data
Valence state	+2	+4	+2

[a]HSDB 2007
[b]Budavari et al. 1989
[c]Lide 1996
[d]Temperature not specified.
[e]Since these compounds exist in the atmosphere in the particulate state, their concentrations are expressed as µg/m^3 only.
[f]Howe 1981
[g]Molecular weight calculated from atomic weights.
[h]Lewis 1993

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

5.1 PRODUCTION

The most important lead ore is galena (PbS) followed by anglesite ($PbSO_4$) and cerussite ($PbCO_3$). The latter two minerals are formed from the weathering of galena. Five lead mines in Missouri plus lead-producing mines in Alaska, Idaho, Montana, and Washington produce most of the primary lead. In 2003, Alaska and Missouri ("lead-belt" in southeastern part of the state) accounted for 96% of domestic mine production. Lead can be recovered from ore deposits of lead, zinc, lead-zinc, and silver. Lead ore is mined underground except when it is mined with copper ores, which are typically open pit mines. The United States is third in world lead production after Australia and China. Together with Peru, Canada, and Mexico, these six countries account for 82% of the world's mine production.

Primary lead is obtained from mined ore. The crude ore is first beneficiated, which involves processes such as crushing, dense-medium separation, grinding, and froth floatation to obtain concentrates with higher lead concentrations. Primary metal is generally produced from the sulfide concentrate by a two-step process involving (1) an oxidative roast to remove sulfur with the formation of PbO and (2) blast furnace reduction of the PbO. Lead concentrates produced from ore were processed into primary metal at two smelter refineries operated by a company in Missouri.

Secondary lead is obtained from scrap lead. Ninety-nine percent of secondary production of lead was produced at 23 plants in the United States, 15 of which had annual capacities of 15,000 tons or more. In 2003, secondary lead accounted for 82% of refined lead production. Secondary lead is obtained primarily from recycled lead-acid batteries. Almost all of the lead recycled in 2003 was produced by 7 companies operating 15 plants in Alabama, California, Florida, Indiana, Louisiana, Minnesota, Missouri, New York, Tennessee, and Texas (USGS 2003).

Tables 5-1 and 5-2 list facilities in each state that respectively manufacture, process, or use lead and lead compounds, the intended use, and the range of maximum amounts of these substances that are stored on site. The data listed in Tables 5-1 and 5-2 are derived from the Toxics Release Inventory (TRI04 2006). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list. In comparing Toxics Release Inventory (TRI) data with that of previous years, it is important to note that starting in 2001 the threshold for reporting lead was reduced to 100 pounds. Previously, reporting was only required of facilities that manufactured or processed 25,000 pounds or more annually or that used 10,000 pounds or more annually. Additionally, in 1998, additional industries were required to report,

Table 5-1. Facilities that Produce, Process, or Use Lead

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	10	100	99,999	1, 5, 7, 9, 12, 13, 14
AL	126	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	74	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AZ	76	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	281	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	56	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CT	104	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DC	4	100	99,999	1, 8, 11, 12, 13
DE	15	100	9,999,999	2, 3, 7, 8, 9, 11, 12, 13, 14
FL	119	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	117	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GU	3	0	999	1, 5, 12
HI	15	0	999,999	1, 7, 8, 11, 12, 13, 14
IA	91	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	37	0	9,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
IL	217	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	174	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	61	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
KY	107	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	77	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	103	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MD	51	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
ME	39	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
MI	176	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	84	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	112	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MS	74	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	19	0	99,999	1, 2, 5, 6, 7, 8, 9, 12, 13, 14
NC	138	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	17	0	99,999	1, 2, 3, 5, 7, 8, 9, 10, 12, 13, 14
NE	58	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NH	44	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
NJ	161	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	28	0	49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 14
NV	55	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
NY	178	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	268	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	93	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OR	75	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-1. Facilities that Produce, Process, or Use Lead

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
PA	238	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	31	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 12
RI	50	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SC	113	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	21	0	499,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TN	156	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	223	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	63	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	109	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VI	3	100	99,999	1, 5, 12, 14
VT	17	0	9,999,999	2, 6, 7, 8, 9, 10, 11, 12, 13, 14
WA	90	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	129	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	64	0	49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14
WY	15	0	999,999	1, 4, 7, 8, 9, 12, 13, 14

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

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

Source: TRI04 2006 (Data are from 2004)

Table 5-2. Facilities that Produce, Process, or Use Lead Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
AK	30	0	999,999,999	1, 2, 4, 5, 7, 9, 10, 12, 13, 14
AL	159	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
AR	111	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
AZ	129	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CA	324	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
CO	87	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
CT	111	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
DE	38	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
FL	136	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GA	187	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
GU	5	0	9,999	1, 2, 3, 4, 5, 7, 9, 12, 13, 14
HI	11	0	99,999	1, 2, 5, 7, 9, 12, 13, 14
IA	107	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ID	41	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
IL	287	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
IN	259	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KS	104	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
KY	148	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	116	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MA	148	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MD	80	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ME	33	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13, 14
MI	209	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MN	103	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MO	161	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MP	4	0	9,999	1, 2, 3, 4, 5, 7, 9, 12, 13, 14
MS	93	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
MT	43	0	10,000,000,000	1, 2, 3, 4, 5, 6, 7, 9, 12, 13, 14
NC	156	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
ND	17	0	999,999	1, 2, 5, 7, 9, 10, 12, 13, 14
NE	65	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NH	51	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NJ	182	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NM	55	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
NV	74	0	999,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
NY	197	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OH	330	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	96	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14

Table 5-2. Facilities that Produce, Process, or Use Lead Compounds

State[a]	Number of facilities	Minimum amount on site in pounds[b]	Maximum amount on site in pounds[b]	Activities and uses[c]
OR	92	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PA	331	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
PR	38	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
RI	59	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SC	123	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
SD	24	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TN	166	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
TX	288	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	88	0	499,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VA	120	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
VI	7	0	999,999	1, 2, 3, 4, 5, 7, 8, 9, 10, 12
VT	18	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 11, 12, 13, 14
WA	113	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WI	136	0	99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
WV	70	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13, 14
WY	36	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 12, 13, 14

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

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

Source: TRI04 2006 (Data are from 2004)

including metal mining, coal mining, electrical utilities, and Resource Conservation and Recovery Act (RCRA)/Solvent Recovery. Table 5-3 lists the producers of primary lead metal and selected lead compounds. Companies listed are those producing lead compounds in commercial quantities, exceeding 5,000 pounds or $10,000 in value annually. Table 5-4 shows the U.S. production volumes for lead for 1999 through 2003. During this time, the primary lead production declined while secondary lead production was fairly constant.

5.2 IMPORT/EXPORT

No lead in ore and concentrates and base bullion were imported into the United States in 2003, while 175,000 metric tons were imported in pigs, bars, and reclaimed scrap. Imports were down from 1999 when 12,300 metric tons, 90 metric tons, and 311,000 metric tons were imported in ore and concentrates; base bullion; and pigs bars and reclaimed scrap, respectively. In 2003, 36,000 metric tons, lead content of lead pigments and compounds were imported in the United States (USGS 2003).

Exports of lead in ore and concentrates and lead materials, excluding scrap, rose from 93,500 and 103,000 metric tons in 1999 to 253,000 and 123,000 metric tons, respectively, in 2003. In 2003, 92,800 metric tons of lead scrap were exported (USGS 2003).

5.3 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 (King and Ramachandran 1995; Shea 1996; Sutherland and Milner 1990). Lead is used in the manufacture of storage batteries; lead alloys used in bearings, brass and bronze and some solders; sheets and pipe for nuclear and x-ray shielding, cable covering, noise control materials; chemical resistant linings; ammunition; and pigments and lead compounds used in glass making, ceramic glazes, plastic stabilizers, caulk, and paints. Consumption of lead in lead-acid batteries, including SLI (Start, Light, Ignition) batteries used in cars, trucks, and other vehicles and industrial type lead acid batteries is the major use of lead today. In 2003, the U.S. consumption for lead was: 84.2%, storage batteries; 3.5%, ammunition, shot, and bullets; 2.6%, other oxides (paint, glass and ceramic products, other pigments and chemicals); 2.3%, casting metals (electrical machinery and equipment, motor vehicles and equipment, other transportation equipment, and nuclear radiation shielding); and 1.7%, sheet lead (building construction, storage tanks, process vessels, etc., and medical radiation

Table 5-3. Current U.S. Manufacturers of Lead Metal and Selected Lead Compounds[a]

Company	Location
Lead metal[b]:	
Doe Run Resources Corp.	St. Louis, Missouri
Lead chromate (Yellow 34):	
Dominion Colour Corp. (USA)	Paterson, New Jersey
Engelhard Corporation	Louisville, Kentucky
Nichem Corp.	Chicago, Illinois
Rockwood Pigments, NA, Inc.	Beltsville, Maryland
Wayne Pigment Corporation	Milwaukee, Wisconsin
Lead fluoborate:	
Atotech USA Inc	Rock Hill, South Carolina
General Chemical Corporation	Claymont, Delaware
OMG Fidelity, Inc.	Newark, New Jersey
Solvay Fluorides, LLC.	St. Louis, Missouri
Lead molybdenum chromate (Red 104):	
Englehard Corporation	Louisville, Kentucky
Wayne Pigment Corporation	Milwaukee, Wisconsin
Lead nitrate:	
GFS Chemicals, Inc.	Columbus, Ohio
Lead oxide, yellow:	
Eagle-Picher Industries, Inc	Joplin, Missouri
Hammond Group, Inc.	Hammond, Indiana, Pottstown, Pennsylvania
OMNI Oxide	Lancaster, Ohio
Lead sulfate:	
Nichem Corp.[c]	Chicago, Illinois
Hammond Group, Inc.[d]	Hammond, Indiana
Eagle-Pitcher Industries, Inc.[e]	Joplin, Missouri

[a]Derived from SRI 2004 unless otherwise noted. SRI reports production of chemicals produced in commercial quantities (defined as exceeding 5,000 pounds or $10,000 in value annually) by the companies listed.
[b]USGS 2004. Primary producer
[c]Lead sulfate, Dibasic lead sulfate ($2PbO.PBSO_4$) and Tribasic lead sulfate ($3PbO.PbSO_4$)
[d]Dibasic lead sulfate ($2PbO.PBSO_4$) and tribasic lead sulfate ($3PbO.PbSO_4$)
[e]Tribasic lead sulfate ($3PbO.PbSO_4$)

Table 5-4. U.S. Lead Production 1999–2003

Production	Production volumes in metric tons				
	1999	2000	2001	2002	2003
Mined (recovered): domestic ores, recoverable lead content	503,000	449,000	454,000	440,000	449,000
Primary (refined): domestic/foreign ores and base bullion	350,000	341,000	290,000	262,000	245,000
Secondary (refined): lead content	1,110,000	1,130,000	1,100,000	1,120,000	1,150,000

Source: USGS 2003

shielding) (USGS 2003). Certain dispersive uses of lead that led to widespread exposure, such as tetraethyl lead in gasoline, water pipe, solder in food cans, lead shot and sinkers, 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, EPA, in 1973, 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 <1% of the amount of lead used in the peak year of 1970 (EPA 1996a).

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 1996a). 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 1996a). 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 1996a). 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 1996a), but tetraethyl lead has not been produced in the United States since March 1991. All gasoline sold for motor vehicle use since January 1, 1996, has been unleaded (EPA 1997).

Table 5-5 lists the uses of the specific lead compounds identified in Chapter 4.

Lead arsenate, basic lead arsenate, and lead arsenite were formerly used as herbicides, insecticides, or rodenticides. Until the 1960s, they were widely used to control pests in fruit orchards, especially apple orchards (EPA 2002; PAN Pesticides Database 2004; Peryea 1998; Wisconsin Department of Health and

Table 5-5. Current and Former Uses of Selected Lead Compounds

Compound	Uses
Lead acetate	Dyeing of textiles, waterproofing, varnishes, lead driers, chrome pigments, gold cyanidation process, insecticide, anti-fouling paints, analytical reagent, hair dye
Lead azide	Primary detonating compound for high explosives
Lead bromide	Photopolymerization catalyst, inorganic filler in fire-retardant plastics, general purpose welding flux
Lead chloride	Preparation of lead salts, lead chromate pigments, analytical reagent
Lead chromate	Pigment in industrial paints, rubber, plastics, ceramic coatings; organic analysis
Lead fluoborate	Salt for electroplating lead; can be mixed with stannous fluoborate to electroplate any composition of tin and lead as an alloy
Lead iodide	Bronzing, printing, photography, cloud seeding
Lead molybdate	Analytical chemistry, pigments
Lead nitrate	Lead salts, mordant in dyeing and printing calico, matches, mordant for staining mother of pearl, oxidizer in the dye industry, sensitizer in photography, explosives, tanning, process engraving, and lithography
Lead oxide, black	Storage batteries, ceramic cements and fluxes, pottery and glazes, glass, chromium pigments, oil refining, varnishes, paints, enamels, assay of precious metal ores, manufacture of red lead, cement (with glycerol), acid-resisting compositions, match-head compositions, other lead compounds, rubber accelerator
Lead phosphate	Stabilizing agent in plastics
Lead styphnate	Primary explosive
Lead sulfate	Storage batteries, paints, ceramics, pigments, Electrical and other vinyl compounds requiring high heat stability
Lead sulfide	Ceramics, infrared radiation detector, semi-conductor, ceramic glaze, source of lead
Tetraethyl lead	Anti-knock agent in aviation gasoline

Sources: Boileau et al. 1987; Carr 1995; EPA 2001

Family Services 2002). All insecticidal use of lead arsenate was officially banned on August 1, 1988. However, all registrations for its insecticidal use had lapsed before that time.

5.4 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). In 2002, about 81% of refined lead production in the United States was recovered from recycled scrap. The primary source was recycled lead-acid batteries. About 6% of recycled lead was obtained from other sources, namely new scrap, obtained from primary lead production, building construction materials, cable covering, and solder. About 99% of the 1.10 million tons of lead recycled in 2002 was produced by 7 companies operating 15 secondary smelter-refineries in Alabama, California, Florida, Indiana, Louisiana, Minnesota, Missouri, New York, Pennsylvania, Tennessee, and Texas. An estimated 90–95% of the lead consumed in the United States is considered to be recyclable. In 1996, 77.1% of U.S. lead consumption was satisfied by recycled lead products (mostly lead-acid batteries). This compares to 69.5% in 1990 and 55.2% in 1980 (Larrabee 1997, 1998; USGS 2002).

Disposal of wastes containing lead or lead compounds is controlled by a number of federal regulations (see Chapter 8). 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 2001e). 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 (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). According to the Battery Council International, 97% of all lead-acid batteries are recycled and new batteries contain between 60 and 80% recycled lead and plastic (Battery Council International 2003).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

Lead has been identified in at least 1,272 of the 1,684 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2006). However, the number of sites evaluated for lead is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 1,258 are located within the United States, 2 are located in Guam, 10 are located in the Commonwealth of Puerto Rico, and 2 are located in the Virgin Islands (not shown).

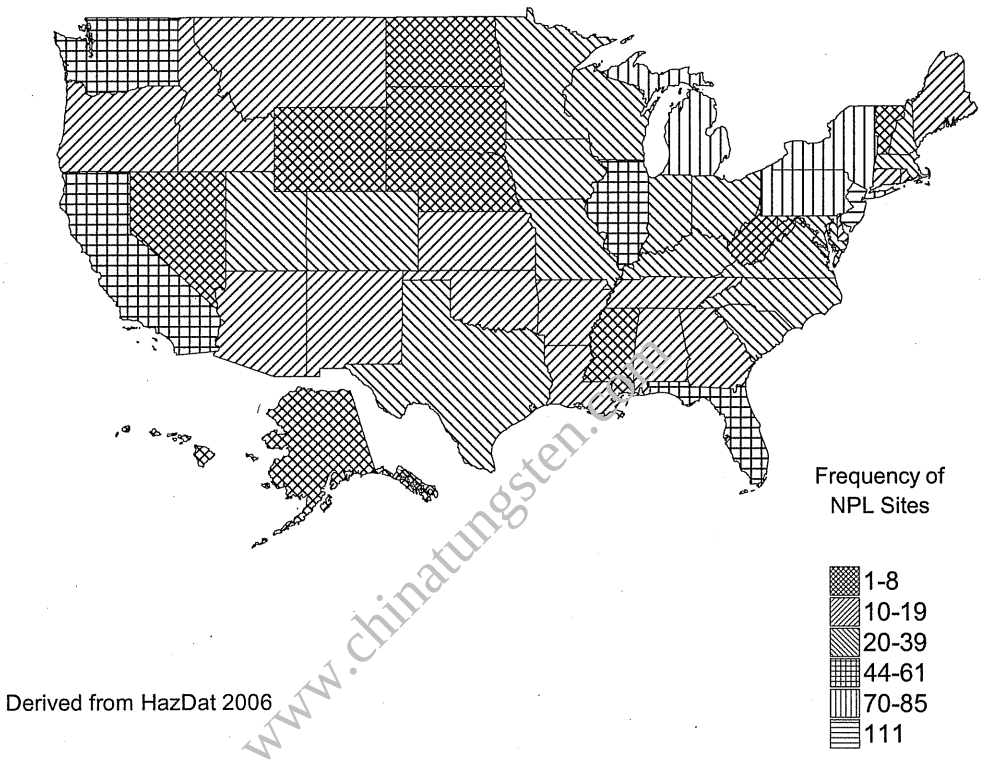
Lead is dispersed throughout the environment primarily as the result of anthropogenic activities. In the air, lead is in the form of particles and is removed by rain or gravitational settling. The solubility of lead compounds in water is a function of pH, hardness, salinity, and the presence of humic material. Solubility is highest in soft, acidic water. The sink for lead is the soil and sediment. Because it is strongly adsorbed to soil, it generally is retained in the upper layers of soil and does not leach appreciably into the subsoil and groundwater. Lead compounds may be transformed in the environment to other lead compounds; however, lead is an element and cannot be destroyed. Anthropogenic sources of lead include the mining and smelting of ore, manufacture of lead-containing products, combustion of coal and oil, and waste incineration. Many anthropogenic sources of lead, most notably leaded gasoline, lead-based paint, lead solder in food cans, lead-arsenate pesticides, and shot and sinkers, have been eliminated or strictly regulated due to lead's persistence and toxicity. Because lead does not degrade, these former uses leave their legacy as higher concentrations of lead in the environment.

Plants and animals may bioconcentrate lead, but lead is not biomagnified in the aquatic or terrestrial food chain.

The general population may be exposed to lead in ambient air, foods, drinking water, soil, and 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 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

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



exposures have occurred 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 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 gradually phased out the use of lead alkyls in gasoline, and by 1990, auto emissions accounted for only 33% of the annual lead emissions (EPA 1996b). Use of lead additives in motor fuels was totally banned after December 31, 1995 (EPA 1996a). 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.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005i). This is not an exhaustive list. Manufacturers, processors, and users of lead and lead compounds are required to report information to the TRI only if they employ 10 or more full-time employees; if they operate in certain industrial sectors; and if their facility produces, imports, processes, or uses at least 100 pounds of lead, (exclusive of that contained in stainless steel, brass, or bronze alloys), or lead compounds in a calendar year. Prior to 2001, the threshold for reporting was much higher for persistent, bioaccumulative, toxic (PBT) chemicals such as lead. Facilities then had to report only when they manufactured, imported, or processed >25,000 pounds or used >10,000 pounds of lead or lead compounds in a calendar year. This higher threshold still applies to lead contained in

stainless steel, brass, or bronze alloys. The threshold for lead is determined using the weight of the metal, whereas the threshold for lead compounds is determined by the weight of the entire compound. Prior to 1998, only facilities classified within the SIC codes 20–39 (Manufacturing Industries) were required to report. After 1998, the industrial sector required to report was enlarged to include other industrial sectors, such as metal mining, coal mining, electrical utilities, and hazardous waste treatment (EPA 2001a).

While lead is a naturally-occurring chemical, it is rarely found in its elemental form. It occurs in the Earth's crust primarily as the mineral galena (PbS), and to a lesser extent as anglesite ($PbSO_4$) and cerussite ($PbCO_3$). Lead minerals are found in association with zinc, copper, and iron sulfides as well as gold, silver, bismuth, and antimony minerals. It also occurs as a trace element in coal, oil, and wood. Typical lead concentration in some ores and fuels are: copper ores, 11,000 ppm; lead and zinc ores, 24,000 ppm; gold ores, 6.60 ppm; bituminous coal, 3–11 ppm; crude oil, 0.31 ppm; No. 6 fuel oil, 1 ppm; and wood, 20 ppm (EPA 2001a).

Lead released from natural sources, such as volcanoes, windblown dust, and erosion, are minor compared with anthropogenic sources. Industrial sources of lead can result from the mining and smelting of lead ores, as well as other ores in which lead is a by-product or contaminant. In these processes, lead may be released to land, water, and air. Electrical utilities emit lead in flue gas from the burning of fuels, such as coal, in which lead is a contaminant. Because of the large quantities of fuel burned by these facilities, large amounts of lead can be released. For example, using the EPA emission factor for lignite coal, $4.2x10^{-4}$ pounds of lead/ton of coal, a boiler burning a million pounds of lignite coal will release 420 pounds of lead into the atmosphere (EPA 2001a). Many of the anthropogenic sources of lead have been eliminated or phased out because of lead's persistence, bioaccumulative nature, and toxicity. These include, most notably, lead in gasoline, lead-based paint, and lead-containing pesticides, and lead in ammunition and sinkers. Because lead does not degrade, these former uses leave their legacy as higher concentrations of lead in the environment.

According to the TRI, in 2004, a total of 12,112,037 pounds of lead were released to the environment from 4,347 reporting facilities (TRI04 2006). Another 4,767,316 pounds were transferred off-site. Table 6-1 lists amounts of lead released from these facilities grouped by state. In addition, a total of 405,285,570pounds of lead compounds were released to the environment from 4,294 reporting facilities and another 20,809,590 pounds were transferred off-site (TRI04 2006). Table 6-2 lists amounts of lead

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Lead[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	7	292	2	0	39,203	13	39,497	13	39,510
AL	115	11,377	625	39	1,857,435	904	1,800,604	69,778	1,870,382
AR	52	2,642	193	0	56,661	35,279	46,126	48,649	94,775
AZ	77	652	6,112	0	56,020	43,185	55,184	50,786	105,969
CA	290	2,208	1,669	359	35,634	47,985	31,094	56,761	87,855
CO	49	424	59	143	115,238	22,117	94,378	43,604	137,981
CT	69	286	36	0	138	11,454	311	11,603	11,914
DC	2	0	0	0	403	0	0	403	403
DE	3	3	1	0	0	0	4	0	4
FL	156	4,640	371	0	152,932	10,593	152,988	15,548	168,536
GA	123	3,786	150	0	78,219	37,659	76,673	43,140	119,813
GU	1	120	0	0	0	0	120	0	120
HI	10	784	1	1	125,691	1,681	126,477	1,682	128,159
IA	76	3,999	446	140	5,939	50,150	8,280	52,395	60,674
ID	20	580	29	0	4,397,661	831	4,398,246	855	4,399,101
IL	220	20,391	1,713	401	156,127	14,987	22,120	171,499	193,619
IN	191	6,973	1,411	176	784,642	825,635	19,525	1,599,312	1,618,837
KS	45	5,123	64	99	42,320	5,206	26,399	26,413	52,812
KY	85	13,914	377	1,250	84,887	101,249	91,819	109,859	201,678
LA	59	1,386	1,913	279	2,400	795	4,914	1,858	6,772
MA	103	722	34	0	3,200	12,226	2,188	13,994	16,182
MD	38	587	34	0	11,669	2,731	10,399	4,622	15,021
ME	18	516	159	0	1,386	15	1,363	714	2,077
MI	182	8,600	526	0	101,768	11,209	14,625	107,478	122,103
MN	97	629	519	0	3,058	800	630	4,376	5,006
MO	90	2,581	262	157	142,943	1,733	125,168	22,508	147,676
MS	57	1,986	393	27	44,196	449	43,659	3,392	47,050
MT	7	366	11	0	332,755	669	332,252	1,549	333,801
NC	141	2,197	563	0	223,107	8,242	212,004	22,104	234,108
ND	10	406	474	0	8,313	200	4,470	4,922	9,392
NE	54	6,788	70	0	5,155	5,535	7,692	9,855	17,547
NH	34	364	121	0	2,171	3,449	644	5,461	6,105
NJ	73	1,612	169	0	1,299	37,414	2,921	37,573	40,494
NM	17	90	0	0	32,544	3,413	32,634	3,413	36,047
NV	21	2,522	0	0	96,301	2,563	98,588	2,798	101,386
NY	169	4,296	7,241	1	26,877	38,864	18,677	58,602	77,279

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Lead[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
OH	311	21,200	6,974	28,852	2,396,501	831,963	2,294,828	990,663	3,285,490
OK	59	6,250	25	162	84,903	712	55,964	36,088	92,052
OR	54	389	17	0	198,334	1,019	198,327	1,432	199,759
PA	229	18,426	2,534	0	44,891	336,150	49,233	352,768	402,001
PR	22	41	0	0	0	420	41	420	461
RI	25	58	46	0	0	2,176	70	2,209	2,280
SC	78	6,116	492	19,107	34,974	18,570	11,829	67,430	79,259
SD	17	105	26	0	11,103	1	11,208	28	11,236
TN	107	8,958	832	198	24,456	33,552	15,650	52,346	67,996
TX	232	19,573	2,036	133,133	339,513	39,359	453,503	80,211	533,714
UT	37	539	74	0	154,967	26,984	145,376	37,189	182,565
VA	91	6,437	1,152	0	385,614	26,809	32,753	387,259	420,012
VI	2	114	0	0	426	23	516	47	563
VT	6	14	18	0	0	2,658	14	2,676	2,691
WA	76	861	1,545	0	864,384	12,312	855,186	23,917	879,102
WI	178	10,688	1,015	0	79,703	32,974	11,181	113,200	124,380
WV	42	1,538	46	0	50,653	6,245	46,684	11,798	58,482
WY	10	66	0	0	27,052	0	27,003	115	27,118
Total	4,337	215,216	42,581	184,525	13,725,870	2,711,160	12,112,037	4,767,316	16,879,353

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

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Lead Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
AK	13	11,686	792	8,493,212	141,141,748	3	149,643,055	4,387	149,647,441
AL	108	30,437	10,300	1,001	1,709,923	786,593	1,450,722	1,087,531	2,538,253
AR	71	7,871	1,744	0	174,136	192,907	137,497	239,162	376,659
AZ	60	14,142	214	0	5,510,961	9,510	5,499,714	35,144	5,534,857
CA	276	9,530	1,462	123	4,989,235	124,884	3,760,943	1,364,291	5,125,234
CO	53	6,310	820	0	6,775,795	2,753	6,577,849	207,830	6,785,679
CT	72	1,842	50,808	0	55,894	46,837	2,552	152,828	155,380
DE	13	2,930	1,161	0	72,923	16,714	31,159	62,568	93,728
FA	110	23,635	2,624	0	505,968	21,557	444,097	109,687	553,784
FL	133	19,762	2,502	0	439,521	15,659	337,497	139,948	477,445
GU	3	4	1	0	4	0	10	0	10
HI	13	3,902	22	11	1,304	206	3,935	1,510	5,444
IA	62	19,705	1,919	3	250,083	104,373	54,916	321,167	376,084
ID	31	4,652	682	0	2,432,819	3,756	2,421,469	20,439	2,441,908
IL	223	27,715	6,780	1,139	2,252,474	166,469	1,752,530	702,047	2,454,577
IN	183	54,164	7,662	1,202	3,736,474	1,318,189	1,273,823	3,843,869	5,117,691
KS	54	11,010	309	0	104,267	83,899	100,975	98,510	199,485
KY	82	22,586	1,937	40	908,615	41,149	865,666	108,660	974,327
LA	76	16,143	26,110	0	1,104,894	3,061	948,072	202,136	1,150,209
MA	135	4,088	243	0	304,852	38,052	9,549	337,686	347,234
MD	38	4,202	1,873	9	261,495	56,339	235,657	88,260	323,918
ME	29	1,346	1,373	0	12,061	9,811	11,991	12,601	24,592
MI	136	23,248	9,161	80	711,353	94,813	296,369	542,284	838,653
MN	74	9,093	948	0	254,293	132,931	89,773	307,491	397,264
MO	111	181,782	10,114	0	28,889,783	3,098	27,669,492	1,415,285	29,084,777
MP	3	1	0	0	1	0	2	0	2
MS	59	14,205	1,624	254,800	112,794	3,928	330,719	56,634	387,352
MT	20	6,339	393	3,098	15,029,303	851	15,030,211	9,772	15,039,984
NC	154	19,778	2,287	13	452,288	365,461	422,797	417,030	839,828
ND	10	7,745	14	66	130,165	80	86,306	51,764	138,070
NE	28	4,918	135	0	52,093	32,663	52,489	37,321	89,810
NH	31	490	71	0	55,741	911	743	56,469	57,213
NJ	98	7,008	8,201	0	496,387	222,789	153,985	580,400	734,385
NM	22	1,252	881	0	596,749	17,894	583,007	33,768	616,776
NV	32	4,073	541	4	105,668,551	5,296	105,667,734	10,731	105,678,465
NY	129	16,840	9,737	0	744,058	168,013	687,725	250,922	938,648
OH	263	60,447	13,753	15,937	1,905,688	568,837	801,235	1,763,427	2,564,663
OK	47	54,622	363	401	290,227	73,571	338,813	80,372	419,184
OR	61	2,037	3,165	0	55,083	530	11,787	49,027	60,814

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use Lead Compounds[a]

		Reported amounts released in pounds per year[b]							
							Total release		
State[c]	RF[d]	Air[e]	Water[f]	UI[g]	Land[h]	Other[i]	On-site[j]	Off-site[k]	On- and off-site
PA	246	69,995	6,769	987	3,479,169	1,229,509	1,714,804	3,071,625	4,786,428
PR	18	2,948	18	0	394	2,936	3,028	3,268	6,296
RI	24	38	67	1	3,701	805	44	4,568	4,612
SC	84	16,757	2,239	0	354,464	28,224	255,034	146,649	401,683
SD	17	1,936	762	0	1,446,132	386	1,446,330	2,884	1,449,215
TN	108	16,735	4,380	0	8,765,194	35,448	8,635,566	186,192	8,821,758
TX	236	45,373	5,779	1,089	2,492,627	54,544	2,015,842	583,571	2,599,413
UT	36	14,630	277	0	59,676,521	298,324	59,596,136	393,616	59,989,752
VA	98	14,524	4,397	558	381,233	35,396	267,225	168,883	436,108
VI	2	389	0	0	0	0	389	0	389
VT	10	25	50	0	2,712	7,136	41	9,882	9,923
WA	87	6,775	6,896	0	2,788,908	792,545	2,759,956	835,168	3,595,124
WI	136	11,702	2,165	0	389,469	56,300	110,108	349,527	459,636
WV	59	4,743	1,970	54	810,502	9,651	597,011	229,908	826,919
WY	17	5,336	20	0	112,415	309	97,189	20,891	118,080
Total	4,294	923,449	218,510	8,773,829	408,893,442	7,285,930	405,285,570	20,809,590	426,095,160

[a]The TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.
[b]Data in TRI are maximum amounts released by each facility.
[c]Post office state abbreviations are used.
[d]Number of reporting facilities.
[e]The sum of fugitive and point source releases are included in releases to air by a given facility.
[f]Surface water discharges, waste water treatment0(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).
[g]Class I wells, Class II0V wells, and underground injection.
[h]Resource Conservation and Recovery Act (RCRA) subtitle C landfills; other on0site landfills, land treatment, surface impoundments, other land disposal, other landfills.
[i]Storage only, solidification/stabilization (metals only), other off0site management, transfers to waste broker for disposal, unknown
[j]The sum of all releases of the chemical to air, land, water, and underground injection wells.
[k]Total amount of chemical transferred off0site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI04 2006 (Data are from 2004)

compounds released from these facilities grouped by state. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Lead has been identified in a variety of environmental media (air, surface water, groundwater, soil, and sediment) collected at 1,272 of the 1,684 current and former NPL hazardous waste sites (HazDat 2006). Lead is the most frequently found metal at hazardous waste sites (Reed et al. 1995).

6.2.1 Air

According to the TRI, in 2004, a total of 215,216 pounds of lead were released to air from 4,337 reporting facilities (TRI04 2006). Table 6-1 lists amounts of lead released from these facilities grouped by state. In addition, a total of 923,449 pounds of lead compounds were released to air from 4,294 reporting facilities (TRI04 2006). Table 6-2 lists amounts of lead compounds released from these facilities grouped by state. Releases of lead and lead compounds to air constitute, respectively, 1.78 and 4 0.23% of all on-site releases. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Lead has been identified in air samples collected at 96 of the 1,272 NPL hazardous waste sites where it was detected in some environmental medium (HazDat 2006).

The emissions of lead and lead compounds to the atmosphere reported to TRI has declined from 2.8 million pounds in 1988 to about 1.1 million pounds in 2004 as new industries were added to TRI reporting requirements (TRI04 2006). In 2000, before the reporting thresholds were drastically reduced, air emissions were 1.5 million pounds. In the past, transportation, particularly automotive sources, were the major contributor to air emissions of lead. Today, industrial processes, especially metal processing, are the major sources of lead emissions to the atmosphere with the highest lead concentrations found around smelters and battery manufacturers (EPA 2003a). Based on emission estimates, EPA reports a 93% reduction in lead emissions to the atmosphere between 1982 and 2002 and a 5% reduction between 1993 and 2002. Air quality levels for lead, namely the maximum quarterly mean concentrations, declined 93% between 1983 and 2002 and 57% between 1993 and 2002. EPA estimated that 78% of emissions in 2001 were from industrial processes, 12% from transportation, and 10% from fuel combustion. It should be noted that aviation gasoline and racing fuels are not regulated for lead content and can use significant quantities of lead (EPA 2003a). Historical trends of lead emissions in the United States are provided in Table 6-3 (EPA 2007a).

Table 6-3. Historic Levels of Lead Emissions to the Atmosphere in the United States

Pounds of lead emitted annually								
1970	1975	1980	1985	1990	1995	2000	2005	2006
$4.4x10^8$	$3.2x10^8$	$1.5x10^8$	$4.6x10^7$	$1.0x10^7$	$8.0x10^6$	$4.0x10^6$	$6.0x10^6$	$4.0x10^6$

Source: EPA 2007a

EPA (2000) estimated lead emission between 1990 and 1993 from all sources, not just those covered by TRI, which is limited to certain industries. During this period, lead emissions were estimated to average 3,307 tons/year. The major contributors to these emissions were: metals processors (840 tons/year), chemical manufacturers (181 tons/year), other manufacturing operations (553 tons/year), waste disposal and recycling (270 tons/year), onroad (e.g., automobiles, trucks, buses, and motorcycles) mobile sources (418 tons/year), and nonroad (e.g., airplanes, boats, railway engines, lawnmowers, and off-road vehicles) mobile sources (778 tons/year).

A study that estimated the historical rate of atmospheric metal fluxes into Central Park Lake, New York City by analyzing sediment cores for levels of trace metals, indicated that lead fluxes were extremely high throughout the 20th century, reaching maximum values (>70 µg cm^{-2} year^{-1}) from the late 1930s to the early 1960. This occurred decades before the maximum emissions from the use of leaded gasoline (Chillrud et al. 1999). The trends closely resemble the history of solid waste incineration in the city. These results, and the widespread use of solid waste incineration during that time, suggest that this may have been the dominant source of lead in urban areas. The decline in the prevalence of small incinerators, increased recycling, and the decline in the use of lead in a variety of consumer and commercial products would indicate that atmospheric releases of lead from solid waste incineration is a much less important source of lead emissions today than it was in the past.

As indicated in Table 6-4, by 1988, transportation (i.e., automotive) emissions were no longer the dominant source of lead emitted to the atmosphere. When such emissions were prevalent, >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 (EPA 1985d). 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. In the early 1980s EPA allowed up to 0.05 g of lead in a gallon of unleaded gasoline (EPA 1982b).

In 1996, estimated mobile transportation source emissions of lead into air for the 48 contiguous states decreased from an average of 1,196 tons/year derived for 1990–1993 to 546.1 tons/year in 1996 (EPA 2000, 2001b). The estimates are based on data obtained from the 1996 National Toxics Inventory. The onroad estimate of 18.9 tons/year for 1996 was a dramatic decrease from the average estimate of

Table 6-4. National Lead Emission Estimates (in 103 Metric Tons/Year), 1979–1989

Source category	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989
Transportation	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 categories may not equal the total because of rounding.

Source: derived from EPA 1991e

418 tons/year given for 1990–1993 (EPA 2000, 2001b). Likewise, nonroad emissions decreased from an average of 778 tons/year in 1990–1993 to 527.2 tons/year in 1996. These decreases were the result of the complete phase-out of leaded gasoline in 1996. Projected estimates of lead emissions in 2007 for onroad and nonroad sources were 22.0 and 585.2 tons/year, respectively. The major onroad lead emissions in 1996 were generated from light-duty gasoline vehicles (13.9 tons/year) and light-duty gasoline trucks (5.0 tons/year). The major generators of lead emissions in 1996 from nonroad sources were airports (526.1 tons/year).

Emissions of lead from electric utility steam generating plants totaled 71.37 tons/year in 1994 (EPA 1998b). The emissions varied depending on the fuel used in the electric generating facility; coal (62 tons/year), oil (8.9 tons/year), and natural gas (0.47 tons/year). It is projected that total lead emissions from electric steam generating plants will increase to 93.08 tons/year in 2010. This increase will be due to increased demand for electric power and an increased use of coal and natural gas as fuel sources to generate electricity. Lead emissions for coal, oil, and natural powered electric steam utilities are projected to be 87, 5.4, and 0.68 tons/year, respectively, in 2010.

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 by sanding or sandblasting can result in high localized concentrations of lead dust in both indoor and outdoor air.

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).

6.2.2 Water

According to the TRI, in 2004, a total of 42,581 pounds of lead were released to water from 4,337 reporting facilities (TRI04 2006). Table 6-1 lists amounts of lead released from these facilities

grouped by state. In addition, a total of 218,510 pounds of lead compounds were released to water from, 4,294 reporting facilities (TRI04 2006). Table 6-2 lists amounts of lead compounds released from these facilities grouped by state. Releases of lead and lead compounds to water constitute, respectively, 0.35 and 0.05 % of all on-site releases. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

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).

Lead is released into surface water from lead shot and lead sinkers. A study of a shooting range in Southwestern Virginia found that the dissolved lead content of surface water ranged up to 473 ppb with the highest concentrations closest to the backstop (Craig et al. 1999). Upstream from the site the lead concentration was 0.5 ppb. In 1991, the U.S. Fish and Wildlife Service banned the use of lead shot when hunting waterfowl, such as geese or ducks, in order to avoid releasing lead directly to surface water.

Although aquatic releases of lead from industrial facilities are expected to be small with respect to emissions to land and air, 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. The age of a home or building and the type of plumbing installed will be a major factor regarding the levels of lead in drinking water (EPA 2005h). Lead-contaminated drinking water is most problematic in buildings and residences that are either very old or very new. It was not uncommon to use lead pipes for interior plumbing purposes at the start of the 20th century in the United States. Also, lead piping was often used for the service connections that join residences to public water supplies (this practice ended only recently in some localities). Plumbing installed before 1930 is most likely to contain lead pipes. In most new homes, copper pipes have replaced lead pipes and lead-free solder is used. However, lead-free means that solders and flux may not contain >0.2% lead, while pipes, pipe fittings, and well pumps may not contain >8% lead. New brass faucets and fittings can also leach lead, which is released directly into the water. Lead levels

decrease as the residence ages because as time passes, mineral deposits form a coating on the inside of the pipes, which insulates the water from the lead.

Lead has been identified in groundwater samples collected at 949 of the 1,272 NPL hazardous waste sites, and in surface water samples collected at 567 of the 1,272 NPL hazardous waste sites where it was detected in some environmental medium (HazDat 2006).

6.2.3 Soil

According to the TRI, in 2004, a total of 13,725,870 pounds of lead were released to the land, both on-site and off-site, by 4,337 reporting facilities (TRI04 2006). Table 6-1 lists amounts of lead released from these facilities grouped by state. In addition, a total of 408,893,442 pounds of lead compounds were released to land, both on-site and off-site, by 4,294 reporting facilities (TRI04 2006). Table 6-2 lists amounts of lead compounds released from these facilities grouped by state. In addition, 184,525 and 8,773,829 pounds of lead and lead compounds, respectively, were injected underground. Ninety-seven percent of lead compounds injected underground were by one facility, Kennecott Greens Creek Mining Co. in Juneau, Alaska. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

While the majority of lead releases are to land, they constitute much lower exposure risks than releases to air and water. In 1997, before new industries were added to TRI, 95% of lead and lead compound releases to land reported to TRI were from the primary metals industrial sector, primarily metal smelters. In 2004, metal mining, coal mining, electrical utilities, and Resource Conservation and Recovery Act (RCRA)/solvent recoveries (hazardous waste facilities), as well as primary metals, are the industrial sectors contributing most heavily to releases to land. Many of these facilities with large releases, such as metal mines, are located in sparsely populated areas. Hazardous waste facilities are highly regulated. Most of the lead released to land becomes tightly bound and immobile.

Lead-containing material from home and commercial use may be sent to municipal landfills. It is important to note that land is the ultimate repository for lead, and lead released to air and water ultimately is deposited in soil or sediment. For example, lead released to the air from leaded gasoline or in stack gas from smelters and power plants will settle on soil, sediment, foliage, or other surfaces. The heaviest contamination occurs near the highway, in the case of leaded gasoline, or near the facility, in the case of a power plant or smelter.

Lead has been identified in soil samples collected at 901 of the 1,272 NPL hazardous waste sites, and in sediment samples collected at 605 of the 1,272 NPL hazardous waste sites where it was detected in some environmental medium (HazDat 2006).

6.2.4 Paint

Although the sale of residential lead-based paint was banned in the United States in 1978, flaking paint, paint chips, and weathered powdered paint, which are most commonly associated with deteriorated housing stock in urban areas, remain major sources of lead exposure for young children residing in these houses, particularly for children afflicted 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 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. 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 >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 dust in air (from sanding and sandblasting) and on exposed surfaces. A study was conducted in New Orleans where power sanding is a common practice during repainting old houses and median, 90th percentile, and maximum lead concentrations in 31 study houses were 35, 126, and 257 mg/g, respectively (Mielke et al. 2001). Lead concentrations in dust and soil samples from one study of a house where the paint chips contained about 90 mg Pb/g were very high. If the house had been sanded down to bare wood, 7.4 kg of lead would have been released to the environment. 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 1988–1991, 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).

6.3 ENVIRONMENTAL FATE

6.3.1 Transport and Partitioning

In the atmosphere, non-organic compounds of lead exist primarily in the particulate form. The median particle distribution for lead emissions from smelters is 1.5 µm with 86% of the particle sizes under 10 µm (Corrin and Natusch 1977). The smallest lead-containing particulate matter (<1 µm) is associated with high-temperature combustion processes. 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, $\mu g/m^3$) 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). While lead particles from automobile emissions are quite small (<0.1 μm in diameter), they may coagulate, resulting in larger particulates (Chamberlain et al. 1979). Lead has been found in sediment cores of lakes in Ontario and Quebec, Canada far from any point sources of lead releases, suggesting that long-range atmospheric transport was occurring (Evans and Rigler 1985). However, the results reported by Allen-Gil et al. (1997) do not support the contention of long-range transport of lead from smelters in the Arctic, based on lead concentrations in sediments obtained from Arctic lakes in the United States. In fact, data summarized by Berndtsson (1993) indicate that local sources dominate the deposition of lead; lead is primarily deposited <10 kilometers from emission sources.

The amount of soluble lead 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 amount of soluble lead. The carbonate concentration is in turn dependent upon the partial pressure of carbon dioxide, pH, and temperature (EPA 1986a).

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 (NSF 1977).

The fate of lead in soil is affected by the 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). Soil samples were extracted from the Powder River Basin in Wyoming to determine the relative distribution and speciation of lead and other metals in acidic environments (Reddy et al. 1995). At near neutral pH, organic carbon-lead complexes were the predominant species in the soil water extracts. At low pH, dissolved lead in ionic form (Pb^{2+}) and ion pairs (e.g., $PbSO_4$) were the predominant species. It was concluded that the mobility of lead will increase in environments having low pH due to the enhanced solubility of lead under acidic conditions. 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 through runoff to surface water or leaching to groundwater except under acidic conditions (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, are converted to the less soluble lead sulfate either by reactions in the atmosphere or by reactions at the soil surface, thus limiting it's mobility in soil. 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 ≥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 occur in water entrapped in soil macro- and micropores (Reed et al. 1995). Lead complexes and precipitates in soil. In soil with 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 1982c). 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 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 (e.g., acid rain) (NSF 1977). Favorable conditions for leaching may be present in some soils near lead smelting and NPL sites. Tetraalkyl lead compounds, such as tetraethyl lead, are insoluble in water and would not be expected to leach in soil. However, they can be transported through a soil column when it is present in a migrating plume of gasoline (USAF 1995). In 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).

Plants and animals may bioconcentrate lead, but biomagnification is not expected. In general, the highest lead concentrations are found in aquatic and terrestrial organisms with habitats 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 and fishing (lead from spent shot or sinkers); 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 adsorption of lead to soil organic matter, the bioavailability increases as the pH and the organic matter content of the soil are reduced. Plants grown in lead-contaminated soils were shown to accumulate low levels of lead in the edible portions of the plant from adherence of dusts and translocation into the tissues (Finster et al. 2004). Thirty-two different types of fruits or vegetables were grown in urban gardens with soils containing high lead levels (27–4,580 mg/kg). Samples were harvested and washed with either water or detergents and analyzed for lead content. Only one fruiting vegetable among 52 samples contained lead levels greater than the detection limit of 10 µg/g

in the edible portion. However, 39% of the leafy vegetables and herbs had lead levels >10 μg/g in the edible shoot portion following washing of the vegetables with detergent and water (Finster et al. 2004).

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 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).

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 1,000 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 low 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 35–80 μg) correlated strongly with the concentration of lead in the soil (0–240 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.

Uptake of lead in animals may occur as a result of inhalation of contaminated ambient air or ingestion of contaminated plants. However, lead is not biomagnified in aquatic or terrestrial food chains. 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 fresh-water 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*), fresh-water 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 up in 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 found to occur. 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.

6.3.2 Transformation and Degradation

6.3.2.1 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 automobile exhaust 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 was released, 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 elemental lead and lead-sulfur compounds, $PbSO_4$, $PbO \cdot PbSO_4$, and PbS (Corrin and Natusch 1977; EPA 1986a; Spear et al. 1998). The lead emitted from the combustion of waste oil was found to be in the form of $PbCl_2$, PbO, and elemental lead (Pb^0) (Nerin et al. 1999). 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).

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 25 °C) and tetramethyl lead (26.0 mm Hg at 20 °C), 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 reactions with hydroxyl radicals during summer is approximately 5.7 hours, based on a rate constant of $6.8x10^{-11}$ cm^3/molecule - sec (Nielsen et al. 1991). The half-life for tetramethyl lead is about 65 hours based on a rate constant of $5.9x10^{-12}$ cm^3/molecule - sec. In the winter, both compounds have half-lives of up to several days since the concentration of atmospheric hydroxyl radicals is lower than in summer months (DeJonghe and Adams 1986). Trialkyl compounds occur almost entirely in the vapor phase and have life-times in air that are 3 times longer than for the corresponding tetraalkyl compounds (Hewitt and Harrison 1986, 1987). 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 would be the major process for removing these compounds from air. Dialkyl lead compounds would be removed from the air 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). Monitoring studies in England indicate that urban air advected to rural areas may contain up to 5% of 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).

6.3.2.2 Water

The chemistry of lead in aqueous solution is highly complex because this element can be found in multiple forms. Lead has a tendency to form compounds of low solubility with the major anions found in natural waters. The amount of lead dissolved in surface waters is dependent on the pH and the dissolved salt content of the water. The maximum solubility of lead in hard water is about 30 µg/L at pH>5.4 and the maximum solubility of lead in soft water is approximately 500 µg/L at pH>5.4 (EPA 1977). 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 pH<5.4, the formation of lead sulfate limits the concentration of soluble lead in water, while at pH>5.4, the formation of lead carbonates limits the amount of soluble lead (EPA 1979). 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 1979).

The speciation of lead was found to differ in fresh water and seawater. In fresh water, lead may partially exist as the divalent cation (Pb^{2+}) at pHs below 7.5, but complexes with dissolved carbonate to form insoluble $PbCO_3$ under alkaline conditions (Long and Angino 1977). Even small amounts of carbonate ions formed in the dissolution of atmospheric CO_2 are sufficient to keep lead concentrations in rivers at the 500 µg/L solubility limit (EPA 1979). Lead chloride and lead carbonate are the primary complexes formed in seawater (Long and Angino 1977). The speciation of lead in water is also dependent on the presence of other ligands in water. Lead is known to form strong complexes with humic acid and other organic matter (Denaix et al. 2001; Gao et al. 1999; Guibaud et al. 2003). Lead-organic matter complexes are stable to a pH of 3 with the affinity increasing with increasing pH, but decreasing with increased water hardness (EPA 1979). In seawater, there is the presence of lead complexed to Fe-Mn oxides, which is due to the content of these oxides in seawater (Elbaz-Poulichet et al. 1984). Sorption of lead to polar particulate matter in freshwater and estuarine environments is an important process for the removal of lead from these surface waters. The adsorption of lead to organic matter, clay and mineral surfaces, and coprecipitation and/or sorption by hydrous iron and manganese oxides increases with increasing pH (EPA 1979).

In water, tetraalkyl lead compounds, such as tetraethyl lead and tetramethyl lead, are subject to photolysis and volatilization. Degradation proceeds from trialkyl species to dialkyl species, and eventually to inorganic lead oxides. Removal of tetraalkyl lead compounds from seawater occurs at rates that provide half-lives measurable in days (DeJonghe and Adams 1986). Some of the degradation products include trialkyl lead carbonates, hydroxides, and halides. These products are more persistent than the original tetraalkyl lead compounds.

6.3.2.3 Sediment and Soil

Lead in its naturally-occurring mineral forms is a very minor component of many soils in the United States. Additional sources of lead are incorporated to soils from atmospheric wet and dry deposition. Since the ban on leaded gasoline, the major source of lead emissions to the environment arise from industrial processes (EPA 1996b). 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 most likely exists primarily as $PbSO_4$ and $PbCO_3$ and is deposited onto soil as lead sulfates and lead carbonates. Organic tetraalkyl lead compounds, once used extensively in motor fuel, are emitted from automobiles primarily in the form of lead bromochloride, which is ultimately transformed to lead sulfate. The organolead

compounds also 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, resulting in a complex variety of lead compounds. The speciation of lead in soils is dependent upon the properties of the soil. In a calcareous soil, PbSO4 and PbCO3 were shown to account for <5% of the total lead content, whereas in road side dust, $PbSO_4$, elemental lead, Pb_3O_4, $PbO{\cdot}PbSO_4$, and $2PbCO_3{\cdot}Pb(OH)_2$ were present in significant quantities (Chaney et al. 1988). It was also reported that after adding 3,000–4,000 mg/kg of lead in the form of PbSO4, subsequent extractions revealed that the lead sulfate was rapidly transformed to other lead compounds in the soil (Chaney et al. 1988).

Nearly all forms of lead that are released to soil from anthropogenic sources, such as $PbSO_4$, $PbCO_3$, PbS, $Pb(OH)_2$, $PbCrO_4$, and PbClBr, are transformed by chemical and biotic processes to adsorbed forms in soil (Chaney et al. 1988). The transformation process involves the formation of lead complexes with binding sites on clay minerals, humic acid and other organic matter, and hydrous iron oxides (Chaney et al. 1988; Chuan et al. 1996; Sauve et al. 1997). The ability of soils to bind lead is dependent on soil pH and the cation exchange capacity of the soil components (e.g., hydrous iron oxides on clay and organic matter) (Chaney et al. 1988; EPA 1986a). Only a small fraction (0.1–1%) of lead appears to remain water-soluble in soil (Khan and Frankland 1983). The solubility of lead in soil is dependent on pH, being sparingly soluble at pH 8 and becoming more soluble as the pH approaches 5 (Chuan et al. 1996). Between pH 5 and 3.3, large increases in lead solubility in soil are observed. These changes in lead solubility appear to correlate with the pH-dependent adsorption and dissolution of Fe-Mn oxyhydroxides. In addition to pH, other factors that influence lead solubility in soil are total lead content and the concentrations of phosphate and carbonate in soils (Bradley and Cox 1988; Ge et al. 2000; Pardo et al. 1990; Sauve et al. 1997).

Since the ban on the use of leaded gasoline, atmospheric lead deposition to soil has decreased considerably. However, the deposited organolead compounds and their transformation products remain in the soil. Limited data indicate that tetraethyl and tetramethyl lead are converted into water-soluble lead compounds in soil through microbial metabolism (Ou et al. 1994). Using an Arredondo fine sand from Florida (92% sand, 7% silt, 1% clay, 11.8 g/kg organic carbon, pH 5.5), tetraethyl lead was shown to degrade sequentially to monoionic triethyl lead, diionic diethyl lead, and eventually Pb^{+2} (Ou et al. 1994). Experiments were conducted using non sterilized and autoclaved soil samples. The presence of monoionic triethyl lead and diionic diethyl lead was generally lower in the autoclaved samples, suggesting that both abiotic and biotic mechanisms are responsible for the degradation of tetraethyl lead. At the end of a 28-day incubation period, no tetraethyl lead was present in the soil; however, there were

significant quantities of monoionic triethyl lead and diionic diethyl lead, which suggest that the degradation products are more persistent than the original species. Although tetraethyl and tetramethyl lead are not expected to leach significantly through soil, their more water-soluble metabolites may be subject to leaching (EPA 1985a).

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). However, Wang et al. (1995) observed that lead migration in forest soils is slowed considerably due to a decrease in solubility when lead moves from the soil surface horizon to streams. Their results suggest that lead is effectively trapped in the subsurface soil horizons, which may greatly reduce its release to streams.

Lead content in plants is largely the result of atmospheric deposition. This is due to the strong retention of particulate matter on plant surfaces that is difficult to remove through washing (EPA 1977). Some plants are capable of taking up lead from soil through their root systems, although this uptake does not appear to be appreciable (IARC 1980; Nwosu et al. 1995). The distribution of lead in plants is mainly in the roots and much less in the stems or leaves (Deng et al. 2004; Nan and Cheng 2001). Eventually, the lead will be returned to soil when these plants decay unless they are harvested (to possibly enter the food chain) or removed (EPA 1986a).

6.4 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. Concentrations of lead in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. 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. The analytical methods available for monitoring lead in a variety of environmental media are detailed in Chapter 7.

6.4.1 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. Lead levels 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. Due to decreases in lead emissions to the atmosphere from automobiles, the level of lead in air has declined significantly over the past 3 decades. Monitoring data from a composite of 147 sampling sites throughout the United States indicated 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 1986a, 1989e). Between 1979 and 1983, 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 >80%. This reduction resulted primarily from the decreased use of leaded gasoline and the use of more efficient emission controls on stationary lead 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 3 of the 12 sites are thought to be 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 1996b). Data from the EPA National Air Quality Monitoring Program indicated that the 2002 average air quality concentration for lead is about 94% lower than in the early 1980s, with a mean atmospheric concentration below 0.05 μg/m^3 in 2002 (EPA 2005k). 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 1990). This decrease was undoubtedly caused by decreased use of leaded gasoline in the period leading up to its total ban after December 1995. Composite urban air concentrations of lead for 1989 and 1991 were 0.11 and 0.08 μg/m^3 (EPA 1996b). Although lead concentration in urban air continues 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 1996b).

Concentrations of lead in ambient air that result from emission, both mobile and stationary, have been estimated to average 0.0058 μg/m^3 in 1996, while the concentration of lead attributed to mobile sources alone was 0.0035 μg/m^3 (EPA 2001a).

Lead concentrations in air and dust in the indoor environment were measured in residential homes as part of the National Human Exposure Assessment Survey (NHEXAS) in EPA Region V (Indiana, Illinois, Michigan, Minnesota, Ohio, and Wisconsin). Mean (±1 standard deviation [SD]) and median concentrations of lead in indoor air from 213 residences were 15.2 ng/m^3 (37.6 ng/m^3) and 6.17 ng/m^3, respectively, with a maximum value of 293.5 ng/m^3 (Bonanno et al. 2001). The median lead concentration in outdoor air was 8.84 ng/m^3 (Clayton et al. 2002). Lead concentrations were higher in households where one or more residents smoked indoors (mean concentration of 21.8 ng/m^3) as compared to households with nonsmoking residents (mean concentration of 7.79 ng/m^3) (Bonanno et al. 2001). In dust collected from the living areas of 238 residences, the mean (±1 SD) and median lead concentrations were 467.4 μg/g (2,100 μg/g) and 131.6 μg/g, respectively, with a maximum value of 30,578 μg/g. Dust samples collected from window sills had mean (±1 SD) and median lead concentrations of 987 μg/g (2,723 μg/g) and 207.5 μg/g, respectively, with a maximum value of 21,120 μg/g. For both indoor air and dust measurements, higher concentrations of lead were correlated with dilapidated and suburban homes.

In another analysis of the NHEXAS EPA Region V data, Pellizzari et al. (1999) looked at potential differences in lead concentrations in indoor air and personal air exposures between minorities (e.g., Hispanics and African-Americans) and nonminorities (e.g., Caucasian). Some differences were noted in the mean (±1 SD) lead concentrations between minorities of 57 ng/m^3 (±24 ng/m^3) and nonminorities of 22 ng/m^3 (±3.4 ng/m^3) in personal air exposures, although the differences were not significant (p=0.147). Similarly, differences were noted between minorities (26±12 ng/m^3) and nonminorities (13±2.6 ng/m^3) in indoor air, although these too were not significantly different (p=0.266). When the age of the home was

considered in the analysis, it was found that lead concentrations were significantly (p=0.036) higher in homes built before 1940 than in homes built between 1960 and 1979, with mean (±1 SD) values of 46 ng/m^3 (±1.6 ng/m^3) and 13 ng/m^3 (±2.1 ng/m^3), respectively. The lead concentrations measured in indoor air in homes built before 1940 were not significantly different from mean (±1 SD) lead concentrations of 22 ng/m^3 (±5.1 ng/m^3) and 23 ng/m^3 (±5.1 ng/m^3) measured in indoor air in homes built between 1940 and 1959 and between 1980 and 1995, respectively.

6.4.2 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). The median lead level in natural river water is 5 µg/L, with a range of 0.6–120 µg/L (Bowen 1966). Lead levels in seawater are estimated as 0.005 µg/L (EPA 1982c). Lead concentrations in surface water are higher in urban areas than in rural areas (EPA 1982c). Using the EPA Storage and Retrieval (STORET) database, from January 1, 2005 to May 16, 2005, lead had been detected in surface water in Washington, Utah at concentrations of 20.5 and 142 µg/L and surface water from Salt Lake City, Utah at 7.75 µg/L (EPA 2005j). Lead was not detected above the detection limits in 224 other surface water samples obtained from various locations in Utah and Iowa over the sampling period (EPA 2005j).

Urban storm water runoff is an important source of lead entering receiving waterways. Lead is found in building material (brick, concrete, painted and unpainted wood, roofing, and vinyl), and automotive sources (brakes, used oil), which contribute to runoff (Davis et al. 2001). The largest contributing sources were siding and roofing.

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 >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 1986a, 1989e); however, it was

estimated that in 1988 the average lead content of drinking water decreased to 17 µg/L (Cohen 1988). In 1986, the Safe Drinking Water Act Amendments banned the use of lead solder or flux containing >0.2% lead and the use of lead pipes or fittings that contained >8% lead (EPA 1986a, 1989e).

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 <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 <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 1989d).

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). In the NHEXAS study that was conducted during 1995–1996, lead concentrations were measured in tap drinking water (flushed for 15 minutes) taken from 82 homes in Arizona (O'Rourke et al. 1999), 441–444 homes in EPA Region V (Thomas et al. 1999), and 381 homes in Maryland (Ryan et al. 2000). Median lead concentrations of 0.4, 0.37, and 0.33 µg/L were determined in the Arizona, EPA Region V, and Maryland regional studies, respectively. Mean values (±1 SD) of 0.84 µg/L (±1.8 µg/L) and 1.08 µg/L (±2.01 µg/L) were calculated for the EPA Region V and Maryland studies, respectively, and are much lower than the mean concentrations of lead in drinking water determined in previous EPA estimates.

According to EPA's National Compliance Report for calendar year 1998 (EPA 1999), 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 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 >10% of tap water samples.

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. Lead concentrations in tap water were found to vary depending on the age of nine homes in New Jersey. In homes built in the 1980s, median lead concentrations in the first-draw sample were higher (17.9 µg/L) than in first-draw samples (1.86 µg/L) taken from homes built in the 1970s (Murphy and Hall 2000). Leaching of lead from kitchen plumbing fixtures was given as the reason for the high lead concentrations in the first-draw samples. An additional water draw (>2 L) found decreased lead concentrations in tap water for all homes. However, the median concentration of lead in samples taken from homes built in the 1980s was higher (2.45 µg/L) than in samples taken from 1970s homes (0.14 µg/L). The lead concentrations in these higher volume samples are attributed to lead leaching from solder joints in basement piping and the water meter on the public water service line that may be more prevalent in the more recently built homes.

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 1986b).

6.4.3 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 1982c; Fitchko and Hutchinson 1975), and concentrations of lead in coastal sediments range from 1 to 912 mg/kg with a mean value of 87 mg/kg (EPA 1982c; 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 1982c). More current data obtained from the EPA STORET database (from January 1, 2004 to May 16, 2005), showed that lead has been detected in sediment samples from Honolulu, Hawaii (0.75–6.2 mg/kg), various locations of South Carolina (<1–21 mg/kg), Dade County, Florida (4.7–17.9 mg/kg), and various locations in Tennessee (6–50 mg/kg) (EPA 2005k). Surface sediment concentrations in Puget Sound ranged from 13 to 53 mg/kg (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). Local sources of lead releases can also contribute significantly to lead content in sediments (Gale et al. 2004). For example, lead concentrations in sediments located near mines and or sites containing mine tailings in the old lead belt of Missouri were greatly elevated, 10,550–12,400 mg/kg sediment (dry weight) compared to unaffected sediments (72–400 mg/kg dry weight) (Gale et al. 2002).

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 >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 <50 and 58 µg/g, respectively. These data suggest that lead-contaminated soil is a major source of lead exposure in urban areas (Mielke 1993). As would be expected, soils in elementary school properties were also found to have the same pattern of lead levels as the soils in the surrounding residences. Lead concentrations in soils collected from inner-city schools in New Orleans were higher (median

concentration of 96.5 μg/g) than soils collected from mid-city (30.0 μg/g) and outer-city (16.4 μg/g) elementary schools (Higgs et al. 1999).

Studies conducted in Maryland and Minnesota indicate that within large, light-industrial, urban settings such as Baltimore, the highest soil lead levels generally occur near inner-city areas, especially where high traffic flows have long prevailed (Mielke et al. 1983, 1984/1985, 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 had been significantly reduced, found that median soil lead levels taken from the foundations of homes, in yards, and adjacent to the street were 700, 210, 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 suggested 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 as high as 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 >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" (MPCA 1987).

Lead was analyzed in dust wipes and soil samples from 67 public housing projects containing 487 dwelling units across the United States (Succop et al. 2001). A total of 5,906 dust wipes and 1,222 soil samples were included in the data set. The median soil levels were 194 ppm near the foundation, 177 ppm near the walkways, and 145 ppm elsewhere in the yard. The maximum level, 3,900 ppm, was found in a foundation sample. Median dust lead loading from kitchens, living rooms, and two children's bedrooms were 151, 936, and 8,560 μg m^{-2} for floor window sills and window troughs, respectively. Thirteen percent of the floor samples and 30% of the window sill samples from the rooms exceeded the HUD Interim Dust Lead Standards of 431 and 2,690 μg m^{-2} for floor and window sill samples, respectively.

Blood lead levels (PbBs) in children have been shown to correlate with lead concentration in soils in urban areas. In a study of children in New Orleans, Mielke et al. (1999) found that those living in areas classified as high (median soil lead concentrations >310 μg/kg) and low (median soil lead concentrations <310 μg/kg) metal census tract regions correlated well with median PbB above and below 9 μg/dL, respectively. In an analysis of data collected in an ATSDR study of children living near four NPL sites, it was concluded that a PbB of 5.99 μg/dL could be predicted for children exposed to soil lead levels of 500 mg/kg (Lewin et al. 1999). However, there was a high degree of uncertainty and variability associated with the predicted correlation between blood and soil lead levels, suggesting the contribution of other factors to PbB, such as lead levels in household dust, interior paint, and drinking water.

In a study of associations between soil lead levels and childhood blood lead levels (PbBs) in urban New Orleans and rural Lafourche Parish in Louisiana, childhood PbBs appeared more closely associated with soil lead levels than with age of housing. In the study, over 2,600 lead-containing soil 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 lead-containing soil levels were associated with new housing, but census tracts with high median lead-containing soil levels were split evenly between old and new housing. The same pattern was also observed for childhood PbBs. High lead-containing soil levels were associated with high PbB, and low lead-containing soil levels were 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 >9 μg/dL and no indication of a statistical association between median PbB and either median lead levels in soil or age of housing (Mielke et al. 1997a).

In the state of Maine, soil samples taken from areas where the risk of lead contamination was considered high (within 1–2 feet of a foundation of a building >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). Environmental health studies conducted near four NPL sites measured mean concentrations of lead in soil ranging from 317 to 529 mg/kg, and mean concentrations of lead in dust ranging from 206 to 469 mg/kg (Agency for Toxic Substances and Disease Registry 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/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 1986b).

6.4.4 Paint

Weathering of lead-based paint can contribute to the lead content of dust and soil. A 1974 study indicated that elevated PbBs 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 (MPCA 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.

6.4.5 Other Sources

Concentrations of lead (wet weight basis) in samples of 11 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); and tomato (0.002).

Lead has been detected in a variety of foods. Lead may be introduced into food through uptake from soil into plants or atmospheric deposition onto plant surfaces, during transport to market, processing, and kitchen preparation (EPA 1986a). In the FDA Total Diet Study (TDS) 1991–1996, food was purchased 4 times/year from each of four geographic regions of the United States and a market basket consisting of about 260 foods from three representative cities within the geographical region analyzed for different elements, including lead (Capar and Cunningham 2000). Lead was below the limit of quantitation in all TDS food in the following food categories: milk and cheese; eggs; meat, poultry, and fish; legumes and nuts; grain and cereal products; vegetables; mixed dishes and meals; desserts; snacks; fats and dressings; and infant and junior foods. Only five products had quantifiable concentrations of lead, namely: canned peaches (0.032 mg/kg), canned pineapple (0.013 mg/kg), canned fruit cocktail (0.031 mg/kg), sweet cucumber pickles (0.036 mg/kg), and dry table wine (0.023 mg/kg). Typical concentrations of lead in various foods are shown in Table 6-5 for the TDS 1991–1996. Results of a previous FDA TDS in which samples were collected in 27 cities between October 1980 and March 1983 are shown for comparison (Gartrell et al. 1986a).

Other factors such as absorption of lead from cooking water and cookware can influence the amount of lead in cooked vegetables. Ceramic dishes may contain lead in their glazes, and lead in glass has been shown to leach into wine. The degree to which lead is released from food once it is consumed also influences a person's uptake of lead.

A survey conducted in five Canadian cities during 1986–1988 in which food was purchased from retail stores and analyzed for lead in composite samples (n=756), determined the lead levels in 11 food categories as well as the average dietary intake of different population groups (Dabeka and McKenzie

Table 6-5. Lead Levels in Various Food Categories

Food category	Mean concentration (µg/g)	
	TDS 1980–1982a	TDS 1991–1996b
Dairy products	0.006	
Milk and cheese		<0.02–<0.05
Eggs		<0.03
Meat, fish, and poultry	0.016	nd–<0.05
Grain and cereal products	0.023	nd–<0.05
Vegetables	0.010–0.041	nd–<0.05
Legumes and nuts	0.124	nd–<0.05
Fruits	0.046–0.060	nd–0.032
Mixed dishes and meals		nd–<0.04
Desserts		nd–<0.04
Snacks		<0.05
Oils, fats, shortenings, and dressings	0.017	nd–<0.04
Sugar, adjuncts, condiments, and sweeteners	0.028	<0.03–0.036
Infant and junior foods		nd–<0.04
Beverages	0.010	nd–0.0.023

[a]Gartrell et al. 1986b
[b]Capar and Cunningham 2000

nd = not detectable (<0.008 µg/g); TDS = Total Dietary Study

1995). Results of this study are found in Table 6-6. The lead level in all of the foods ranged from <0.4 to 523.4 ng/g with a mean of 23.2 ng/g for all food categories. The highest mean Pb levels were found in canned luncheon meats (163 ng/g), canned beans (158 ng/g), canned citrus fruit (126 ng/g), and canned peaches (133 ng/g). In canned foods, mean Pb levels decreased from 73.6 ng/g in 1985 to 46 ng/g in 1988, at which time it was estimated that 97–99% of Canadian canned foods were in lead-free cans. 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). A survey conducted in five Canadian cities during 1986–1988 in which food was purchased from retail stores and analyzed for lead in composite samples (n=756), determined the lead levels in 11 food categories as well as the average dietary intake of different population groups (Dabeka and McKenzie 1995). Results of this study are found in Table 6-6. The lead level in all of the foods ranged from <0.4 to 523.4 ng/g with a mean of 23.2 ng/g for all food categories. The highest mean Pb levels were found in canned luncheon meats (163 ng/g), canned beans (158 ng/g), canned citrus fruit (126 ng/g), and canned peaches (133 ng/g). In canned foods, mean Pb levels decreased from 73.6 ng/g in 1985 to 46 ng/g in 1988, at which time it was estimated that 97–99% of Canadian canned foods were in lead-free cans. 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 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 1995. For lead, the geometric mean, maximum, and 85th percentile concentrations (µg/g wet weight) were 0.11, 4.88, and 0.22, respectively. 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).

Table 6-6. Lead Levels in Canadian Foods 1986–1988

Food category	Number of samples	Concentration (ng/g)		
		Mean	Median	Maximum
Milk and milk products	64	7.7	3.9	44.7
Meat and poultry	89	20.2	8.2	523.2
Fish	28	19.3	13.7	72.8
Soups	20	15.5	8.7	48.7
Bakery goods and cereals	120	13.7	10.5	66.4
Vegetables	190	24.4	8.7	331.7
Fruits and fruit juices	127	44.4	15.9	372.7
Fats and oils	15	9.6	<8.8	19.7
Sugar and candies	35	18.3	10.3	111.6
Beverages	35	9.9	<3.1	88.8
Miscellaneous	33	41.7	23.4	178.9
All categories	756	23.2	9.2	523.4

Source: Dabeka and McKenzie 1995

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 2007, 8 advisories restricting the consumption of lead-contaminated fish and shellfish were in effect in 5 states (Hawaii, Idaho, Washington, Kansas, and Missouri) and 1 territory (American Samoa) (EPA 2007b).

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 that 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.

The FDA investigated the prevalence and concentration of lead in a variety of dietary supplements with an emphasis on botanical-based products (Dolan et al. 2003). The concentration of lead in the 95 major product components tested was <20–48,600 µg/kg and the median concentration was 403 µg/kg. Levels of lead found in 11 products would result in exposures that exceed the tolerable lead intakes for children and women of child-bearing age, particularly pregnant women, 6 and 25 µg Pb/day. Of the 136 brands of nutritional supplements containing calcium (calcium supplements, mineral-vitamin supplements, antacids, and baby formulas) purchased in California in 1996, two-thirds failed to meet the 1999 California criteria for acceptable lead levels in consumer products, >1.5 µg lead/g calcium (Scelfo and Flegal 2000). The lowest levels were found in infant formulas and antacids, which all contained either synthesized or refined calcium. Lead concentrations were undetectable (<0.02 µg/g) in all infant formulas tested. Of the natural calcium supplements, none of the dolomite brands (n=5), five of the oyster shell brands (n=26), and half of the bonemeal brands (n=9) met the 1999 California criteria, while two dolomite brands and one oyster shell brand exceeded the federal limit, 7.5 µg Pb/g calcium.

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. Lead was the most common heavy metal contaminant/adulterant found in samples (n=54) of Asian traditional remedies available at health food stores and Asian groceries in Florida, New York, and New Jersey (Garvey et al. 2001). Sixty percent of the remedies tested would give a daily dose of lead in excess of 300 mg when taken according to labeling instructions. 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). Ayurveda is a traditional form of medicine practiced in India and other South Asian countries; the medications used often contain herbs, minerals, metals, or animal products and are made in standardized and nonstandardized formulations (CDC 2004). During 2000–2003, 12 cases of lead poisoning among adults were reported in five states due to the use of ayurveda medications obtained from ayurvedic physicians (CDC 2004).

Because lead concentrations in urban soil can be very high, a pilot study was conducted in an urban neighborhood in Chicago in order to gauge the levels of lead in an array of fruits, vegetables, and herbs (Finster et al. 2004). The soil lead concentrations where the plants were sampled varied from 27 to 4,580 ppm (median 800 ppm, geometric mean 639 ppm). Detectable lead levels in the edible fruit,

vegetables, and herbs sampled ranged from 11 to 81 ppm. Only one fruiting vegetable (cucumber 81 ppm) among the 52 sampled had detectable levels of lead in the edible portion. However, 12 of the 31 leafy vegetables and herbs sampled contained lead in the edible shoot part of the plant (range, 11–60 ppm). The lead concentrations in the four samples of root vegetables ranged from 10 to 21 ppm. No significant correlation was found between the lead concentrations in the edible portion of plant and the soil lead level.

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). This lead may have been due to the use of lead arsenate pesticides or lead-containing vehicle exhaust contaminating the tobacco plants. While no recent data were found on the concentration of lead in tobacco, higher levels of lead in indoor air and PbBs are associated with households with smokers (Bonanno et al. 2001; Mannino et al. 2003).

Hair dyes and some cosmetics may contain lead compounds (Cohen and Roe 1991). Hair dyes formulated with lead acetate may have lead concentrations 3–10 times the allowable concentration in paint. Measured lead concentrations of 2,300–6,000 µg of lead/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). Of the 115 suspected moonshine samples seized by local law enforcement between 1995 and 2001 and analyzed by the Bureau of Alcohol, Tobacco, and Firearms, 33 samples (28.7%) contained lead levels >300 μg/dL. The median and maximum levels were 44.0 and 53,200 μg/dL, respectively (Parramore et al. 2001).

Use of lead ammunition may result in exposure to lead dust generated during gun or rifle discharge at levels up to 1,000 $\mu g/m^3$ (EPA 1985c), from lead pellets ingested by or imbedded in animals that are used as food sources, and from lead pellets or fragments imbedded in humans from shooting incidents (Burger et al. 1998; Johnson and Mason 1984; Raymond et al. 2002). Exposures to airborne lead dust from firearm discharge in indoor shooting ranges has been shown to result in increases in blood lead concentration that are 1.5–2 times higher than preexposure concentrations (Greenberg and Hamilton 1999; Gulson et al. 2002). However, the use of copper-jacketed bullets, nonlead primers, and well-ventilated indoor firing ranges lessen the impact of airborne lead on blood lead levels (Gulson et al. 2002).

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.

Inexpensive metallic jewelry items specifically intended for children and teenagers have been shown to contain varying levels of lead (Maas et al. 2005). A total of 311 chemical assays conducted using 285 jewelry items purchased in 20 different stores in California revealed that a considerable amount of lead was added to the items, presumably to increase their weight or to impart some type of metallic coating to the surface of the item. The mean weight percentage of lead for all 311 assays was 30.6%. Of the 311 samples tested, 169 contained at least 3% lead by weight in at least one portion of the jewelry piece and 123 of the samples were found to contain >50% lead by weight (Maas et al. 2005). In addition, 62 pieces of the purchased jewelry were tested for surface levels of lead that could potentially be transferred dermally through the routine handling of these pieces. Using standard laboratory wipes, the surface of the jewelry pieces were wiped for a total of 20 seconds and subsequently analyzed for lead content. Mean lead levels in the wipes ranged from 0.06 to 541.97 µg. The authors characterized the potential lead exposure from these dermal transfer experiments as either low exposure (<1 µg of lead transferred to the laboratory wipe), moderate exposure (1–10 µg of lead transferred to the laboratory wipe), high exposure (10–50 µg of lead transferred to the laboratory wipe), and very high exposure (>50 µg of lead transferred to the laboratory wipe). Approximately 35% of the 62 pieces tested were characterized as having low exposure, 48% were characterized as moderate exposure, 11% were characterized as high exposure, and 5% were characterized as very high exposure (Maas et al. 2005).

6.5 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 6.6) 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 soil concentrations of lead at a range in Michigan were 10–100 times greater than background level of 25 mg/kg; mobilization of lead appeared to be occurring and may present a threat to groundwater and surface water (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 lead concentration ratio was assumed to be approximately 0.8, yielding an estimated lead exposure of 1.0 $\mu g/m^3$ for adults. This estimate assumed a 2-hour/day exposure to an outdoor 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 6.4.1).

Using the EPA National Air Quality Monitoring System, the average maximum 24-hour atmospheric lead concentration in the United States was 0.84 $\mu g/m^3$ in 2004 (EPA 2005k). There were two maximum 24-hour monitoring values measured in 2004 in which the 10 $\mu g/m^3$ level was exceeded (11.76 and 11.53 $\mu g/m^3$ in Muncie, Indiana). All other atmospheric lead levels measured throughout the rest of the United States were <10 $\mu g/m^3$ threshold in 2004.

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. The contribution of various food categories to the 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, are shown in Table 6-7 (Gartrell et al. 1986b). This value is only slightly higher

Table 6-7. Contribution of Various Food Categories to the Average Daily Intake (AVDI) of Lead in Adults (1980–1982)

Food category	AVDI (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
Leafy legumes	9.18
Root vegetables	1.39
Garden fruit	4.44
Fruits	10.00
Oils, fats, and shortenings	1.23
Sugar and adjuncts	2.34
Beverages	6.86
Total	56.50

Source: Gartrell et al. 1986b

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 (Bolger et al. 1991; Gunderson 1988), dietary values for average daily intake of lead by different population groups from 1980 to 1990 have been estimated (Table 6-8). The estimates of lead intake presented in Table 6-8 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). Data from the 1990–1991 Total Diet Survey indicate that dietary lead intake ranged 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). The daily dietary intake of lead estimated from the 1986–1988 Canadian Survey was 24 µg/day for all ages, male and female (Dabeka and McKenzie 1995). The highest contribution among 11 food categories to Pb intake was beverages (20.9%) and bakery goods and cereals (20.6%). The FDA Total Diet Survey (TDS) 1991–1996 tested 18 market baskets consisting of about 260 foods collected from three cities (representing standard metropolitan statistical areas) within four different geographical regions (Capar and Cunningham 2000). Mean and median Pb concentrations in all foods were 0.005 and 0 mg/kg, respectively. These results are similar to those in previous TDS 1982–1988 and 1990–1991 surveys except those in canned foods. The lower Pb concentrations in canned foods for TDS 1991–1996 is attributed to the reduction and ultimate ban in 1995 on the use of lead-soldered food cans in the United States.

More recent data on lead intakes from the U.S. diet come from the results of the NHEXAS studies. Mean and median dietary intakes of lead for study participants in the EPA Region V study were calculated to be 0.25 and 0.10 µg/kg body weight/day, respectively, or 17.5 and 7.0 µg/day for a 70-kg adult, respectively (Thomas et al. 1999). These results were obtained from measurement of concentrations in water and dietary samples. The median dietary lead intake for the Region V population agrees with the 0.09–0.10 µg/kg body weight/day calculated in the FDA TDS (1986–1991) (Gunderson 1995), but is

Table 6-8. Daily Average Intake of Lead (µg Lead/Day)

Age	Sex	1980[a]	1982[a]	1984[a]	1986[a]	1988[a]	1990–1991[b]
6–11 Months	Male/female	≈34	20	16.7	10	5	1.82
2 Years	Male	≈45	25.1	23.0	12.8	5.0	1.87
	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	2.63
	Male	No data	No data	40.9	21.8	8.2	3.24
25–30 Years	Female	No data	32.0	28.7	14.8	7.9	3.28
	Male	84	45.2	40.9	21.2	10.0	4.17
60–65 Years	Female	No data	No data	30.4	15.6	No data	3.05
	Male	No data	No data	37.6	19.1	No data	3.46

[a]Bolger et al. 1991
[b]Bolger et al. 1996

substantially lower than the average in the 1986–1988 Canadian study of 0.4 µg/kg body weight/day (calculated from an average intake of 24 µg/day for a 60-kg person (Dabeka and McKenzie 1995). Higher mean daily intakes of lead of 8.14 mg/day were reported from the NHEXAS Maryland study (Ryan et al. 2001). This intake was determined from the consumption levels determined in the NHEXAS Maryland study and the concentration in food from the 1997 ATSDR Toxicological Profile for Lead, 11.0 ppb. This intake would be much lower if the more recent levels of lead in food as reported in Capar and Cunningham (2000) were used. The mean and median concentrations of lead in combined solids and liquids in the EPA Region V study were 4.5 and 3.1 µg/kg, respectively. The mean (median) Pb intakes from dietary, water, and inhalation routes were 10.9 (7.3), 1.7 (0.66), and 0.333 (0.156) µg/day, respectively. While water lead contributed significantly to dietary intake, dietary intake was greater than that calculated for intake from home tap water. Mean and median flushed tap water from Region V homes contained 0.84 and 0.33 µg/L, while standing tap water contained 3.9 and 1.9 µg/L of lead, respectively.

In another approach to determining daily lead intake within subpopulations in the United States, Moschandreas et al. (2002) used the Dietary Exposure Potential Model (DEPM) and data obtained from Combined National Residue Database (CNRD) to estimate dietary lead intake based on food consumption patterns in 19 subpopulation groups. The food items used in the model are based on 11 food groups consisting of approximately 800 exposure core foods that represent 6,500 common food items. The results of their model (Table 6-9) yielded an average dietary lead intake in the U.S. population of 1.009 µg/kg body weight/day, or 70.6 µg/day for a 70-kg adult. Of the various subpopulation groups, nonnursing infants and children ages 1–6 years had much higher lead intakes/kg body weight than the general population, 3.117 and 1.952 µg/kg body weight, respectively.

The NHEXAS Arizona study evaluated exposure to lead for a study population from multiple media and pathways (O'Rourke et al. 1999). The concentrations of lead in the various media sampled are presented in Table 6-10 and the estimated total human exposure to the study population and various subpopulations is shown in Table 6-11. The daily total lead intake to the study population from all media ranged from 11 to 107 µg/day, with a mean of 36 µg/day. This compares with a range of 15–312 µg/day reported by the World Health Organization (WHO 1995).

Moonshine consumption was strongly associated with elevated PbBs (Morgan and Parramore 2001). A 2000 study found a median PbB of 11 µg/dL among 35 moonshine consumers versus 2.5 µg/dL in 68 randomly-selected nonmoonshine consumers. Gulson et al. (2001b) studied the contribution of lead

Table 6-9. Dietary Exposure Estimates of U.S. Populations to Lead Based on the Dietary Exposure Potential Model (DEPM)

Subpopulation	Lead intake (µg/kg body weight/day)
U.S. population	1.009
Age/gender	
Nonnursing infants	3.117
Children 1–6	1.952
Children 7–12	1.164
Females 13–19	0.824
Females 20+	0.920
Females 55+	0.946
Males 13–19	0.890
Males 20+	0.895
Males 55+	0.918
Ethnicity	
Hispanic	1.177
Non-Hispanic white	1.095
Non-Hispanic black	0.797
Non-Hispanic other	0.871
Geographic region[a]	
North central	0.611
Northeast	0.968
Southern	0.966
Western	1.133
Family income[b]	
Poverty 0–130%	1.094
Poverty 131%+	0.986

[a]The regional classification is as defined by the U.S. Department of Agriculture, and is based upon U.S. Census Bureau regions.
[b]Annual household income as a percentage of the Poverty Index

Source: Moschandreas et al. 2002

Table 6-10. Lead Concentrations for Various Media From the NHEXAS Arizona Study

Media	Number of samples	Percent BDL	Lead concentration—percentile			
			Units	50th	75th	90th
Air—indoors	119	100	ng/m^3	BDL	BDL	BDL
Air—outdoors	116	100	ng/m^3	BDL	BDL	BDL
Dust	135	86	µg/g	BDL	BDL	131.0
Soil	139	85	µg/g	BDL	BDL	118.1
Food	159	0.6	µg/kg	6.4	9.2	16.1
Beverage	154	29	µg/kg	1.9	4.1	7.1
Drinking water consumed	73	51	µg/L	BDL	0.4	2.0
Tap water consumed	82	1	µg/L	0.4	0.9	1.3

BDL = below detection limit

Source: O'Rourke et al. 1999

Table 6-11. Total Lead Exposure of Subject Population From the NHEXAS Arizona Study

Exposure population	Number of subjects	Lead intake (µg/day)		
		Mean	Median	Range
All subjects	176	36	31	11–107
Adult male (>18 years of age)	55	42	37	16–107
Adult female (>18 years of age)	86	35	30	11–96
Children (<18 years of age)	35	27	25	15–45
Hispanic	54	40	34	14–107
Non-Hispanic	119	34	29	11–-96

Source: O'Rourke et al. 1999

from calcium supplements to blood lead in 21 adults divided into three treatment groups over a 6-month period. One treatment group received a complex calcium supplement (carbonate/phosphate/citrate), another group received calcium carbonate, and the last, the control group, received no supplement. The isotopic composition of the supplements differed from that of the subject's blood allowing the investigators to estimate the contribution of the supplements to PbBs. While the changes from baseline to treatment in isotopic composition were significant in the treatment groups, there was no discernable increase in PbB concentration during the study. The change in isotopic contribution, however, indicates that there is a limited input of lead from the diet into the blood in adults. These results are consistent in other investigations that showed minimal gastrointestinal absorption of lead in the presence of calcium in adults.

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 1992). 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 NHANES revealed that between 1976 and 1991, the mean PbBs of the U.S. population aged from 1 to 74 years dropped 78%, from 12.8 to 2.8 µg/dL. The prevalence of PbBs ≥10 µg/dL also decreased sharply from 77.8 to 4.3%. The major cause of the observed decline in PbBs is most likely the removal of 99.8% of lead from gasoline and the removal of lead from soldered cans (Pirkle et al. 1994). PbBs 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 noncentral-city residents. PbBs also correlated with low income, low educational attainment, and residence in the Northeast region of the United States. Data analyses of the PbBs from NHANES surveys 1991–1994 and 1999–2002 are provided in Table 6-12 (CDC 2005a). Geometric means as well as 95% confidence intervals were calculated, and the results were organized by age, race/ethnicity, and sex. For 1999–2002, the overall prevelance of elevated PbBs (≥10 µg/dL) was 0.7%, down from 2.2% in the 1991–1994 survey. Children aged 1–5 years had the highest prevelance, 1.6%, of all age groups for levels ≥10 µg/dL in the 1999–2002 survey. This percentage is down from 4.4% in the 1991–1994 NHANES survey (CDC 2005a). Approximately 310,000 children in this age group were at risk of exposure to harmful levels of lead. The largest decline (72%) in elevated PbB in the two surveys, from 11.2 to 3.1%, was among non-Hispanic black children aged 1–5 years. In 2000, the year that had been targeted for the elimination of PbBs, >25 µg/dL in children aged 6 months–5 years, a total of 8,723 children had been identified with PbBs ≥25 µg/dL. Lead surveillance data collected by states between 1997 and 2001 also show a decline in the number of children aged 1–5 years with PbBs ≥10 µg/dL from 130,512 in 1997 to 74,887 in 2001 (Meyer et al. 2003).

The Adult Blood Lead Epidemiology and Surveillance (ABLES) program, which tracks cases of adult (aged ≥16 years) elevated PbBs from workplace exposure, reported updated results from 25 participating states for the period 1998–2001 (Roscoe et al. 2002). During that period, the prevalence of adults with PbBs ≥25 µg/dL was 13.4 per 100,000 employed adults, compared with 15.2 per 100,000 for 1994–1997. For adults with blood lead levels ≥40 µg/dL, the prevalence rate was 2.9 per 100,000 during 1998–2001, compared with 3.9 per 100,000 for 1994–1997. ABLES surveillance data from 2004 tracked the blood lead levels of females of childbearing age (16–44 years) in 37 different states (CDC 2007). The results indicated that 0.06 per 100,000 had PbBs ≥40 µg/dL, 0.7 per 100,000 had PbBs ≥25 µg/dL, 3.9 per 100,000 had PbBs ≥10 µg/dL, and 10.9 per 100,000 had PbBs ≥5 µg/dL (CDC 2007).

A 1992 survey of lead in blood of 492 Inuit adults from the Arctic region of Quebec, Canada resulted in geometric mean lead concentrations of 0.42 µmol/L, with a range of 0.04–2.28 µmol/L. Analysis of variance revealed that smoking, age, and consumption of waterfowl were associated with elevated lead levels (Dewailly et al. 2001). A Swedish study was aimed at characterizing PbBs in 176 men and 248 women, 49–92 years of age (Baecklund et al. 1999). Blood lead levels ranged from 5.6 to 150 µg Pb/L (median 27 µg Pb/L) and were higher in men than in women (median 30 versus 24 µg Pb/L). In both men and women, PbBs decreased between 50 and 70 years of age, which was thought to be a result of decreased energy intake. In women, PbBs peaked at 50–55 years of age, which is probably related to

Table 6-12. Geometric Mean Blood Lead Levels (µg/dL) and the 95th Percentile Confidence Interval, by Race/Ethnicity, Sex, and Age

Sex/age (years)	Number in sample	All racial/ethnic groups	White, non-Hispanic	Black, non-Hispanic	Mexican American
NHANES 1991–1994 geometric mean (95% confidence interval)					
			Both sexes		
≥1	13,472	2.3 (2.1–2.4)	2.2 (2.0–2.3)	2.8 (2.5–3.0)	2.4 (2.3–2.6)
1–5	2,392	2.7 (2.5–3.0)	2.3 (2.1–2.6)	4.3 (3.6–5.0)	3.1 (2.7–3.5)
6–19	2,960	1.7 (1.5–1.8)	1.5 (1.4–1.7)	2.3 (2.1–2.6)	2.0 (1.8–2.1)
20–59	5,596	2.2 (2.1–2.3)	2.1 (2.0–2.2)	2.6 (2.4–2.8)	2.5 (2.4–2.6)
≥60	2,524	3.4 (3.2–3.5)	3.3 (3.2–3.4)	4.3 (3.7–4.9)	3.1 (2.7–3.6)
			Males		
≥1	6,204	2.8 (2.6–2.9)	2.6 (2.5–2.8)	3.6 (3.3–4.0)	3.1 (2.9–3.3)
1–5	1,211	2.8 (2.5–3.1)	2.3 (2.1–2.6)	4.7 (3.9–5.5)	3.3 (2.9–3.6)
6–19	1,443	1.9 (1.7–2.1)	1.7 (1.5–1.9)	2.7 (2.4–3.1)	2.3 (2.0–2.5)
20–59	2,365	2.9 (2.7–3.1)	2.7 (2.5–3.0)	3.6 (3.2–3.9)	3.4 (3.2–3.6)
≥60	1,185	4.2 (4.0–4.4)	4.0 (3.8–4.2)	6.3 (5.4–7.1)	4.1 (3.5–4.8)
			Female		
≥1	7,268	1.9 (1.8–2.0)	1.8 (1.7–1.9)	2.2 (2.0–2.4)	1.9 (1.8–2.1)
1–5	1,181	2.7 (2.4–2.9)	2.3 (2.0–2.6)	4.0 (3.2–4.8)	2.9 (2.4–3.4)
6–19	1,517	1.5 (1.3–1.7)	1.4 (1.2–1.6)	2.0 (1.7–2.2)	1.7 (1.5–1.9)
20–59	3,231	1.7 (1.6–1.8)	1.6 (1.5–1.7)	1.9 (1.8–2.1)	1.8 (1.7–1.9)
≥60	1,339	2.9 (2.7–3.0)	2.8 (2.7–3.0)	3.3 (2.8–3.8)	2.5 (2.1–2.9)
NHANES 1999–2002 geometric mean (95% confidence interval)					
			Both sexes		
≥1	16,825	1.6 (1.5–1.6)	1.5 (1.5–1.6)	1.8 (1.7–1.9)	1.6 (1.6–1.7)
1–5	1,160	1.9 (1.8–2.1)	1.8 (1.6–2.0)	2.8 (2.5–3.1)	1.9 (1.8–2.0)
6–19	6,283	1.1 (1.1–1.2)	1.1 (1.0–1.1)	1.5 (1.4–1.6)	1.3 (1.2–1.4)
20–59	5,876	1.5 (1.5–1.6)	1.5 (1.4–1.5)	1.7 (1.6–1.8)	1.8 (1.6–1.9)
≥60	3,056	2.2 (2.1–2.3)	2.2 (2.1–2.3)	2.7 (2.5–2.8)	2.1 (1.9–2.3)
			Males		
≥1	8,202	1.9 (1.8–2.0)	1.9 (1.8–1.9)	2.1 (1.4–1.6)	2.0 (1.9–2.2)
1–5	846	1.9 (1.8–2.1)	1.8 (1.6–2.0)	2.8 (2.5–3.2)	2.0 (1.8–2.1)
6–19	3,158	1.3 (1.3–1.4)	1.2 (1.1–1.3)	1.7 (1.5–1.8)	1.5 (1.4–1.6)
20–59	2,689	2.0 (1.9–2.0)	1.9 (1.8–2.0)	2.1 (2.0–2.3)	2.3 (2.2–2.5)
≥60	1,509	2.7 (2.6–2.8)	2.6 (2.5–2.7)	3.4 (3.1–3.6)	2.6 (2.3–2.8)
			Female		
≥1	8,623	1.3 (1.3–1.3)	1.3 (1.2–1.3)	1.5 (1.4–1.6)	1.3 (1.2–1.4)
1–5	764	1.9 (1.8–2.1)	1.8 (1.5–2.1)	2.8 (2.5–3.2)	1.8 (1.7–2.0)
6–19	3,125	1.0 (0.9–1.0)	0.9 (0.8–1.0)	1.3 (1.2–1.5)	1.1 (1.0–1.2)
20–59	3,187	1.2 (1.2–1.2)	1.2 (1.1–1.2)	1.4 (1.3–1.5)	1.3 (1.2–1.4)
≥60	1,547	1.9 (1.8–2.0)	1.9 (1.8–2.0)	2.3 (2.1–2.4)	1.8 (1.6–2.0)

Source: CDC 2005a

postmenopausal bone mineralization. Increases in PbBs after age 70 was thought to be a result from higher lead exposure in the past for this group. Nash et al. (2004) reported median adjusted PbBs that were 25–30% higher than for premenopausal women (2.0 µg/dL). Users of hormone replacement therapy had significant lower median PbBs. Lead stored in the bones of women is released into the blood during post menopausal bone mineral resorption.

Mourning doves and other game birds consume lead pellets from hunting fields for grit. Recreational and subsistence hunters and their families who consume large amounts of these birds may ingest lead from this source (Burger et al. 1998).

Lead is a component of tobacco and tobacco smoke, and smokers often have higher lead blood levels than nonsmokers (Bonanno et al. 2001; Mannino et al. 2003). Using data from the NHEXAS EPA Region V study, PbB levels in smokers and nonsmokers were analyzed and a correlation between tobacco smoke and exposure levels was observed (Bonanno et al. 2001). The mean PbBs in smokers, nonsmokers exposed to environmental tobacco smoke (ETS), and nonsmokers without ETS were 2.85, 2.06, and 1.81 µg/dL, respectively (Bonanno et al. 2001).

Table 6-13 provides geometric means and selected percentiles of lead levels in the urine in segments of the U.S. population (CDC 2003, 2005b). These data will continue to be updated as new information becomes available.

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 2005d; Tripathi and Llewellyn 1990). NIOSH has estimated that >1 million American workers were occupationally exposed to inorganic lead in >100 occupations (NIOSH 1978a). According to NOES, conducted by NIOSH between 1980 and 1983, an estimated 25,169 workers 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 nonferrous foundries, lead smelters, and battery plants; 3,902 workers were exposed to lead chloride; and 576,579 workers 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 et al. 1992).

Table 6-13. Geometric Mean and Selected Percentile Urine Concentrations (µg/L) of Lead in the U.S. Population From 1999 to 2002

Group and survey years	Geometric mean	Percentile				
		50th	75th	90th	95th	Sample size
Age 6 and older						
1999–2000	0.766	0.800	1.30	2.10	2.90	2,465
2001–2002	0.677	0.600	1.20	2.00	2.60	2,690
6–11 Years						
1999–2000	1.07	1.00	1.50	2.40	3.40	340
2001–2002	0.753	0.800	1.20	2.00	2.60	368
12–19 Years						
1999–2000	0.659	0.600	1.10	1.70	2.20	719
2001–2002	0.564	0.600	0.900	1.50	1.90	762
20 Years and older						
1999–2000	0.752	0.700	1.40	2.10	2.90	1,406
2001–2002	0.688	0.700	1.20	1.90	2.80	1,560
Males						
1999–2000	0.923	0.900	1.60	2.40	3.40	1,227
2001–2002	0.808	0.700	1.30	2.40	3.20	1,335
Females						
1999–2000	0.642	0.600	1.20	1.90	2.40	1,238
2001–2002	0.573	0.500	1.00	1.50	2.20	1,335
Mexican Americans						
1999–2000	1.02	1.00	1.70	2.80	4.10	884
2001–2002	0.833	0.80	1.50	2.40	3.20	683
Non-Hispanic blacks						
1999–2000	1.11	1.10	1.90	2.90	4.20	568
2001–2002	0.940	0.900	1.50	2.60	3.70	667
Non-Hispanic whites						
1999–2000	0.695	0.700	1.30	1.90	2.60	882
2001–2002	0.610	0.600	1.00	1.80	2.40	1,132

Source: CDC 2003, 2005b

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 (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 Boffetta 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 PbBs of 56 radiator shop mechanics in the Boston area revealed that 80% had PbBs >30 μg/dL and 16 had PbBs 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 and Llewellyn 1990). When jacketed bullets were used, breathing zone levels decreased to 8.7 μg/m^3 or less. PbBs 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 and Llewellyn 1990). At an outdoor uncovered range in Los Angeles, instructors who spent an average of 15–20 hours/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 nondetectable 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 nonstudent dormitories (dust-lead concentration range of 116–546 μg/g with a geometric mean of 214 μg/g in the student's rooms versus a dust-lead concentration range of 50–188 μg/g with a geometric mean of 65 μg/g for the nonstudent 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 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 PbBs in workers; improvement of hygienic practices proved to be more effective at lowering PbBs 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, PbBs, urinary coproporphyrin levels, or δ-aminolevulinic acid [ALA] levels) rather than monitoring the workplace environment for lead concentrations (EPA 1986a; NIOSH 1978a). An 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 PbBs), 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 (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 PbBs ranging from 16 to 135 μg/dL. Approximately 30% of the workforce was found to be on medical leave as a result of their PbBs exceeding 40 μg/dL. An analysis of PbBs among family members of the exposed workers gave revealed 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).

Data from the NHANES III was used to compile statistics regarding the PbBs in U.S. workers (Yassin et al. 2004). The greatest levels tended to occur in mechanical and construction trades, while the lowest levels were observed for workers involved in professional labor categories such as managerial positions and health care professionals. Lead levels increased with age, decreased with education level, and male workers had a much higher geometric mean blood level, 3.3 μg/dL, than female workers, 1.8 μg/dL. Tables 6-14 and 6-15 summarize the results from these data for different industries and occupations. Okun et al. (2004) evaluated trends in occupational lead exposure in U.S. industries following the establishment of the general industrial lead standard in 1978 and the construction lead standard in 1993. They used data collected by OSHA under their compliance and consultation programs. On the basis of

Table 6-14. Median, Range, and Weighted Geometric Mean Blood Lead Levels in U.S. Workers, Ages 18–64 in 1988–1994

Occupation	Number of workers	µg/dL		
		Median	Range	WGM (GSD)
Vehicle mechanics	169	5.10	0.70–28.10	4.80 (3.88)
Food service workers	700	2.30	0.70–27.00	2.00 (2.69)
Management, professional, technical and sales	4,768	2.20	0.70–39.40	2.13 (4.05)
Personal service workers	1,130	2.90	0.70–25.90	2.48 (4.52)
Agricultural workers	498	3.80	0.70–23.40	2.76 (4.02)
Production workers: machine operators, material movers, etc.	1,876	3.30	0.70–52.90	2.88 (4.24)
Laborers other than construction	137	4.70	0.70–21.80	3.47 (3.36)
Transportation workers	530	3.85	0.70–22.30	3.49 (5.10)
Mechanics other than vehicles	227	4.10	0.70–16.60	3.50 (4.91)
Construction trades people	470	4.30	0.70–16.90	3.66 (4.64)
Construction workers	122	4.70	1.20–36.00	4.44 (7.84)
Health service workers	499	2.00	0.70–22.40	1.76 (2.24)
All	11,126	2.80	0.70–52.90	2.42 (6.93)

GSD = geometric standard deviation; WGM = weighted geometric mean

Source: Yassin et al. 2004

Table 6-15. Median, Range, and Weighted Geometric Mean Blood Lead Levels in U.S. Workers, Ages 18–64 by Industrial Categories[a]

Industry	Number of workers	Blood lead (µg/dL)		
		Median	Range	WGM (GSD)
Repair services (SIC 75–76)	188	4.80	0.70–28.10	4.54 (5.05)
Wholesale and retail trade (SIC 50–59)	2,229	2.50	0.70–39.40	2.25 (3.38)
Finance, insurance, and real estate (SIC 60–65, 67)	1,117	2.40	0.70–28.70	2.30 (2.74)
Agriculture (SIC 01–02, 07–08)	493	3.80	0.70–23.40	2.68 (4.09)
Transportation and utility (SIC 40–49)	764	3.10	0.70–22.30	2.58 (3.49)
Manufacturing (SIC 20–32, 34–39)	2,008	3.10	0.70–41.80	2.66 (4.51)
Metal (SIC 33)	188	3.80	0.70–52.90	3.50 (2.91)
Construction (SIC 15–17)	671	4.40	0.70–36.00	3.68 (5.66)
Mining (SIC 10, 12–14	47	3.90	1.10–12.90	4.66 (6.23)
Services (SIC 770, 72–73, 78–79, 80–84, 86–89, 91–97)	3,449	2.30	0.70–23.70	2.05 (4.39)
All	11,148	2.80	0.70–52.90	2.42 (6.93)

[a]Working population aged 18–64: U.S. Third National Health and Nutrition Examination Survey, 1988–1994

GSD = standard deviation of geometric mean, SIC = standard industrial code; WGM = weighted geometric mean

Source: Yassin et al. 2004

these data, there has been a decline in occupational lead exposures for general industry facilities since 1979. The median exposure level for these facilities declined 5–10-fold. With the exception of retail trade, these declines were for the major industry divisions and the majority of four-digit SIC codes including some high risk industries. A decline was not observed in the construction industry, but in this case, the data are only for a limited number of years.

6.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in Section 3.7, 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, 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, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

The American Academy of Pediatrics (AAP) (1998) has concluded that although monitoring data demonstrate a decline in the prevalence of PbBs, 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 PbBs 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 PbBs 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 PbBs in children were correlated with soil lead levels, which were highest in inner-city areas; soil lead levels and PbBs 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).

The results of successive NHANES monitoring studies suggest that from 1976 to 2002, PbBs have declined, but were consistently higher for younger children than for older children (CDC 1997b, 1997d, 2003, 2005a, 2005b; Pirkle et al. 1994). In general, PbBs also correlated with low income, low educational attainment, and residence in the Northeast region of the United States. Data from Phase II of NHANES III (conducted during October 1991 to September 1994) and the most recent data (1999–2002) indicate that PbBs in the U.S. population aged ≥1 year continued to decrease and that PbBs 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, 2003. 2005a, 2005b; Pirkle et al. 1998). 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 PbBs ≥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 PbBs ≥15 µg/dL and 0.4% had PbBs ≥20 µg/dL. For the NHANES III Phase II data, the geometric mean PbBs 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). For the most recent 1999–2002 NHANES sample, the geometric mean PbB for children ≥1 year was 1.6 µg/dL and among those aged 1–5 years, approximately 1.6% had PbBs ≥10 µg/dL (CDC 2005a). These data have been summarized in Table 6-12.

The U.S. Navy instituted a pediatric lead surveillance program in 1995 because of public health concerns over pediatric PbBs (Bohnker et al. 2003). The database contained 38,502 samples from 1995 to 2001 with 1.6% containing levels ≥10 µg/dL. Samples were obtained at the time of the 12-month well-child visit. Results were similar to those for the NHANES survey.

Fetuses are at even greater risk. As discussed in Section 3.5, 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 PbBs 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 PbBs were strongly dependent on time elapsed since immigration to the United States, with PbBs being highest in those women who had immigrated most recently. Elevated PbBs in immigrant women were also associated with pica and with low dietary calcium during pregnancy (Rothenberg et al. 1999a, 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 25 lived in agricultural areas with low air pollution. The mean lead concentrations (expressed as mean±SD) for the women living in areas with high air pollution were 3.72±0.47 µg/dL in maternal blood and 2.0±0.34 µg/dL in umbilical cord blood (correlation coefficient, r=0.57). The mean lead concentrations for the women living in areas with low air pollution were 2.05±0.56 µg/dL in maternal blood and 1.29±0.36 µg/dL in umbilical cord blood (correlation coefficient, r=0.70). The authors concluded that the placenta demonstrates a dynamic protective function that is amplified when maternal PbBs 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 concentrations of umbilical cord blood were 6.56±3.19 µg/dL for the 1980 group and 1.19±1.32 µg/dL for the 1990 group (Hu et al. 1996b).

In a study of blood samples collected from 113 mothers of 23 different nationalities and from their neonates (cord blood), mean maternal PbBs were 14.9±2.14 µg/dL (range, 6.6–27.8 µg/dL) and mean cord PbBs were 13±2.5 µg/dL (range, 6.0–30 µg/dL). Sixteen percent of mothers and nearly 10% of cord blood samples had PbBs >20 µg/dL (Al Khayat et al. 1997b).

Malcoe et al. (2002) assessed lead sources and their effect on blood lead in rural Native American and white children living in a former mining region. Blood samples, residential environmental samples (soil, dust, paint, water) and caregiver interviews (hand-mouth behaviors, socioeconomic conditions) were obtained from a representative sample of 245 children ages 1–6. There were no ethnic differences in the results. However poor children were especially vulnerable. Regression analysis showed that mean floor dust lead loading >10.1 µg/ft^2 and yard soil lead >165.3 mg/kg were independently associated with blood lead levels ≥10 µg/dL.

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 <1 year old (Cohen 1988). 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 for children has dropped dramatically since the late 1970s. Results summarizing the CDC NHANES II and NHANES III, Phases I and II, study of blood lead levels for children aged 1–5 years are provided in Table 6-16 (CDC 1997b, 1997d, 2005a).

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 6.4.1).

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 PbBs in young children, the major source of moderately elevated PbBs (30–80 µg/dL) in inner city children is most 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 PbBs in over 200 urban and suburban infants followed from birth to 2 years of age; however, the PbBs 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 PbBs (>8.8 µg/dL) were 72 µg/wipe (window sill dust) and 1,011 µg/g, respectively; children with low PbBs (<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 PbBs had

Table 6-16. Blood Levels of Lead in Children (1–5 Years) in 1976–2002

Children (1–5 Years)	NHANES			
	1976–1980	1988–1991	1991–1994	1999–2002
Geometric mean (µg/dL)	15.0	3.6	2.7	1.9
Blood lead ≥10 µg/dL	88.2%	8.9%	4.4%	1.6%

NHANES = National Health and Nutrition Examination Survey

Sources: CDC 1997b, 1997d, 2005a; Pirkle 1994

been renovated, while only 56% of the homes of children with low PbBs 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). Regular use of dust control methods (e.g., wet mopping of floors, damp-sponging of horizontal surfaces, high-efficiency vacuum cleaner) has been shown in some, although not all, cases to reduce indoor dust, lead dust, and blood lead levels in some, although not all, older homes containing leaded paints (Lanphear et al. 2000b; Rhoads et al. 1999). Decreases of between 17 and 43% in blood lead concentrations were observed in children where regular dust control methods had been used to reduce indoor levels of lead (Rhoads et al. 1999).

Lanphear and Roghmann (1997) and Lanphear et al. (1996a, 1996b, 1998b) studied factors affecting PbBs in urban children and found the following independent predictors of children's PbBs: 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 PbBs. 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 and Roghmann 1997). Community characteristics such as residence within a city, proportion of 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 PbBs 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 PbBs. 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 >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 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).

EPA conducted the Urban Soil Lead Abatement Demonstration Project (USLADP), also known as the "Three City Lead Study," in Boston, Baltimore, and Cincinnati (EPA 1996c). The purpose was to determine whether abatement of lead in soil could reduce PbBs of inner-city children. No significant evidence was found that soil abatement had any direct impact on children's PbBs 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 postabatement (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 PbBs (2.2–2.7 μg/dL). EPA reanalyzed the data from the USLADP in an integrated report (EPA 1996c). 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 PbBs in children. These include the site-specific exposure scenario, the magnitude of the remediation, and the magnitude of additional sources of lead exposure.

Authors of a study of PbBs in children in Toronto, Canada, before and after abatement of lead-contaminated soil and house dust found that 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).

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 PbBs 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, cerussite, 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 bioavailabilities 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.

Seasonal variations in PbBs in children have been observed in a number of studies. Mean PbBs in the State of New York have been shown to increase by 15–30% in the late summer as compared to mean values obtained during late winter/early spring (Haley and Talbot 2004). Blood lead measurements taken from children aged 0–6 years in Syracuse, New York over a 48-month period beginning in January 1992, showed a regular yearly periodicity in blood lead concentrations, which peaked in the late summer (Johnson and Bretsch 2002). These seasonal variations in PbBs have been attributed to ingestion of lead in soil. Indeed, the work of Johnson and Bretsch (2002), which looked at the relationship between PbBs measured in children and soil lead concentrations within small regional grids (600 m by 600 m) laid out over the City of Syracuse, New York, showed a correlation between the geometric mean PbBs and the median soil lead concentrations (r^2>0.65).

In addition to the ingestion of hand soil/dust through normal hand-to-mouth activity, some children engage in pica behavior (consumption of nonfood 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/day and that a pica child may ingest 5,000 mg or more of soil/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/day from this source alone (Mielke et al. 1989), and a pica child may be exposed to >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 6–71 months of age in a multi-site study (Agency for Toxic Substances and Disease Registry 1995).

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 PbBs ≥20 µg/dL that were considered to be attributable to residential renovation and remodeling (CDC 1997d).

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 4 to 63 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 that of the control subject. The pharmacokinetic model for lead may be complex since >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. Women who resided in homes that were >30 years old, lived in high-traffic areas for >5 years, or had drunk three 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. (1998a, 2001c) 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%. Lead release during maternal bone loss and maternal diet appear to be the major sources of lead in breast milk fed infants. Other sources of lead, such as air, soil, and dust are considered to contribute minimally to lead concentrations in infant blood. Mean lead concentration (±SD) in breast milk for participants in the study was 0.73±0.70 µg/kg.

Sowers et al. (2002b) examined the relationship between lead concentrations in breast milk, maternal blood lead concentration, and maternal bone loss in 15 mothers who breast-fed compared to 30 mothers who bottle-fed commercial formula. The data showed a modest correlation ($p<0.07$) between maternal blood lead and breast milk concentrations at 1–2 months postpartum. However, a stronger correlation ($p<0.001$) was observed between the mean extent of bone loss (5.6%) and lead concentrations in breast milk in women who breast-fed between 1.5 and 6 months postpartum.

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 40 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 5–30 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 PbBs in infants drinking water (or formula reconstituted using water) drawn from the same tap. Predicted PbBs 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. PbBs 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 PbBs (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). Based upon data collected from 1987–1994, children aged 1–5 years (n=139) of workers whose occupation resulted in lead exposure had a geometric mean PbB of 9.3 µg/dL as compared to a U.S. population geometric mean of 3.6 µg/dL (Roscoe et al. 1999). Of this group, 52% of the children had PbBs ≥10 µg/dL compared to 8.9% of the U.S. population and 21% had PbBs ≥20 µg/dL compared to 1.1% of the U.S. population (Roscoe et al. 1999). 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 6.5. 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. Recent data by Maas et al. (2005) indicate that high levels of lead are prevalent in inexpensive cosmetic jewelry that is sold to the general public at retail stores (see Section 6.4.5).

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 6.4.5) 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).

Children may be exposed to lead through the inhalation of second-hand smoke. Mannino et al. (2003) employed data from the NHANES III and analyzed PbBs of children aged 4–16 who were exposed to high, low, and intermediate levels of second-hand smoke. Serum levels of the nicotine biomarker cotinine were used to classify the children into one of the three second-hand smoke exposure categories. The geometric mean PbBs were 1.5, 1.9, and 2.6 μg/dL for children with low (≤0.050–0.104 ng/mL), intermediate (0.105–0.562 ng/mL), and high (0.563–14.9 ng/mL) serum cotinine levels, respectively (Mannino et al. 2003).

6.7 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 6.6), individuals living near sites where lead was produced or sites where lead was disposed, and individuals living near one of the 1,272 NPL hazardous waste sites where lead has been detected in some

environmental media (EPA 1986b; HazDat 2006; Murgueytio et al. 1998) also may be at risk for exposure to high levels of lead. Since lead is often detected in tobacco and tobacco smoke, persons who use chewing tobacco or smoke, may have higher PbB levels than persons that do not use these products (Bonanno et al. 2001).

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; 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). Populations living near any of the 1,272 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 2006). 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.

6.8 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 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.

6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of lead and its compounds are sufficiently characterized to permit an estimation of the environmental fate of lead to be made (Howe 1981; Lide 1996; Budavari et al. 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, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2004, became available in May of 2006. This database is updated yearly and should provide a list of industrial production facilities and emissions.

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). Exports of lead in ore and concentrates and lead materials, excluding scrap, rose from 93,500 and 103,000 metric tons in 1999 to 253,000 and 123,000 metric tons, respectively, in 2003. In 2003, 92,800 metric tons of lead scrap were exported (USGS 2003).

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.

Environmental Fate. Lead released to the atmosphere partitions to surface water, soil, and sediment (EPA 1986a; 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 1979). Inorganic lead compounds are strongly adsorbed to minerals and organic matter in soils and sediments (Chaney et al. 1988; Chuan et al. 1996; EPA 1986a; Gerritse et al. 1981; Sauve et al. 1997). Some work has been conducted to assess the speciation of lead in air, water, and soil (Chaney et al. 1988; Corrin and Natusch 1977; EPA 1986a; Long and Angino 1977; Nerin et al. 1999; Spear et al. 1998). 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. Additional data regarding the chemical speciation and the transformation pathways of lead in soils and water with varying properties such as pH, oxygen content and salinity are necessary to fully understand the environmental fate of lead in soils and water.

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 (MPCA 1987). 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). Dermal absorption models of lead would be useful in modeling total exposure pathways of lead.

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 1982c, 1986a, 1988b, 1989d, 1989e, 1990; Lee et al. 1989; Maenhaut et al. 1979; Mielke 1993; Mielke et al. 1983, 1984/1985, 1989). More current data (1995–1996) on lead in ambient and indoor air, drinking water, and foodstuffs for residents in Arizona, EPA Region V (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin), and Maryland are available through the NHEXAS (Bonanno et al. 2001; Clayton et al. 2002; O'Rourke et al. 1999; Pellizzari et al. 1999; Ryan et al. 2000; Thomas et al. 1999). 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. Lead has been found in tobacco and tobacco smoke and higher levels of lead have been detected in indoor air of the homes of smokers when compared to non smokers (Bonanno et al. 2001; Mannino et al. 2003). It is unclear whether the source of this lead is from plant uptake, atmospheric deposition of lead compounds to the surface of tobacco plants, or from tobacco plants being grown in soils that had previously been treated with arsenate pesticides. A study to determine the source of this lead in tobacco is needed in order to help reduce the risk of lead exposure to smokers and those that may inhale second hand smoke.

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 burden 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 1977b, 1977c; Que Hee and Boyle 1988; Que Hee et al. 1985a; Wielopolski et al. 1986). The most common method of assessing human exposure involves measurement of lead in blood (PbB) (Aguilera de Benzo et al. 1989; Delves and Campbell 1988; Manton and Cook 1984; NIOSH 1977b, 1977c; Que Hee et al. 1985a). PbBs have been correlated with ambient air exposure levels and dust, and dietary intake levels (Rabinowitz et al. 1985). In their critical evaluation of reports of historic occupational aerosol exposure to lead, Vincent and Werner (2003) recommended that exposure measurements be made using sampling techniques and strategies that relate to the health effects underlying the need for exposure assessment. Additionally, sufficient detail must be included so that the quality and value of the data can be judged. This is necessary so the data can be pooled for broad hazard surveillance purposes. 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. The most recent NHANES Report, containing data from 1999 to 2002 and released in 2005, contains blood lead levels for the U.S. population (CDC 2005a, 2005b). The data pertaining to lead levels in the U.S. population are summarized in Tables 6-12 and 6-13. 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. Lead levels in blood (CDC 2005a, 2005b) and urine

(CDC 2003, 2005b) of children are available from the NHANES monitoring data, and have been summarized in Tables 6-12 and 6-13.

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

Exposure Registries. No exposure registries for lead were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries 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.

6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2005) database provides additional information obtainable from a few ongoing studies that may fill in some of the data needs identified in Section 6.8.1. These studies are summarized in Table 6-17.

Table 6-17. Ongoing Research Regarding the Environmental Fate and Exposure of Humans to Lead

Investigator	Affiliation	Research description	Sponsor
Blum CB	Columbia University, New York, New York	The estimation of bioavailability to lead and arsenic from soil currently use assumptions based on bioavailability data from animal or *in vitro* models. Using the technique of stable Pb isotope dilution, a method was developed for estimating soil Pb bioavailability in humans. This model examines changes in the ratio of ^{206}Pb to ^{207}Pb in blood, following the ingestion of trace quantities of Pb-contaminated soils.	National Institute of Environmental Health Sciences
Cochran JK and Veron A	SUNY at Stony Brook, Stony Brook, New York	This three-year award for United States-France collaboration in environmental geochemistry involves State University of New York at Stony Brook and the Centre Europeen de Recherche et d'Enseignement de Geosciences in Marseilles, France. The investigators will determine the history of input rates and sources of stable lead to coastal areas.	National Science Foundation
Basta NK and Lower SK	Ohio State University, Columbus, Ohio	The goals of this project are to: (1) determine the ability of chemical speciation methods that measure heavy metal bioavailability; (2) estimate ecotoxicity of contaminated soil; (3) determine the effect of soil chemical properties on chemical speciation and heavy metal bioavailability in contaminated soil and the ability of soil chemical properties to define ecotoxicity categories in development of ecological soil screening levels; (4) determine the ability of diammonium phosphate to reduce bioavailable chemical species of heavy metal contaminants in soil.	Department of Agriculture
Spraks DL	University of Delaware, Newark, Delaware	The goals of this project are to (1) determine the effect of reaction conditions and residence time on sorption/release of important metals/metalloids (Cu, Cd, Cr, Ni, Pb, As) on soil components and Delaware soils; and (2) ascertain metal/metalloid reaction mechanisms on soil components/soils using molecular level spectroscopic (e.g., x-ray absorption fine structure [XAFS] and microscopic [atomic force microscopy (AFS]) techniques. Metal/metalloid sorption studies will be examined as a function of residence time, pH, and total metal loading on soil components/soils, using a pH-stat batch method.	Department of Agriculture

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7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, measuring, and/or monitoring lead, its metabolites, and other biomarkers of exposure and effect to lead. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and 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 modify previously used methods to obtain lower detection limits and/or to improve accuracy and precision.

7.1 BIOLOGICAL MATERIALS

Blood, Urine, Serum, Cerebrospinal Fluid. Several analytical methods are available to analyze the level of lead in biological samples. The most common methods employed 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). 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) for flame AAS measurements, while flameless AAS measurements can detect blood lead levels at about 1 ng/mL (Flegal and Smith 1995). A detection limit of 0.05 ng/mL has been achieved for lead in blood samples analyzed by GFAAS (Flegal and Smith 1995). ICP/MS is also a very powerful tool for trace analysis of lead and other metals. Although ICP/MS instruments are more costly than GFAA instruments, their ability to analyze multiple metals from a single sample, low detection limits, reliability, and ease of use have increasingly made them popular for trace metal analysis. 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 7-1.

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. OSHA mandates biological monitoring of blood as a measure of workplace exposure to lead (Goyer 2001). 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 1977c). 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 1977b; 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 1977b, 1977c; 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 1994c). 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).

An indirect fluorescent method to quantify the level of Pb^{+2} in intracellular fluids has been published (Dyatlov et al. 1998). Although there are no commercially available fluorescent probes specific to Pb^{2+}, the fluorescent probe (fluo-3) frequently used to quantify levels of Ca^{2+} was employed as a means to estimate Pb^{2+} levels in calcium containing solution. The presence of Pb^{2+} depresses the fluorescent signal

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
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 0.05 µg/mL (urine)	99 (±10.8%)	NIOSH 1994e
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
Blood and tissue	Digestion of sample with $HNO_3/HClO_4/H_2SO_4$; heat	ICP/AES (Method 8005)	0.01 µg/g (blood) 0.2 µg/g (tissue)	113	NIOSH 1994b
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	Collect 50 mL urine sample and add 5 mL concentrated HNO_3 as preservative. Extraction-filter samples through cellulose membrane, adjust pH to 8, ash filters and resins in low temperature oxygen plasma for 6 hours	ICP/AES (Method 8310)	0.1 µg/ sample (50–200 mL sample volume)	100	NIOSH 1994f
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	10B50 µg/L	85 (serum) >80 (urine, blood)	Que Hee and Boyle 1988

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Urine (δ-amino-levulinic 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-amino-levulinic 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-amino-levulinic 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
Serum and cerebro-spinal 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; dissolution 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

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Bone	Partially polarized photon directed at second phalanx of left forefinger (noninvasive technique)	K-XRF	20 µg/g	No data	Christoffersson et al. 1986
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; redissolution in buffer solution	ASV	No data	83–114	Rabinowitz et al. 1989
Teeth	Dry ashing of sample; crushing; dry ashing again; dissolution 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; ^{206}Pb = lead 206

observed in the emission spectrum of the fluo-3 Ca^{2+} complex at 530 nm, and the concentration of Pb^{2+} in solution was correlated with the observed decrease of intensity in the emission spectra.

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 to 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 of 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 range (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. Lead accumulates over a lifetime in bones, so these measurements represent a metric cumulative dose, whereas measurements of lead in blood represent a more recent dose. Typical analyses encompass L x-rays of the tibia produced 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* bone K x-ray fluorescence (Batuman et al. 1989; Hu et al. 1989, 1990, 1991, 1998). The K x-ray fluorescence technique has been more widely used and validated than the L x-ray method, which has limitations regarding its utility for the determination of lead levels in bone (Hu et al. 1998; Preiss and Tariq 1992). The more energetic K x-rays penetrate the cortical bone deeper (2 cm) than the soft L x-rays, and are therefore more suitable for determining the average lead content 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 (Landrigan 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 range 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. A limitation of x-ray fluorescence measurements is that its precision is dependent upon the mass of the bone being studied (Hu et al. 1998). Therefore, thin bones of children have greater measurement errors than mature bones found in adults. 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 range (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.

7.2 ENVIRONMENTAL SAMPLES

The primary methods of analyzing for lead in environmental samples are AAS, GFAAS, ASV, ICP/AES, and XRFS (EPA 1993). 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 for the analysis of trace metals (including lead) has increased in recent years due to its high sensitivity and ease of sample preparation. ICP/MS is generally 3 orders of magnitude more sensitive than ICP/AES; however, it is more costly than other spectroscopic methods and is not universally available (Al-Rashdan et al. 1991; California Department of Fish and Game 2004). 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 analyzing lead concentrations in the atmosphere, a distinction between the levels of inorganic lead, which exists predominantly in the particulate phase, and alkyl lead, which occurs predominantly in the vapor phase, is necessary. Particulate-phase lead can be separated from the gas phase 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. Table 7-2 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, and 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 1981, 1994a, 1994c, 2003; 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 1977a, 1977d). 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 a wide range as well as high sensitivity. It is relatively inexpensive compared to other methods (NIOSH 1977a).

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (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 (NIOSH Method 7105)	0.02 µg/ sample (1–1,500 L sample)	85–115	NIOSH 1994d
Air (particulate lead)	Collection of particulate matter onto membrane filter; wet ashing with HNO_3	AAS flame (Method 7082)	2.6 µg/sample (200–1,500 L sample)	97–100	NIOSH 1994c
Air (particulate lead)	Collection of particulate matter onto cellulose acetate membrane filter; wet ashing with $HNO_3/HClO_4$	ICP/AES (NIOSH Method 7300)	25 ng/mL	101–109	NIOSH 2003
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 electro-deposition; 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 1994a
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

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
Air (tetramethyl and tetraethyl lead)	Adsorption of volatile compounds in filtered sample onto XAD-2 resin, desorption with pentane	GC/PID (NIOSH Method 2534 [TML] and 2533 [TEL])	0.4 µg/sample (15–100 L sample) (TML); 0.1 µg/ sample (30–200 L sample) (TEL)	97	NIOSH 1994g; 1994h
Air (particulate and organo-lead)	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
Air (particulate and organo-lead)	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 1994a
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 1983
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

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
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 1983
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)	Acidification, addition of ammoniacal citrate-cyanide reducing solution; extraction with chloroform containing dithizone.	(Standard Method 3500-PbB)	No data	No data	NEMI 2005b
Water	Filtration, acidification, aspiration into a flame	AAS (Standard Method 3111B)	0.5 mg/L	No data	NEMI 2005a
Water	Digestion, analysis	GFAAS (Standard Method 3113B)	1 µg/L	101%	NEMI 2005c
Water and waste water (dissolved, total)	Filtration/acidification and analysis for dissolved; digestion followed by analysis for total	ICP/AES (Standard Method 3120B)	10 µg/L	109%	NEMI 2005d
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; 90B104% (6B28% RSD) for solid samples	EPA 1994d
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	10B50 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

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
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
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 ground-water	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 1986c
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

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (percent recovery)	Reference
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 vegetation)	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 7-2. Analytical Methods for Determining Lead in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Accuracy (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
Feathers	Clean feathers with non ionic detergent; rinse with deionized water for 2–3 minutes.	ICP/MS	10 ppb	No data	California Department of Fish and Game 2004

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; ICP/MS = inductively coupled plasma-mass spectrometry; IDMS = isotope dilution mass spectrometry; LAMMA = laser microprobe mass analysis; MS = mass spectrometry; NaOH = sodium hydroxide; NG = nanogram; NIOSH = National Institute for Occupational Safety and Health; ^{206}Pb = lead 206; PID = photoionization detector; TAL = tetraalkyl leads; TEL = tetraethyl lead; THF = tetrahydrofuran; TML = tetramethyl lead; XRD = X-ray diffraction; XRF = X-ray fluorescence

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 has 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 1994d). Chelation/extraction can also be used to recover lead from aqueous matrices (APHA 1998). 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 (EPA 1986c).

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 1986c; 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 1986c; 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 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).

7.3 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 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.

7.3.1 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 1977b, 1977c, 1994c, 2003; 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 (Moore 1995; Rabinowitz et al. 1985). Methods of quantifying lead in tissues, bone, teeth, and hair are generally reliable, but are only sensitive at relatively high exposure concentrations. Since the elimination half-time of lead in blood is approximately 30 days, PbBs generally reflect relatively recent exposures. Lead in bone is considered 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. 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). Lead interferes with the conversion of zinc protoporphyrin (ZPP) to heme by the enzyme ferrochelatase and a correlation has been observed between lead blood levels and ZPP; therefore, levels of ZPP can also be used as a biomarker of lead exposure (Goyer 2001). The methods for determining these biomarkers are generally sensitive and reliable. 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 (NEMI 2005a, 2005b, 2005c, 2005d; Eckel and Jacob 1988; EPA 1982a, 1986a, 1988b, 1989d, 1989e, 1990, 1994d; Lee et al. 1989; Maenhaut et al. 1979; Mielke 1993; Mielke et al. 1983, 1984/1985, 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 1981, 1994c, 2003; 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.

7.3.2 Ongoing Studies

Ongoing studies regarding analytical methods for lead were reported in the Federal Research in Progress database (FEDRIP 2005), and are summarized in Table 7-3.

Table 7-3. Ongoing Research Regarding the Analytical Methods for Lead in Environmental and Biological Samples

Investigator	Affiliation	Research description	Sponsor
Chillrud S	Columbia University, New York, New York	Core-Geochemistry Laboratory: A laboratory is being developed to support several ongoing research projects, including projects involving the analytical measurement of lead in environmental samples and human tissue. The instrumentation that will be used includes a VG sector 54-30 Thermal Ionization Mass Spectrometer (TIMS), a Hitachi Z8200 Graphite Furnace Atomic Absorption Spectrophotometer (GFAAS), a VG High-Resolution inductively coupled plasma-mass spectrometry (ICP-MS).	National Institute of Environmental Health Sciences
Mutti A	University of Parma, Parma Italy	Metals in exhaled breath condensate as chronic obstructive pulmonary disease (COPD) biomarkers: Develop biomarkers for COPD involving the analysis of exhaled breath condensate for the presence of lead by electro-thermal atomic absorption spectroscopy (ETAAS) and ICP-MS.	National Heart, Blood, and Lung Institute
Parsons PJ	New York State Department of Health, Human Toxicology and Molecular Epidemiology	Bone Lead Standardization Program: The aim of this proposal is to create a Standardization Program for Bone Lead measurements (BLSP) obtained via reference methods and via *in vivo* x-ray fluorescence (XRF).	National Institute of Environmental Health Sciences

Source: FEDRIP 2005

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8. REGULATIONS AND ADVISORIES

The international and national regulations and guidelines regarding lead and lead compounds in air, water, and other media are summarized in Table 8-1.

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 2005).

EPA has assigned lead a weight-of-evidence carcinogen classification of B2, probable human carcinogen, based on inadequate information in humans and sufficient data in animals (IRIS 2005). The International Agency for Research on Cancer (IARC) has classified inorganic lead compounds as probably carcinogenic to humans (Group 2A) based on limited evidence of carcinogenicity in humans and sufficient evidence in animals (IARC 2004). IARC also determined that organic lead compounds are not classifiable as to their carcinogenicity to humans (Group 3) based on inadequate evidence of carcinogenicity in humans and animals (IARC 2004). The Department of Health and Humans Services (DHHS) has determined that lead and lead compounds are reasonably anticipated to be human carcinogens based on limited evidence from studies in humans and sufficient evidence from studies in experimental animals (NTP 2005). 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 2004). 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 2004).

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

Table 8-1. Regulations and Guidelines Applicable to Lead and Lead Compounds

Agency	Description	Information	Reference
INTERNATIONAL			
Guidelines:			
IARC	Carcinogenicity classification		IARC 2004
	Lead compounds, inorganic	Group 2A[a]	
	Lead compounds, organic	Group 3[b]	
WHO	Air quality guidelines	0.5 µg/m^3	WHO 2000
	Drinking water quality guidelines	0.01 mg/L	WHO 2004
NATIONAL			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (TWA)		ACGIH 2004
	Lead, inorganic	0.05 mg/m^3	
EPA	Hazardous air pollutant	Yes	EPA 2004b 42 USC 7412
	National primary and secondary ambient air quality standards[c]	1.5 µg/m^3	EPA 2005b 40 CFR 50.12
NIOSH	REL (TWA)[d]	0.05 mg/m^3	NIOSH 2005
	IDLH	100 mg/m^3	
OSHA	PEL (8-hour TWA) for toxic and hazardous substances for lead	50 µg/m^3	OSHA 2005d 29 CFR 1910.1025
	PEL (8-hour TWA) for general industry for tetraethyl lead[e]	0.075 mg/m^3	OSHA 2005c 29 CFR 1910.1000
	PEL (8-hour TWA) for construction industry for tetraethyl lead[e]	0.1 mg/m^3	OSHA 2005b 29 CFR 1926.55
	PEL (8-hour TWA) for shipyard industry for tetraethyl lead[e]	0.1 mg/m^3	OSHA 2005a 29 CFR 1915.1000
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act	Yes	EPA 2005a 40 CFR 116.4
	Lead acetate, lead chloride, lead fluoroborate, lead iodide, lead nitrate, lead sulfate, lead sulfide, and tetraethyl lead		
	National primary drinking water standards		EPA 2002
	MCLG	Zero	
	MCL	Treatment technique[f]	
	Action level	0.015 mg/L	
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act	10 pounds	EPA 2005c 40 CFR 117.3
	Lead acetate, lead chloride, lead fluoroborate, lead iodide, lead nitrate, lead sulfate, lead sulfide, and tetraethyl lead		

Table 8-1. Regulations and Guidelines Applicable to Lead and Lead Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Residential lead hazards standards – TSCA Section 403		EPA 2005l
	Floors	40 µg/ft^2	
	Interior window sills	250 µg/ft^2	
	Bare soil in children's play areas	400 ppm	
	Bare soil in rest of yard	1,200 ppm average	
c. Food			
FDA	Action level (µg/mL leaching solution)		FDA 2000
	Ceramicware		
	Flatware (average of 6 units)	3.0 µg/mL	
	Small hollowware (other than cups and mugs) (any 1 of 6 units)	2.0 µg/mL	
	Large hollowware (other than pitchers) (any 1 of 6 units)	1.0 µg/mL	
	Cups and mugs (any 1 of 6 units) and pitchers (any 1 of 6 units)	0.5 µg/mL	
	Silver-plated hollowware		
	Product intended for use by adults (average of 6 units)	7 µg/mL	
	Product intended for use by infants and children (any 1 of 6 units)	0.5 µg/mL	
	Bottled drinking water	0.005 mg/L	FDA 2004 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification		ACGIH 2004
	Lead	A3[g]	
	Biological exposure indices (lead in blood)[h]	30 µg/100 mL	
ATSDR	Action level for children	10 µg/dL	Agency for Toxic Substances and Disease Registry 1997
EPA	Carcinogenicity classification	Group B2[i]	IRIS 2005
	Oral slope factor	Not available	
	Inhalation unit risk	Not available	
	RfC	Not available	
	RfD	Not applicable[j]	
	Superfund, emergency planning, and community right-to-know		
	Designated CERCLA hazardous substance	10 pounds	EPA 2005d 40 CFR 302.4
	Reportable quantity		
	Lead, lead acetate, lead chloride, lead fluoroborate, lead iodide, lead nitrate, lead phosphate, lead sulfate, lead sulfide, and tetraethyl lead		

Table 8-1. Regulations and Guidelines Applicable to Lead and Lead Compounds

Agency	Description	Information	Reference
NATIONAL *(cont.)*			
EPA	Superfund, emergency planning, and community right-to-know		
	Effective date of toxic chemical release reporting for lead	01/01/87	EPA 2005g 40 CFR 372.65
	Extremely hazardous substances		EPA 2005e 40 CFR 355, Appendix A
	Tetraethyl lead		
	Reportable quantity	10 pounds	
	Threshold planning quantities	100 pounds	
	Superfund, emergency planning, and community right-to-know		
	Threshold amounts for manufacturing (including importing), processing, and otherwise using such toxic chemicals	100 pounds	EPA 2005f 40 CFR 372.28
NTP	Carcinogenicity classification	Reasonably anticipated to be human carcinogens	NTP 2005

[a]Group 2A: probably carcinogenic to humans
[b]Group 3: not classifiable as to carcinogenicity to humans
[c]National primary and secondary ambient air quality standards for lead and its compounds, measured as elemental lead by a reference method based on Appendix G to 40 CFR 50.12, or by an equivalent method, are: 1.5 μg/m^3, maximum arithmetic mean averaged over a calendar quarter.
[d]The REL also applies to other lead compounds (as Pb), including metallic lead, lead oxides, and lead salts (including organic salts such as lead soaps but excluding lead arsenate). The NIOSH REL for lead (10-hour TWA) is 0.050 mg/m^3; air concentrations should be maintained so that worker blood lead remains less than 0.060 mg Pb/100 g of whole blood.
[e]Skin designation
[f]Treatment Technique: lead is regulated by a Treatment Technique that requires systems to control the corrosiveness of their water. If more than 10% of tap water samples exceed the action level, water systems must take additional steps. For lead, the action level is 0.015 mg/L.
[g]A3: confirmed animal carcinogen with unknown relevance to humans
[h]BEI: Women of child-bearing potential, whose blood exceeds 10 μg/dL, are at risk of delivering a child with a blood Pb over the current CDC guideline of 10 μg/dL. If the blood Pb of such child remains elevated, they may be at increased risk of cognitive deficits.
[i]Group B2: probable human carcinogen
[j]See IRIS record for complete oral RfD discussion (IRIS 2005).

ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; BEI = biological exposure indices; CDC = Centers for Disease Control and Prevention; CERCLA = Comprehensive Environmetnal Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TSCA = Toxic Substances Control Act; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

occupational exposure of 50 μg/m^3 (0.006 ppm) or lower, based on an 8-hour TWA (OSHA 2005d). When employee exposures to lead cannot be maintained ≤50 μg/m^3 through engineering and work practice controls, the employer is required to provide the employees with respirators as a means of supplemental 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 2005d). Under the requirements for medical surveillance and biological monitoring, the blood lead level (PbB) of employees exposed to lead above the action level for >30 days/year must be monitored at least every 6 months. The frequency for sampling an employee's PbB increases to once every 2 months if the results of his or hers previous blood analysis indicated a PbB ≥40 μg/dL (OSHA 2005d). OSHA requires continuing the 2-month sampling protocol until the employee's PbB is below 40 μg/dL for two 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 PbB ≥50 μg/dL, the employer is required to remove the employee from that work area (OSHA 2005d). The relocation of an employee may also be instituted if the average of the three most recent blood tests or the average of all blood tests given over the most recent 6-month period indicates a PbB ≥50 μg/dL. If however, the last single blood test taken during this period indicates a PbB ≤40 μg/dL, relocation of the employee may not be required (OSHA 2005d). 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 2005f), can be found in 29 CFR 1910.1025 (OSHA 2005d). 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 2005e). More detailed requirements for protecting construction workers from occupational exposures to lead can be found in 29 CFR 1926.62 (OSHA 2005e).

The EPA regulates lead under the Clean Air Act (CAA) and has designated lead as a hazardous air pollutant (HAP) (EPA 2004b). 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 1996a). 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 <1% of the amount of lead used in the peak year of 1970 (EPA 1996a). 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 per gallon 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 that contains lead or lead additives. The effective date for this prohibition was January 1, 1996 (EPA 1996a). 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/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 1996a).

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 waste water 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 as well as 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 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 and 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 five states (Hawaii, Louisiana, Missouri, Ohio, and Tennessee), and one U.S. Territory (American Samoa) restricting the consumption of lead-contaminated fish and shellfish (EPA 2004d). 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 >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).

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 1990). 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 that 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 childcare 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 <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 (HUD 1998). 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 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 five categories of lead-based paint professionals: supervisors, workers, inspectors, risk assessors, and project designers; and three 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 >10 ft^2 of deteriorated paint on exterior surface areas and >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 of ≥40 $\mu g/ft^2$ on uncarpeted floors and ≥250 $\mu g/ft^2$ on interior window sills (EPA 2005l). 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 Native American 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 1998c). 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. Local, certified (licensed) lead-based paint inspectors, risk assessors, 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 2000). In 1993, the FDA has established an action level for lead in fruit beverages (80 μg/kg) packaged in lead-soldered cans (FDA 1998b); in 1995, the use of lead-

soldered cans was banned by the FDA. Lead solders are alloys of metals that 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 allowable concentrations of lead ranging from 0.1 to 10 ppm (FDA 1998a).

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 CDC of grants for additional lead screening and referral programs for children and infants (Congressional Record 1988). The CPSC has declared paints and similar surface coating having a lead content that exceeds the 0.06% by weight limit to be "banned hazardous products" (CPSC 1977). 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 1977). 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 1977).

The CDC determined in 1991 that PbBs >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 a PbB exceeding the CDC guideline value are at risk of delivering children with a PbB >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 PbB 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 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/week. The BEI for lead is 30 µg/dL (ACGIH 2004). The recommended exposure level (REL) for lead in the air adopted by the NIOSH is 0.05 mg/m^3 (NIOSH 2005). NIOSH also recommends maintaining air concentrations so that worker blood lead remains at <60 µg/dL (NIOSH 1997a).

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9. REFERENCES

Abadin HG, Hibbs BF, Pohl HR. 1997b. Breast-feeding exposure of infants to cadmium, lead, and mercury: A public health viewpoint. Toxicol Ind Health 15(4):1-24.

Abadin HG, Wheeler JS, Jones DE, et al. 1997a. A framework to guide public health assessment decisions at lead sites. J Clean Technol Environ Toxicol Occup Med 6:225-237.

Abbate C, Buceti R, Munao F, et al. 1995. Neurotoxicity induced by lead levels: An electrophysiological study. Int Arch Occup Environ Health 66:389-392.

ACGIH. 1986. Documentation of the threshold limit values and biological exposure indices. 5th ed. Cincinnati, OH: American Conference of Governmental Industrial Hygienists, BEI-19 to BEI-23.

ACGIH. 1998. 1998 TLVs and BEIs. Threshold limit values for chemical substances and physical agents. Biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienist.

ACGIH. 2004. Lead. Threshold limit values for chemical substances and physical agents and biological exposure indices. Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

Adebonojo FO. 1974. Hematologic status of urban black children in Philadelphia: Emphasis on the frequency of anemia and elevated blood lead levels. Clin Pediatr 13:874-888.

Adhikari N, Sinha N, Narayan R, et al. 2001. Lead-induced cell death in testes of young rats. J Appl Toxicol 21:275-277.

Adinolfi M. 1985. The development of the human blood-CSF-brain barrier. Dev Med Child Neurol 27:532-537.

Agency for Toxic Substances and Disease Registry. 1989. Decision guide for identifying substance-specific data needs related to toxicological profiles; notice. Fed Regist 54(174):37618-37634.

Agency for Toxic Substances and Disease Registry. 1995. Multisite lead and cadmium exposure study with biological markers incorporated. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Agency for Toxic Substances and Disease Registry. 1997. Public health statement for lead. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

Agency for Toxic Substances and Disease Registry. 2004a. Interaction profile for arsenic, cadmium, chromium, and lead. Atlanta, GA: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/interactionprofiles/ip04.html. July 22, 2005.

Agency for Toxic Substances and Disease Registry. 2004b. Interaction profile for lead, manganese, zinc, and copper. Atlanta, GA: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/interactionprofiles/ip06.html. July 22, 2005.

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*Not cited in text

9. REFERENCES

Agency for Toxic Substances and Disease Registry. 2006. Interaction profile for chlorpyrifos, lead, mercury, and methylmercury. Atlanta, GA: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/interactionprofiles/IP-11/ip11.pdf. June 14, 2007.

Aguilera de Benzo Z, Fraile R, Carrion N, et al. 1989. Determination of lead in whole blood by electrothermal atomization atomic absorption spectrometry using tube and platform atomizers and dilution with Triton X-100. J Anal Atom Spectrom 4:397-400.

Ahamed M, Verma S, Kumar A, et al. 2005. Environmental exposure to lead and its correlation with biochemical indices in children. Sci Total Environ 346(1-3):48-55.

Ahlgren L, Liden S, Mattson, et al. 1976. X-ray fluorescence analysis of lead in human skeleton *in vivo*. Scand J Work Environ Health 2:82-86.

*Ahmed NS, El-Gendy KS, El-Refaie AK et al. 1987. Assessment of lead toxicity in traffic controllers of Alexandria, Egypt, road intersections. Arch Environ Health 42:92-95.

Aiba Y, Ohshiba S, Horiguchi S, et al. 1999. Peripheral hemodynamics evaluated by acceleration plethysmography in workers exposed to lead. Ind Health 37:3-8.

Åkesson A, Stal P, Vahter M. 2000. Phlebotomy increases cadmium uptake in hemochromatosis. Environ Health Perspect 108:289-291.

Al-Hakkak ZSH, Hamamy HA, Murad AMB, et al. 1986. Chromosome aberrations in workers at a storage battery plant in Iraq. Mutat Res 171:53-60.

Al Khayat A, Habibullah J, Koutouby A, et al. 1997b. Correlation between maternal and cord blood lead levels. Int J Environ Health Res 7(4):323-328.

Al Khayat A, Menon NS, Alidina MR. 1997a. Acute lead encephalopathy in early infancy-clinical presentation and outcome. Ann Trop Paediatr 17(1):39-44.

Al-Modhefer AJA, Bradbury MWB, Simmons TJB. 1991. Observations on the chemical nature of lead in human blood serum. Clin Sci 81:823-829.

Al-Neamy FR, Almehdi AM, Alwash R, et al. 2001. Occupational lead exposure and amino acid profiles and liver function tests in industrial workers. Int J Environ Health Res 11(2):181-188.

Al-Rashdan A, Heitkemper D, Caruso JA. 1991. Lead speciation by HPLC-ICP-AES and HPLC-ICP-MS. J Chromatogr Sci 29(3):98-102.

Al-Saleh I, Nester M, DeVol E, et al. 2001. Relationship between blood lead concentrations, intelligence, and academic achievement of Saudi Arabian schoolgirls. Int J Hyg Environ Health 204:165-174.

Al-Saleh I, Shinwari N, Mashour A, et al. 2005. Is lead considered as a risk factor for high blood pressure during menopause period among Saudi women? Int J Hyg Environ Health 208(5):341-356.

Alessio L. 1988. Relationships between “chelatable lead” and the indicators of exposure and effect in current and past occupational life. Sci Total Environ 71:293-299.

9. REFERENCES

Alessio L, Bertazzi PA, Monelli O, et al. 1976. Free erythrocyte protoporphyrin as an indicator of the biological effect of lead in adult males: II. Comparison between free erythrocyte protoporphyrin and other indicators of effect. Int Arch Occup Environ Health 37:89-105.

Alexander FW, Delves HT. 1981. Blood lead levels during pregnancy. Int Arch Occup Environ Health 48:35-39.

Alexander BH, Checkoway H, Costa-Mallen P, et al. 1998b. Interaction of blood lead and δ-aminolevulinic acid dehydratase genotype on markers of heme synthesis and sperm production in lead smelter workers. Environ Health Perspect 106:213-216.

Alexander BH, Checkoway H, Faustman EM, et al. 1998a. Contrasting associations of blood and semen lead concentrations with semen quality among lead smelter workers. Am J Ind Med 34:464-469.

Alexander BH, Checkoway H, van Netten C, et al. 1996. Semen quality of men employed at a lead smelter. Occup Environ Med 53:411-416.

Alexander FW, Clayton BE, Delves HT. 1974. Mineral and trace-metal balances in children receiving normal and synthetic diets. QJ Med 43:89-111.

Allen LB, Siitonen PH, Thompson HC. 1998. Determination of copper, lead, and nickel in edible oils by plasma and furnace atomic spectroscopies. J Am Oil Chem Soc 75(4):477-481.

Allen-Gil SM, Gubala CP, Landers DH, et al. 1997. Heavy metal accumulation in sediment and freshwater fish in U.S. arctic lakes. Environ Toxicol Chem 16(4):733-741.

Alomran AH, Shleamoon MN. 1988. The influence of chronic lead exposure on lymphocyte proliferative response and immunoglobulin levels in storage battery workers. J Biol Sci Res 19:575-585.

Altman PL, Dittmer DS. 1974. Biological handbooks: Biology data book. Vol. III. 2nd ed. Bethesda, MD: Federation of American Societies for Experimental Biology, 1987-2008, 2041.

Altmann L, Sveinsson K, Kraemer U, et al. 1998. Visual functions in 6-year-old children in relation to lead and mercury levels. Neurotoxicol Teratol 20(1):9-17.

Alvares AP, Kapelner S, Sassa S, et al. 1975. Drug metabolism in normal children, lead-poisoned children, and normal adults. Clin Pharmacol Ther 17:179-183.

American Academy of Pediatrics. 1998. Screening for elevated blood lead levels. Policy statement. Committee on environmental health. Pediatrics 101(6):1072-1078.

Amitai Y, Graef JW, Brown MJ, et al. 1987. Hazards of deleading homes of children with lead poisoning. Am J Dis Child 141:758-760.

Anders E, Bagnell CR, Krigman M, et al. 1982. Influence of dietary protein composition on lead absorption in rats. Bull Environ Contam Toxicol 28:61-67.

Andersen ME, Krishnan K. 1994. Relating in vitro to in vivo exposures with physiologically based tissue dosimetry and tissue response models. In: Salem H, ed. Animal test alternatives: Refinement, reduction, replacement. New York: Marcel Dekker, Inc., 9-25.

9. REFERENCES

Andersen ME, Clewell HJ III, Gargas ML, et al. 1987. Physiologically based pharmacokinetics and the risk assessment process for methylene chloride. Toxicol Appl Pharmacol 87:185-205.

Anderson RJ. 1987. Peripheral nerve conduction velocities and excitability. In: Lowndes HE, ed. Electrophysiology in neurotoxicology, Vol. 11. Piscataway, NJ: Department of Pharmacology and Toxicology, 51-69.

Angle CR, Kuntzelman DR. 1989. Increased erythrocyte protoporphyrins and blood lead--a pilot study of childhood growth patterns. J Toxicol Environ Health 26:149-156.

Angle CR, McIntire MS. 1978. Low level lead and inhibition of erythrocyte pyrimidine nucleotidase. Environ Res 17:296-302.

Angle CR, Manton WI, Stanek KL. 1995. Stable isotope identification of lead sources in preschool children: The Omaha study. Clin Toxicol 33(6):657-662.

Angle CR, Marcus A, Cheng I-H, et al. 1984. Omaha childhood blood lead and environmental lead: A linear total exposure model. Environ Res 35:160-170.

Angle CR, McIntire MS, Swanson MS, et al. 1982. Erythrocyte nucleotides in children--increased blood lead and cytidine triphosphate. Pediatr Res 16:331-334.

Annesi-Maesano I, Pollitt R, King G, et al. 2003. In utero exposure to lead and cord blood total IgE. Is there a connection? Allergy 58:589-594.

Anttila A, Heikkila P, Nykyri E, et al. 1996. Risk of nervous system cancer among workers exposed to lead. J Occup Environ Med 38(2):131-136.

Anttila A, Heikkila P, Pukkala E, et al. 1995. Excess lung cancer among workers exposed to lead. Scand J Work Environ Health 21:460-469.

APHA. 1998. Method 3111. Metals by flame atomic absorption spectrometry. In: Clesceri LS, Greenberg AE, Eaton AD, eds. Standard methods for the examination of water and wastewater. 20th ed. Washington, DC: American Public Health Association. American Water Works Association. Water Environmental Federation, 3-13 to 3-22.

Apostoli P, Bellini A, Porru S, et al. 2000a. The effect of lead on male fertility: A time to pregnancy (TTP) study. Am J Ind Med 38:310-315.

Apostoli P, Maranelli G, Cas LD, et al. 1990. Blood lead and blood pressure: A cross sectional study in a general population group. Cardiologia 35(7):597-603.

Araki S, Aono H, Yokoyama K, et al. 1986. Filterable plasma concentration, glomerular filtration, tubular reabsorption and renal clearance of heavy metals and organic substances in metal workers. Arch Environ Health 41:216-221.

Araki S, Honma T, Yanagihara S, et al. 1980. Recovery of slowed nerve conduction velocity in lead-exposed workers. Int Arch Occup Environ Health 46:151-157.

Araki S, Murata K, Aono H. 1987. Central and peripheral nervous system dysfunction in workers exposed to lead, zinc and copper. Int Arch Occup Environ Health 59:177-187.

9. REFERENCES

Araki S, Sata F, Katsuyuki M. 1990. Adjustment for urinary flow rate and improved approach to biological monitoring. Int Arch Environ Health 62:471-477.

Araki S, Sato H, Yokoyama K, et al. 2000. Subclinical neurophysiological effects of lead: A review on peripheral, central, and autonomic nervous system effects in lead workers. Am J Ind Med 37:193-204.

Ariza ME, Bijur GN, Williams MV. 1998. Lead and mercury mutagenesis: Role of H2O2, superoxide dismutase, and xanthine oxidase. Environ Mol Mut 31:352-361.

Arnvig E, Grandjean P, Beckmann J. 1980. Neurotoxic effects of heavy lead exposure determined with psychological tests. Toxicol Lett 5:399-404.

Aroza I, Bonilla M, Madrid Y, et al. 1989. Combination of hydride generation and graphite furnace atomic absorption spectrometry for the determination of lead in biological samples. J Anal Atmos Spectro 4:163-166.

Aschengrau A, Beiser A, Bellinger D, et al. 1994. The impact of soil lead abatement on urban children's blood lead levels: Phase II results from the Boston lead-in-soil demonstration project. Environ Res 67:125-148.

Assennato G, Paci C, Baser ME, et al. 1987. Sperm count suppression without endocrine dysfunction in lead-exposed men. Arch Environ Health 42:124-127.

ASTM. 1998a. ASTM E 1613. Standard test method for analysis of digested samples for lead by inductively coupled plasma atomic emission spectrometry (ICP-AES). Flame atomic absorption (FAAS), or graphite furnace atomic absorption (GFAA) techniques. In: Annual book of ASTM standards. Philadelphia, PA: American Society for Testing and Materials, 669-674.

ASTM. 1998b. ASTM E 1644. Standard practice for hot plate digestion of dust wipe samples for the determination of lead by atomic spectrometry. In: Annual book of ASTM standards. Philadelphia, PA: American Society for Testing and Materials, 684-687.

ASTM. 1998c. ASTM E 1645. Standard practice for the preparation of dried paint samples for subsequent lead analysis by atomic spectrometry. In: Annual book of ASTM standards. Philadelphia, PA: American Society for Testing and Materials, 688-692.

ASTM. 1998d. ASTM E 1726. Standard practice for sample digestion of soils for the determination of lead by atomic spectrometry. In: Annual book of ASTM standards. Philadelphia, PA: American Society for Testing and Materials, 918-921.

ASTM. 1998e. ASTM E 1727. Standard practice for field collection of soil samples for lead determination by atomic spectrometry techniques. In: Annual book of ASTM standards. Philadelphia, PA: American Society for Testing and Materials, 922-924.

ASTM. 1998f. ASTM E 1728. Standard practice for field collection of settled dust samples using wipe sampling methods for lead determination by atomic spectrometry techniques. In: Annual book of ASTM standards. Philadelphia, PA: American Society for Testing and Materials, 925-927.

ASTM. 1998g. ASTM E 1729. Standard practice for field collection of dried paint samples for lead determination by atomic spectrometry techniques. In: Annual book of ASTM standards. Philadelphia, PA: American Society for Testing and Materials, 928-930.

Astrin KH, Bishop DF, Wetmur JG, et al. 1987. Delta-aminolevulinic acid dehydratase isozymes and lead toxicity. Ann NY Acad Sci 514:23-29.

Atchison WD. 2004. Neurotoxicants and synaptic function: Session VII-B summary and research needs. Neurotoxicology 25:515-519.

Aufderheide AC, Wittmers LE. 1992. Selected aspects of the spatial distribution of lead in bone. Neurotoxicology 13:809-820.

Aungst BJ, Fung HL. 1981. Kinetic characterization of an *in vitro* lead transport across the rat small intestine. Toxicol Appl Pharmacol 61:38-47.

Aungst BJ, Doice JA, Fung H-L. 1981. The effect of dose on the disposition of lead in rats after intravenous and oral administration. Toxicol Appl Pharmacol 61:48-57.

Aviv A, John E, Bernstein J, et al. 1980. Lead intoxication during development: Its late effect on kidney function and blood pressure. Kidney Int 17:430-437.

Awad El Karim MA, Hamed AS, Elhaimi YAA, et al. 1986. Effects of exposure to lead among lead-acid battery factory workers in Sudan. Arch Environ Health 41:261-265.

Azar A, Snee RD, Habibi K. 1975. An epidemiologic approach to community air lead exposure using personal air samplers. In: Griffin TB, Knelson JH, eds. Lead. Stuttgart, West Germany: Georg Thieme Publishers, 254-290.

Azar A, Trochimowicz HJ, Maxfield ME. 1973. Review of lead studies in animals carried out at Haskell Laboratory: Two year feeding study and response to hemorrhage study. In: Barth D, Berlin A, Engel R, et al., eds. Environmental health aspects of lead: Proceedings, International Symposium, October 1972, Amsterdam, The Netherlands. Luxembourg: Commission of the European Communities, 199-210.

Baecklund M, Pedersen NL, Bjorkman L, et al. 1999. Variation in blood concentrations of cadmium and lead in the elderly. Environ Res 80(3):222-230.

Bagci C, Bozkurt AI, Cakmak EA, et al. 2004. Blood lead levels of the battery and exhaust workers and their pulmonary function tests. Int J Clin Pract 58(6):568-572.

Baghurst PA, McMichael AJ, Tong S, et al. 1995. Exposure to environmental lead and visual-motor integration at age 7 years: The Port Pirie cohort study. Epidemiology 6(2):104-109.

Baghurst PA, McMichael AJ, Wigg NR, et al. 1992. Environmental exposure to lead and children's intelligence at the age of seven years. New Engl J Med 327:1279-1284.

Baghurst PA, Robertson EF, McMichael AJ, et al. 1987. The Port Pirie cohort study: Lead effects on pregnancy outcome and early childhood development. Neurotoxicology 8:395-401.

Baker EL, Feldman RG, White RF, et al. 1983. The role of occupational lead exposure in the genesis of psychiatric and behavioral disturbances. Acta Psychiatr Scand Suppl 67:38-48.

9. REFERENCES

*Baker EL, Goyer RA, Fowler BA, et al. 1980. Occupational lead exposure, nephropathy, and renal cancer. Am J Ind Med 1:138-148.

Baker EL, Hayes CG, Landrigan PH, et al. 1977. A nationwide survey of heavy metal absorption in children living near primary copper, lead, and zinc smelters. Am J Epidemiol 106(4):261-273.

Baker EL, Landrigan PJ, Barbour AG, et al. 1979. Occupational lead poisoning in the United States: Clinical and biochemical findings related to blood lead levels. Br J Ind Med 36:314-322.

Balbus-Kornfeld JM, Stewart W, Bolla KI, et al. 1995. Cumulative exposure to inorganic lead and neurobehavioural test performance in adults: An epidemiological review. Occup Environ Med 52(1):2-12.

Ballew C, Khan LK, Kaufmann R, et al. 1999. Blood lead concentration and children's anthropometric dimensions in the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. J Pediatr 134:623-630.

Balo J, Bajtai A, Szenda B. 1965. [Experimental adenomas of the kidney produced by chronic administration of lead phosphate.] Magyar Onkol 9:144-151. (Hungarian)

Baloh RW, Spivey GH, Brown CP, et al. 1979. Subclinical effects of chronic increased lead absorption--a prospective study: 11. Results of baseline neurologic testing. J Occup Med 21:490-496.

Banks EC, Ferretti LE, Shucard DW. 1997. Effects of low level lead exposure on cognitive function in children: A review of behavioral, neuropsychological and biological evidence. Neurotoxicology 18(1):237-282.

Bannon DI, Abounader R, Lees PSJ, et al. 2003. Effect of DMT1 knockdown on iron, cadmium, and lead uptake in Caco-2 cells. Am J Physiol Cell Physiol 284:C44-C50.

Bannon DI, Olivi L, Bressler J. 2000. The role of anion exchange in the uptake of Pb by human erythrocytes and Madin-Darby canine kidney cells. Toxicology 147:101-107.

Bannon DI, Portnoy ME, Olivi L, et al. 2002. Uptake of lead and iron by divalent metal transport 1 in yeast and mammalian cells. Biochem Biophys Res Commun 295:978-984.

Barltrop D, Khoo HE. 1975. The influence of nutritional factors on lead absorption. Postgrad Med J 51:795-800.

Barltrop D, Meek F. 1979. Effect of particle size on lead absorption from the gut. Arch Environ Health 34:280-285.

Barnes RM. 1990. Childhood soil ingestion: How much dirt do kids eat? Anal Chem 62:1023-1033.

Barnes DG, Dourson M. 1988. Reference dose (RfD): Description and use in health risk assessments. Regul Toxicol Pharmacol 8:471-486.

Barratt CLR, Davies AG, Bansal MR, et al. 1989. The effects of lead on the male rat reproductive system. Andrologia 21:161-166.

9. REFERENCES

Barregård L, Svalander C, Schütz A, et al. 1999. Cadmium, mercury, and lead in kidney cortex of the general Swedish population: A study of biopsies from living kidney donors. Environ Health Perspect 107(11):867-871.

Barry PSI. 1975. A comparison of concentrations of lead in human tissue. Br J Ind Med 32:119-139.

Barry PSI. 1981. Concentrations of lead in the tissues of children. Br J Ind Med 38:61-71.

Barth A, Schaffer AW, Osterode W, et al. 2002. Reduced cognitive abilities in lead-exposed men. Int Arch Occup Environ Health 75:394-398.

Barton JC. 1984. Active transport of lead-210 by everted segments of rat duodenum. Am J Physiol 247:G193-G198.

Barton JC, Conrad ME. 1981. Effect of phosphate on the absorption and retention of lead in the rat. Am J Clin Nutr 34:2192-2198.

Barton JC, Conrad ME, Harrison L, et al. 1978a. Effects of calcium on the absorption and retention of lead. J Lab Clin Med 91:366-376.

Barton JC, Conrad ME, Harrison L, et al. 1980. Effects of vitamin D on the absorption and retention of lead. Am J Physiol 238:G124-G130.

Barton JC, Conrad ME, Nuby S, et al. 1978b. Effects of iron on the absorption and retention of lead. J Lab Clin Med 92:536-547.

Barton JC, Patton MA, Edwards CQ, et al. 1994. Blood lead concentrations in hereditary hemochromatosis. J Lab Clin Med 124(2):193-198.

Basaran N, Ündeger U. 2000. Effects of lead on immune parameters in occupationally exposed workers. Am J Ind Med 38:349-354.

Batra N, Nehru B, Bansal MP. 2001. Influence of lead and zinc on rat male reproduction at 'biochemical and histopathological levels'. J Appl Toxicol 21:507-512.

Battery Council International. 2003. Battery recycling. Chicago, IL: Battery Council International. http://www.batterycouncil.org/recycling.html. May 12, 2005.

Battistuzzi G, Petrucci R, Silvagni L, et al. 1981. Delta-aminolevulinate dehydrase: A new genetic polymorphism in man. Ann Hum Gen 45:223-229.

Batuman V, Wedeen RP, Bogden JD, et al. 1989. Reducing bone lead content by chelation treatment in chronic lead poisoning: An *in vivo* X-ray fluorescence and bone biopsy study. Environ Res 48:70-75.

Bauchinger M, Schmid E. 1972. Chromosomenanalvsen in zellkulturen des chinesischen hamsters nach applikation von bleiacetat. Mutat Res 14:95-100.

Bauchinger M, Dresp J, Schmid E, et al. 1977. Chromosome analyses of children after ecological lead exposure. Mutat Res 56:75-79.

9. REFERENCES

Baum CR, Shannon MW. 1997. The lead concentration of reconstituted infant formula. J Toxicol Clin Toxicol 35(4):371-5.

Beck BD, Mattuck RL, Bowers TS, et al. 2001. The development of a stochastic physiologically-based pharmacokinetic model for lead. Sci Total Environ 274:15-19.

Beek B, Obe G. 1974. Effect of lead acetate on human leukocyte chromosomes *in vitro*. Experientia 30:1006-1007.

Beek B, Obe G. 1975. The human leukocyte test system: VI. The use of sister chromatid exchanges as possible indicators for mutagenic activities. Humangenetik 29:127-134.

Bell RR, Spickett JT. 1981. The influence of milk in the diet on the toxicity of orally ingested lead in rats. Food Cosmet Toxicol 19:429-436.

Bellinger DC. 1995. Interpreting the literature on lead and child development: The neglected role of the "experimental system". Neurotoxicol Teratol 17:201-212.

Bellinger DC. 2000. Effect modification in epidemiologic studies of low-level neurotoxicant exposures and health outcomes. Neurotoxicol Teratol 22:133-140.

Bellinger DC. 2004. Lead. Pediatrics 113(4):1016-1022.

Bellinger DC, Needleman HL. 1983. Lead and the relationship between maternal and child intelligence. J Pediatr 102:523-527.

Bellinger DC, Needleman HL. 2003. Intellectual impairment and blood lead levels. N Engl J Med 349(5):500-502.

Bellinger DC, Hu H, Titlebaum L, et al. 1994. Attentional correlates of dentin and bone lead levels in adolescents. Arch Environ Health 49(2):98-105.

Bellinger DC, Leviton A, Needleman HL, et al. 1986a. Low-level lead exposure and infant development in the first year. Neurobehav Toxicol Teratol 8:151-161.

Bellinger DC, Leviton A, Rabinowitz M, et al. 1986b. Correlates of low-level lead exposure in urban children at two years of age. Pediatrics 77:826-833.

Bellinger DC, Leviton A, Waternaux C, et al. 1985a. A longitudinal study of the developmental toxicity of low-level lead exposure in the prenatal and early postnatal periods. In: Lekkas TD, ed. International conference on heavy metals in the environment, Athens, Greece, September, Vol. 1. Edinburgh, United Kingdom: CEP Consultants, Ltd., 32-34.

Bellinger DC, Leviton A, Watemaux C, et al. 1985b. Methodological issues in modeling the relationship between low-level lead exposure and infant development: Examples from the Boston lead study. Environ Res 38:119-129.

Bellinger DC, Leviton A, Waternaux C, et al. 1987a. Longitudinal analyses of prenatal and postnatal lead exposure and early cognitive development. N Engl J Med 316:1037-1043.

9. REFERENCES

Bellinger DC, Leviton A, Waternaux C, et al. 1989a. Low-level lead exposure and early development in socioeconomically advantaged urban infants. In: Smith M, Grant LD, Sors A, eds. Lead exposure and child development: An international assessment. Lancaster, UK: Kluwer Academic Publishers, 345-356.

Bellinger DC, Leviton A, Waternaux C, et al. 1989b. Low-level lead exposure, social class, and infant development. Neurotoxicol Teratol 10:497-504.

Bellinger DC, Needleman HL, Leviton A, et al. 1984. Early sensory-motor development and prenatal exposure to lead. Neurobehav Toxicol Teratol 6:387-402.

Bellinger DC, Sloman J, Leviton A, et al. 1987b. Low level lead exposure and child development: Assessment at age 5 of a cohort followed from birth. In: Lindberg SE, Hutchinson TC, eds. International Conference on Heavy Metals in the Environment. New Orleans, LA, September, Vol. 1. Edinburgh, UK: CEP Consultants, Ltd., 49-53.

Bellinger DC, Sloman J, Leviton A, et al. 1991. Low-level lead exposure and children's cognitive function in the preschool years. Pediatrics 87:219-227.

Bellinger DC, Stiles KM, Needleman HL. 1992. Low-level lead exposure, intelligence and academic achievement: A long-term follow-up study. Pediatrics 90:855-861.

Benetou-Marantidou A, Nakou S, Michelovannis J. 1988. Neurobehavioral estimation of children with life-long increased lead exposure. Arch Environ Health 43:392-395.

Bergdahl IA, Skerfving S. 1997. Partition of circulating lead between plasma and red cells does not seem to be different for internal and external sources of lead. Letter to the editor. Am J Ind Med 32:317-318.

Bergdahl IA, Gerhardsson L, Liljelind IE, et al. 2006. Plasma-lead concentration: Investigations into its usefulness for biological monitoring of occupational lead exposure. Am J Ind Med 49(2):93-101.

Bergdahl IA, Gerhardsson L, Schutz A, et al. 1997b. Delta-aminolevulinic acid dehydratase polymorphism: Influence on lead levels and kidney function in humans. Arch Environ Health 52(2):91-96.

Bergdahl IA, Grubb A, Schutz A, et al. 1997a. Lead binding to δ-aminolevulinic acid dehydratase (ALAD) in human erythrocytes. Pharmacol Toxicol 81:153-158.

Bergdahl IA, Schutz A, Grubb A. 1996. Application of liquid chromatography-Inductively coupled plasma mass spectrometry to the study of protein-bond lead in human erythrocytes. J Anal Atom Spectrom 11:735-738.

Bergdahl IA, Sheveleva M, Schutz A, et al. 1998. Plasma and blood lead in humans: Capacity-limited binding to δ-aminolevulinic acid dehydratase and other lead-binding components. Toxicol Sci 46:247-253.

Bergdahl IA, Vahter M, Counter SA, et al. 1999. Lead in plasma and whole blood from lead-exposed children. Environ Res 80:25-33.

9. REFERENCES

Berkowitz GS, Wolff MS, Lapinski RH, et al. 2004. Prospective study of blood and tibia lead in women undergoing surgical menopause. Environ Health Perspect 112(17):1673-1678.

Berlin CM, Gorman RL, May DG, et al. 1995. Treatment guidelines for lead exposure in children. Pediatrics 96(1):155-160.

Bernard BP, Becker CE. 1988. Environmental lead exposure and the kidney. Clin Toxicol 26:1-34.

Bernard AM, Vyskocil A, Roels H, et al. 1995. Renal effects in children living in the vicinity of a lead smelter. Environ Res 68:91-95.

Berndtsson R. 1993. Small-scale spatial patterns of bulk atmospheric deposition. J Environ Qual 22:349-360.

Bert JL, Van Dusen LJ, Grace JR. 1989. A generalized model for the prediction of lead body burdens. Environ Res 48:117-127.

Betts PR, Astley R, Raine DN. 1973. Lead intoxication in children in Birmingham. Br Med J 1:402-406.

Beyer WN, Cromartie EJ. 1987. A survey of Pb, Cu, Zn, Cd, Cr, As, and Se in earthworms and soil from diverse sites. Environ Monit Assess 8:27-36.

*Bhattacharya A, Shukla R, Bornschein R, et al. 1988. Postural disequilibrium quantification in children with chronic lead exposure: A pilot study. Neurotoxicology 9:327-340.

Bhattacharya A, Shukla R, Dietrich KN, et al. 1993. Functional implications of postural disequilibrium due to lead exposure. Neurotoxicology 14:179-190.

*Bhattacharya A, Smelser DT, Berger O, et al. 1998. The effect of succimer therapy in lead intoxication using postural balance as a measure: A case study in a nine year old child. Neurotoxicology 19(1):57-64.

Biagini G, Caudarelia R, Vangelista A. 1977. Renal morphological and functional modification in chronic lead poisoning. In: Brown SS, ed. Clinical chemistry and chemical toxicology of metals. Elsevier/North-Holland Biomedical Press, 123-126.

Biggins PDE, Harrison RM. 1979. Atmospheric chemistry of automotive lead. Environ Sci Technol 13:558-565.

Billick IH, Gray VE. 1978. Lead based paint poisoning research: Review and evaluation 1971-1977. Washington, DC: U.S. Department of Housing and Urban Development.

Binder S, Sokal D, Maugham D. 1986. Estimating soil ingestion: The use of tracer elements in estimating the amount of soil ingestion by young children. Arch Environ Health 41:341-345.

Birch J, Harrison RM, Laxen DPH. 1980. A specific method for 24-48 hour analysis of tetraalkyl lead in air. Sci Total Environ 14:31-42.

Bizarro P, Acevedo S, Nino-Cabrera G, et al. 2003. Ultrastructural modifications in the mitochondrion of mouse Sertoli cells after inhalation of lead, cadmium or lead–cadmium mixture. Reprod Toxicol 17:561-566.

Blake KCH, Mann M. 1983. Effect of calcium and phosphorus on the gastrointestinal absorption of ^{203}Pb in man. Environ Res 30:188-194.

Blake KCH, Barbezat GO, Mann M. 1983. Effect of dietary constituents on the gastrointestinal absorption of ^{203}Pb in man. Environ Res 30:182-187.

Blakley BR, Archer DL. 1982. Mitogen stimulation of lymphocytes exposed to lead. Toxicol Appl Pharmacol 62:183-189.

Blakley BR, Archer DL, Osborne L. 1982. The effect of lead on immune and viral interferon production. Can J Comp Med 46:43-46.

Bleecker ML, Ford DP, Lindgren KN, et al. 2003. Association of chronic and current measures of lead exposure with different components of brainstem auditory evoked potentials. Neurotoxicology 24:625-631.

Bleecker ML, Ford DP, Lindgren KN, et al. 2005. Differential effects of lead exposure on components of verbal memory. Occup Environ Med 62(3):181-187.

Bloch P, Garavaglia G, Mitchell G, et al. 1976. Measurement of lead content of children's teeth in situ by x-ray fluorescence. Phys Med Biol 20:56-63.

Bloom NS, Crecelius EA, 1987. Distribution of silver, mercury, lead, copper, and cadmium in Central Puget Sound sediments. Mar Chem 21:377-390.

Böckelmann I, Pfister EA, McGauran N, et al. 2002. Assessing the suitability of cross-sectional and longitudinal cardiac rhythm tests with regard to identifying effects of occupational chronic lead exposure. J Occup Environ Med 44:59-65.

Bogden JD, Kemp FW, Han S, et al. 1995. Dietary calcium and lead interact to modify maternal blood pressure, erythropoiesis, and fetal and neonatal growth in rats during pregnancy and lactation. J Nutr 125:990-1002.

Bohnker BK, Schwartz E, McGinnis J, et al. 2003. Effects of pediatric blood lead surveillance on Navy population health (1995-2001). Mil Med 168(5):391-393.

Boileau J, Fauquignon C, Napoly C. 1987. Explosives. In: Ullmann's encyclopedia of industrial chemistry. 5th edition. New York, NY: VCH Publishers, 143-172.

Bolanowska W. 1968. Distribution and excretion of triethyllead in rats. Br J Ind Med 25:203-208.

Bolanowska W, Piotrowski J, Garczynski H. 1967. Triethyllead in the biological material in cases of acute tetraethyllead poisoning. Arch Toxicol 22:278-282.

Bolger PM, Carrington CD, Capar SG, et al. 1991. Reductions in dietary lead exposure in the United States. Chem Speciation Bioavail 3(314):31-36.

Bolger PM, Yess NJ, Gunderson EL, et al. 1996. Identification and reduction of sources of dietary lead in the United States. Food Addit Contam 13(1):53-60.

9. REFERENCES

Bonanno LJ, Freeman NCG, Greenburg M, et al. 2001. Multivariate analysis on levels of selected metals, particulate matter, VOC, and household characteristics and activities from the midwestern states NHEXAS. Appl Occup Environ Hyg 16(9):859-874.

Bonde JP, Kolstad H. 1997. Fertility of Danish battery workers exposed to lead. Int J Epidemiol 26(6):1281-1288.

Bonde JP, Joffe M, Apoatoli P, et al. 2002. Sperm count and chromatin structure in men exposed to inorganic lead: Lowest adverse effect levels. Occup Environ Med 59:234-242.

Bonithon-Kopp C, Huel G, Grasmick C, et al. 1986c. Effects of pregnancy on the inter-individual variations in blood lead levels of lead, cadmium and mercury. Biol Res Preg 7:37-42.

*Bonithon-Kopp C, Huel G, Moreau T. 1986a. [Lead and psychomotor development in children: A critical analysis of arguments of epidemiologic origin.] Neuropsychiatr Enfanc Adolesc 34:383-394. (French)

*Bonithon-Kopp C, Huel G, Moreau T, et al. 1986b. Prenatal exposure to lead and cadmium and psychomotor development of the child at 6 years. Neurobehav Toxicol Teratol 8:307-310.

*Borella P, Picco P, Masellis G. 1986. Lead content in abortion material from urban women in early pregnancy. Int Arch Occup Environ Health 57:93-99.

Borja-Aburto VH, Hertz-Picciotto I, Lopez MR, et al. 1999. Blood lead levels measured prospectively and risk of spontaneous abortion. Am J Epidemiol 150:590-597.

Borjesson J, Gerhardsson L, Schuetz A, et al. 1997. In vivo measurements of lead in fingerbone in active and retired lead smelters. Int Arch Occup Environ Health 69(2):97-105.

Bornschein RL, Grote J, Mitchell T, et al. 1989. Effects of prenatal lead exposure on infant size at birth. In: Smith M, Grant LD, Sors A, eds. Lead exposure and child development: An international assessment. Lancaster, UK: Kluwer Academic Publishers, 307-319.

Bornschein RL, Succop PA, Krafft KM, et al. 1986. Exterior surface dust lead, interior house dust lead and childhood lead exposure in an urban environment. In: Hemphil DD, ed. Trace substances in environmental health. Vol. 20. Columbia, MO: University of Missouri 322-332.

Bos AJJ, can der Stap CCAH, Valkovic V, et al. 1985. Incorporation routes of elements into human hair: Implications for hair analysis used for monitoring. Sci Total Environ 42:157-169.

Boscolo P, Carmignani M. 1988. Neurohumoral blood pressure regulation in lead exposure. Environ Health Perspect 78:101-106.

*Boscolo P, Galli G, Iannaccone A, et al. 1981. Plasma renin activity and urinary kallikrein excretion in lead-exposed workers as related to hypertension and nephropathy. Life Sci 28:175-184.

Bost L, Primatesta P, Dong W, et al. 1999. Blood lead and blood pressure: Evidence from the health survey for England 1995. J Hum Hypertens 13(22):123-128.

Boudene C, Despaux-Pages N, Comoy E, et al. 1984. Immunological and enzymatic studies of erythrocytic 8-aminolevulinate dehydratase. Int Arch Occup Environ Health 55:87-96.

9. REFERENCES

Boudene C, Malet D, Masse R. 1977. Fate of 210Pb inhaled by rats. Toxicol Appl Pharmacol 41:271-276.

Bouton C, Pevsner J. 2000. Effects of lead on gene expression. Neurotoxicology 21(6):1045-1056.

Bowen HJM. 1966. Trace elements in biochemistry. New York, NY: Academic Press, 31-32.

Bowers TS, Beck BD. 2006. What is the meaning of non-linear dose-response relationships between blood lead concentrations and IQ? Neurotoxicology 27:520-524.

Bowers TS, Mattuck RL. 2001. Further comparisons of empirical and epidemiological data with predictions of the integrated exposure uptake biokinetic model for lead in children. Hum Ecol Risk Assess 7(6):1699-1713.

Bowers TS, Beck BD, Karam HS. 1994. Assessing the relationship between environmental lead concentrations and adult blood lead levels. Risk Anal 14(2):183-189.

Bradley JE, Baumgartner RJ. 1958. Subsequent mental development of children with lead encephalopathy, as related to type of treatment. J Pediatr 53:311-315.

Bradley SB, Cox JJ. 1988. The potential availability of cadmium, copper, iron, lead, manganese, nickel, and zinc in standard river sediment (NBS 1645). Environ Technol Lett 9:733-739.

Bradley JE, Powell AE, Niermann W, et al. 1956. The incidence of abnormal blood levels of lead in a metropolitan pediatric clinic: With observation on the value of coproporphyrinuria as a screening test. J Pediatr 49:1-6.

Bradman A, Eskenazi B, Sutton P, et al. 2001. Iron deficiency associated with higher blood lead in children living in contaminated environments. Environ Health Perspect 109(10):1079-1084.

Brady HR, Brenner BM, Clarkson MR, et al. 2000. Acute renal failure. In: Brenner BM, ed. The kidney. New York, NY: W.B. Saunders Co., 1202.

Braithwaite RA, Brown SS. 1987. The need for accuracy in trace metal analysis: A case study of childhood exposure to lead. Occup Environ Health 9:35-49.

Braunstein GD, Dahlgren J, Loriaux DL. 1978. Hypogonadism in chronically lead-poisoned men. Infertility 1:33-51.

Bress WC, Bidanset JH. 1991. Percutaneous in vivo and in vitro absorption of lead. Vet Hum Toxicol 33:212-214.

Bressler J, Kim K, Chakraborti T, et al. 1999. Molecular mechanisms of lead neurotoxicity. Neurochem Res 24(4):595-600.

Bressler JP, Olivi L, Kim Y, et al. 2005. Plasma membrane transporters for lead and cadmium. J Appl Pharmacol 13(1):1-6.

Brewer GJ, Hill GM, Dick RD, et al. 1985. Interactions of trace elements: Clinical significance. J Am Coll Nutr 4:33-38.

Brito JA, McNeill FE, Webber CE, et al. 2005. Grid search: An innovative method for the estimation of the rates of lead exchange between body compartments. J Environ Monit 7(3):241-247.

Brockel BJ, Cory-Slechta DA. 1998. Lead, attention, and impulsive behavior: Changes in a fixed-ratio waiting-for-reward paradigm. Pharmacol Biochem Behav 60(2):545-552.

Brody DJ, Pirkle JL, Kramer RA, et al. 1994. Blood lead levels in the US population. Phase 1 of the Third National Health and Nutrition Examination Survey (NHANES III, 1988 to 1991). J Am Med Assoc 272:277-283.

Bronner F, Pansu S, Stein WD. 1986. An analysis of intestinal calcium transport across the rat intestine. Am J Physiol 250:G561-G569

Bruce WR, Heddle JA. 1979. The mutagenic activity of 61 agents as determined by the micronucleus, Salmonella and sperm abnormality assays. Can J Genet Cytol 21:319-334.

Buc HA, Kaplan JC. 1978. Red-cell pyrimidine 5'-nucleotidase and lead poisoning. Clin Chim Acta 87:49-55.

Buchanan LH, Counter SA, Ortega F, et al. 1999. Distortion product oto-acoustic emissions in Andean children and adults with chronic lead intoxication. Acta Otolaryngol (Stockh)119:652-658.

Buchet JP, Roels H, Bernard A, et al. 1980. Assessment of renal function of workers exposed to inorganic lead, cadmium, or mercury vapor. J Occup Med 22:741-750.

Budavari S, O'Neil MJ, Smith A, et al. eds. 1989. The Merck index. An encyclopedia of chemicals, drugs, and biologicals. 11th ed. Rahway, NJ: Merck & Co., Inc., 851-854.

Bull RJ, Lutkenhoff SD, McCarty GE, et al. 1979. Delays in the postnatal increase of cerebral cyochrome concentrations in lead-exposed rats. Neuropharmacology 18:83-92.

Bulsma JB, De France HF. 1976. Cytogenetic investigations in volunteers ingesting inorganic lead. Int Arch Occup Environ Health 28:145-148.

Bunn TL, Dietert RR, Ladics GS, et al. 2001c. Developmental immunotoxicology assessment in the rat: Age, gender, and strain comparisons after exposure to lead. Toxicol Meth 11:41-58.

Bunn TL, Parsons PJ, Kao E, et al. 2001a. Exposure to lead during critical windows of embryonic development: Differential immunotoxic outcome based on stage of exposure and gender. Toxicol Sci 64:57-66.

Bunn TL, Parsons PJ, Kao E, et al. 2001b. Gender-based profiles of developmental immunotoxicity to lead in the rat: Assessment in juveniles and adults. J Toxicol Environ Health A 64:223-240.

Burger J, Kennamer RA, Brisbin IL, et al. 1998. A risk assessment for consumers of mourning doves. Risk Anal 18(5):563-573.

Bushnell PJ, Bowman RE. 1979a. Effects of chronic lead ingestion on social development in infant Rhesus monkeys. Neurobehav Toxicol 1:207-219.

9. REFERENCES

Bushnell PJ, Bowman RE. 1979b. Persistence of impaired reversal learning in young monkeys exposed to low levels of dietary lead. J Toxicol Environ Health 5:1015-1023.

Bushnell PJ, Levin ED. 1983. Effects of zinc deficiency on lead toxicity in rats. Neurobehav Toxicol Teratol 5:283-288.

Bushnell PJ, Bowman RE, Allen JR, et al. 1977. Scotopic vision deficits in young monkeys exposed to lead. Science 196:333-335.

Byczkowski JZ, Gearhart JM, Fisher JW. 1994. Occupational exposure of infants to toxic chemicals via breast milk. Nutrition 10(1):43-48.

Byers RK, Lord EE. 1943. Late effects of lead poisoning on mental development. Am J Dis Child 66(5):471-494.

Cake KM, Bowins RJ, Vaillancourt C, et al. 1996. Partition of circulating lead between serum and red cells is different for internal and external sources of exposure. Am J Ind Med 29:440-445.

Calabrese EJ. 1978. Pollutants and high-risk groups: The biological basis of increased human susceptibility to environmental and occupational pollutants. New York, NY: John Wiley and Sons, 43-49, 71-72, 106-107, 135-138.

Calabrese EJ, Barnes R, Stanek EJ III, et al. 1989. How much soil do young children ingest: An epidemiological study. Regul Toxicol Pharmacol 10:123-137.

Calabrese EJ, Stanek EJ, James RC, et al. 1997b. Soil ingestion: A concern for acute toxicity in children. Environ Health Perspect 105:1354-1358.

Calabrese EJ, Stanek EJ, Pekow P, et al. 1997a. Soil ingestion estimates for children residing on a Superfund site. Ecotoxicol Environ Saf 36:258-268.

Calderon-Salinas JV, Quintanar-Escorcia MA, Gonzalez-Martinez MT, et al. 1999. Lead and calcium transport in human erythrocyte. Hum Exp Toxicol 18:327-332.

California Department of Fish and Game. 2004. Analysis of lead in California condor feathers: Determination of exposure and depuration during feather growth. Sacramento, CA: California Department of Fish and Game.

Campara P, D'Andrea F, Micciolo R, et al. 1984. Psychological performance of workers with blood-lead concentration below the current threshold limit value. Int Arch Occup Environ Health 53:233-246.

Campbell JR, Toribara TY. 2001. Hair-root lead to screen for lead toxicity. J Trace Elem Exp Med 14:69-72.

*Campbell BC, Beattie AD, Moore MR, et al. 1977. Renal insufficiency associated with excessive lead exposure. Br Med J 1:482-485.

*Campbell BC, Meredith PA, Scott JJC. 1985. Lead exposure and changes in the renin-angiotensin-aldosterone system in man. Toxicol Lett 25:25-32.

Campbell JR, Moss ME, Raubertas RF. 2000a. The association between caries and childhood lead exposure. Environ Health Perspect 108(11):1099-1102.

Campbell JR, Rosier RN, Novotny L, et al. 2004. The association between environmental lead exposure and bone density in children. Environ Health Perspect 112(11):1200-1203.

Campbell TF, Needleman HL, Riess JA, et al. 2000b. Bone lead levels and language processing performance. Dev Neuropsychol 18(2):171-186.

Canfield RL, Gendle MH, Cory-Slechta DA. 2004. Impaired neuropsychological functioning in lead-exposed children. Dev Neuropsychol 26(1):513-540.

Canfield RL, Henderson CR, Cory-Slechta DA, et al. 2003. Intellectual impairment in children with blood lead concentrations below 10 microgram per deciliter. N Engl J Med 348(16):1517-1526.

Canonne-Hergaux F, Gruenheid S, Ponka P, et al. 1999. Cellular and subcellular localization of the Nramp2 iron transporter in the intestinal brush border and regulation by dietary iron. Blood 93(12):4406-4417.

Capar SG, Cunningham WC. 2000. Element and radionuclide concentrations in food: FDA total diet study 1991-1996. J AOAC Int 83(11):157-177.

Capar SG, Rigsby EJ. 1989. Survey of lead in canned evaporated milk. J Assoc Off Anal Chem 72:416-417.

Carbone R, Laforgia N, Crollo E, et al. 1998. Maternal and neonatal lead exposure in southern Italy. Biol Neonate 73:362-366.

Cardenas A, Roels H, Bernard AM, et al. 1993. Markers of early renal changes induced by industrial pollutants. II. Application to workers exposed to lead. Br J Ind Med 50:28-36.

Cardozo dos Santos A, Colacciopo S, Bo CMRD, et al. 1994. Occupational exposure to lead, kidney function tests, and blood pressure. Am J Ind Med 26:635-643.

Carlisle JC, Wade MJ. 1992. Predicting blood lead concentrations from environmental concentrations. Regul Toxicol Pharmacol 16:280-289.

Carmignani M, Boscolo M, Poma P, et al. 1999. Kininergic system and arterial hypertension following chronic exposure to inorganic lead. Immunopharmacology 44:105-110.

Carmignani M, Boscolo P, Preziosi P. 1988. Cardiovascular actions of lead in rats as related to the level of chronic exposure. Arch Toxicol Supp 12:326-329.

Carmignani M, Volpe AR, Boscolo P, et al. 2000. Catcholamine and nitric oxide systems as targets of chronic lead exposure in inducing selective functional impairment. Life Sci 68:401-415.

Carmouche JJ, Puzas JE, Zhang X, et al. 2005. Lead exposure inhibits fracture healing and is associated with increased chondrogenesis, delay in cartilage mineralization, and a decrease in osteoprogenitor frequency. Environ Health Perspect 113:749-755.

Carpenter SJ. 1982. Enhanced teratogenicity of orally administered lead in hamsters fed diets deficient in calcium or iron. Toxicology 24:259-271.

Carr DS. 1995. Lead compounds: Lead salts. In: Kirk-Othmer encyclopedia of chemical technology. 4th edition. New York, NY: John Wiley and Sons, 132-152.

Carta P, Carta R, Girei E, et al. 2003. [Cognitive and performance capacity among adolescents living near a lead and zinc smelter.] G Ital Med Lav Ergon 25(Suppl 3):43-45.

Case JM, Reif CB, Timko A. 1989. Lead in the bottom sediments of Lake Nuangola and fourteen other bodies of water in Luzerne County, Pennsylvania. J PA Acad Sci 63:67-72.

Casteel WS, Cowart RP, Weis CP, et al. 1997. Bioavailability of lead to juvenile swain dosed with soil from the Smuggler Mountain NLP site of Aspen, Colorado. Fundam Appl Toxicol 36:177-187.

Cavalleri A, Minoia C, Pozzoli L, et al. 1978. Determination of plasma lead levels in normal subjects and in lead-exposed workers. Br J Ind Med 35:21-26.

Cavalleri A, Trimarchi F, Gelmi C, et al. 1982. Effects of lead on the visual system of occupationally exposed subjects. Scand J Work Environ Health 8:148-151.

CDC. 1985. Preventing lead poisoning in young children. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. Publication No. 99-2230, 7-19.

CDC. 1991. Preventing lead poisoning in young children. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention.

*CDC. 1997a. Adult blood lead epidemiology and surveillance-United States Fourth Quarter 1996. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 46(16):358-359, 367.

CDC. 1997b. Update: Blood lead levels. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 46(7):141-146.

CDC. 1997c. Screening young children for lead poisoning: Guidance for state and local public health officials. Centers for Disease Control and Prevention. Atlanta, GA: U.S. Department of Health & Human Services.

CDC. 1997d. Children with elevated blood lead levels attributed to home renovation and remodeling activities - New York 1993-1994. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 45(51&52):1120-1123.

CDC. 1998. Lead poisoning associated with imported candy and powdered food coloring - California and Michigan. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 47(48):1041-1043.

CDC. 2003. Second national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention. Atlanta, GA: U.S. Department of Health and Human Services.

CDC. 2004. Lead poisoning associated with ayurvedic medications - five states, 2000-2003. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 53(26):582-584.

CDC. 2005a. Blood lead levels - United States, 1999-2002. Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 54(20):513-516.

CDC. 2005b. Third national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention. Atlanta, GA: U.S. Department of Health and Human Services.

CDC. 2007. Lead exposure among females of childbearing age-United States, 2004. MMWR Morb Mortal Wkly Rep 56(16):397-400. http://www.cdc.gov/mmwr/PDF/wk/mm5616.pdf. June 05, 2007.

Cerklewski FL. 1979. Influence of dietary zinc on lead toxicity during gestation and lactation in the female rat. J Nutr 109:1703-1709.

Cerklewski FL. 1980. Reduction in neonatal lead exposure by supplemental dietary iron during gestation and lactation in the rat. J Nutr 110:1453-1457.

Cerklewski FL, Forbes RM. 1976. Influence of dietary zinc on lead toxicity in the rat. J Nutr 106:689-696.

Chakraborti D, DeJonghe WRA, Mol WE, et al. 1984. Determination of ionic alkyllead compounds in water by gas chromatography/atomic absorption spectrometry. Anal Chem 56:2692-2697.

Chamberlain A. 1983. Effect of airborne lead on blood lead. Atmos Environ 17:677-692.

Chamberlain A, Heard C, Little MJ, et al. 1978. Investigations into lead from motor vehicles. Harwell, United Kingdom: United Kingdom Atomic Energy Authority. Report no. AERE-9198. 1979. The dispersion of lead from motor exhausts. Philos Trans R Soc Lond A 290:557-589.

Chamberlain A, Heard C, Little P, et al. 1979. The dispersion of lead from motor exhausts. Philos Trans R Soc Lond A 290:557-589.

Chan WH, Tang JS, Chung DH, et al. 1986. Concentration and deposition of trace metals in Ontario 1982. Water Air Soil Pollut 29:373-389.

Chaney RL, Mielke HW, Sterret SB. 1988. Speciation, mobility and bioavailability of soil lead. Environ Geochem Health 9:105-129.

Chang H-R, Chen S-S, Chen T-J, et al. 1996. Lymphocyte β_{-2}-adrenergic receptors and plasma catecholamine levels in lead-exposed workers. Toxicol Appl Pharmacol 139:1-5.

Charney E, Sayre J, Coulter M. 1980. Increased lead absorption in inner city children: Where does the lead come from? Pediatrics 65:226-231.

Chau YK, Wong PTS, Bengert GA, et al. 1979. Determination of tetraalkyl-lead compounds in water, sediments, and fish samples. Anal Chem 51:186-188.

Chau YK, Wong PTS, Kramar O, et al. 1980. Occurrence of tetraalkylead compounds in the aquatic environment. Bull Environ Contam Toxicol 24:265-269.

ChemIDplus. 2005. Lead and lead compounds. Bethesda, MD: U.S. National Library of Medicine.

9. REFERENCES

Chen A, Dietrich KN, Ware JH, et al. 2005. IQ and blood lead from 2 to 7 years of age: Are the effects in older children the residual of high blood lead concentrations in 2-year-olds? Environ Health Perspect 113(5):597-601.

Chen A, Rhoads GG, Cai B, et al. 2006. The effect of chelaton on blood pressure in lead-exposed children: A randomized study. Environ Health Perspect 114(4):579-583.

Cheng Y, Schwartz J, Sparrow D, et al. 2001. Bone lead and blood lead levels in relation to baseline blood pressure and the prospective development of hypertension. Am J Epidemiol 153(2):164-171.

Cheng Y, Schwartz J, Vokonas PS, et al. 1998. Electrocardiographic conduction disturbances in association with low-level lead exposure (the Normative Aging Study). Am J Cardiol 82:594-599.

Chettle DR, Scott MC, Somervaille LJ. 1991. Lead in bone: Sampling and quantitation using K X-rays excited by 109Cd. Environ Health Perspect 91:45-55.

Chia KS, Jeyaratnam J, Lee J, et al. 1995b. Lead-induced nephropathy: Relationship between various biological exposure indices and early markers of nephrotoxicity. Am J Ind Med 27:883:895.

Chia KS, Jeyaratnam J, Tan C, et al. 1995a. Glomerular function of lead-exposed workers. Toxicol Letters 77:319-328.

Chia KS, Mutti A, Tan C, et al. 1994. Urinary N-acetyl-D-glucosaminidase activity in workers exposed to inorganic lead. Occup Environ Med 51:125-129.

Chia SE, Chia HP, Ong CN, et al. 1996b. Cumulative concentrations of blood lead and postural stability. Occup Environ Med 53(4):264-268.

Chia SE, Chia KS, Chia HP, et al. 1996a. Three-year follow-up of serial nerve conduction among lead-exposed workers. Scand J Work Environ Health 22(5):374-80.

Chia SE, Zhou H, Tham MT, et al. 2005. Possible influence of δ-aminolevulinic acid dehydratase polymorphism and susceptibility to renal toxicity of lead: A study of a Vietnamese population. Environ Health Perspect 113(10):1313-1317.

Chillrud SN, Bopp RF, Simpson HJ, et al. 1999. Twentieth century atmospheric metal fluxes into Central Park Lake, New York City. Environ Sci Technol 33(5):657-662.

Chiodo LM, Jacobson SW, Jacobson JL. 2004. Neurodevelopmental effects of postnatal lead exposure at very low levels. Neurotoxicol Teratol 26(3):359-371.

Chisolm JJ. 1962. Aminoaciduria as a manifestation of renal tubular injury in lead intoxication and a comparison with patterns of aminoaciduria seen in other diseases. J Pediatr 60:1-17.

Chisolm JJ. 1965. Chronic lead intoxication in children. Dev Med Child Neurol 7:529-536.

Chisolm JJ. 1968. The use of chelating agents in the treatment of acute and chronic lead intoxication in childhood. J Pediatr 73:1-38.

9. REFERENCES

Chisolm JJ. 1981. Dose-effect relationships for lead in young children: Evidence in children for interactions among lead, zinc, and iron. In: Lynam DR, Piantanida LG, Cole JF, eds. Environmental lead: Proceedings on the second international symposium on environmental lead research, December, 1978, Cincinnati, Ohio. New York, NY: Academic Press, 1-7.

Chisolm JJ. 1986. Removal of lead paint from old housing: The need for a new approach. Am J Public Health 76:236-237.

Chisolm JJ. 2000. Safety and efficacy of meso-2,3-dimercaptosuccinic acid (DMSA) in children with elevated blood lead concentrations. Clin Toxicol 38(4):365-375.

Chisolm JJ, Harrison HE. 1956. The exposure of children to lead. Pediatrics 18:943-958.

*Chisolm JJ, Harrison HC, Eberlein WR, et al. 1955. Aminoaciduria, hypophosphatemia, and rickets in lead poisoning: Study of a case. Am J Dis Child 89:159-168.

Chisolm JJ, Mellits ED, Barrett MB. 1976. Interrelationships among blood lead concentration, quantitative daily ALA-U and urinary lead output following calcium EDTK. In: Nordberg GF, ed. Proceedings of third meeting of the subcommittee on the toxicology of metals under the Permanent Commission and International Association on Occupational Health, November 1974, Tokyo, Japan. Amsterdam, Netherlands: Elsevier Publishing Co., 416-433.

Chisolm JJ, Thomas DJ, Hamill TG. 1985. Erythrocyte porphobilinogen synthase activity as an indicator of lead exposure to children. Clin Chem 31:601-605.

Choie DD, Richter GW. 1972. Lead poisoning: Rapid formation of intranuclear inclusions. Science 177:1194-1195.

Chowdhury AR, Chinoy NJ, Gautam AK, et al. 1986. Effect of lead on human semen. Adv Contracept Deliv Syst 2:208-211.

Christoffersson JO, Ahlgren L, Schutz A, et al. 1986. Decrease of skeletal lead levels in man after end of occupational exposure. Arch Environ Health 41:312-318.

Chu NF, Liou SH, Wu TN, et al. 1999. Reappraisal of the relation between blood lead concentration and blood pressure among the general population in Taiwan. Occup Environ Med 56:30-33.

Chuan MC, Shu GY, Liu JC. 1996. Solubility of heavy metals in a contaminated soil: Effects of redox potential and pH. Water Air Soil Pollut 90:543-556.

Chuang HY, Chao KY, Tsai SY. 2005. Reversible neurobehavioral performance with reductions in blood lead levels-A prospective study on lead workers. Neurotoxicol Teratol 27(3):497-504.

Chuang HY, Schwartz J, Gonzales-Cossio T, et al. 2001. Interrelations of lead levels in bone, venous blood, and umbilical cord blood with exogenous lead exposure through maternal plasma lead in peripartum women. Environ Health Perspect 109(5):527-532.

Cikrt M, Tichy M. 1975. Role of bile in intestinal absorption of ^{203}Pb in rats. Experientia 31:1320-3121.

Clark CS, Bornschein RL, Succop P, et al. 1985. Conditions and type of housing as an indicator of potential environmental lead exposure and pediatric blood lead levels. Environ Res 38:46-53.

Clausing P, Brunekreef B, van Wijen JH. 1987. A method for estimating soil ingestion by children. Int Arch Occup Environ Health 59:73-82.

Clayton CA, Pellizzari ED, Quackenboss JJ. 2002. National Human Exposure Assessment Survey: Analysis of exposure pathways and routes for arsenic and lead in EPA Region 5. J Expo Anal Environ Epidemiol 12:29-43.

Clewell HJ III, Andersen ME. 1985. Risk assessment extrapolations and physiological modeling. Toxicol Ind Health 1(4):111-131.

Coate D, Fowles R. 1989. Is there statistical evidence for a blood lead-blood pressure relationship? J Economics 8:173-184.

Cocco P, Carta P, Flore C, et al. 1996. Mortality of lead smelter workers with the glucose-6-phosphate dehydrogenase-deficient phenotype. Cancer Epidemiol Biomarkers Prev 5(3):223-225.

Cocco P, Cocco E, Anni MS, et al. 1991. Occupational exposure to lead and blood cholesterol in glucose-6-phosphate dehydrogenase deficient and normal subjects. Res Commun Chem Pathol Pharmacol 72(1):81-95.

Cocco P, Dosemeci M, Heineman EF. 1998a. Brain cancer and occupational exposure to lead. J Occup Environ Med 40(11):937-942.

Cocco P, Hua F, Boffetta P, et al. 1997. Mortality of Italian lead smelter workers. Scand J Work Environ Health 23(1):15-23.

Cocco P, Ward MH, Dosemeci M. 1998b. Occupational risk factors for cancer of the gastric cardia. J Occup Environ Med 40(10):855-861.

Cohen J. 1988. Revisions to dietary lead estimates for case-study exposure analyses. Memo to the files. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. September 9, 1988.

Cohen AJ, Roe FJC. 1991. Review of lead toxicology relevant to the safety assessment of lead acetate as a hair colouring. Food Chem Toxicol 29(7):485-507.

Congiu L, Corongiu FP, Dore M, et al. 1979. The effect of lead nitrate on the tissue distribution of mercury in rats treated with methylmercury chloride. Toxicol Appl Pharmacol 51:363-366.

Congressional Record. 1988. Lead contamination control act of 1988. Congressional Record-House. (October 5, 1988):49645-49648.

Cools A, Salle HJA, Verberk MM, et al. 1976. Biochemical response of male volunteers ingesting inorganic lead for 49 days. Int Arch Occup Environ Health 38:129-139.

*Cooney GH, Bell A, McBride W, et al. 1989a. Low-level exposures to lead: The Sydney lead study. Dev Med Child Neurol 31:640-649.

*Cooney GH, Bell A, McBride W, et al. 1989b. Neurobehavioral consequences of prenatal low level exposures to lead. Neurotoxicol Teratol 11:95-104.

Cooper WC. 1988. Deaths from chronic renal disease in US battery and lead production workers. Environ Health Perspect 78:61-63.

Cooper WC, Wong O, Kheifets L. 1985. Mortality among employees of lead battery plants and lead producing plants, 1947-1980. Scand J Work Environ Health 11:331-345.

Corrin ML, Natusch DFS. 1977. Physical and chemical characteristics of environmental lead. In: Boggess WR, Wixson BG, eds. Lead in the environment. Washington, DC: National Science Foundation, 7-31.

*Cory-Slechta DA. 1990. Lead exposure during advanced age: Alterations in kinetics and biochemical effects. Toxicol Appl Pharmacol 104:67-78.

Cory-Slechta DA. 1995. Relationships between lead-induced learning impairments and changes in dopaminergic, cholinergic, and glutamatergic neurotransmitter system functions. Ann Rev Pharmacol Toxicol 35:391-415.

Cory-Slechta DA. 1997. Relationships between Pb-induced changes in neurotransmitter system function and behavioral toxicity. Neurotoxicology 18(3):673-688.

Cory-Slechta DA. 2003. Lead-induced impairments in complex cognitive function: Offerings from experimental studies. Neuropsychol Dev Cogn C Child Neuropsychol 9(1):54-75.

Cory-Slechta DA. 2006. Interactions of lead exposure and stress: Implications for cognitive dysfunction. Int Rev Res Ment Retard 30:87-139.

Cory-Slechta DA, Thompson T. 1979. Behavioral toxicity of chronic postweaning lead exposure in the rat. Toxicol Appl Pharmacol 47:151-159.

Cory-Slechta DA, Bissen ST, Young AM, et al. 1981. Chronic post-weaning lead exposure and response duration performance. Toxicol Appl Pharmacol 60:78-84.

Cory-Slechta DA, Virgolini MB, Thiruchelvam M, et al. 2004. Maternal stress modulates the effects of developmental lead exposure. Environ Health Perspect 112(6):717-730.

Cory-Slechta DA, Weiss B, Cox C. 1983. Delayed behavioral toxicity of lead with increasing exposure concentrations. Toxicol Appl Pharmacol 71:342-352.

Cory-Slechta DA, Weiss B, Cox C. 1985. Performance and exposure indices of rats exposed to low concentrations of lead. Toxicol Appl Pharmacol 78:291-299.

Cory-Slechta DA, Weiss B, Cox C. 1987. Mobilization and redistribution of lead over the course of calcium disodium ethylenediamine tetraacetate chelation therapy. J Pharmacol Exp Ther 243:804-813.

*Coscia GC, Discalzi G, Ponzetti C. 1987. Immunological aspects of occupational lead exposure. Med Lav 78:360-364.

Coscia JM, Ris MD, Succop PA, et al. 2003. Cognitive development of lead exposed children from ages 6 to 15 years: An application of growth curve analysis. Neuropsychol Dev Cogn C Child Neuropsychol 9(1):10-21.

Costa LG, Aschner M, Vitalone A, et al. 2004. Developmental neuropathology of environmental agents. Annu Rev Pharmacol Toxicol 44:87-110.

Costa M, Cantoni O, DeMars M, et al. 1982. Toxic metals produce S-phase-specific cell cycle block. Res Commun Chem Pathol Pharmacol 38:405-419.

Coste J, Mandereau L, Pessione F, et al. 1991. Lead-exposed workmen and fertility: A cohort study on 354 subjects. Eur J Epidemiol 7:154-158.

Counter SA. 2002. Brainstem neural conduction biomarkers in lead-exposed children of Andean lead-glaze workers. J Occup Environ Med 44(9):855-864.

Counter SA, Buchanan LH. 2002. Neuro-ototoxicity in Andean adults with chronic lead and noise exposure. J Occup Environ Med 44:30-38.

Counter SA, Buchanan LH, Ortega F, et al. 1997a. Normal auditory brainstem and cochlear function in extreme pediatric plumbism. J Neurol Sci 152(1):85-92.

Counter SA, Buchanan LH, Ortega F, et al. 2000. Blood lead and hemoglobin levels in Andean children with chronic lead intoxication. Neurotoxicology 21(3):301-308.

Counter SA, Vahter M, Buchanan LH, et al. 1997b. High lead exposure and auditory sensory-neural function in Andean children. Environ Health Perspecp 105:522-526.

CPSC. 1977. Ban of lead-containing products bearing lead-containing paint. Consumer Product Safety Commission. Code of Federal Regulations. 16 CFR 1303.

CPSC. 1996. CPSC finds lead poisoning hazard for young children in imported vinyl miniblinds. U.S. Consumer Product Safety Commission. http://www.cpsc.gov/cpscpub/prerel/prhtml96/96150.html. February 25, 1999.

Craig JR, Rimstidt JD, Bonnaffon CA, et al. 1999. Surface water transport of lead at shooting range. Bull Environ Contam Toxicol 63:312-319.

Cramer K, Goyer RA, Jagenburg R, et al. 1974. Renal ultrastructure, renal function, and parameters of lead toxicity in workers with different periods of lead exposure. Br J Ind Med 31:113-127.

Cremin JD, Luck ML, Laughlin NK, et al. 1999. Efficacy of succimer chelation for reducing brain lead in a primate model of human lead exposure. Toxicol Appl Pharmacol 161:283-293.

Crump K. 1997. Evaluation of the Boston study of effectiveness of soil abatement in reducing children's blood lead, with particular emphasis upon the EPA (1996) reevaluation. ICF Kaiser: Ruston, LA. Report to Seeger, Potter, Richardson, Luxton, Joselow & Brooks. March 13, 1997.

Cullen MR, Kayne RD, Robins JM. 1984. Endocrine and reproductive dysfunction in men associated with occupational inorganic lead intoxication. Arch Environ Health 39:431-440.

Dabeka RW, McKenzie AD. 1988. Lead and cadmium levels in commercial infant foods and dietary intake by infants 0-1 year old. Food Addit Contam 5:333-342.

9. REFERENCES

Dabeka RW, McKenzie AD. 1995. Survey of lead, cadmium, fluoride, nickel, and cobalt in food composites and estimation of dietary intakes of these elements by Canadians in 1986-1988. J AOAC Int 78(4):897-909.

Dabeka RW, Karpinski KF, McKenzie AD, et al. 1988. Survey of lead and cadmium in human milk and correlation of levels with environmental and food factors. Sci Total Environ 71:65-66.

Dabeka RW, McKenzie AD, Lacroix GMA. 1987. Dietary intakes of lead, cadmium, arsenic and fluoride by Canadian adults: A 24-hour duplicate diet study. Food Addit Contam 4:89-102.

Daggett DA, Oberley TD, Nelson SA, et al. 1998. Effects of lead on rat kidney and liver: GST expression and oxidative stress. Toxicology 128:191-206.

Dalpra L, Tibiletti MG, Nocera G, et al. 1983. SCE analysis in children exposed to lead emission from a smelting plant. Mutat Res 120:249-256.

Damm D, Grandjean P, Lyngbye T, et al. 1993. Early lead exposure and neonatal jaundice: Relation to neurobehavioral performance at 15 years of age. Neurotoxicol Teratol 15:173-181.

Danadevi K, Rozati R, Banu BS, et al. 2003. DNA damage in workers exposed to lead using comet assay. Toxicology 187:183-193.

Davis JM, Svendsgaard DJ. 1987. Lead and child development. Nature 329:297-300.

Davis JM, Svendsgaard DJ. 1990. Nerve conduction velocity and lead: A critical review and meta-analysis. In: Johnson BL, Anger WK, Durao A, et al., eds. Advances in neurobehavioral toxicology. Chelsea, MI: Lewis Publishers, 353-376.

Davis A, Ruby MV, Bergstrom PD. 1992. Bioavailability of arsenic and lead in soils from the Butte, Montana, mining district. Environ Sci Technol 26:461-468.

Davis A, Ruby MV, Bergstrom, PD. 1994. Factors controlling lead bioavailability in the Butte mining district, Montana, USA. Environ Geochem Health 16:147-157.

Davis A, Shokouhian M, Ni S. 2001. Loading estimates of lead, copper, cadmium, and zinc in urban runoff from specific sources. Chemosphere 44:997-1009.

Dearth RK, Hiney JK, Srivastava V, et al. 2002. Effects of lead (Pb) exposure during gestation and lactation on female pubertal development in the rat. Reprod Toxicol 16:343-352.

Dearth RK, Hiney JK, Srivastava V, et al. 2004. Low level lead (Pb) exposure during gestation and lactation: Assessment of effects on pubertal development in Fisher 344 and Sprague-Dawley female rats. Life Sci 74:1139-1148.

De Gennaro LD. 2002. Lead and the developing nervous system. Growth Dev Aging 66:43-50.

Dehpour AR, Essalat M, Ala S, et al. 1999. Increase by NO synthase inhibitor of lead-induced release of N-acetyl-beta-D-glucosaminidase from perfused rat kidney. Toxicology 132:119-125.

DeJonghe WRA, Adams FC. 1986. Biogeochemical cycling of organic lead compounds. Adv Environ Sci Technol 17:561-594.

DeJonghe WRA, Chakraborti D, Adams FC. 1981. Identification and determination of individual tetraalkyl lead species in air. Environ Sci Technol 15:1217-1222.

Deknudt G, Gerber GB. 1979. Chromosomal aberrations in bone-marrow cells of mice given a normal or a calcium-deficient diet supplemented with various heavy metals. Mutat Res 68:163-168.

Deknudt G, Colle A, Gerber GB. 1977. Chromosomal abnormalities in lymphocytes from monkeys poisoned with lead. Mutat Res 45:77-83.

de Kort WLAM, Zwennis WCM. 1988. Blood lead and blood pressure: Some implications for the situation in the Netherlands. Environ Health Perspect 78:67-70

de Kort WL, Verschoor MA, Wibowo AAE, et al. 1987. Occupational exposure to lead and blood pressure: A study of 105 workers. Am J Ind Med 11:145-156.

de la Burde B, Choate MS. 1972. Does asymptomatic lead exposure in children have latent sequelae? J Pediatr 81:1088-1091.

de la Burde B, Choate MS. 1975. Early asymptomatic lead exposure and development at school age. J Pediatr 87:638-642.

Delves HT, Campbell MJ. 1988. Measurements of total lead concentrations and of lead isotope ratios in whole blood by use of inductively coupled plasma source mass spectrometry. J Anal At Spectrom 3:343-348.

Denaix L, Semlali RM, Douay F. 2001. Dissolved and colloidal transport of Cd, Pb, and Zn in a silt loam soil affected by atmospheric industrial deposition. Environ Pollut 113:29-38.

Deng H, Ye ZH, Wong MH. 2004. Accumulation of lead, zinc, copper and cadmium by 12 wetland plant species thriving in metal-contaminated sites in China. Environ Pollut 132:29-40.

Den Hond E, Nawrot T, Staessen JA. 2001. Relationship between blood pressure and blood lead in NHANES III. J Hypertens 19(2):S57.

Den Hond E, Nawrot T, Staessen JA. 2002. The relationship between blood pressure and blood lead in NHANES III. J Hum Hypertens 16:563-568.

DeSilva PE. 1981. Determination of lead in plasma and studies on its relationship to lead in erythrocytes. Br J Ind Med 38:209-217.

Dewailly E, Ayotte P, Bruneau S, et al. 2001. Exposure of the Inuit population of Nunavik (Arctic Quebec) to lead and mercury. Arch Environ Health 56(4):350-357.

Dhawan M, Flora SJS, Singh S, et al. 1989. Chelation of lead during, co-exposure to ethanol. Biochem Int 19:1067-1075.

Diamond GL. 1988. Biological monitoring of urine for exposure to toxic metals. In: Clarkson TW, Nordberg G, Sager PF, et al., eds. Scientific basis and practical applications of biological monitoring of toxic metals. New York, NY: Plenum Press, 515-529.

Diamond GL. 2005. Risk assessment of nephrotoxic metals. In: Tarloff J, Lash L, eds. The toxicology of the kidney. London: CRC Press, 1099-1132.

Dick RD, Pinkerton LE, Krieg EF, et al. 1999. Evaluation of postural stability in workers exposed to lead at a secondary lead smelter. Neurotoxicology 20(4):595-607.

Dieter MP, Matthews HB, Jeffcoat RA, et al. 1993. Comparison of lead bioavailability in F344 rats fed lead acetate, lead oxide, lead sulfide, or lead ore concentrate from Skagway, Alaska. J Toxicol Environ Health 39:79-93.

Dietert RR, Lee JE, Bunn TL. 2002. Developmental immunotoxicology: Emerging issues. Hum Exp Toxicol 21:479-485.

Dietert RR, Lee JE, Hussain I, et al. 2004. Developmental immunotoxicology of lead. Toxicol Appl Pharmacol 198:86-94.

Dietrich KN, Berger OG, Succop PA. 1993b. Lead exposure and the motor development status of urban six-year-old children in the Cincinnati Prospective study. Pediatrics 91:301-307.

Dietrich KN, Berger OG, Succop PA, et al. 1993a. The developmental consequences of low to moderate prenatal and postnatal lead exposure: Intellectual attainment in the Cincinnati lead study cohort following school entry. Neurotoxicol Teratol 15:37-44.

Dietrich KN, Krafft KM, Bier M, et al. 1986. Early effects of fetal lead exposure: Neurobehavioral findings at 6 months. Int J Biosoc Med Res 8:151-168.

Dietrich KN, Krafft KM, Bier M, et al. 1989. Neurobehavioral effects of foetal lead exposure: The first year of life. In: Smith M, Grant LD, Sors A, eds. Lead exposure and child development: An international assessment. Lancaster, UK: Kluwer Academic Publishers, 320-331.

Dietrich KN, Krafft KM, Bornschein RL, et al. 1987a. Low-level fetal lead exposure effect on neurobehavioral development in early infancy. Pediatrics 80:721-730.

Dietrich KN, Krafft KM, Shukla R, et al. 1987b. The neurobehavioral effects of early lead exposure. Monogr Am Assoc Ment Defic 8:71-95.

Dietrich KN, Ris MD, Succop PA, et al. 2001. Early exposure to lead and juvenile delinquency. Neurotoxicol Teratol 23:511-518.

Dietrich KN, Succop PA, Berger OG, et al. 1991. Lead exposure and the cognitive development of urban preschool children: The Cincinnati cohort lead study at age 4 years. Neurotoxicol Teratol 13:203-211.

Dietrich KN, Ware JH, Salganik M, et al. 2004. Effect of chelation therapy on the neuropsychological and behavioral development of lead-exposed children after school entry. Pediatrics 114(1):19-26.

Ding Y, Gonick HC, Vaziri ND, et al. 2001. Lead-induced hypertension. Increased hydroxyl radical production. Am J Hypertens 14:169-173.

Ding Y, Vaziri ND, Gonick HC. 1998. Lead-induced hypertension: II. Response to sequential infusions of l- arginine, superoxide dismutase, and nitroprusside. Environ Res 76(2):107-113.

Dixon S, Tohn E, Rupp R, et al. 1999. Achieving dust lead clearance standards after lead hazard control projects: An evaluation of the HUD-recommended cleaning procedure and an abbreviated alternative. Appl Occup Environ Hyg 14(5):339-334.

Dolan SP, Nortrup DA, Bolger PM, et al. 2003. Analysis of dietary supplements for arsenic, cadmium, mercury, and lead using inductively coupled plasma mass spectrometry. J Agric Food Chem 51(5):1307-1312.

Dolenc P, Staessen JA, Lauwerys RR, et al. 1993. Short report: Low-level lead exposure does not increase the blood pressure in the general population. J Hypertens 11:589-593.

Drasch G, Bohm J, Baur C. 1987. Lead in human bones: Investigation of an occupationally nonexposed population in southern Bavaria (F.R.G.): I. Adults. Sci Total Environ 64:303-315.

*Drasch G, Kretschmer E, Lochner C. 1988. Lead and sudden infant death: Investigations on blood samples of SID babies. Eur J Pediatr 147:79-84.

Drasch G, Wanghofer E, Roider G. 1997. Are blood, urine, hair, and muscle valid biomonitors for the internal burden of men with the heavy metals mercury, lead and cadmium? Trace Elem Electrolytes 14(3):116-123.

Duggan MJ, Inskip MJ. 1985. Childhood exposure to lead in surface dust and soil: A community health problem. Public Health Rev 13:1-54.

Dundar B, Oktem F, Arslan MK, et al. 2006. The effect of long-term low-dose lead exposure on thyroid function in adolescents. Environ Res 101(1):140-145.

Dunkel VC, Zieger E, Brusick D, et al. 1984. Reproducibility of microbial mutagenicity assays: 1. Tests with Salmonella typhimurim and Escherichia coli using a standardized protocol. Environ Mutagen 6 (Suppl. 2):1-254.

Dursun N, Tutus A. 1999. Chronic occupational lead exposure and thyroid function. J Trace Elem Exp Med 12:45-49.

DuVal GE, Fowler BA. 1989. Preliminary purification and characterization studies of a low molecular weight, high affinity cytosolic lead-binding protein in rat brain. Biochem Biophys Res Commun 159:177-184.

Duydu Y, Suzen HS, Aydin A, et al. 2001. Correlation between lead exposure indicators and sister chromatid exchange (SCE) frequencies in lymphocytes from inorganic lead exposed workers. Arch Environ Contam Toxicol 41:241-246.

Dyatlov VA, Platoshin AV, Lawrence DA, et al. 1998. Lead potentiates cytokine- and glutamate-mediated increases in permeability of blood-brain barrier. Neurotoxicology 19:283-292.

Dye BA, Hirsch R, Brody DJ. 2002. The relationship between blood lead levels and periodontal bone loss in the United States, 1988-1994. Environ Health Perspect 110(10):997-1002.

Eaton DL, Stacey NH, Wong KL, et al. 1980. Dose response effects of various metal ions on rat liver metallothionein, glutathione, heme oxygenase, and cytochrome P-450. Toxicol Appl Pharmacol 55:393-402.

Eckel WP, Jacob TA. 1988. Ambient levels of 24 dissolved metals in U.S. surface and ground waters. Am Chem Soc Div Environ Chem 28:371-372.

Ehle A. 1986. Lead neuropathy and electrophysiological studies in low level lead exposure: A critical review. Neurotoxicity 7:203-216.

Ehle AL, McKee DC. 1990. Neuropsychological effect of lead in occupationally exposed workers: A critical review. Crit Rev Toxicol 20(4):237-255.

Ehrlich R, Robins T, Jordaan E, et al. 1998. Lead absorption and renal dysfunction in a South African battery factory. Occup Environ Med 55:453-460.

Eisenreich SJ, Looney BB, Thornton JD. 1981. Airborne organic contaminants in the Great Lakes ecosystem. Environ Sci Technol 15:30-38.

Eisenreich SJ, Metzer NA, Urban NR, et al. 1986. Response of atmospheric lead to decreased use of lead in gasoline. Environ Sci Technol 20:171-174.

Eisler R. 1988. Lead hazards to fish, wildlife, and invertebrates: A synoptic review. Laurel, MD: U.S. Department of the Interior, Fish and Wildlife Service. Biol Report 85 (1.14).

Elbaz-Poulichet F, Holliger P, Huang WW, et al. 1984. Lead cycling in estuaries, illustrated by the Gironde Estuary, France. Nature 308:409-414.

Eldred RA, Cahill TA. 1994. Trends in elemental concentrations of fine particles at remote sites in the United Sates of America. Atmos Environ 28:1009-1019.

Ellen G, Van Loon JW. 1990. Determination of cadmium and lead in foods by graphite furnace atomic absorption spectrometry with Zeeman background correction: Test with certified reference materials. Food Addit Contam 7:265-273.

Ellenhorn MJ, ed. 1997. Lead. In: Medical toxicology: Diagnosis and treatment of human poisoning. Metals and related compounds. 2nd ed. Baltimore, MD: Williams and Wilkins, 1563-1579.

Elwood PC, Davey-Smith G, Oldham PD, et al. 1988a. Two Welsh surveys of blood lead and blood pressure. Environ Health Perspect 78:119-121.

Elwood PC, Yarnell JWG, Oldham PD, et al. 1988b. Blood pressure and blood lead in surveys in Wales. Am J Epidemiol 127:942-945.

Emory E, Ansari Z, Pattillo R, et al. 2003. Maternal blood lead effects on infant intelligence at age 7 months. Am J Obstet Gynecol 188(4):S26-32.

EPA. 1977. Standards of performance for secondary lead smelters. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60; Subpart L.

EPA. 1979. Water-related environmental fate of 129 priority pollutants. Volume 1: Introduction and technical background, metals and inorganic pesticides and PCBs. Washington, DC: U.S. Environmental Protection Agency. EPA440479029a, 13-1 - 43-19.

EPA 1982a. Standards of performance for lead-acid battery manufacturing plants. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 60. Subpart KK.

EPA. 1982b. Test methods. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 80.3.

EPA. 1982c. Exposure and risk assessment for lead. Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards, Monitoring and Data Support Division. EPA440485010, PB85220606.

EPA. 1983. Methods for chemical analysis of water and wastes. Methods 239.1 and 239.2. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Research and Development, Environmental Monitoring and Support Laboratory. EPA600479020.

EPA. 1985a. Controls applicable to gasoline refiners and importers. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 80.20.

EPA. 1985b. Determination of reportable quantities. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3.

EPA. 1985c. Lead exposures in the human environment. Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. EPA600D86185, PB86241007.

EPA. 1985d. Regulation of fuels and fuel additives; gasoline lead content. Fed Regist 50(45):9386-9399.

EPA. 1986a. Air quality criteria for lead. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA600883028F.

EPA. 1986b. Superfund record of decision (EPA Region 5): Forest waste disposal site, Genesee County, Michigan. PB87189890.

EPA. 1986c. Test methods for evaluating solid waste SW-846: Physical/chemical methods. Method Nos. 7420 and 7421. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

EPA. 1988a. Specific toxic chemical listings. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65.

EPA. 1988b. Hazard constituents. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261, Appendix VIII.

EPA. 1989c. Exposure factors handbook. Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. EPA600889043.

EPA. 1989d. National primary drinking water regulations. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141, 142.

EPA. 1989e. Supplement to the 1986 EPA air quality criteria for lead. Vol. 1: Addendum. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. ECAO-R-0297, EPA600889049A, PB89181374.

EPA. 1990. Toxicity characteristic. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 261.24, Table 1.

EPA. 1991a. Control of lead and copper. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 141, Subpart I (40 CFR 141.80 - 40 CFR 141.90).

*EPA. 1991b. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 142.19.

EPA. 1991c. Reference air concentrations. Health based limits for exclusion of waste-derived residues. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 266, Appendices IV and VII.

EPA. 1991d. Maximum contaminant level goals and national primary drinking water regulations for lead and copper. Fed Regist 56:26461-26564.

EPA. 1991e. National air quality and emissions trends report 1989. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA450491003.

EPA. 1993. Pb-based paint laboratory operations guidelines: Analysis of Pb in paint, dust, and soil. Washington, DC: U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA747R92006.

EPA. 1994a. Guidance manual for the integrated exposure uptake biokinetic model for lead in children. U.S. Environmental Protection Agency. EPA540R93081, PB93963510.

EPA. 1994b. Technical support document: Parameters and equations used in integrated exposure uptake biokinetic model for lead in children (v0.99d). U.S. Environmental Protection Agency. EPA540R94040, PB94963505.

EPA. 1994c. Validation strategy for the integrated exposure uptake biokinetic model for lead in children. U.S. Environmental Protection Agency. EPA540R94039, PB94963504.

EPA. 1994d. Method 6020: Inductively coupled plasma-mass spectrometry, revision 0 (1994), SW-846. Test methods for evaluating solid waste, Volume 1A: Laboratory manual, physical/chemical methods. Washington, DC: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

*EPA. 1995a. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 421, Subparts P-AB, and AE.

EPA. 1995b. Guidance for assessing chemical contaminant data for use in fish advisories. Washington, DC: U.S. Environmental Protection Agency, Office of Science and Technology, Office of Water. EPA823R95007.

EPA. 1995c. Report on the national survey of lead based paint in housing - base report. U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. EPA747R95003. http://www.hud.gov/lea/leadwnlo.html. January 15, 2005.

EPA. 1996a. U.S. Environmental Protection Agency. Fed Regist 61:3832.

EPA. 1996b. National air quality and emissions trends report 1995. Office of Air Quality Planning and Standards. U.S. Environment Protection Agency.

EPA. 1996c. Urban soil lead abatement demonstration project. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600P93001.

EPA. 1997. Controls and prohibitions. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 80.22. http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?YEAR=1997&TITLE=40&PART=80&SECTION=22&SUBPART=&TYPE=TEXT. May 22, 2007.

EPA. 1998a. Lead; requirements for hazard education before renovation of target housing; final rule. U.S. Environmental Protection Agency. Fed Regist 63:29908.

EPA. 1998b. Lead; identification of dangerous levels of lead; notice of proposed rulemaking. U.S. Environmental Protection Agency. Fed Regist 63:30302.

EPA. 1998c. Lead-based paint poisoning prevention in certain residential structures. U.S. Environmental Protection Agency. Code of Federal Regulations. 440 CFR 745.

EPA. 1999. National characteristics of drinking water systems serving populations under 10,000. U.S. Environmental Protection Agency. EPA816R99010. http://www.epa.gov/safewater/ndwac/smallsys/smallsys.pdf. November 06, 2007.

EPA. 2000. National air pollutant emission trends, 1900-1998. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA454R00002.

EPA. 2001a. Lead and lead compounds. Guidance for reporting releases and other waste management quantities of toxic chemicals. Washington, DC: U.S. Environmental Protection Agency.

EPA. 2001b. The projection of mobile source air toxics from 1996 to 2007: Emissions and concentrations. U.S. Environmental Protection Agency. EPA420R01038.

EPA. 2001c. Final human health risk assessment for the Coeur d'Alene Basin extending from Harrison to Mullan on the Coeur d'Alene River and Tributaries remedial investigation/feasibility study. Washington, DC: U.S. Environmental Protection Agency, Idaho Department of Environmental Quality.

EPA. 2001d. National air quality and emissions trend report, 1999. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA454R01004.

EPA. 2001e. Emergency planning and community right-to-know act-section 313: Guidance for reporting releases and other waste management quantities of toxic chemicals: Lead and lead compounds. Washington, DC: U.S. Environmental Protection Agency. EPA2660B01027.

EPA. 2002. National primary drinking water regulations. Washington, DC: U.S. Environmental Protection Agency. EPA816F02013. http://www.epa.gov/safewater/mcl.html. February 15, 2005.

EPA. 2003a. National air quality and emissions trends report. 2003 Special studies edition. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA454R03005.

EPA. 2003b. Recommendations of the technical review workgroup for lead for an approach to assessing risks associated with adult expsoures to lead in soil. Washington, DC: U.S. Environmental Protection Agency. EPA540R03001.

*EPA. 2004a. Air Emissions Trends-Continued Progress Through 2003. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/airtrends/reports.html. March 17, 2005.

EPA. 2004b. Hazardous air pollutants. Washington, DC: U.S. Environmental Protection Agency. United States Code 42 USC 7412. http://www.epa.gov/ttn/atw/orig189.html. February 15, 2005.

EPA. 2004c. Estimation of relative bioavailability of lead in soil and soil-like materials using in vivo and in vitro methods. Washington, DC: U.S. Environmental Protection Agency. OSWER 9285777.

EPA. 2004d. Fact sheet: National listing of fish advisories. Washington, DC: Office of Water, U.S. Environmental Protection Agency. EPA823F04016.

EPA. 2005a. Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 116.4. http://www.epa.gov/ttn/atw/orig189.html. February 15, 2005.

EPA. 2005b. National primary and secondary ambient air quality standards for lead. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 50.12. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 15, 2005.

EPA. 2005c. Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 117.3. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 16, 2005.

EPA. 2005d. Superfund, emergency planning, and community right-to-know programs. Designation, reportable quantities, and notifications. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 302.4. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 15, 2005.

EPA. 2005e. Superfund, emergency planning, and community right-to-know programs. Extremely hazardous substances and their threshold planning quantities. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 355, Appendix A. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 15, 2005.

EPA. 2005f. Superfund, emergency planning, and community right-to-know programs. Lower thresholds for chemicals of special concern. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.28. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 16, 2005.

EPA. 2005g. Superfund, emergency planning, and community right-to-know programs. Toxic chemical release reporting. Washington, DC: U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR 372.65. http://www.epa.gov/epacfr40/chapt-I.info/chi-toc.htm. February 16, 2005.

EPA. 2005h. Lead in drinking water. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/safewater/lead/leadfacts.html. April 19, 2005.

EPA. 2005i. Toxic chemical release inventory reporting forms and instructions: Revised 2004 version. Section 313 of the Emergency Planning and Community Right-to-Know Act (Title III of the Superfund Amendments and Reauthorization Act of 1986). U.S. Environmental Protection Agency. Office of Environmental Information. EPA260B05001.

EPA. 2005j. EPA STORET database. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/storet/dbtop.html. May 20, 2005.

EPA. 2005k. EPA national air quality monitoring system. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/air/data/. May 20, 2005.

EPA. 2005l. Residential lead hazards standards - TSCA Section 403. Washington, DC: U.S. Environmental Protection Agency. http://www.epa.gov/opptintr/lead/leadhaz.htm. May 26, 2005.

EPA. 2006. Substance registry system. Lead (II) styphnate. U.S. Environmental Protection Agency. http://iaspub.epa.gov/srs/srs_proc_qry.navigate?P_SUB_ID=198986. June 11, 2007.

EPA. 2007a. Air quality and emissions-progress continues in 2006. U.S. Environmental Protection Agency. http://www.epa.gov/airtrends/econ-emissions.html. June 14, 2007.

EPA. 2007b. The national listing of fish advisories. Advisory report output. U.S. Environmental Protection Agency. http://map1.epa.gov/. June 07, 2007.

Erenberg G, Rinsler SS, Fish BG. 1974. Lead neuropathy and sickle cell disease. Pediatrics 54:438-441.

Erfurth EM, Gerhardsson L, Nilsson A, et al. 2001. Effects of lead on the endocrine system in lead smelter workers. Arch Environ Health 56(5):449-455.

Ericson JE. 2001. Enamel lead biomarker for prenatal exposure assessment. Environ Res 87:136-140.

Erkkila J, Armstrong R, Riihimaki V, et al. 1992. In vivo measurements of lead in bone at four anatomical sites: Long term occupational and consequent endogenous exposure. Br J Ind Med 49:631-644.

Ernhart CB, Greene T. 1990. Low-level lead exposure in prenatal and early preschool periods: Language development. Arch Environ Health 45:342-354.

*Ernhart CB, Landa B, Schell NB. 1981. Subclinical levels of lead and developmental deficit--a multivariate follow-up reassessment. Pediatrics 67:911-919.

Ernhart CB, Morrow-Tlucak M, Marler MR, et al. 1987. Low level lead exposure in the prenatal and early preschool periods: Early preschool development. Neurotoxicol Teratol 9:259-270.

9. REFERENCES

Ernhart CB, Morrow-Tlucak M, Wolf AW. 1988. Low level lead exposure and intelligence in the preschool years. Sci Total Environ 71:453-459.

Ernhart CB, Wolf AW, Kennard MJ, et al. 1985. Intrauterine lead exposure and the status of the neonate. In: Lekkas TD, ed. International conference on heavy metals in the environment, Athens, Greece. September, Vol. 1. Edinburgh, United Kingdom: CEP Consultants, Ltd, 35-37.

Ernhart CB, Wolf AW, Kennard MJ, et al. 1986. Intrauterine exposure to low levels of lead: The status of the neonate. Arch Environ Health 41:287-291.

ESA. 1998. LeadCare childhood blood lead testing. Chelmsford, MA: ESA, Inc. http://www.esainc.com/esaproducts/esaleadcare.html. October 15, 1998.

Escribano A, Revilla M, Hernandez ER, et al. 1997. Effect of lead on bone development and bone mass: A morphometric, densitometric, and histomorphometric study in growing rats. Calcif Tissue Int 60(2):200-203.

Eskew AE, Crutcher JC, Zimmerman SL, et al. 1961. Lead poisoning resulting from illicit alcohol consumption. J Forensic Sci 6:337-350.

Esteban E, Rubin CH, Jones RL, et al. 1999. Hair and blood substrates for screening children for lead poisoning. Arch Environ Health 54(6):436-440.

Ettinger AS, Tellez-Rojo MM, Amarasiriwardena C, et al. 2006. Influence of maternal bone lead burden and calcium intake on levels of lead in breast milk over the course of lactation. Am J Epidemiol 163(1):48-56.

Evans RD, Rigler FH. 1985. Long distance transport of anthropogenic lead as measured by lake sediments. Water Air Soil Pollut 24:141-151.

Everson J, Patterson CC. 1980. "Ultra-clean" isotope dilution/mass spectrometric analyses for lead in human blood plasma indicate that most reported values are artificially high. Clin Chem 26:1603-1607.

Ewers U, Brockhaus A, Dolgner R, et al. 1990. Levels of lead and cadmium in blood of 55-66 year old women living in different areas of Northrhine-Westphalia-Chronological trend 1982-1988. Zentralb Hyg Umveltmed 189:405-418.

Ewers U, Stiller-Winkler R, ldel H. 1982. Serum immunoglobulin, complement C3, and salivary IgA level in lead workers. Environ Res 29:351-357.

Exon JH, Koller LD, Kerkvliet NI. 1979. Lead-cadmium interaction: Effects on viral-induced mortality and tissue residues in mice. Arch Environ Health 34:469-475.

Factor-Litvak P, Graziano JH, Kline JK, et al. 1991. A prospective study of birthweight and length of gestation in population surrounding a lead smelter in Kosovo, Yugoslavia. Int J Epidemiol 20:722-728.

Factor-Litvak P, Kline JK, Popovac D, et al. 1996. Blood lead and blood pressure in young children. Epidemiology 7(6):633-637.

Factor-Litvak P, Slavkovich V, Liu X, et al. 1998. Hyperproduction of erythropoietin in nonanemic lead-exposed children. Environ Health Perspect 106(6):361-364.

Factor-Litvak P, Wasserman G, Kline JK, et al. 1999. The Yugoslavia prospective study of environmental lead exposure. Environ Health Perspect 107:9-15.

Fahim MS, Khare NK. 1980. Effects of subtoxic levels of lead and cadmium on urogenital organs of male rats. Arch Androl 4:357.

*Fahim MS, Fahim Z, Hall DG. 1976. Effects of subtoxic lead levels on pregnant women in the state of Missouri. Res Commun Chem Pathol Pharmacol 13:309-331.

Faith RE, Luster MI, Kimmel CA. 1979. Effect of chronic developmental lead exposure on cell-mediated immune functions. Clin Exp lmmunol 35:413-420.

Falcón M, Vinas P, Luna A. 2003. Placental lead and outcome of pregnancy. Toxicology 185:59-66.

Fanning D. 1988. A mortality study of lead workers, 1926-1985. Arch Environ Health 43:247-251.

Farias P, Echavarria M, Hernandez-Avila M, et al. 2005. Bone, blood and semen lead in men with environmental and moderate occupational exposure. Int J Environ Health Res 15(1):21-31.

Fayerweather WE, Karns ME, Nuwayhid IA, et al. 1997. Case-control study of cancer risk in tetraethyl lead manufacturing. Am J Ind Med 31:28-35.

FDA. 1992. Lead in ceramic foodware; revised compliance policy guide; availability. Washington, DC: Department of Health and Human Services, U.S. Food and Drug Administration. Fed Regist 57:29734.

FDA. 1995. Substances prohibited from use in human food. Substances prohibited from indirect addition to human food through food-contact surfaces. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 189.240.

FDA. 1996. Tin-coated lead foil capsules for wine bottles. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 189.301.

FDA. 1998a. Direct food substances affirmed as generally recognized as safe. U.S. Food and Drug Administration. Code of Federal Regulations. 21 CFR 184.

FDA. 1998b. Hazard analysis and critical control point (HACCP); procedures for the safe and sanitary processing and importing of juice. U.S. Food and Drug Administration. Fed Regist 63(79):20449-20486. http://www.cfsan.fda.gov/lrd/fr98424a.html. May 25, 2007.

FDA. 2000. Action levels for poisonous or deleterious substances in human food and animal feed. Washington, DC: Food and Drug Administration. http://www.cfsan.fda.gov/lrd/fdaact.html. February 15, 2005.

FDA. 2004. Bottled water. U.S. Environmental Protection Agency. Code of Federal Regulations.21 CFR 165.110 http://a257.g.akamaitech.net/7/257/2422/12feb20041500/edocket.access.gpo.gov/cfr_2004/aprqtr/pdf/21cfr165.110.pdf. September 22, 2007.

FEDRIP. 2005. FEDRIP literature search for lead. Palo Alto, CA: Federal Research in Progress. Dialog Information Service.

Feldman RG. 1978. Urban lead mining: Lead intoxication among deleaders. N Engl J Med 298(20):1143-1145.

Fell GS. 1984. Review article: Lead toxicity: Problems of definition and laboratory evaluation. Ann Clin Biochem 21:453-460.

Fels LM, Wünsch M, Baranowski J, et al. 1998. Adverse effects of chronic low level lead exposure on kidney function - a risk group study in children. Nephrol Dial Transplant 13:2248-2256.

Fergusson DM, Fergusson JE, Horwood LJ, et al. 1988. A longitudinal study of dentine lead levels, intelligence, school performance and behavior: Part III. Dentine lead levels and attention activity. J Child Psychol Psychiatry 29:811-824.

Fewtrell LJ, Pruss-Ustun A, Landrigan P, et al. 2004. Estimating the global burden of disease of mild mental retardation and cardiovascular diseases from environmental lead exposure. Environ Res 94:120-133.

Finster ME, Gray KA, Binns HJ. 2004. Lead levels of edibles grown in contaminated residential soils: A field survey. Sci Total Environ 320:245-257.

Fischbein A, Anderson KE, Sassa S, et al. 1981. Lead poisoning from do-it- yourself heat guns for removing lead-based paint: Report of two cases. Environ Res 24:425-431.

Fischbein A, Tsang P, Luo J, et al. 1993. Phenotypic aberrations of CD3 and CD4 cells and functional impairments of lymphocytes at low-level occupational exposure to lead. Clin Immunol Immunopathol 66:163-168.

Fischbein A, Wallace J, Sassa S, et al. 1992. Lead poisoning from art restoration and pottery work unusual exposure source and household risk. J Environ Path Toxicol Oncol 11(1):7-11.

Fitchko J, Hutchinson TC. 1975. A comparative study of heavy metal concentrations in river mouth sediments around the Great Lakes. J Great Lakes Res 1:46-78.

Flanagan PR, Hamilton DL, Haist J, et al. 1979. Inter-relationships between iron and absorption in iron-deficient mice. Gastroenterology 77:1074-1081.

Flegal AR, Smith DR. 1995. Measurements of environmental lead contamination and human exposure. Rev Environ Contam Toxicol 143:1-45.

Fleming DEB, Boulay D, Richard NS, et al. 1997. Accumulated body burden and endogenous release of lead in employees of a lead smelter. Environ Health Perspect 105(2):224-233.

Fleming DEB, Chettle DR, Wetmur JG, et al. 1998b. Effect of the δ-aminolevulinate dehydratase polymorphism on the accumulation of lead in bone and blood in lead smelter workers. Environ Res 77:49-61.

Fleming MD, Romano MA, Su MA, et al. 1998a. Nramp2 is mutated in the anemic Belgrade (b) rat: Evidence of a role for Nramp2 in endosomal iron transport. Proc Natl Acad Sci U S A 95:1148-1153.

Flora SJS, Tandon SK. 1987. Effect of combined exposure to lead and ethanol on some biochemical indices in the rat. Biochem Pharm 36:537-541.

Fomon SJ. 1966. Body composition of the infant: Part I: The male reference infant. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 239-246.

Fomon SJ, Haschke F, Ziegler EE, et al. 1982. Body composition of reference children from birth to age 10 years. Am J Clin Nutr 35:1169-1175.

Forbes GB, Reina JC. 1972. Effect of age on gastrointestinal absorption (Fe, Sr, Pb) in the rat. J Nutr 102:647-652.

Forni A, Camiaghi G, Sechi GC. 1976. Initial occupational exposure to lead: Chromosome and biochemical findings. Arch Environ Health 31:73-78.

Foster WG. 1992. Reproductive toxicity of chronic lead exposure in the female Cynomolgus monkey. Reprod Toxicol 6:123-131.

Foster WG, McMahon A, Rice DC. 1996. Sperm chromatin structure is altered in Cynomolgus monkeys with environmentally relevant blood lead levels. Toxicol Ind Health 12(5):723-735.

Foster WG, Singh A, McMahon A, et al. 1998. Chronic lead exposure effects in the Cynomolgus monkey (*Macaca fascicularis*) testis. Ultrastruct Pathol 22(1):63-71.

Fowler BA. 1989. Biological roles of high affinity metal-binding proteins in mediating cell injury. Comments Toxicol 3:27-46.

Fowler BA, DuVal G. 1991. Effects of lead on the kidney: Roles of high-affinity lead-binding proteins. Environ Health Perspect 91:77-89.

Fowler BA, Kimmel CA, Woods JS, et al. 1980. Chronic low-level lead toxicity in the rat: III. An integrated assessment of long-term toxicity with special reference to the kidney. Toxicol Appl Pharmacol 56:59-77.

Fox DA, Chu LWF. 1988. Rods are selectively altered by lead: II. Ultrastructure and quantitative histology. Exp Eye Res 46:613-625.

Fox DA, Farber DB. 1988. Rods are selectively altered by lead: I. Electrophysiology and biochemistry. Exp Eye Res 46:597-611.

Fox DA, Katz LM. 1992. Developmental lead exposure selectively alters the scotopic ERG component of dark and light adaptation and increases rod calcium content. Vision Res 32:249-255.

Fox DA, Rubinstein SD. 1989. Age-related changes in retinal sensitivity, rhodopsin content and rod outer segment length in hooded rats following low-level lead exposure during development. Exp Eye Res 48:237-249.

Fox DA, Campbell ML, Blocker YS. 1997. Functional alterations and apoptotic cell death in the retina following developmental or adult lead exposure. Neurotoxicology 18(3):645-664.

Fox DA, Katz LM, Farber DB. 1991. Low level developmental lead exposure decreases the sensitivity, amplitude and temporal resolution of rods. Neurotoxicology 12:641-654.

Fracasso ME, Perbellini L, Solda S, et al. 2002. Lead induced DNA strand breaks in lymphocytes of exposed workers: Role of reactive oxygen species and protein kinase C. Mutat Res 515:159-169.

Franklin CA, Inskip MJ, Baccanale CL, et al. 1997. Use of sequentially administered stable lead isotopes to investigate changes in blood lead during pregnancy in a nonhuman primate (*Macaca fascicularis*). Fundam Appl Toxicol 39:109-119.

Franks PA, Laughlin NK, Dierschke DJ, et al. 1989. Effects of lead on luteal function in Rhesus monkeys. Biol Reprod 41:1055-1062.

Freeman GB, Dill JA, Johnson JD, et al. 1996. Comparative absorption of lead from contaminated soil and lead salts by weanling Fischer 344 rats. Fundam Appl Toxicol 33:109-119.

Freeman GB, Johnson JD, Killinger JM, et al. 1992. Relative bioavailability of lead from mining waste soil in rats. Fundam Appl Toxicol 19:388-398.

Freeman GB, Johnson JD, Liao SC, et al. 1994. Absolute bioavailability of lead acetate and mining waste lead in rats. Toxicology 91:151-163.

Friedlander MA. 1981 Blood pressure and creatinine clearance in lead-exposed children: Effect of treatment. Arch Environ Health 36:310-315.

Frisancho AR, Ryan AS. 1991. Decreased stature associated with moderate blood lead concentrations in Mexican-American children. Am J Clin Nutr 54:516-519.

Froom P, Kristal-Boneh E, Benbassat J, et al. 1998. Predictive values of determinations of zinc protoporphyrin for increase blood lead concentrations. Clin Chem 44:1283-1288.

Froom P, Kristal-Boneh E, Benbassat J, et al. 1999. Lead exposure in battery-factory workers is not associated with anemia. J Occup Environ Med 41(2):120-123.

Fu H, Boffetta P. 1995. Cancer and occupational exposure to inorganic lead compounds: A meta-analysis of published data. Occup Environ Med 52(2):73-81.

Fujita H, Sato K, Sano S. 1982. Increase in the amount erythrocyte δ-aminolevulinic acid dehydratase in workers with moderate lead exposure. Int Arch Occup Environ Health 50:287-297.

Fukunaga M, Kurachi Y, Mizuguchi Y. 1982. Action of some metal ions at yeast chromosomes. Chem Pharm Bull 30:3017-3019.

Fullmer CS, Rosen JF. 1990. Effect of dietary calcium and lead status on intestinal calcium absorption. Environ Res 51:91-99.

Fullmer CS, Edelstin S, Waserman RH. 1985. Lead-binding properties of intestinal calcium-binding proteins. J Biol Chem 260:6816-6819.

Fulton M, Raab G, Thomson G, et al. 1987. Influence of blood lead on the ability and attainment of children in Edinburgh. Lancet 1:1221-1226.

Gale NL, Adams CD, Wixson BG, et al. 2002. Lead concentrations in fish and river sediments in the old lead belt of Missouri. Environ Sci Technol 36:4262-4268.

Gale NL, Adams CD, Wixson BG, et al. 2004. Lead, zinc, copper, and cadmium in fish and sediments from the Big River and Flat River Creek of Missouri's Old Lead Belt. Environ Geochem Health 26:37-49.

Gant VA. 1938. Lead poisoning. Ind Med 7:679-699.

Gao K, Pearce J, Jones J, et al. 1999. Interaction between peat, humic acid and aqueous metal ions. Environ Geochem Health 21:13-26.

Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986a. Pesticides, selected elements, and other chemicals in infant and toddler total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 69:123-145.

Gartrell MJ, Craun JC, Podrebarac DS, et al. 1986b. Pesticides, selected elements, and other chemicals in adult total diet samples, October 1980-March 1982. J Assoc Off Anal Chem 69:146-161.

Gartside PS. 1988. The relationship of blood lead levels and blood pressure in NHANES II: Additional calculations. Environ Health Perspect 78:31-34.

Garvey GJ, Hahn G, Lee RV, et al. 2001. Heavy metal hazards of Asian traditional remedies. Int J Environ Health Res 11(1):63-71.

Gasiorek K, Bauchinger M. 1981. Chromosome changes in human lymphocytes after separate and combined treatment with divalent salts of lead, cadmium, and zinc. Environ Mutat 3:513-518.

Ge Y, Murray P, Hendershot WH. 2000. Trace metal speciation and bioavailability in urban soils. Environ Pollut 107:137-144.

Gemmel A, Tavares M, Alperin S, et al. 2002. Blood lead level and dental caries in school-age children. Environ Health Perspect 110(10):625-630.

Gennart J-P, Bernard A, Lauwerys R. 1992a. Assessment of thyroid, testes, kidney and autonomic nervous system function in lead-exposed workers. Int Arch Occup Environ Health 64:49-57.

Gennart J-P, Buchet J-P, Roels H, et al. 1992b. Fertility of male workers exposed to cadmium, lead or manganese. Am J Epidemiol 135:1208-1219.

Gercken B, Barnes RM. 1991. Determination of lead and other trace element species in blood by size exclusion chromatography and inductively coupled plasma/mass spectrometry. Anal Chem 63:283-287.

Gerhardsson L, Brune D, Nordberg GF, et al. 1986a. Distribution of cadmium, lead, and zinc in lung, liver, and kidney in long-term exposed smelter workers. Sci Total Environ 50:65-85.

Gerhardsson L, Chettle DR, Englyst V, et al. 1992. Kidney effects in long term exposed lead smelter workers. Br J Ind Med 49:186-192.

Gerhardsson L, Endlyst V, Lundstrom NG, et al. 1995b. Lead in tissues of deceased lead smelter workers. J Trace Elem Med Biol 9:136-143.

Gerhardsson L, Hagmar L, Rylander L, et al. 1995a. Mortality and cancer incidence among secondary lead smelter workers. Occup Environ Med 52:667-672.

Gerhardsson L, Lundstrom NG, Nordberg G, et al. 1986b. Mortality and lead exposure: A retrospective cohort study of Swedish smelter workers. Br J Ind Med 43:707-712.

Gerhardt RE, Crecelius EA, Hudson JB. 1980. Trace element content of moonshine. Arch Environ Health 35:332-334.

Gerlach RF, Cury JA, Krug FJ, et al. 2002. Effect of lead on dental enamel formation. Toxicology 14(175(1-3)):27-34.

Gerlach RF, Toledo DB, Novaes PD, et al. 2000. The effect of lead on the eruption rates of incisor teeth in rats. Arch Oral Biol 45:951-955.

Gerr F, Letz R, Stokes L, et al. 2002. Association between bone lead concentration and blood pressure among young adults. Am J Ind Med 42:98-106.

Gerritse RG, Vriesema R, Dalenberg H, et al. 1981. Trace element mobility in soils effect of sewage sludge. Heavy Met Environ Int Conf 4th 1:180-184.

Gersberg RM, Gaynor K, Tenczar D, et al. 1997. Quantitative modeling of lead exposure from glazed ceramic pottery in childhood lead poisoning cases. Int J Environ Health Res 7(3):193-202.

Gibbs PNB, Gore MG, Jordan PM. 1985. Investigation of the effect of metal ions on the reactivity of thiol groups in human 5-aminolaevulinate dehydratase. Biochem J 225:573-580.

Giddings JC, ed. 1973. Lead in gasoline. In: Chemistry, man, and environmental change: An integrated approach. New York, NY: Harper & Row, Publishers, Inc., 351-353.

Gilbert ME, Lasley SM. 2002. Long-term consequences of developmental exposure to lead or polychlorinated biphenyls: Synaptic transmission and plasticity in the rodent CNS. Environ Toxicol Pharmacol 12:105-117.

Giwercman A, Carlsen E, Keiding N, et al. 1993. Evidence for increasing incidence of abnormalities of the human testis: A review. Environ Health Perspect Suppl 101(2):65-71.

Glenn BS, Stewart WF, Links JM, et al. 2003. The longitudinal association of lead with blood pressure. Epidemiology 14:30-36.

Glenn BS, Stewart WF, Schwartz BS, et al. 2001. Relation of alleles of the sodium- potassium adenosine triphosphatase α2 gene with blood pressure and lead exposure. Am J Epidemiol 153:537-545.

Glickman L, Valciukas JA, Lilis R, et al. 1984. Occupational lead exposure: Effects on saccadic eye movements. Int Arch Occup Environ Health 54:115-125.

Goering PL. 1993. Lead-protein interactions as a basis for lead toxicity. Neurotoxicology 14:45-60.

Goering PL, Fowler BA. 1984. Regulation of lead inhibition of delta-aminolevulinic acid dehydratase by a high affinity renal lead-binding protein. J Pharmacol Exp Ther 231:66-71.

Goering PL, Fowler BA. 1985. Mechanisms of renal lead-binding protein protection against lead-inhibition of delta-aminolevulinic acid dehydratase. J Pharmacol Exp Ther 234:365-371.

Goering PL, Fowler BA. 1987. Metal constitution of metallothionein influences inhibition of delta-aminolevulinic acid dehydratase (porphobiligen synthase) by lead. Biochem J 245:339-345.

Goering PL, Mistry P, Fowler BA. 1986. A high affinity lead binding protein attenuates lead inhibition of delta-aminolevulinic acid dehydratase: Comparison with a renal lead-binding protein. J Pharmacol Exp Ther 237:220-225.

Goldberg AM, Meredith PA, Miller S, et al. 1978. Hepatic drug metabolism and heme biosynthesis in lead-poisoned rats. Br J Pharmacol 62:529-536.

Goldberg RL, Hicks AM, O'Leary LM, et al. 1991. Lead exposure at uncovered outdoor firing ranges. J Occup Med 33(6):718-719.

Goldman RH, Baker EL, Hannan M, et al. 1987. Lead poisoning in automobile radiator mechanics. N Engl J Med 317:214-218.

Goldstein GW. 1993. Evidence that lead acts as a calcium substitute in second messenger metabolism. Neurotoxicology 14:97-102.

Goldstein GW, Ar D. 1983. Lead activates calmodulin sensitive processes. Life Sci 33:1001-1006.

Gomaa A, Howard H, Bellinger D, et al. 2002. Maternal bone lead as an independent risk factor for fetal neurotoxicity: A prospective study. Pediatrics 110(1):110-118.

Gomes VE, Rosario de Sousa ML, Barbosa F, et al. 2004. In vivo studies on lead content of deciduous teeth superficial enamel of preschool children. Sci Total Environ 320:25-35.

Gong JK, Arnold JS, Cohn SH. 1964. Composition of trabecular and cortical bone. Anatmol Rec 149:325-331.

Gonick HC, Ding Y, Bondy SC, et al. 1997. Lead-induced hypertension. Interplay of nitric oxide and reactive oxygen species. Hypertension 30:1487-1492.

Gonick HC, Ding Y, Bondy SC, et al. 1998. Effect of low lead exposure on eicosanoid excretion in rats. Prost Lipid Med 55:77-82.

Gonzalez-Riola J, Hernandez ER, Escribano A, et al. 1997. Effect of lead on bone and cartilage in sexually mature rats: A morphometric and histomorphometry study. Environ Res 74(1):91-93.

Goodman M, LaVerda N, Clarke C, et al. 2002. Neurobehavioural testing in workers occupationally exposed to lead: Systematic review and meta-analysis of publications. Occup Environ Med 59:217-223.

Goodrum PE, Diamond GL, Hassett JM, et al. 1996. Monte Carlo modeling of childhood lead exposure: Development of a probabilistic methodology for use with the USEPA IEUBK model for lead in children. Hum Ecol Risk Assess 2(4):681-708.

Gorell JM, Johnson CC, Rybicki BA, et al. 1997. Occupational exposures to metals as risk factors for Parkinson's disease. Neurology 48(3):650-658.

Gorell JM, Johnson CC, Rybicki BA, et al. 1999. Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. Neurotoxicology 20(2-3):239-248.

Goyer RA. 1968. The renal tubule in lead poisoning. I. Mitochondrial swelling and aminoaciduria. Lab Invest 19:71-77.

Goyer RA. 1971. Lead toxicity: A problem in environmental pathology. Am J Pathol 64:167-179.

Goyer RA. 1986. Toxic effect of metals. In: Klaassen CD, ed. Casarett and Doull's toxicology: The basic science of poisons. 3rd ed. New York, NY: Macmillan Publishing Co., 582-588, 598-605.

Goyer RA. 1989. Mechanisms of lead and cadmium nephrotoxicity. Toxicol Lett 46:153-162.

Goyer RA. 1990. Transplacental transport of lead. Environ Health Perspect 89:101-105.

Goyer RA. 1993. Lead toxicity: Current concerns. Environ Health Perspect 100:177-187.

Goyer RA. 2001. Lead. In: Bingham E, Cohrssen B, Powell CH, eds. Patty's toxicology. 5th edition. New York, NY: John Wiley & Sons, Inc., 611-675.

Goyer RA, Krall R. 1969. Ultrastructural transformation in mitochondria isolated from kidneys of normal and lead-intoxicated rats. J Cell Biol 41:393-400.

Goyer RA, Leonard DL, Moore JF, et al. 1970a. Lead dosage and the role of the intranuclear inclusion body. Arch Environ Health 20:705-711.

Goyer RA, May P, Cates MM, et al. 1970b. Lead and protein content of isolated intranuclear inclusion bodies from kidneys of lead-poisoned rats. Lab Invest 22(3):245-251.

Grabo TN. 1997. Unknown toxic exposures. Arts and crafts materials. AAOHN 45(3):124-130.

Grandjean P. 1979. Occupational lead exposure in Denmark: Screening with the haematofluorometer. Br J Ind Med 36:52-58.

Grandjean P, Bach E. 1986. Indirect exposures: The significance of bystanders at work and at home. Am Ind Hyg Assoc J 47:819-824.

Grandjean P, Lintrup J. 1978. Erythrocyte-Zn-protoporphyrin as an indicator of lead exposure. Scand J Clin Lab Invest 38:669-675.

Grandjean P, Olsen B. 1984. Lead. In: Vercruysse A, ed. Techniques and instrumentation in analytical chemistry. Volume 4: Evaluation of analytical methods in biological systems: Part B. Hazardous metals in human toxicology. New York, NY: Elsevier Science Publishing Co., Inc., 153-169.

Grandjean P, Hollnagel H, Hedegaard L, et al. 1989. Blood lead-blood pressure relations: Alcohol intake and hemoglobin as confounders. Am J Epidemiol 129:732-739.

Grandjean P, Jorgensen PJ, Viskum S, et al. 1991. Temporal and interindividual variation in erythrocytezine-protoporphyrin in lead exposed workers. Br J Ind Med 48:254-257.

Grandjean P, Wulf HC, Niebuhr E. 1983. Sister chromatid exchange in response to variations in occupational lead exposure. Environ Res 32:199-204.

Grant LD, Kimmel CA, West GL, et al. 1980. Chronic low-level lead toxicity in the rat: II. Effects on postnatal physical and behavioral development. Toxicol Appl Pharmacol 56:42-58.

Graziano JH. 1994. Validity of lead exposure markers in diagnosis and surveillance. Clin Chem 40:1387-1390.

Graziano JH, Blum C. 1991. Lead exposure from lead crystal. Lancet 333:141-142.

Graziano JH, Blum CB, Lolacono NJ, et al. 1996. A human in vivo model for determination of lead bioavailability using stable isotope dilution. Environ Health Perspect 104:176-179.

Graziano JH, Popovac D, Factor-Litvak P, et al. 1990. Determinants of elevated blood lead during pregnancy in a population surrounding a lead smelter in Kosovo, Yugoslavia. Environ Health Perspect 89:95-100.

Graziano JH, Slavkovic V, Factor-Litvak P, et al. 1991. Depressed serum erythropoietin in pregnant women with elevated blood lead. Arch Environ Health 46(6):347-350.

Graziano JH, Slavkovich V, Liu X, et al. 2004. A prospective study of prenatal and childhood lead exposure and erythropoietin production. J Occup Environ Med 46:924-929.

Greenberg M, Hamilton R. 1999. Lack of blood lead elevations in police officers following small arms qualification on an indoor range [Abstract]. J Toxicol Clin Toxicol 37(5):627.

Greene T, Ernhart CB. 1991. Prenatal and preschool age lead exposure: Relationship with size. Neurotoxicol Teratol 13:417-427.

Griffin S, Goodrum PE, Diamond GL, et al. 1999. Application of a probabilistic risk assessment methodology to a lead smelter site. Hum Ecol Risk Assess 5(4):845-868.

Griffin TB, Coulston F, Wills H. 1975. [Biological and clinical effects of continuous exposure to airborne particulate lead.] Arh Hig Toksikol 26:191-208. (Yugoslavian)

Grobler SR, Rossouw RJ, Kotze D. 1988. Effect of airborne lead on the blood lead levels of rats. S Afr J Sci 84:260-262.

Gross M, Kumar R. 1990. Physiology and biochemistry of vitamin D-dependent calcium binding proteins. Am J Physiol 259:F195-F209.

Gross SB, Pfitzer EA, Yeager DW, et al. 1975. Lead in human tissues. Toxicol Appl Pharmacol 32:638-651.

Grosse SD, Matte TD, Schwartz J, et al. 2002. Economic gains resulting from the reduction in children's exposure to lead in the United States. Environ Health Perspect 110(6):563-569.

9. REFERENCES

Gruber HE, Gonick HC, Khalil-Manesh F, et al. 1997. Osteopenia induced by long-term, low- and high-level exposure of the adult rat to lead. Miner Electrolyte Metab 23 (2):65-73.

Guibaud G, Tixier N, Bouju A, et al. 2003. Relation between extracellular polymers' composition and its ability to complex Cd, Cu and Pb. Chemosphere 52:1701-1710.

Guilarte TR, Toscano CD, McGlothan JL, et al. 2003. Environmental enrichment reverses cognitive and molecular deficits induced by developmental lead exposure. Ann Neurol 53:50-56.

Gulson BL. 1996. Tooth analyses of sources and intensity of lead exposure in children. Environ Health Perspect 104:306-312.

Gulson BL. 2000. Revision of estimates of skeletal contribution to blood during pregnancy and postpartum period. J Lab Clin Med 136:250-251.

Gulson BL, Wilson D. 1994. History of lead exposure in children revealed from isotopic analyses of teeth. Arch Environ Health 49(4):279-283.

*Gulson BL, Gray B, Mahaffey KR, et al. 1999a. Comparison of the rates of exchange of lead in the blood of newly born infants and their mothers with lead in their current environment. J Lab Clin Med 133:171-178.

Gulson BL, James M, Giblin AM, et al. 1997a. Maintenance of elevated lead levels in drinking water from occasional use and potential impact on blood leads in children. Sci Total Environ 205(2-3):271-275.

Gulson BL, Jameson CW, Mahaffey KR, et al. 1997b. Pregnancy increases mobilization of lead from maternal skeleton. J Lab Clin Med 130(1):51-62.

Gulson BL, Jameson CW, Mahaffey KR, et al. 1998a. Relationships of lead in breast milk to lead in blood, urine, and diet of the infant and mother. Environ Health Perspect 106(10):667-674.

Gulson BL, Mahaffey KR, Jameson CW, et al. 1998b. Mobilization of lead from the skeleton during the postnatal period is larger than during pregnancy. J Lab Clin Med 131:324-329.

Gulson BL, Mahaffey KR, Jameson CW, et al. 1999c. Impact of diet on lead in blood and urine in female adults and relevance to mobilization of lead from bone stores. Environ Health Perspect 107(4):257-263.

Gulson BL, Mizon KJ, Korsch MJ, et al. 1996. Impact on blood lead in children and adults following relocation from their source of exposure and contribution of skeletal tissue to blood lead. Bull Environ Contam Toxicol 56:543-550.

*Gulson BL, Mizon KJ, Korsch MJ, et al. 2001a. Dietary intakes of selected elements from longitudinal 6-day duplicate diets for pregnant and nonpregnant subjects and elemental concentrations of breast milk and infant formula. Environ Res 87:160-174.

Gulson BL, Mizon KJ, Korsch MJ, et al. 2003. Mobilization of lead from human bone tissue during pregnancy and lactation - a summary of long-term research. Sci Total Environ 303:79-104.

Gulson BL, Mizon KJ, Palmer JM, et al. 2001b. Contribution of lead from calcium supplements to blood lead. Environ Health Perspect 109(3):283-288.

Gulson BL, Mizon KJ, Palmer JM, et al. 2001c. Longitudinal study of daily intake and excretion of lead in newly born infants. Environ Res 85:232-245.

Gulson BL, Mizon KJ, Palmer JM, et al. 2004. Blood lead changes during pregnancy and postpartum with calcium supplementation. Environ Health Perspect 12(15):1499-1507.

Gulson BL, Palmer JM, Bryce A. 2002. Changes in blood lead of a recreational shooter. Sci Total Environ 293(1-3):143-150.

Gulson BL, Pounds JG, Mushak P, et al. 1999b. Estimation of cumulative lead releases (lead flux) from the maternal skeleton during pregnancy and lactation. J Lab Clin Med 134(6):631-640.

Gump BB, Stewart P, Reihman J, et al. 2005. Prenatal and early childhood blood lead levels and cardiovascular functioning in 9 1/2 year old children. Neurotoxicol Teratol 27(4):655-665.

Gunderson EL. 1988. FDA total diet study, April 1982-April 1984, dietary intakes of pesticides, selected elements and other chemicals. J Assoc Off Anal Chem 71:1200-1209.

Gunderson EL. 1995. FDA Total diet study, July 1986-April 1991, Dietary intakes of pesticides, selected elements, and other chemicals. J AOAC Int 78(6):1353-1363.

Gurer-Orhan H, Sabir HU, Ozgunes H. 2004. Correlation between clinical indicators of lead poisoning and oxidative stress parameters in controls and lead-exposed workers. Toxicology 195:147-154.

Gustafson A, Hedner P, Schutz A, et al. 1989. Occupational lead exposure and pituitary function. Int Arch Occup Environ Health 61:277-281.

Guzelian PS, Henry CJ, Olin SS, eds. 1992. Similarities and differences between children and adults: Implications for risk assessment. Washington, DC: International Life Sciences Institute Press.

*Haas T, Wieck AG, Schaller KH, et al. 1972. [The usual lead load in new-born infants and their mothers.] Zentralbl Bakteriol [B] 155:341-349. (German)

Habermann HC, Crowell K, Janicki P. 1983. Lead and other metals can substitute for Ca^2 in calmodulin. Arch Toxicol 54:61-70.

Haeger-Aronsen B, Schutz A, Abdulla M. 1976. Antagonistic effect in vivo of zinc on inhibition of δ-aminolevulinic acid dehydratase by lead. Arch Environ Health 31:215-220.

Haenninen H, Hernberg S, Mantere P, et al. 1978. Psychological performance of subjects with low exposure to lead. J Occup Med 20:683-689.

Häenninen H, Mantere P, Hernberg S, et al. 1979. Subjective symptoms in low-level exposure to lead. Neurotoxicology 1:333-347.

Haley VB, Talbot TO. 2004. Seasonality and trend in blood lead levels of New York State children. BMC Pediatr 4:8.

Hamilton DL. 1978. Interrelationships of lead and iron retention in iron- deficient mice. Toxicol Appl Pharmacol 46:651-661.

Hamilton JD, O'Flaherty EJ. 1994. Effects of lead exposure on skeletal development in rats. Fundam Appl Toxicol 22(4):594-604.

Hamilton JD, O'Flaherty EJ. 1995. Influence of lead on mineralization during bone growth. Fundam Appl Toxicol 26(2):265-271.

Hammad TA, Sexton M, Langenberg P. 1996. Relationship between blood lead and dietary iron intake in preschool children. A cross-section study. Ann Epidemiol 6(1):30-33.

Hammond PB, Bornschein RL, Succop P. 1985. Dose-effect and dose-response relationships of blood lead to erythrocytic protoporphyrin in young children. Environ Res 38:187-196.

Hänninen H, Aitio A, Kovala T, et al. 1998. Occupational exposure to lead and neuropsychological dysfunction. Occup Environ Med 55:202-209.

Hansen ON, Trillingsgaard A, Beese I, et al. 1989. A neuropsychological study of children with elevated dentine lead level: Assessment of the effect of lead in different socioeconomic groups. Neurotoxicol Teratol 11:205-213.

Harlan WR. 1988. The relationship of blood lead levels to blood pressure in the US population. Environ Health Perspect 78:9-13.

Harlan WR, Landis JR, Schmouder RL, et al. 1985. Blood lead and blood pressure: Relationship in the adolescent and adult U.S. population. JAMA 253:530-534.

Hart C. 1987. Art hazards: An overview for sanitarians and hygienists. J Environ Health 49:282-286.

*Harvey PG, Hamlin MW, Kumar R, et al. 1984. Blood lead, behavior and intelligence test performance in preschool children. Sci Total Environ 40:45-60.

Harvey PG, Hamlin MW, Kumar R, et al. 1988. Relationships between blood lead, behavior, psychometric and neuropsychological test performance in young children. Br J Dev Psychol 6:145-156.

Harville EW, Hertz-Picciotto I, Schramm M, et al. 2005. Factors influencing the difference between maternal and cord blood lead. Occup Environ Med 62:263-269.

Hashmi NS, Kachru DN, Khandelwal S, et al. 1989. Interrelationship between iron deficiency and lead intoxication: Part 2. Biol Trace Elem Res 22:299-307.

*Hawk BA, Schroeder SR, Robinson G, et al. 1986. Relation of lead and social factors to IQ of low-SES children: A partial replication. Am J Ment Defic 91:178-183.

HazDat. 2006. HazDat database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry. www.atsdr.cdc.gov/hazdat.html. October 14, 2006.

He L, Poblenz AT, Medrano CJ, et al. 2000. Lead and calcium produce rod photoreceptor cell apoptosis by opening the mitochondrial permeability transition pore. J Biol Chem 275:12175-12184.

Healy MA, Harrison PG, Aslam M, et al. 1982. Lead sulfide and traditional preparations: Routes for ingestion, and solubility and reactions in gastric fluid. J Clin Hosp Pharmacol 7:169-173.

Heard MJ, Chamberlain AC. 1982. Effect of minerals and food on uptake of lead from the gastrointestinal tract in humans. Hum Toxicol 1:411-416.

Heard MJ, Chamberlain AC. 1983. Uptake of lead by humans and effects of minerals and food. Sci Total Environ 30:245-253.

Heard MJ, Wells AC, Newton D, et al. 1979. Human uptake and metabolism of tetra ethyl and tetramethyl lead vapour labelled with ^{203}Pb. In: International Conference on Management and Control of Heavy Metals in the Environment, London, England, September. Edinburgh, United Kingdom: CEP Consultants, Ltd., 103-108.

Hense HW, Filipiak B, Keil U. 1993. The association of blood lead and blood pressure in population surveys. Epidemiology 4:173-179.

Heo Y, Lee BK, Ahn KD, et al. 2004. Serum IgE elevation correlates with blood lead levels in battery manufacturing workers. Hum Exp Toxicol 23:209-213.

Heo Y, Lee WT, Lawrence DA. 1998. Differential effects of lead and cAMP on development and activities of TH1- and Th2-lymphocytes. Toxicol Sci 43:172-185.

Herber RFM. 1980. Estimation of blood lead values from blood porphyrin and urinary delta-aminolevulinic acid levels in workers. Int Arch Occup Environ Health 45:169-179.

Hermes-Lima M, Pereira B, Bechara EJH. 1991. Are free radicals involved in lead poisoning? Xenobiotica 21:1085-1090.

Hernandez-Avila M, Gonzalez-Cossio T, Hernandez-Avila JE, et al. 2003. Dietary calcium supplements to lower blood lead levels in lactating women: A randomized placebo-controlled trial. Epidemiology 14(2):206-212.

Hernandez-Avila M, Gonzalez-Cossio T, Palazuelos E, et al. 1996. Dietary and environmental determinants of blood and bone lead levels in lactating postpartum women living in Mexico City. Environ Health Perspect 104:1076-1082.

Hernández-Avila M, Peterson KE, Gonzalez-Cossio T, et al. 2002. Effect of maternal bone lead on length and head circumference of newborns and 1-month-old infants. Arch Environ Health 57(5):482-488.

Hernandez-Avila M, Smith D, Meneses F, et al. 1998. The influence of bone and blood lead on plasma lead levels in environmentally exposed adults. Environ Health Perspect 106(8):473-477.

Hernandez-Avila M, Villalpano CG, Palazuelos E, et al. 2000. Determinants of blood lead levels across the menopausal transition. Arch Environ Health 53:355-360.

Hernandez-Ochoa I, Carcia-Vargas G, Lopez-Carrillo L, et al. 2005. Low lead environmental exposure alters semen quality and sperm chromatin condensation in northern Mexico. Reprod Toxicol 20(2):221-228.

Hernberg S, Nikkanen J. 1970. Enzyme inhibition by lead under normal urban conditions. Lancet 1:63-64.

Hernberg S, Nikkanen J, Mellin G, et al. 1970. δ-Aminolevulinic acid dehydrase as a measure of lead exposure. Arch Environ Health 21:140-145.

Hertz-Picciotto I, Croft J. 1993. Review of the relation between blood lead and blood pressure. Epidemiol Rev 15:352-373.

Hewitt PJ. 1988. Accumulation of metals in the tissues of occupationally exposed workers. Environ Geochem Health 10:113-116.

Hewitt CN, Harrison RM. 1986. Formation and decomposition of trialkyllead compounds in the atmosphere. Environ Sci Technol 20(8):797-802.

Hewitt CN, Harrison RM. 1987. Atmospheric concentrations and chemistry of alkyl lead compounds and environmental alkylation of lead. Environ Sci Technol 21:260-266.

Higgs FJ, Mielke HW, Brisco M. 1999. Soil lead at elementary public schools: Comparison between school properties and residential neighbourhoods of New Orleans. Environ Geochem Health 21:27-36.

Hirata M, Kosaka H. 1993. Effects of lead exposure on neurophysiological parameters. Environ Res 63:60-69.

Hodgkins DG, Robins TG, Hinkamp DL, et al. 1992. A longitudinal study of the relation of lead in blood to lead in air concentrations among battery workers. Br J Ind Med 49:241-248.

Hoffman DJ, Niyogi SK. 1977. Metal mutagens and carcinogens affect RNA synthesis rates in a distinct manner. Science 198:513-514.

Hogan K, Marcus A, Smith R, et al. 1998. Integrated exposure uptake biokinetic model for lead in children: Empirical comparisons with epidemiological data. Environ Health Perspect 106:1557-1567.

Hogstedt C, Hane M, Agrell A, et al. 1983. Neuropsychological test results and symptoms among workers with well-defined long-term exposure to lead. Br J Ind Med 40:99-105.

Holmgren GGS, Meyer MW, Chaney RL, et al. 1993. Cadmium, lead, cooper, and nickel in agricultural soils of the United States of America. J Environ Qual 22:335-348.

Holness DL, Nethercott JR. 1988. Acute lead intoxication in a group of demolition workers. Appl Ind Hyg 3:338-341.

Homan CS, Brogan GX, Orava RS. 1998. Lead toxicity. In: Viccellio P, ed. Emergency toxicology. Philadelphia, PA: Lippincott-Raven Publishers, 363-378.

Hong CD, Hanenson IB, Lerner S, et al. 1980. Occupational exposure to lead: Effects on renal function. Kidney Int 18:489-494.

Hoppin JA, Aro A, Hu H, et al. 1997. In vivo bone lead measurement in suburban teenagers. Pediatrics 100(3 Pt 1):365-370.

Horn J. 1970. [Isolation and examination of inclusion bodies of the rat kidney after chronic lead poisoning.] Virchows Arch B Cell Pathol 6:313-317. (German)

Hotter G, Fels LM, Closa D, et al. 1995. Altered levels of urinary prostanoids in lead-exposed worker. Toxicol Lett 77:309-312.

Howe HE. 1981. Lead. In: Kirk-Othmer encyclopedia of chemical technology. 3rd ed., Vol. 14. New York, NY: John Wiley and Sons, 98-139.

Hryhirczuk DO, Rabinowitz RB, Hessl SM, et al. 1985. Elimination kinetics of blood lead in workers with chronic lead intoxication. Am J Ind Med 8:33-42.

HSDB. 2007. Lead. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. June 13, 2007.

Hsiao C-Y, Wu H-DI, Lai J-S, et al. 2001. A longitudinal study of the effects of long-term exposure to lead among lead battery factory workers in Taiwan (1989-1999). Sci Total Environ 279:151-158.

Hsieh LL, Liou SH, Chen YH, et al. 2000. Association between aminolevulinate dehydrogenase genotype and blood lead levels in Taiwan. J Occup Environ Med 42(2):151-155.

Hsu FS, Krook L, Pond WG, et al. 1975. Interactions of dietary calcium with toxic levels of lead and zinc in pigs. J Nutr 105:112-118.

Hsu PC, Hsu CC, Liu MY, et al. 1998a. Lead-induced changes in spermatozoa function and metabolism. J Toxicol Environ Health A 55:45-64.

Hsu PC, Liu MY, Hsu CC, et al. 1998b. Effects of vitamin E and/or C on reactive oxygen species-related lead toxicity in the rat sperm. Toxicology 128:169-179.

Hu H. 1991a. A 50-year follow-up of childhood plumbism. Hypertension, renal function, and hemoglobin levels among survivors. Am J Dis Child 145:681-687.

Hu H. 1991b. Knowledge of diagnosis and reproductive history among survivors of childhood plumbism. Am J Public Health 81:1070-1072.

Hu H, Aro A, Payton M, et al. 1996a. The relationship of bone and blood lead to hypertension. The normative study. JAMA 275:1171-1176.

Hu H, Aro A, Rotnitzky A. 1995. Bone lead measured by x-ray fluorescence: Epidemiologic methods. Environ Health Perspect 103(Suppl 1):105-110.

Hu H, Hashimoto D, Besser M. 1996b. Levels of lead in blood and bone of women giving birth in a Boston hospital. Arch Environ Health 51(1):52-58.

Hu H, Milder FL, Burger DE. 1989. X-ray fluorescence: Issues surrounding the application of a new tool for measuring burden of lead. Environ Res 49:295-317.

Hu H, Milder FL, Burger DE. 1990. X-ray fluorescence measurements of lead burden in subjects with low-level community lead exposure. Arch Environ Health 45(6):335-341.

Hu H, Pepper L, Goldman R. 1991. Effect of repeated occupational exposure to lead, cessation of exposure, and chelation on levels of lead in bone. Am J Ind Med 20:723-735.

Hu H, Rabinowitz M, Smith D. 1998. Bone lead as a biological marker in epidemiologic studies of chronic toxicity: Conceptual paradigms. Environ Health Perspect 106(1):1-8.

Hu H, Tellez-Rojo MM, Bellinger D, et al. 2006. Fetal lead exposure at each stage of pregnancy as a predictor of infant mental health. Environ Health Perspect 114(11):1730-1735.

Hu H, Watanabe H, Payton M, et al. 1994. The relationship between bone lead and hemoglobin. JAMA 272(19):1512-1517.

Hu H, Wu M-T, Cheng Y, et al. 2001. The δ-aminolevulinic acid dehydratase (ALAD) polymorphism and bone and blood lead levels in community-exposed men: The normative aging study. Environ Health Perspect 109(8):827-832.

*Huang JX, He FS, Wu YG, et al. 1988a. Observations on renal function in workers exposed to lead. Sci Total Environ 71:535-537.

Huang XP, Feng ZY, Zhai WL, et al. 1988b. Chromosomal aberrations and sister chromatid exchanges in workers exposed to lead. Biomed Environ Sci 1:382-387.

Hubermont G, Buchet J, Roels H, et al. 1976. Effect of short-term administration of lead to pregnant rats. Toxicology 5:379-384.

HUD. 1997. Guidelines for the evaluation and control of lead-based paint hazards in housing. Chapter 7: Lead-based paint inspection. 1997 Revision. U.S. Department of Housing and Urban Development.

HUD. 1998. Lead-based paint poisoning prevention in certain residential structures. U.S. Department of Housing and Urban Development. Code of Federal Regulations. 24 CFR 35.

Hursh JB, Mercer TT. 1970. Measurement of ^{212}Pb loss rate from human lungs. J Appl Physiol 28:268-274.

Hursh JB, Suomela J. 1968. Absorption of ^{212}Pb from the gastrointestinal tract of man. Acta Radiol 7(2):108-120.

Hursh JB, Clarkson TW, Miles EF, et al. 1989. Percutaneous absorption of mercury vapor by man. Arch Environ Health 44(2):120-127.

Hursh JB, Schraub A, Sattler EL, et al. 1969. Fate of ^{212}Pb inhaled by human subjects. Health Phys 16:257-267.

*Huseman CA, Moriarty CM, Angle CR. 1987. Childhood lead toxicity and impaired release of thyrotropin-stimulating hormone. Environ Res 42:524-533.

Huseman CA, Varma MM, Angle CR. 1992. Neuroendocrine effects of toxic and low blood lead levels in children. Pediatrics 90:186-189.

Hwang K-Y, Schwartz BS, Byung-Kook L, et al. 2001. Associations of lead exposure and dose measures with erythrocyte protein kinase C activity in 212 current Korean lead workers. Toxicol Sci 62:280-288.

Iannaccone A, Boscolo P, Carmignani M. 1981. Neurogenic and humoral mechanisms in arterial hypertension of chronically lead-exposed rats. Medicina del Lavoro 72:13-21.

IARC. 1980. IARC monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 23: Some metals and metallic compounds. Lyons France: World Health Organization, International Agency for Research on Cancer, 325-415.

IARC. 2004. Overall evaluations of carcinogenicity to humans: As evaluated in IARC Monographs volumes 1-82 (at total of 900 agents, mixtures and exposures). Lyon, France: International Agency for Research on Cancer. http://www-cie.iarc.fr/monoeval/crthall.html. February 15, 2005.

Iavicoli I, Carelli G, Stanek EJ, et al. 2004. Effects of low doses of dietary lead on puberty onset in female mice. Reprod Toxicol 19(1):35-41.

Inskip MJ, Franklin CA, Baccanale CL, et al. 1996. Measurement of the flux of lead from bone to blood in a nonhuman primate (*Macaca fascicularis*) by sequential administration of stable lead isotopes. Fundam Appl Toxicol 33:235-245.

IPCS. 1995. Inorganic lead. International Programme on Chemical Safety. Environmental Health Criteria 165 ed. Geneva, Switzerland: WHO (World Health Organization).

IRIS. 2005. Lead. U.S. Environmental Protection Agency. Washington, DC: Integrated Risk Information System. http://www.epa.gov/iris/. March 26, 2005.

Ishida M, Ishizaki M, Yamada Y. 1996. Decreases in postural change in finger blood flow in ceramic painters chronically exposed to low level lead. Am J Ind Med 29(5):547-553.

Ito Y, Niiya Y, Otani M, et al. 1987. Effect of food intake on blood lead concentration in workers occupationally exposed to lead. Toxicol Lett 37:105-114.

Iwata T, Yano E, Karita K, et al. 2005. Critical dose of lead affecting postural balance in workers. Am J Epidemiol 48(5):319-325.

Jackson LW, Correa-Villasenor A, Lees PS, et al. 2004. Parental lead exposure and total anomalous pulmonary venous returrn. Birth Defects Res A Clin Mol Teratol 70(4):185-193.

Jacquet P, Tachon P. 1981. Effects of long-term lead exposure on monkey leukocyte chromosomes. Toxicol Lett 8:165-169.

Jacquet P, Leonard A, Gerber GB. 1977. Cytogenetic investigations on mice treated with lead. J Toxicol Environ Health 2:619-624.

Jagetia GC, Aruna R. 1998. Effect of various concentrations of lead nitrate on the induction of micronuclei in mouse bone marrow. Mutat Res 415:131-137.

James AC, Stahlhofen W, Rudolf G, et al. 1994. Deposition of inhaled particles. Ann ICRP 24(1-3):231-299.

James HM, Hilburn ME, Blair JA. 1985. Effects of meals and meal times on uptake of lead from the gastrointestinal tract of humans. Hum Toxicol 4:401-407.

Janakiraman V, Ettinger A, Mercado-Garcia A, et al. 2003. Calcium supplements and bone resorption in pregnancy: A randomized crossover trial. Am J Prev Med 24(3):260-264.

Janin Y, Couinaud C, Stone A, et al. 1985. The “lead-induced colic” syndrome in lead intoxication. Surg Ann 17:287-307.

Jason KM, Kellogg CK. 1981. Neonatal lead exposure: Effects on development of behavior and striatal dopamine neurons. Pharmacol Biochem Behav 15:641-649.

Jelliffe-Pawlowski LL, Miles SQ, Courtney JG, et al. 2006. Effect of magnitude and timing of maternal pregnancy blood lead (Pb) levels on birth outcomes. J Perinatol 26(3):154-162.

Jemal A, Graubard BI, Devesa SS, et al. 2002. The association of blood lead level and cancer mortality among whites in the United States. Environ Health Perspect 110(4):325-329.

Jin Y, Liao Y, Lu C, et al. 2006. Health effects in children aged 3-6 years induced by environmental lead exposure. Ecotoxicol Environ Saf 63(2):313-317.

Joffe M, Bisanti L, Apostoli P, et al. 2003. Time to pregnancy and occupational lead exposure. Occup Environ Med 60:752-758.

Johanson CE. 1980. Permeability and vascularity of the developing brain: Cerebellum vs cerebral cortex. Brain Res 190:3-16.

Johnson BL, Mason RW. 1984. A review of public health regulations on lead. Neurotoxicity 5:1-22.

Johnson DL, Bretsch JK. 2002. Soil lead and children's blood lead levels in Syracuse, NY, USA. Environ Geochem Health 24:375-385.

Johnson NE, Tenuta K. 1979. Diets and lead blood levels of children who practice pica. Environ Res 18:369-376.

*Joselow MM, Flores J. 1977. Application of the zinc protoporphyrin (ZP) test as a monitor of occupational exposure to lead. Am Ind Hyg Assoc J 38:63-66.

Joseph CLM, Havstad S, Ownby DR, et al. 2005. Blood lead levels and risk of asthma. Environ Health Perspect 113(7):900-904.

Kamel F, Umbach DM, Munsat TL, et al. 2002. Lead exposure and amyotrophic lateral sclerosis. Epidemiology 13:311-319.

Kapoor SC, Van Rossum GDV, O’Neill KJ et al. 1985. Uptake of inorganic lead in vitro by isolated mitochondria and tissue slices of rat renal cortex. Biochem Pharmacol 34:1439-1448.

Karmaus W, Brooks KR, Nebe T, et al. 2005. Immune function biomarkers in children exposed to lead and organochlorine compounds: A cross-sectional study. Environ Health 4:5. http://www.ehjournal.net/content/4/1/5. February 1, 2007.

Kaufmann RB, Staes CJ, Matte TD. 2003. Deaths related to lead poisoning in the United States, 1979–1998. Environ Res 91:78-84.

Kaye WE, Novotny TE, Tucker M. 1987. New ceramics-related industry implicated in elevated blood lead levels in children. Arch Environ Health 42:161-164.

Kehoe RA. 1961. The metabolism of lead in man in health and disease: Present hygienic problems relating to the absorption of lead: The Harben lectures, 1960. J R Inst Public Health Hyg 24:177-203.

Kehoe RA. 1987. Studies of lead administration and elimination in adult volunteers under natural and experimentally induced conditions over extended periods of time. Food Chem Toxicol 25:425-493.

Kehoe RA, Thamann F. 1931. The behavior of lead in the animal organism: II. Tetraethyl lead. Am J Hyg 13:478-498.

Kerper LE, Hinkle PM. 1997b. Cellular uptake of lead is activated by depletion of intracellular calcium stores. J Biol Chem 272(13):8346-8352.

Kerper LE, Hinkle PM. 1997a. Lead uptake in brain capillary endothelial cells: Activation by calcium store depletion. Toxicol Appl Pharmacol 146:127-133.

Khalil-Manesh F, Gonick HC, Cohen AH, et al. 1992a. Experimental model of lead nephropathy. I. Continuous high-dose lead administration. Kidney Int 41:1192-1203.

Khalil-Manesh F, Gonick HC, Cohen A, et al. 1992b. Experimental model of lead nephropathy. II. Effect of removal from lead exposure and chelation treatment with dimercaptosuccinic acid (DMSA). Environ Res 58:35-54.

Khalil-Manesh F, Gonick HC, Weiler EWJ. 1993. Lead-induced hypertension: Possible role of endothelial factors. Am J Hypertens 6:723-729.

Khan DH, Frankland B. 1983. Chemical forms of cadmium and lead in some contaminated soils. Environ Pollut Ser B 6:15-31.

Kharab P, Singh I. 1985. Genotoxic effects of potassium dichromate, sodium arsenite, cobalt chloride and lead nitrate in diploid yeast. Mutat Res 155:117-120.

*Khera AK, Wibberley DG, Dathan JG. 1980a. Placental and stillbirth tissue lead concentration in occupationally exposed women. Br J Ind Med 37:394-396.

*Khera AK, Wibberley DG, Edwards KW, et al. 1980b. Cadmium and lead levels in blood and urine in a series of cardiovascular and normotensive patients. Int J Environ Stud 14:309-312.

Khoury GA, Diamond GL. 2003. Risks to children from exposure to lead in air during remedial or removal activities at superfund sites: A case study of the RSR lead smelter superfund site. Toxicol Sci 72:394.

Kim JS, Hamilton DL, Blakley BR, et al. 1992. The effects of thiamin on lead metabolism: Organ distribution of lead 203. Can J Vet Res 56:256-259.

Kim R, Hu H, Rotnitzky A, et al. 1995. A longitudinal study of chronic lead exposure and physical growth in Boston children. Environ Health Perspect 103:952-957.

Kim R, Hu H, Rotnitzky A, et al. 1996b. Longitudinal relationship between dentin lead levels in childhood and bone lead levels in young adulthood. Arch Environ Health 51(5):375-382.

Kim R, Landrigan C, Mossmann P, et al. 1997. Age and secular trends in bone lead levels in middle-aged and elderly men: Three-year longitudinal follow-up in the normative aging study. Am J Epidemiol 146(4):586-591.

Kim R, Rotnitzky A, Sparrow D, et al. 1996a. A longitudinal study of low-level lead exposure and impairment of renal function. The normative aging study. JAMA 275:1177-1181.

Kimber I, Stonard MD, Gidlow DA, et al. 1986. Influence of chronic low- level exposure to lead on plasma immunoglobin concentration and cellular immune function in man. Int Arch Occup Environ Health 57:117-125.

Kimmel EC, Fish RH, Casida JE. 1977. Bioorganotin chemistry: Metabolism of organotin compounds in microsomal monoxygenase systems and in mammals. J Agric Food Chem 25:1-9.

King M, Ramachandran V. 1995. Lead. In: Kirk-Othmer encyclopedia of chemical technology. 4th edition. New York, NY: John Wiley & Sons, 69-113.

Kirkby H, Gyntelberg F. 1985. Blood pressure and other cardiovascular risk factors of long-term exposure to lead. Scand J Work Environ Health 11:15-19.

Klaassen CD, Shoeman DW. 1974. Biliary excretion of lead in rats, rabbits, and dogs. Toxicol Appl Pharmacol 1(9):434-446.

Klauder DS, Petering HB. 1975. Protective value of dietary copper and iron against some toxic effects of lead in rats. Environ Health Perspect 12:77-80.

Kohler K, Lilienthal H, Guenther E, et al. 1997. Persistent decrease of the dopamine synthesizing enzyme tyrosine hydroxylase in the Rhesus monkey retina after chronic lead exposure. Neurotoxicology 18(3):623-632.

Koller LD. 1985. Immunological effects of lead. In: Mahaffey KR, ed. Dietary and environmental lead: Human health effects. Amsterdam, The Netherlands: Elsevier Publishers B.V., 339-353.

Koller K, Brown T, Spurgeon A, et al. 2004. Recent developments in low-level lead exposure and intellectual impairment in children. Environ Health Perspect 112(9):987-994.

Koller LD, Kerkvliet NI, Exon JH. 1985. Neoplasia induced in male rats fed lead acetate, ethylurea and sodium nitrite. Toxicologic Pathol 13:50-57

Komori M, Nishio K, Kitada M, et al. 1990. Fetus-specific expression of a form of cytochrome P-450 in human livers. Biochemistry 29:4430-4433.

Koo WWR, Succop PA, Bornschcin RL, et al. 1991. Serum vitamin D metabolites and bone mineralization in young children with chronic low to moderate lead exposure. Pediatrics 87:680-687.

Kordas K, Canfield RL, Lopez P, et al. 2006. Deficits in cognitive function and achievement in Mexican first-graders with low blood lead concentrations. Environ Res 100(3):371-386.

Kordas K, Stoltzfus RJ, Lopez P, et al. 2005. Iron and zinc supplementation does not improve parent or teacher ratings of behavior in first grade Mexican children exposed to lead. J Pediatr 147(5):632-639.

Koren G, Chang N, Gonen R, et al. 1990. Lead-exposure among mothers and their newborns in Toronto. Can Med Assoc J 142:1241-1244.

Korrick SA, Hunter DJ, Rotnitzky A, et al. 1999. Lead and hypertension in a sample of middle-aged women. Am J Public Health 89(3):330-335.

Korrick SA, Schwartz J, Tsaih SW, et al. 2002. Correlates of bone and blood lead levels among middle-aged and elderly women. Am J Epidemiol 156(4):335-343.

Kosmider S, Petelenz T. 1962. [Electrocardiographic changes in elderly patients with chronic professional lead poisoning.] Pol Arch Med Wewn 32:437-442. (Polish)

Kosnett MJ. 2004. Lead. In: Olson KR, Anderson IB, Benowitz NL, et al, eds. Poisoning & drug overdose. 4th ed. New York, NY: McGraw-Hill Companies, Inc., 238-242.

Kosnett MJ, Becker CE, Osterloh JD, et al. 1994. Factors influencing bone lead concentration in a suburban community assessed by noninvasive K x-ray fluorescence. JAMA 271:197-203.

Kostial K, Kello D, Jugo S, et al. 1978. Influence of age on metal metabolism and toxicity. Environ Health Perspect 25:81-86.

*Kotok D. 1972. Development of children with elevated blood levels: A controlled study. J Pediatr 80:57-61.

*Kotok D, Kotok R, Heriot T. 1977. Cognitive evaluation of children with elevated blood lead levels. Am J Dis Child 131:791-793.

Kramer HJ, Gonick HC, Lu E. 1986. In vitro inhibition of Na-K-ATPase by trace metals: Relation to renal and cardiovascular damage. Nephron 44:329-336.

Krieg EF, Chrislip DW, Crespo CJ, et al. 2005. The relationship between blood lead levels and neurobehavioral test performance in NHANES III and related occupational studies. Public Health Rep 120(3):240-251.

Krishnan K, Andersen ME. 1994. Physiologically based pharmacokinetic modeling in toxicology. In: Hayes AW, ed. Principles and methods of toxicology. 3rd ed. New York, NY: Raven Press, Ltd., 149-188.

Krishnan K, Andersen ME, Clewell HJ III, et al. 1994. Physiologically based pharmacokinetic modeling of chemical mixtures. In: Yang RSH, ed. Toxicology of chemical mixtures: Case studies, mechanisms, and novel approaches. San Diego, CA: Academic Press, 399-437.

Kristal-Boneh E, Coller D, Froom P, et al. 1999. The association between occupational lead exposure and serum cholesterol and lipoprotein levels. Am J Public Health 89(7):1083-1087.

Kromhout D. 1988. Blood lead and coronary heart disease risk among elderly men in Zutphen, The Netherlands. Environ Health Perspect 78:43-46.

Kromhout D, Wibowo AAE, Herber RFM, et al. 1985. Trace metals and coronary heart disease risk indicators in 152 elderly men (the Zutphen study). Am J Epidemiol 122:378-385.

Krueger JA, Duguay KM. 1989. Comparative analysis of lead in Maine urban soils. Bull Environ Contam Toxicol 42:574-581.

*Kuhnert PM, Erhard P, Kuhnert BR. 1977. Lead and δ-aminolevulinic acid dehydratase in RBC's of urban mothers and fetuses. Environ Res 14:73-80.

Kumar BD, Krishnaswamy K. 1995. Detection of occupational lead nephropathy using early renal markers. Clin Toxicol 33(4):331-335.

Kumar S, Jain S, Aggarwal CS, et al. 1987. Encephalopathy due to inorganic lead exposure in an adult. Jpn J Med 26:253-254.

Kutbi II, Ahmed M, Saber A, et al. 1989. Measurement of blood-lead levels in school children of Jeddah Saudi Arabia and assessment of sub-toxic levels of lead on some sensitive hematological parameters. J Environ Sci Health A24:943-955.

Kwong WT, Friello P, Semba RD. 2004. Interactions between iron deficiency and lead poisoning: Epidemiology and pathogenesis. Sci Total Environ 330:21-37.

Lacey RF, Moore MR, Richards WN. 1985. Lead in water, infant diet and blood: The Glasgow duplicate diet stud. Sci Total Environ 41:235-257.

Lagerkvist BJ, Ekesrydh S, Englyst V, et al. 1996. Increased blood lead and decreased calcium levels during pregnancy: A prospective study of Swedish women living near a smelter. Am J Public Health 86:1247-1252.

LaGoy P. 1987. Estimated soil ingestion rates for use in risk assessment. Risk Anal 7:355-359.

Lai JS, Wu TN, Liou SH, et al. 1997. A study of the relationship between ambient lead and blood lead among lead battery workers. Int Arch Occup Environ Health 69(4):295-300.

Lancranjan I, Popescu HI, Gavanescu O, et al. 1975. Reproductive ability of workmen occupationally exposed to lead. Arch Environ Health 30:396-401.

Landis JR, Flegal KM. 1988. A generalized Mantel-Haenszel analysis of the regression of blood pressure on blood lead using NHANES II data. Environ Health Perspect 78:35-41.

Landrigan PJ. 1989. Toxicity of lead at low dose. Br J Ind Med 46:593-596.

Landrigan PJ, Baker EL. 1981. Exposure of children to heavy metals from smelters: Epidemiology and toxic consequences. Environ Res 25:204-224.

Landrigan PJ, Todd AC. 1994. Lead poisoning [see comments]. West J Med 161(2):153-159.

Landrigan PJ, Baker EL, Feldman RG, et al. 1976. Increased lead absorption with anemia and slowed nerve conduction in children near a lead smelter. J Pediatr 89:904-910.

Landrigan PJ, Boffetta P, Apostoli P. 2000. The reproductive toxicity and carcinogenicity of lead: A critical review. Am J Ind Med 38:231-243.

Landrigan PJ, Schechter CB, Lipton JM, et al. 2002. Environmental pollutants and disease in American children: Estimates of morbidity, mortality, and costs for lead poisoning, asthma, cancer, and developmental disabilities. Environ Health Perspect 110:721-728.

Langlois P, Smith L, Fleming S, et al. 1996. Blood lead levels in Toronto children and abatement of lead-contaminated soil and house dust. Arch Environ Health 51(1):59-67.

Lannefors H, Hansson HC, Granat L. 1983. Background aerosol composition in southern Sweden -- Fourteen micro and macro constituents measured in seven particle size intervals at one site during one year. Atmos Environ 17:87-101.

Lanphear BP, Roghmann KJ. 1997. Pathways of lead exposure in urban children. Environ Res 74(1):67-73.

Lanphear BP, Burgoon DA, Rust SW, et al. 1998a. Environmental exposures to lead and urban children's blood lead levels. Environ Res 76(2):120-130.

Lanphear BP, Byrd RS, Auinger P, et al. 1998b. Community characteristics associated with elevated blood lead levels in children. Pediatrics 101(2):264-271.

Lanphear BP, Dietrich K, Auinger P, et al. 2000a. Cognitive deficits associated with blood lead concentrations <10 µg/dL in US children and adolescents. Public Health Rep 115(6):521-529.

Lanphear BP, Eberly S, Howard CR. 2000b. Long-term effect of dust control on blood lead concentrations. Pediatrics 106(4):1-4.

Lanphear BP, Hornung R, Khoury J, et al. 2005. Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. Environ Health Perspect 113(7):894-899.

Lanphear BP, Weitzman M, Eberly S. 1996a. Racial differences in urban children's environmental exposures to lead. Am J Public Health 86(10):1460-1463.

Lanphear BP, Weitzman M, Winter NL, et al. 1996b. Lead-contaminated house dust and urban children's blood lead levels. Am J Public Health 86(10):1416-1421.

Lansdown R, Yule W, Urbanowicz MA, et al. 1986. The relationship between blood lead concentrations, intelligence, attainment and behavior in a school population: The second London study. Int Arch Occup Environ Health 57:225-235.

*Laraque D, McCormick M, Norman M, et al. 1990. Blood lead, calcium status, and behavior in preschool children. Am J Dis Child 144:186-189.

Larrabee D. 1997. U.S. industry & trade outlook. New York, NY: McGraw Hill Inc., 14-10 to 14-13.

Larrabee D. 1998. Comments on chapter 4 of the draft toxicological profile for lead/metals division. U.S. Department of Commerce, February 11, 1998.

Larson JK, Buchan RM, Blehm KD, et al. 1989. Characterization of lead fume exposure during gas metal arc welding on carbon steel. Appl Ind Hyg 4:330-333.

Larsson B, Slorach SA, Hagman U, et al. 1981. WHO collaborative breast feeding study. Acta Paediatr Scand 70:281-284.

Lasky RE, Luck ML, Torre P, et al. 2001. The effects of early lead exposure on auditory function in rhesus monkeys. Neurotoxicol Teratol 23:639-649.

Lasky RE, Maier MM, Snodgrass EB, et al. 1995. The effects of lead on otoacoustic emissions and auditory evoked potentials in monkeys. Neurotoxicol Teratol 17:633-644.

Lasley SM, Gilbert ME. 2000. Glutamatergic components underlying lead-induced impairments in hippocampal synaptic plasticity. Neurotoxicology 21(6):1057-1068.

Laug EP, Kunze FM. 1948. The penetration of lead through the skin. J Ind Hyg Toxicol 30:256-259.

*Lauwers MC, Hauspie RC, Susanne C, et al. 1986. Comparison of biometric data of children with high and low levels of lead in the blood. Am J Phys Anthropol 69:107-116.

Lauwerys R, Buchet J-P, Roels HA, et al. 1974. Relationship between urinary delta-aminolevulinic acid excretion and the inhibition of red cell delta-aminolevulinate dehydratase by lead. Clin Toxicol 7:383-388.

Lauwerys R, Buchet J-P, Roels HA, et al. 1978. Placental transfer of lead, mercury, cadmium, and carbon monoxide in women: I. Comparison of the frequency distributions of the biological indices in maternal and umbilical cord blood. Environ Res 15:278-289.

Lawton LJ, Donaldson WE. 1991. Lead-induced tissue fatty acid alterations and lipid peroxidation. Biol Trace Elem Res 28:83-97.

Laxen DP, Raab GM, Fulton M. 1987. Children's blood lead and exposure to lead in household dust and water--a basis for an environmental standard for lead in dust. Sci Total Environ 66:235-244.

Lee BK, Lee GS, Stewart WF, et al. 2001. Associations of blood pressure and hypertension with lead dose measures and polymorphisms in the vitamin D receptor and δ-aminolevulinic acid dehydratase genes. Environ Health Perspect 109(4):383-389.

Lee RG, Becker WC, Collins DW. 1989. Lead at the tap: Sources and control. J Am Water Works Assoc 81:52-62.

Leeder JS, Kearns GL. 1997. Pharmcogenetics in pediatrics: Implications for practice. Pediatr Clin North Am 44(1):55-77.

Legare ME, Barhoumi R, Hebert E, et al. 1998. Analysis of Pb^2 entry into cultured astroglia. Toxicol Sci 46:90-100.

Leggett RW. 1993. An age-specific kinetic model of lead metabolism in humans. Environ Health Perspect 101:598-616.

Leikin JB, Paloucek FP. 2002. Poisoning and toxicology handbook. 3rd edition. Hudson, OH: Lexi-Comp Inc., 725-731.

Lenga RE. 1988. The Sigma-Aldrich library of chemical safety data. Edition II, Volume 1. Milwaukee, WI: Sigma-Aldrich Corporation, 2071.

Le Quesne PM. 1987. Clinically used electrophysiological end-points. In: Lowndes HE, ed. Electrophysiology in neurotoxicology. Vol. 1. Piscataway, NJ: Department of Pharmacology and Toxicology, Rutgers, 103-116.

Lerda D. 1992. Study of sperm characteristics in persons occupationally exposed to lead. Am J Ind Med 22:567-571.

Leung H. 1993. Physiologically-based pharmacokinetic modelling. In: Ballentyne B, Marrs T, Turner P, eds. General and applied toxicology. Vol. 1. New York, NY: Stockton Press, 153-164.

Levey AS, Bosch JP, Lewis JB, et al. 1999. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med 130(6):461-479.

Levin ED, Bowman RE. 1986. Long-term lead effects on the Hamilton Search Task and delayed alternation in monkeys. Neurobehav Toxicol Teratol 8:219-224.

Lewin MD, Sarasua S, Jones PA. 1999. A multivariate linear regression model for predicting children's blood lead levels based on soil lead levels: A study at four Superfund sites. Environ Res 81:52-61.

Lewis RJ. 1993. Hawley's condensed chemical dictionary. New York, NY: Van Nostrand Reinhold Company, 686-693.

Li S, Zhengyan Z, Rong L, et al. 2005. Decrease of $CD4^+$ T-lymphocytes in children exposed to environmental lead. Biol Trace Elem Res 105(1-3):19-25.

Lide DR, ed. 1996. CRC handbook of chemistry and physics. Boca Raton, FL: CRC Press, Inc., 4-119.

Lidsky TI, Schneider JS. 2003. Lead neurotoxicity in children: Basic mechanisms and clinical correlates. Brain 126:5-19.

Liebelt EL, Schonfeld DJ, Gallagher P. 1999. Elevated blood lead levels in children are associated with lower erythropoietin concentrations. J Pediatr 134:107-109.

Lilienthal H, Winneke G. 1996. Lead effects on the brain stem auditory evoked potentials in monkeys during and after the treatment phase. Neurotoxicol Teratol 18:17-32.

Lilienthal H, Kohler K, Turfeld M, et al. 1994. Persistent increases in scotopic B-wave amplitudes after lead exposure in monkeys. Exp Eye Res 59:203-209.

Lilienthal H, Lenaerts C, Winneke G, et al. 1988. Alternation of the visual evoked potential and the electroretinogram in lead-treated monkeys. Neurotoxicol Teratol 10:417-422.

9. REFERENCES

*Lilis R. 1981. Long-term occupational lead exposure, chronic nephropathy, and renal cancer: A case report. Am J Ind Med 2:293-297.

Lilis R, Eisinger J, Blumberg W, et al. 1978. Hemoglobin, serum iron, and zinc protoporphyrin in lead-exposed workers. Environ Health Perspect 25:97-102.

Lilis R, Fischbein A, Valciukas JA, et al. 1980. Kidney function and lead: Relationships in several occupational groups with different levels of exposure. Am J Ind Med 1:405-412.

Lilis R, Gavrilescu N, Nestorescu B, et al. 1968. Nephropathy in chronic lead poisoning. Br J Ind Med 25:196-202.

Lilley SG, Florence TM, Stauber JL. 1988. The use of sweat to monitor lead absorption through the skin. Sci Total Environ 76:267-278.

Lin JL, Tan DT, Hsu KH, et al. 2001. Environmental lead exposure and progressive renal insufficiency. Arch Intern Med 161:264-271.

Lin S, Hwang S, Marshall EG, et al. 1996. Fertility rates among lead workers and professional bus drivers: A comparative study. Ann Epidemiol 6:201-208.

Lindgren KN, Ford DP, Bleecker ML. 2003. Pattern of blood levels over working lifetime and neuropsychological performance. Arch Environ Health 58(6):373-379.

Lindgren KN, Masten VL, Ford DP, et al. 1996. Relation of cumulative exposure to inorganic lead and neuropsychological test performance. Occup Environ Med 53(7):472-477.

Liu X, Dietrich KM, Radcliffe J, et al. 2002. Do children with falling blood lead levels have improved cognition? Pediatrics 110(4):787-791.

Lloyd RD, Mays CW, Atherton DR, et al. 1975. ^{210}Pb studies in beagles. Health Phys 28:575-583.

Lockett CJ, Arbuckle D. 1987. Lead, ferritin, zinc, and hypertension. Bull Environ Contam Toxicol 38:975-980.

Loghman-Adham M. 1997. Renal effects of environmental and occupational lead exposure. Environ Health Perspect 105:928-939.

Long DT, Angino EE. 1977. Chemical speciation of Cd, Cu, Pb, and Zn in mixed freshwater, seawater, and brine solutions. Geochim Cosmochim Acta 41:1183-1191.

Long GJ, Rosen JF. 1994. Lead perturbs 1,25 dihydroxyvitamin D3 modulation of intracellular calcium metabolism in clonal rat osteoblastic (ros 17/2.8) cells. Life Sci 54(19):1395-1402.

Lopez CM, Pineiro AE, Nunez N, et al. 2000. Thyroid hormone changes in males exposed to lead in the Buenos Aires area (Argentina). Pharmacol Res Commun 42(6):599-602.

Lorenzana RM, Troast R, Klotzbach JM, et al. 2005. Issues related to time averaging of exposure in modeling risks associated with intermittent exposures to lead. Risk Anal 25:169-178.

Louis ED, Jurewicz EC, Applegate L, et al. 2003. Association between essential tremor and blood lead concentration. Environ Health Perspect 111(14):1707-1711.

Lucas SR, Sexton M, Langenberg P. 1996. Relationship between blood lead and nutritional factors in preschool children: A cross-sectional study. Pediatrics 97(1):74-78.

Lucchini R, Albini E, Cortesi I, et al. 2000. Assessment of neurobehavioral performance as a function of current and cumulative occupational lead exposure. Neurotoxicology 21(5):805-812.

Lundstrom NG, Nordberg G, Englyst V, et al. 1997. Cumulative lead exposure in relation to mortality and lung cancer morbidity in a cohort of primary smelter workers. Scand J Work Environ Health 23(1):24-30.

Lustberg M, Silbergeld E. 2002. Blood lead levels and mortality. Arch Intern Med 162:2443-2449.

Luster MI, Faith RE, Kimmel CA. 1978. Depression of humoral immunity in rats following chronic developmental lead exposure. J Environ Pathol Toxicol 1:397-402.

Lutz PM, Wilson TJ, Ireland J, et al. 1999. Elevated immunoglobulin E (IgE) levels in children with exposure to environmental lead. Toxicology 134:63-78.

*Lyngbye T, Hansen ON, Grandjean P. 1987. The influence of environmental factors on physical growth in school age: A study of low level lead exposure. In: Lindberg SE, Hutchinson TC, eds. International conference on heavy metals in the environment, Vol. 2, New Orleans, LA. Edinburgh, UK: CEP Consultants, Ltd., 210-212.

*Lyngbye T, Hansen ON, Grandjean P. 1989. Neurological deficits in children: Medical risk factors and lead exposure. Neurotoxicol Teratol 10:531-537.

Lyngbye T, Jorgensen PJ, Grandjean P, et al. 1990b. Validity and interpretation of blood lead levels: A study of Danish school-children. Scand J Clin Lab Invest 50:441-449.

Maas RP, Patch SC, Pandolfo TJ, et al. 2005. Lead content and exposure from children's and adult's jewelry products. Bull Environ Contam Toxicol 74:437-444.

Maddaloni M, Ballew M, Diamond G, et al. 2005. Assessing non-residential lead risks at hazardous waste sites. Hum Ecol Risk Assess 11:967-1003.

Maddaloni M, Lolacono N, Manton W, et al. 1998. Bioavailability of soil-borne lead in adults by stable isotope dilution. Environ Health Perspect 106:1589-1594.

Maenhaut W, Zoller WH, Duce RA, et al. 1979. Concentration and size distribution of particulate trace elements in the south polar atmosphere. J Geophys Res 84:2421-2431.

Mahaffey KR, Annest JL. 1986. Association of erythrocyte protoporphyrin with blood lead level and iron status in the Second National Health and Nutrition Examination Survey, 1976-1980. Environ Res 41:327-338.

Mahaffey KR, Gartside PS, Glueck CJ. 1986. Blood lead levels and dietary calcium intake in 1- to 11-year-old children: The Second National Health and Nutrition Examination Survey, 1976 to 1980. Pediatrics 78:257-262.

Mahaffey KR, Goyer R, Haseman JK. 1973. Dose-response to lead ingestion in rats fed low dietary calcium. J Lab Clin Med 82:92-100.

Mahaffey KR, Rosen JF, Chesney RW, et al. 1982. Association between age, blood lead concentration, and serum 1,25-dihydroxycholecalciferol levels in children. Am J Clin Nutr 35:1327-1331.

Maheswaran R, Gill JS, Beevers DG. 1993. Blood pressure and industrial lead exposure. Am J Epidemiol 137(6):645-653.

Maizlish NA, Parra G, Feo O. 1995. Neurobehavioral evaluation of Venezuelan workers exposed to inorganic lead. Occup Environ Med 52:408-414.

Mäki-Paakkanen J, Sorsa M, Vainio H. 1981. Chromosome aberrations and sister chromatid exchanges in lead-exposed workers. Hereditas 94:269-275.

Malcoe LH, Lynch RA, Keger MC, et al. 2002. Lead sources, behaviors, and socioeconomic factors in relation to blood lead of native and white children: A community-based assessment of a former mining area. Environ Health Perspect Suppl 110:221-231.

Malcolm D, Barnett HAR. 1982. A mortality study of lead workers: 1925-76. Br J Ind Med 39:404-410.

Maldonado-Vega M, Cerbón-Solorzano J, Albores-Medina A, et al. 1996. Lead: Intestinal absorption and bone mobilization during lactation. Hum Exp Toxicol 15:872-877.

Malkin R, Brandt-Rauf P, Graziano J, et al. 1992. Blood lead levels in incinerator workers. Environ Res 59:265-270.

Manceau A, Boisset M-C, Sarret G, et al. 1996. Direct determination of lead speciation in contaminated soils by EXAFS spectroscopy. Environ Sci Technol 30(5):1540-1552.

Mannino DM, Albalak R, Grosse S, et al. 2003. Second-hand smoke exposure and blood lead levels in U.S. children. Epidemiology 14(6):719-727.

Mantere P, Haenninen H, Hernberg S. 1982. Subclinical neurotoxic lead effects: Two-year follow-up studies with psychological test methods. Neurobehav Toxicol Teratol 4:725-727.

Manton WI. 1977. Sources of lead in blood. Identification by stable isotopes. Arch Environ Health 32:149-159.

Manton WI. 1998. Isotope ratios and the source of lead in lead poisoning. J Toxicol Clin Toxicol 36(7):705-706.

Manton WI, Cook JD. 1984. High-accuracy (stable isotope dilution) measurements of lead in serum and cerebrospinal fluid. Br J Ind Med 41:313-319.

Manton WI, Angle CR, Stanek KL, et al. 2003. Release of lead from bone in pregnancy and lactation. Environ Res 92:139-151.

9. REFERENCES

Manton WI, Rothenberg SJ, Manalo M. 2001. The lead content of blood serum. Environ Res 86:263-273.

*Maranelli G, Apostoli P. 1987. Assessment of renal function in lead poisoned workers. Occup Environ Chem Hazards 344-348.

Marcus AH. 1985a. Multicompartment kinetic models for lead: I. Bone diffusion models for long-term retention. Environ Res 36:441-458.

Marcus AH. 1985b. Multicompartment kinetic models for lead: II. Linear kinetics and variable absorption in humans without excessive lead exposure. Environ Res 36:459-472.

Marcus AH. 1985c. Multicompartment kinetic models for lead: III. Lead in blood plasma and erythrocytes. Environ Res 36:473-489.

Marcus AH, Schwartz J. 1987. Dose-response curves for erythrocyte protoporphyrin vs blood lead: Effects of iron status. Environ Res 44:221-227.

Marino PE, Franzblau A, Lilis R, et al. 1989. Acute lead poisoning in construction workers: The failure of current protective standards. Arch Environ Health 44:140-145.

Markowitz ME, Rosen JF. 1981. Zinc (Zn) and copper (Cu) metabolism in CaNa2 EDTA-treated children with plumbism. Pediatr Res 15:635.

Markowitz ME, Weinberger HL. 1990. Immobilization-related lead toxicity in previously lead-poisoned children. Pediatrics 86:455-457.

Marques M, Millas I, Jimenez A, et al. 2001. Alteration of the soluble guanylate cyclase system in the vascular wall of lead-induced hypertension in rats. J Am Soc Nephrol 12:2594-2600.

Martin D, Glass TA, Bandeen-Roche K, et al. 2006. Association of blood lead and tibia lead with blood pressure and hypertension in a community sample of older adults. Am J Epidemiol 163(5):467-478.

Matte TD, Figueroa JP, Burr G, et al. 1989. Lead exposure among lead-acid battery workers in Jamaica. Am J Ind Med 16:167-177.

McBride WG, Black BP, English BJ. 1982. Blood lead levels and behavior of 400 preschool children. Med J Aust 10:2(l):26-29.

McCabe MJ, Singh KP, Reiners JJ. 1999. Lead intoxication impairs the generation of a delayed type hypersensitivity response. Toxicology 139:255-264.

McClain RM, Becker BA. 1972. Effects of organolead compounds on rat embryonic and fetal development. Toxicol Appl Pharmacol 21:265-274.

McDonald ME. 1985. Acid deposition and drinking water. Environ Sci Technol 19:772-776.

McDonald JA, Potter NU. 1996. Lead's legacy? Early and late mortality of 454 lead-poisoned children. Arch Environ Health 51:116-121.

McMichael AJ, Baghurst PA, Vimpani GV, et al. 1994. Tooth lead levels and IQ in school-age children: The Port Pirie cohort study. Am J Epidemiol 140:489-499.

McMichael AJ, Baghurst PA, Wigg NR, et al. 1988. Port Pirie cohort study: Environmental exposure to lead and children's abilities at the age of four years. N Engl J Med 319:468-476.

McMichael AJ, Vimpani GV, Robertson EF, et al. 1986. The Port Pirie cohort study: Maternal blood lead and pregnancy outcome. J Epidemiol Community 40:18-25.

Meredith PA, Moore MR. 1979. The influence of lead on heme biosynthesis and biodegradation in the rat. Biochem Soc Trans 7:637-639.

Meredith PA, Moore MR, Campbell BC, et al. 1978. Delta-aminolevulinic acid metabolism in normal and lead-exposed humans. Toxicology 9:1-9.

Meyer-Baron M, Seeber A. 2000. A meta-analysis for neurobehavioural results due to occupational lead exposure with blood lead concentrations <70 µg/100 ml. Arch Toxicol 73:510-518.

Meyer PA, Pivetz T, Dignam TA, et al. 2003. Surveillance for elevated blood lead levels among children - United States, 1997-2001. MMWR Morb Mortal Wkly Rep 52(10):1-21.

Michaels D, Zoloth SR, Stern FB. 1991. Does low-level lead exposure increase risk of death? A mortality study of newspaper printers. Int J Epidemiol 20:978-983.

Michaelson A, Sauerhoff MW. 1974. An improved model of lead-induced brain dysfunction in the suckling rat. Toxicol Appl Pharmacol 28:88-96.

Mielke HW. 1991. Lead in residential soils: Background and preliminary results of New Orleans. Water Air Soil Pollut 57-58:111-119.

Mielke HW. 1993. Lead dust contaminated U.S.A. communities: Comparison of Louisiana and Minnesota. Appl Geochem (Suppl 2):257-261.

Mielke HW, Adams JL, Reagan PL, et al. 1989. Soil-dust lead and childhood lead exposure as a function of city size and community traffic flow: The case for lead abatement in Minnesota. Environ Chem Health 9(Supp):253-271.

Mielke HW, Anderson JC, Berry KJ, et al. 1983. Lead concentrations in inner-city soils as a factor in the child lead problem. Am J Public Health 73:1366-1369.

Mielke HW, Burroughs S, Wade R, et al. 1984/1985. Urban lead in Minnesota: Soil transect results of four cities. Minnesota Academy of Science 50:19-24.

Mielke HW, Dugas D, Mielke PW, et al. 1997a. Associations between soil lead and childhood blood lead in urban New Orleans and rural Lafourche Parish of Louisiana. Environ Health Perspect 105(9):950-954.

Mielke HW, Gonzales CR, Smith MK, et al. 1999. The urban environment and children's health: Soils as an integrator of lead, zinc, and cadmium in New Orleans, Louisiana, U.S.A. Environ Res 81:117-129.

Mielke HW, Powell ET, Shah A, et al. 2001. Multiple metal contamination from house paints: Consequences of power sanding and paint scraping in New Orleans. Environ Health Perspect 109(9):973-978.

Mielke HW, Taylor MD, Gonzales CR, et al. 1997b. Lead-based hair coloring products: Too hazardous for household use. J Am Pharm Assn 37:85-89.

Milburn H, Mitran E, Crockford GW. 1976. An investigation of lead workers for subclinical effects of lead using three performance tests. Ann Occup Hyg 19:239-249.

Miller EK, Friedland AJ. 1994. Lead migration in forest soils: Response to changing atmospheric inputs. Environ Sci Technol 28:662-669.

Miller MB, Curry SC, Kunkel DB, et al. 1996. Pool cue chalk: A source of environmental lead. Pediatrics 97(6 Pt 1):916-917.

Miller TE, Golemboski KA, Ha RS, et al. 1998. Developmental exposure to lead causes persistent immunotoxicity in Fischer 344 rats. Toxicol Sci 42:129-135.

Minder B, Das-Smaal EA, Orlebeke JF. 1998. Cognition in children does not suffer from very low lead exposure. J Learn Disabil 31(55):494-502.

Mishra KP, Singh VK, Rani R, et al. 2003. Effect of lead exposure on the immune response of some occupationally exposed individuals. Toxicology 188:251-259.

Mistry P, Lucier GW, Fowler BA. 1985. High affinity lead binding proteins from rat kidney cytosol mediate cell-free nuclear translocation of lead. J Pharmacol Exp Ther 232:462-469.

Mistry P, Mastri C, Fowler BA. 1986. Influence of metal ions on renal cytosolic lead-binding proteins and nuclear uptake of lead in the kidney. Biochem Pharmacol 35:711-713.

Moller L, Kristensen TS. 1992. Blood lead as a cardiovascular risk factor. Am J Epidemiol 136(9):1091-1100.

Monteiro HP, Bechara EJH, Abdalla DSP. 1991. Free radicals involvement in neurological porphyrias and lead poisoning. Mol Cell Biochem 103:73-83.

Moore PV. 1995. Lead toxicity-by the Agency for Toxic Substances and Disease Registry. AAOHN J 43(8):428-438.

Moore MR, Goldberg A. 1985. Health implication of the hematopoietic effects of lead. In: Mahaffey KR, ed. Dietary and environmental lead: Human health effects. Amsterdam, The Netherlands: Elsevier Science Publishers B.V., 261-314.

Moore MR, Meredith PA. 1979. The carcinogenicity of lead. Arch Toxicol 42:87-94.

Moore JF, Goyer RA, Wilson M. 1973. Lead-induced inclusion bodies. Solubility, amino acid content, and relationship to residual acidic nuclear proteins. Lab Invest 29(5):488-494.

Moore MR, Goldberg A, Pocock SJ, et al. 1982. Some studies of maternal and infant lead exposure in Glasgow. Scott Med J 27:113-122.

Moore MR, Goldberg A, Yeung-Laiwah AAC. 1987. Lead effects on the heme biosynthetic pathway: Relationship to toxicity. Ann NY Acad Sci 514:191-203.

Moore MR, Meredith PA, Watson WS, et al. 1980. The percutaneous absorption of lead-203 in humans from cosmetic preparations containing lead acetate, as assessed by whole-body counting and other techniques. Food Cosmet Toxicol 18:399-405.

*Mooty J, Ferrand CF, Harris P. 1975. Relationship of diet to lead poisoning in children. Pediatrics 55:636-639.

Moreau T, Hannaert P, Orssaud G, et al. 1988. Influence of membrane sodium transport upon the relation between blood lead and blood pressure in a general male population. Environ Health Perspect 78:47-51.

Moreau T, Orssaud G, Juguet B, et al. 1982. [Blood lead levels and arterial pressure: Initial results of a cross sectional study of 431 male subjects.] Rev Epidemiol Sante Publique 39:395-397. (French)

Morgan A, Holmes A. 1978. The fate of lead in petrol-engine exhaust particulates inhaled by the rat. Environ Res 15:44-56.

Morgan B, Parramore C. 2001. Elevated blood lead levels associated with the consumption of illicitly distilled moonshine. J Toxicol Clin Toxicol 39(5):551.

Morita Y, Sakai T, Araki S, et al. 1997. Nicotinamide adenine dinucleotide synthetase activity in erythrocytes as a tool for the biological monitoring of lead exposure. Int Arch Occup Environ Health 70(3):195-198.

Morris C, McCarron DA, Bennett WM. 1990. Low-level lead exposure, blood pressure, and calcium metabolism. Am J Kidney Dis 15:568-574.

Morris V, Markowitz ME, Rosen JF. 1988. Serial measurements of aminolevulinic acid dehydratase in children with lead toxicity. J Pediatr 112:916-919.

Morrison JN, Quarterman J. 1987. The relationship between iron status and lead absorption in rats. Biol Trace Element Res 14:115-126.

Morrison JN, Quarterman J, Humphries WR. 1977. The effect of dietary calcium and phosphate on lead poisoning in lambs. J Comp Pathol 87:417-429.

Morrison NA, Yeoman R, Kelly PJ, et al. 1992. Contribution of trans-acting factor alleles to normal physiological variability: Vitamin D receptor gene polymorphisms and circulating osteocalcin. Proc Natl Acad Sci U S A 89:6665-6669.

Morrow PE, Beiter H, Amato F, et al. 1980. Pulmonany retention of lead: An experimental study in man. Environ Res 21:373-384.

Morselli PL, Franco-Morselli R, Bossi L. 1980. Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. Clin Pharmacokin 5:485-527.

Mortada WI, Sobh MA, El-Defrawy MM, et al. 2001. Study of lead exposure from automobile exhaust as a risk for nephrotoxicity among traffic policemen. Am J Nephrol 21:274-279.

Moschandreas DJ, Karuchit S, Berry MR, et al. 2002. Exposure apportionment: Ranking food items by their contribution to dietary exposure. J Expo Anal Environ Epidemiol 12:233-243.

Moser R, Oberley TD, Daggett DA, et al. 1995. Effects of lead administration on developing rat kidney. I. Glutathione S-transferase isoenzymes. Toxicol Appl Pharmacol 131:85-93.

Moss ME, Lanphear BP, Auinger P. 1999. Association of dental caries and blood lead levels. JAMA 281(24):2294-2298.

MPCA. 1987. Soil lead report to the Minnesota State Legislature. St. Paul, MN: Minnesota Pollution Control Agency, XII, 13, 28, 29.

Muijser H, Hoogendijk EM, Hooisma J, et al. 1987. Lead exposure during demolition of a steel structure coated with lead-based paints. II. Reversible changes in the conduction velocity of the motor nerves in transiently exposed workers. Scand J Work Environ Health 13:56-61.

Muldoon SB, Cauley JA, Kuller LH, et al. 1996. Effects of blood lead levels on cognitive function of older women. Neuroepidemiology 15(2):62-72.

Muntner P, He J, Vupputuri S, et al. 2003. Blood lead and chronic kidney disease in the general United States population: Results from NHANES III. Kidney Int 63:1044-1050.

Murakami M, Kawamura R, Nishii S, et al. 1983. Early appearance and localization of intranuclear inclusions in the segments of renal proximal tubules of rats following ingestion of lead. Br J Exp Pathol 64:144-155.

Murata K, Araki S, Yokoyama K, et al. 1995. Autonomic and central nervous system effects of lead in female glass workers in China. Am J Ind Med 28(2):233-244.

Murgueytio AM, Evans GR, Sterling DA, et al. 1998. Relationship between lead mining and blood lead levels in children. Arch Environ Health 53(6):414-423.

Muro LA, Goyer RA. 1969. Chromosome damage in experimental lead poisoning. Arch Pathol 87:660-663.

Murphy EA, Hall GS. 2000. Determination of lead sources in water samples using isotope ratios. Bull Environ Contam Toxicol 65:314-321.

Murphy MJ, Graziano JH, Popovac D, et al. 1990. Past pregnancy outcomes among women living in the vicinity of a lead smelter in Kosovo, Yugoslavia. Am J Public Health 80:33-35.

Murray K, Bazzi A, Carter C, et al. 1997. Distribution and mobility of lead in soils at an outdoor shooting range. J Soil Contam 6(1):79-93.

Mushak P. 1991. Gastro-intestinal absorption of lead in children and adults: Overview of biological and biophysico-chemical aspects. Chem Speciat Bioavail 3:87-104.

9. REFERENCES

Mushak P, Crocetti AF. 1996. Lead and nutrition. I. Biologic interactions of lead with nutrients. Nutr Today 31:12-17.

Mykkänen HM, Wasserman RH. 1981. Gastro-intestinal absorption of lead (^{203}Pb) in chicks: Influence of lead, calcium and age. J Nutr 111:1757-1765.

Mykkänen HM, Wasserman RH. 1982. Effect of vitamin D on the intestinal absorption of ^{203}Pb and 47Ca in chicks. J Nutr 112:520-527.

Nakagawa K. 1991 Decreased glutathione S-transferase activity in mice livers by acute treatment with lead, independent of alteration in glutathione content. Toxicol Lett 56:13-17.

Nan Z, Cheng G. 2001. Accumulation of Cd and Pb in spring wheat (*Triticum aestivum* L.) grown in calcareous soil irrigated with wastewater. Bull Environ Contam Toxicol 66:748-754.

NAS. 1972. Lead: Airborne lead in perspective. Washington, DC: National Academy of Sciences, 71-177, 281-313.

NAS. 1980. Lead in the human environment. Washington, DC: National Academy of Sciences, Committee on Lead in the Human Environment.

NAS/NRC. 1989. Report of the oversight committee. In: Biologic markers in reproductive toxicology. Washington, DC: National Academy of Sciences, National Research Council, National Academy Press.

Nash D, Magder L, Lustberg M, et al. 2003. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. JAMA 289:1523-1532.

Nash D, Magder LS, Sherwin R, et al. 2004. Bone density-related predictors of blood lead level among peri- and postmenopausal women in the United States: The Third National Health and Nutrition Examination Survey, 1988–1994. Am J Epidemiol 160(9):901-911.

Navas-Acien A, Selvin E, Sharrett AR, et al. 2004. Lead, cadmium, smoking, and increased risk of peripheral arterial disease. Circulation 109(25):3196-3201.

Nawrot TS, Thijs L, Hond EMD, et al. 2002. An epidemiological re-appraisal of the association between blood pressure and blood lead: A meta-analysis. J Hum Hypertens 16:123-131.

Neal R, Aykin-Burns N, Ercal N, et al. 2005. Pb^2 exposure alters the lens αA-crystallin protein profile in vivo and induces cataract formation in lens organ culture. Toxicology 212(1):1-9.

Needleman HL. 2004. Lead poisoning. Annu Rev Med 55:209-222.

Needleman HL, Gatsonis CA. 1990. Low-level lead exposure and the IQ of children: A meta-analysis of modern studies. J Am Med Assoc 263(5):673-678.

*Needleman HL, Geiger SK, Frank R. 1985. Lead and IQ scores: A reanalysis (letter). Science 227:701-704.

Needleman HL, Gunnoe C, Leviton A, et al. 1979. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N Engl J Med 300:689-695.

Needleman HL, McFarland C, Ness RB, et al. 2002. Bone lead levels in adjudicated delinquents a case control study. Neurotoxicol Teratol 24:711-717.

Needleman HL, Rabinowitz M, Leviton A, et al. 1984. The relationship between prenatal exposure to lead and congenital anomalies. JAMA 251:2956-2959.

Needleman HL, Riess JA, Tobin MJ, et al. 1996. Bone lead levels and delinquent behavior. JAMA 275(5):363-369.

Needleman HL, Schell A, Bellinger D, et al. 1990. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. N Engl J Med 322:83-88.

NEMI. 2005a. Method 3111B. Direct air-acetylene flame method. NEMI method summary. Washington, DC: National Environmental Methods Index. http://web1.er.usgs.gov/nemi/method_summary.jsp?param_method_id=5703. June 10, 2005.

NEMI. 2005b. Method 3500-Pb B. Dithizone method. NEMI method summary. Washington, DC: National Environmental Methods Index. http://web1.er.usgs.gov/nemi/method_summary.jsp?param_method_id=7396. June 10, 2005.

NEMI. 2005c. Method 3113 B. Metals in water by electrothermal atomic absorption spectrometry. NEMI method summary. Washington, DC: National Environmental Methods Index. http://web1.er.usgs.gov/nemi/method_summary.jsp?param_method_id=4698. June 10, 2005.

NEMI. 2005d. Method 3120 B. Metals in water by plasma emission spectroscopy. NEMI method summary. Washington, DC: National Environmental Methods Index. http://web1.er.usgs.gov/nemi/method_summary.jsp?param_method_id=4699. June 10, 2005.

Neri LC, Hewitt D, Orser B. 1988. Blood lead and blood pressure: Analysis of cross-sectional and longitudinal data from Canada. Environ Health Perspect 78:123-126.

Nerin C, Domeno C, Garcia JI, et al. 1999. Distribution of Pb, V, Cr, Ni, Cd, Cu and Fe in particles formed from the combustion of waste oils. Chemosphere 38(7):1533-1540.

Nerin C, Olavide S, Cacho J, et al. 1989. Determination of lead in airborne particulate by hybrid generation. Water Air Soil Pollut 44:339-345.

Nestmann ER, Matula TI, Douglas GR, et al. 1979. Detection of the mutagenic activity of lead chromate using a battery of microbial tests. Mutat Res 66:357-365.

Neuman DR, Dollhopf DJ. 1992. Lead levels in blood from cattle residing near a lead smelter. J Environ Qual 21:181-184.

Nevin R. 2000. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environ Res 83:1-22.

Ng TP, Goh HH, Ong HY, et al. 1991. Male endocrine functions in workers with moderate exposure to lead. Br J Ind Med 48:485-491.

Ni Z, Hou S, Barton CH, et al. 2004. Lead exposure raises superoxide and hydrogen peroxide in human endothelial and vascular smooth muscle cells. Kidney Int 66(6):2329-2336.

Niebuhr E, Wulf HC. 1984. Genotoxic effects. In: Grandjean P, ed. Biological effects of organo-lead compounds. Boca Raton, FL: CRC Press, 117-124.

Nielsen T. 1984. Chapter 6: Atmospheric occurrence of organolead compounds. In: Grandjean P, ed. Biological effects of organolead compounds. Boca Raton, FL: CRC Press, 43-62.

Nielsen OJ, O'Farrell DJ, Treacy JJ, et al. 1991. Rate constants for the gas-phase reactions of hydroxyl radicals with tetramethyllead and tetraethyllead. Environ Sci Technol 25(6):1098-1103.

Nielsen T, Jensen KA, Grandjean P. 1978. Organic lead in normal human brains. Nature 274:602-603.

Nielson KB, Atkin CL, Winge DR. 1985. Distinct metal-binding configurations in metallothionein. J Biol Chem 260:5342-5350.

Nihei MK, Guilarte TR. 2002. Molecular mechanisms of low-level Pb^2 neurotoxicity. In: Massaro EJ, eds. Handbook of neurotoxicology. Totowa, NJ: Humana Press, 107-133.

Nilsson U, Attewell R, Christoffersson JO, et al. 1991. Kinetics of lead in bone and blood after end of occupational exposure. Pharmacol Toxicol 69:477-484.

NIOSH. 1974. Evaluation of behavioral functions in workers exposed to lead. In: Xintaras C, Johnson BL, De Groot 1, eds. Behavioral toxicology: Early detection of occupational hazards. Cincinnati, OH: U.S. Department of Health, Education and Welfare, National Institute for Occupational Safety and Health, 248-266.

NIOSH. 1977a. Manual of analytical methods. 2nd ed, vol. 1. Method No. P&CAM 173. Cincinnati, OH: U.S. Department of Health, Education, and Welfare. Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

NIOSH. 1977b. Manual of analytical methods. 2nd ed, vol. 1. Method No. P&CAM 208. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

NIOSH. 1977c. Manual of analytical methods. 2nd ed, vol. 1. Method No. P&CAM 262. Cincinnati, OH: U.S. Department of Health, Education and Welfare. Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

NIOSH. 1977d. Manual of analytical methods. 2nd ed, vol. 3. Method No. S341. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health.

NIOSH. 1978a. Criteria for a recommended standard: Occupational exposure to inorganic lead revised criteria. 1978. Cincinnati, OH: U.S. Department of Health. Education, and Welfare, Centers for Disease Control, National Institute for Occupational Safety and Health.

NIOSH. 1978b. Manual of analytical methods. 2nd ed, vol. 4. Method No. 383 and 384. Cincinnati, OH: U.S. Department of Health, Education and Welfare, Centers for Disease Control, National Institute for Occupational Safety and Health, S383-1 to S383-10, S384-1 to S384-10.

NIOSH. 1981. Manual of analytical methods. Vol. 7. Method P&CAM 351. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health, 351-1 to 351-11.

NIOSH. 1990. Manual of analytical methods. 3rd ed, vol. I. Method No. 7105. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health.

NIOSH. 1994a. NIOSH manual of analytical methods, 4th ed. Methods 7082 (lead by flame AAS), 7105 (lead by HGAAS), 7505 (lead sulfide), 8003 (lead in blood and urine), 9100 (lead in surface wipe samples), U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health.

NIOSH. 1994b. Method 8005. Elements in blood or tissue. NIOSH manual of analytical methods (NMAM). Cincinnati, OH: National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/8005.pdf. July 26, 2005.

NIOSH. 1994c. Method 7082. Lead by flame AAS. NIOSH manual of analytical methods (NMAM). Cincinnati, OH: National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/7082.pdf. July 26, 2005.

NIOSH. 1994d. Method 7105. Lead by GFAAS. NIOSH manual of analytical methods (NMAM). Cincinnati, OH: National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/7105.pdf. July 26, 2005.

NIOSH. 1994e. Method 8003. Lead in blood and urine. NIOSH manual of analytical methods (NMAM). Cincinnati, OH: National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/8003.pdf. July 26, 2005.

NIOSH. 1994f. Method 8310. Metals in urine. NIOSH manual of analytical methods (NMAM). Cincinnati, OH: National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/8310.pdf. July 26, 2005.

NIOSH. 1994g. Method 2533. Tetraethyl lead (as Pb). NIOSH manual of analytical methods (NMAM). Cincinnati, OH: National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/2533.pdf. July 26, 2005.

NIOSH. 1994h. Method 2534. Tetramethyl lead (as Pb). NIOSH manual of analytical methods (NMAM). Cincinnati, OH: National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/2534.pdf. July 26, 2005.

NIOSH. 1995. Report to Congress on workers' home contamination. Study conducted under the Workers' Family Protection.

NIOSH. 1996. NIOSH health hazard evaluation report, HETA 91-0346-2572, FBI Academy, Quantico, Virginia. Michael E Barsan and Aubrey Miller, U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health.

NIOSH. 1997a. NIOSH pocket guide to chemical hazards. Washington, DC: U.S. Department of Health and Human Services. Public Health Service. Centers for Disease Control and Prevention. National Institute for Occupational Safety and Health, 302.

NIOSH. 1997b. Protecting workers exposed to lead-based paint hazards. A report to congress. DHHS (NIOSH) Publication No. 98-112. January 1997. U.S. Department of Health and Human Services, Center for Disease Control and Prevention, and National Institute for Occupational Safety and Health, 1-74.

NIOSH. 2003. Method 7300. Elements by ICP (Nitric/perchloric acid ashing). NIOSH manual of analytical methods (NMAM). Cincinnati, OH: National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/7300.pdf. July 26, 2005.

NIOSH. 2005. NIOSH pocket guide to chemical hazards. Atlanta, GA: National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/npg/npgdname.html. February 15, 2005.

Nishioka H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat Res 31:185-189.

Nordenson I, Beckman G, Beckman L, et al. 1978. Occupational and environmental risks in and around a smelter in northern Sweden: IV. Chromosomal aberrations in workers exposed to lead. Hereditas 88:263-267.

*Nordstrom S, Beckman L, Nordensen I. 1978. Occupational and environmental risks in and around a smelter in northern Sweden: I. Variations in birth weight. Hereditas 88:43-46.

Nordstrom S, Beckman L, Nordensen I. 1979. Occupational and environmental risks in and around a smelter in northern Sweden: V. Spontaneous abortion among female employees and decreased birth weight in their offspring. Hereditas 90:291-296.

NRC. 1993. National Research Council. Pesticides in the diets of infants and children. Washington, DC: National Academy Press.

Nriagu JO. 1978. Lead in soils, sediments and major rock types. In: Nriagu JO, ed. The biogeochemistry of lead in the environment. Part A. Ecological cycles. New York, NY: Elsevier/North-Holland Biomedical Press, 15-72.

NSF. 1977. Transport and distribution in a watershed ecosystem. In: Boggess WR, ed. Lead in the environment. Washington, DC: National Science Foundation. Report No. NSFRA770214, 105-133.

NTP. 2005. Report on carcinogens. 11th ed. Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program. http://ntp-server.niehs.nih.gov/ntp/roc/toc11.html. February 15, 2004.

Nwosu JU, Harding AK, Linder G. 1995. Cadmium and lead uptake by edible crops grown in a silt loam soil. Bull Environ Contam Toxicol 54:570-578.

Nye LJJ. 1929. An investigation of the extraordinary incidence of chronic nephritis in young people in Queensland. Med J Aust 2:145-159.

O'Connor ME, Rich D. 1999. Children with moderately elevated lead levels: Is chelation with DMSA helpful? Clin Pediatr 38(6):325-331.

Odland JO, Nieboer E, Romanova N, et al. 1999. Blood lead and cadmium and birth weight among sub-arctic and arctic populations of Norway and Russia. Acta Obstet Gynecol Scand 78:852-860.

O'Flaherty EJ. 1986. The rate of decline of blood lead in lead industry workers during medical removal: The effect of job tenure. Fundam Appl Toxicol 6:372-380.

O'Flaherty EJ. 1987. Modeling: An introduction. Pharmacokinetics in risk assessment. Drinking water and health. Vol. 8. Washington, DC: U.S. Environmental Protection Agency, 27-35. PB89203319.

O'Flaherty EJ. 1991a. Physiologically based models for bone-seeking elements. II. Kinetics of lead disposition in rats. Toxicol Appl Pharmacol 111:313-331.

O'Flaherty EJ. 1991b. Physiologically based models for bone-seeking elements. III. Human skeletal and bone growth. Toxicol Appl Pharmacol 111:332-341.

O'Flaherty EJ. 1993. Physiologically based models for bone-seeking elements. IV. Kinetics of lead disposition in humans. Toxicol Appl Pharmacol 118:16-29.

O'Flaherty EJ. 1995a. Physiologically based models for bone-seeking elements. V. Lead absorption and disposition in childhood. Toxicol Appl Pharmacol 131:297-308.

O'Flaherty EJ. 1995b. PBK modeling for metals. Examples with lead, uranium, and chromium. Toxicol Lett 82/83:367-372.

O'Flaherty EJ, Hammond PB, Lerner SI. 1982. Dependence of apparent blood lead half-life on the length of previous lead exposure in humans. Fundam Appl Toxicol 2:49-54.

O'Flaherty EJ, Inskip MJ, Franklin CA, et al. 1998. Evaluation and modification of a physiologically based model of lead kinetics using data from a sequential isotope study in Cynomolgus monkeys. Toxicol Appl Pharmacol 149:1-16.

Oishi H, Nomiyama H, Nomiyama K, et al. 1996. Fluorometric HPLC determination of delta-aminolevulinic acid (ALA) in the plasma and urine of lead workers: Biological indicators of lead exposure. J Anal Toxicol 20(2):106-110.

Okun A, Cooper G, Bailer AJ, et al. 2004. Trends in occupational lead exposure since the 1978 OSHA lead standard. Am J Ind Med 45(6):558-572.

Oldereid NB, Thomassen Y, Attramadal A, et al. 1993. Concentrations of lead, cadmium and zinc in the tissues of reproductive organs of men. J Reprod Fertil 99:421-425.

Olson KW, Skogerboe RK. 1975. Identification of soil lead compounds from automotive sources. Environ Sci Technol 9:227-230.

Omae K, Sakurai H, Higashi T, et al. 1990. No adverse effects of lead on renal function in lead-exposed workers. Ind Health 28:77-83.

Omar M, Ibrahim M, Assem H, et al. 2001. Teeth and blood lead levels in Egyptian schoolchildren: Relationship to health effects. J Appl Toxicol 21:349-352.

Onalaja AO, Claudio L. 2000. Genetic susceptibility to lead poisoning. Environ Health Perspect Suppl 108:23-28.

Ong CN, Lee WR. 1980a. Distribution of lead-203 in human peripheral blood *in vitro*. Br J Ind Med 37:78-84

Ong CN, Lee WR. 1980c. High affinity of lead for fetal hemoglobin. Br J Ind Med 37:292-298.

Ong CN, Lee WR. 1980b. Interaction of calcium and lead in human erythrocytes. Br J Ind Med 37:70-77.

*Ong CN, Endo G, Chia KS, et al. 1987. Evaluation of renal function in workers with low blood lead levels. In: Fao V, Emmett EA, Maroni M, et al., eds. Occupational and environmental chemical hazards. Chichester: Ellis Horwood Limited, 327-333.

Ong CN, Phoon WO, Law HY, et al. 1985. Concentrations of lead in maternal blood, cord blood, and breast milk. Arch Dis Child 60:756-759.

Oomen AG, Tolls J, Sips AJAM, et al. 2003a. Lead speciation in artificial human digestive fluid. Arch Environ Contam Toxicol 44:107-115.

Oomen AG, Rompelberg CJM, Bruil MA, et al. 2003b. Development of an in vitro digestion model for estimation of bioaccessibility of soil contaminants. Arch Environ Contam Toxicol 44(3):281-287.

Opler MGA, Brown AS, Graziano J, et al. 2004. Prenatal lead exposure, δ-aminolevulinic acid, and schizophrenia. Environ Health Perspect 112(5):548-552.

O'Riordan ML, Evans HJ. 1974. Absence of significant chromosome damage in males occupationally exposed to lead. Nature 247:50-53.

O'Rourke MK, Van de Water PK, Jin S, et al. 1999. Evaluations of primary metals from NHEXAS Arizona: Distributions and preliminary exposures. J Expo Anal Environ Epidemiol 9:435-445.

Orssaud G, Claude JR, Moreau T, et al. 1985. Blood lead concentration and blood pressure. Br Med J 290:244.

OSHA. 1993. Lead exposure in construction. Interim Final Rule. U.S. Department of Labor. Occupational Safety and Health Administration. May 4, 1993. Fed Regist 58:26590.

OSHA. 2005a. Air contaminants. Occupational safety and health standards for shipyard employment. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1915.1000. http://www.osha.gov/comp-links.html. February 15, 2005.

OSHA. 2005b. Gases, vapors, fumes, dusts, and mists. Safety and health regulations for construction. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1926.55, Appendix A. http://www.osha.gov/comp-links.html. February 15, 2005.

OSHA. 2005c. Limits for air contaminants. Occupational safety and health standards. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1000. http://www.osha.gov/comp-links.html. February 15, 2005.

OSHA. 2005d. Toxic and Hazardous Substances. Occupational safety and health standards. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 29 CFR 1910.1025. http://www.osha.gov/comp-links.html. March 25, 2005.

OSHA. 2005e. Occupational safety and health standards for shipyard. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 40 CFR 1915.1025. http://www.osha.gov/comp-links.html. May 26, 2005.

OSHA. 2005f. Occupational safety and health standards for shipyard. Washington, DC: Occupational Safety and Health Administration. Code of Federal Regulations. 40 CFR 1926.62. http://www.osha.gov/comp-links.html. May 26, 2005.

Oskarsson A, Fowler BA. 1985. Effects of lead inclusion bodies on subcellular distribution of lead in rat kidney: The relationship to mitochondrial function. Exp Mol Pathol 43:397-408.

Oskarsson A, Jorhem L, Sundberg J, et al. 1992. Lead poisoning in cattle-transfer of lead to milk. Sci Total Environ 111:83-94.

Osman K, Pawlas K, Schutz A, et al. 1999. Lead exposure and hearing effects in children in Katowice, Poland. Environ Res 80:1-8.

Osterode W, Barnas U, Geissler K. 1999. Dose dependent reduction of erythroid progenitor cells and inappropriate erythropoietin response in exposure to lead: New aspects of anaemia induced by lead. Occup Environ Med 56:106-109.

Otto D, Fox DA. 1993. Auditory and visual dysfunction following lead exposure. Neurotoxicology 14(2-3):191-208.

*Otto D, Benignus VA, Muller K, et al. 1981. Effects of age and body lead burden on CNS function in young children: I. Slow cortical potentials. Electroencephalogr Clin Neurophysiol 52:229-239.

*Otto D, Benignus V, Muller K, et al. 1982. Effects of low to moderate lead exposure on slow cortical potential in young children: Two year follow-up study. Neurobehav Toxicol Teratol 4:733-737.

Otto D, Robinson G, Baumann S, et al. 1985. Five-year follow-up study of children with low-to-moderate lead absorption: Electrophysiological evaluation. Environ Res 38:168-186.

Ou L-T, Jing W, Thomas JE. 1995. Biological and chemical degradation of ionic ethyllead compounds in soil. Environ Toxicol Chem 14(4):545-551.

Ou LT, Thomas JE, Jing TW. 1994. Biological and chemical degradation of tetraethyl lead in soil. Bull Environ Contam Toxicol 52:238-245.

Owen GM, Brozek J. 1966. Influence of age, sex and nutrition on body composition during childhood and adolescence. In: Falkner F, ed. Human development. Philadelphia, PA: WB Saunders, 222-238.

Paglia DE, Valentine WN, Dahigren JG. 1975. Effects of low-level lead exposure on pyrimidine 5'-nucleotidase and other erythrocyte enzymes: Possible role of pyrimidine 5'-nucleotidase in the pathogenesis of lead-induced anemia. J Clin Invest 56:1164-1169.

Paglia DE, Valentine WN, Fink K. 1977. Lead poisoning: Further observations on erythrocyte pyrimidine-nucleotidase deficiency and intracellular accumulation of pyrimidine nucleotides. J Clin Invest 60:1362-1366.

Pagliuca A, Mufti GJ, Baldwin D, et al. 1990. Lead-poisoning: Clinical, biochemical, and hematological aspects of a recent outbreak. J Clin Path 43:277-281.

Palmer KT, Kucera CL. 1980. Lead contamination of sycamore and soil from lead mining and smelting operations in eastern Missouri. J Environ Qual 9:106-111.

PAN Pesticides Database. 2004. PAN pesticides database-chemicals. San Francisco, CA: Pesticide Action Network. http://www.pesticideinfo.org/List_Chemicals.jsp?. March 23, 2005.

Pardo R, Barrado E, Perez L, et al. 1990. Determination and speciation of heavy metals in sediments of the Pisuerga River. Water Res 24(3):373-379.

Parkinson DK, Hodgson MJ, Bromet EJ, et al. 1987. Occupational lead exposure and blood pressure. Br J Ind Med 44:744-748.

Parkinson DK, Ryan C, Bormet J, et al. 1986. A psychiatric epidemiologic study of occupational lead exposure. Am J Epidemiol 123:261-269.

Parramore CS, Morgan BW, Ethridge MW. 2001. Lead contaminated moonshine: A report of ATF analyzed samples. J Toxicol Clin Toxicol 39(5):520.

Pasternak G, Becker CE, Lash A, et al. 1989. Cross-sectional neurotoxicology study of lead-exposed cohort. Clin Toxicol 27:37-51.

Payton M, Hu H, Sparrow D, et al. 1994. Low-level lead exposure and renal function in the normative aging study. Am J Epidemiol 140(9):821-829.

Payton M, Riggs KM, Spiro A III, et al. 1998. Relations of bone and blood lead to cognitive function: The VA normative aging study. Neurotoxicol Teratol 20(1):19-27.

Peden DB. 2000. Development of atopy and asthma: Candidate environmental influences and important periods of exposure. Environ Health Perspect 108(suppl 3):475-482.

Pellizzari ED, Perritt RL, Clayton CA. 1999. National human exposure assessment survey (NHEXAS): Exploratory survey of exposure among population subgroups in EPA region V. J Expo Anal Environ Epidemiol 9:49-55.

Pérez-Bravo F, Ruz M, Moran-Jimenez MJ, et al. 2004. Association between aminolevulinate dehydrase genotypes and blood lead levels in children from a lead-contaminated area in Antofagasta, Chile. Arch Environ Contam Toxicol 47:276-280.

Pergande M, Junk K, Precht S, et al. 1994. Changed excretion or urinary proteins and enzymes by chronic exposure to lead. Nephrol Dial Transplant 9:613-618.

Perneger TW, Nieto FJ, Whelton PK, et al. 1993. A prospective study of blood pressure and serum creatinine: Results from the 'clue' study and the ARIC study. JAMA 269:488-93.

Peryea FJ. 1998. Historical use of lead arsenate insecticides, resulting soil contamination and implications for soil remediation. Wenatchee, WA: Tree Fruit Research and Extension Center, Washington State University.

Peterson KE, Salganik M, Campbell C, et al. 2004. Effect of succimer on growth of preschool children with moderate blood lead levels. Environ Health Perspect 112(2):233-237.

Piccinini F, Favalli L., Chiari MC. 1977. Experimental investigations on the contraction induced by lead in arterial smooth muscle. Toxicology 8:43-51.

Pierzynski GM, Schwab AP. 1993. Bioavailability of zinc, cadmium, and lead in a metal contaminated alluvial soil. J Environ Qual 22:247-254.

Pinkerton LE, Biagini RE, Ward EM, et al. 1998. Immunologic findings among lead-exposed workers. Am J Ind Med 33(4):400-408.

Pinto de Almeida AR, Carvalho FM, Spinola AG, et al. 1987. Renal dysfunction in Brazilian lead workers. Am J Nephrol 7:455-458.

Piomelli S, Seaman C, Zullow D, et al. 1982. Threshold for lead damage to heme synthesis in urban children. Proc Natl Acad Sci 7:3335-3339.

Pirkle JL, Brody DJ, Gunter EW, et al. 1994. The decline in blood lead levels in the United States. The National Health and Nutrition Examination Surveys (NHANES). JAMA 272:284-291.

Pirkle JL, Kaufmann RB, Brody DJ, et al. 1998. Exposure of the U.S. population to lead, 1991-1994. Environ Health Perspect 106(11):745-750.

Pirkle JL, Schwartz J, Landis JR, et al. 1985. The relationship between blood lead levels and blood pressure and its cardiovascular risk implications. Am J Epidemiol 121:246-258.

Platt B, Busselberg D. 1994. Combined actions of Pb^2, Zn^2, and Al^3 on voltage-activated calcium channel currents. Cell Mol Neurobiol 14:831-840.

Pocock SJ, Ashby D, Smith MA. 1987. Lead exposure and children's intellectual performance. Int J Epidemiol 16:57-67.

*Pocock SJ, Ashby D, Smith MA. 1989. Lead exposure and children's intellectual performance: The Institute of Child Health/Southhampton Study. In: Smith M, Grant LD, Sors A, eds. Lead exposure and child development: An international assessment. Hingham, MA: Kluwer Academic Publishers, 149-165.

Pocock SJ, Shaper AG, Ashby D, et al. 1984. Blood lead concentration, blood pressure, and renal function. Br Med J 289:872-874.

*Pocock SJ, Shaper AG, Ashby D, et al. 1985. Blood lead and blood pressure in middle-aged men. In: Lekkas TD, ed. International Conference on Heavy Metals in the Environment, Vol. 1, Athens, Greece, September. Edinburgh, United Kingdom: CEP Consultants, Ltd., 303-305.

Pocock SJ, Shaper AG, Ashby D, et al. 1988. The relationship between blood lead, blood pressure, stroke, and heart attacks in middle-aged British men. Environ Health Perspect 78:23-30.

Pocock SJ, Shaper AG, Walker M, et al. 1983. Effects of tap water lead, water hardness, alcohol, and cigarettes on blood lead concentrations. J Epidemiol Community Health 37:1-7.

Pocock SJ, Smith M, Baghurst P. 1994. Environmental lead and children's intelligence: A systematic review of the epidemiological evidence. Br Med J 309:1189-1197.

Pollock CA, Ibels LS. 1986. Lead intoxication in paint removal workers on the Sidney Harbour Bridge. Med J Aust 145:635-639.

Poma A, Pittaluga E, Tucci A. 2003. Lead acetate genotoxicity on human melanoma cells *in vitro*. Melanoma Res 13(6):563-566.

Porru S, Alessio L. 1996. The use of chelating agents in occupational lead poisoning. Occup Med 46(1):41-48.

*Poulos L, Qammaz S, Athanaselis S, et al. 1986. Statistically significant hematopoietic effects of low blood lead levels. Arch Environ Health 41:384-386.

Pounds JG. 1984. Effect of lead intoxication on calcium homeostasis and calcium-mediated cell function: A review. Neurotoxicology 5:295-332.

Pounds JG, Long GJ, Rosen JF. 1991. Cellular and molecular toxicity of lead in bone. Environ Health Perspect 91:17-32.

Pounds JG, Marlar RJ, Allen JR. 1978. Metabolism of lead-210 in juvenile and adult Rhesus monkeys Macaca mulatta. Bull Environ Contam Toxicol 19:684-691.

Preiss IL, Tariq MA. 1992. On the use of L X-ray fluorescence for bone lead evaluation. J Radioanal Nucl Chem 164:381-387.

Proctor SP, Rotnitzky A, Sparrow D, et al. 1996. The relationship of blood lead and dietary calcium to blood pressure in the normative aging study. Int J Epidemiol 25(3):528-536.

Prpic-Majic D, Bobic J, Simic D, et al. 2000. Lead absorption and psychological function in Zagreb (Croatia) school children. Neurotoxicol Teratol 22:347-356.

Pueschel SM, Kopito L, Schwachman H. 1972. Children with an increased lead burden: A screening and follow-up study. JAMA 222:462-466.

Purchase NG, Fergusson JE. 1986. Lead in teeth: The influence of the tooth type and the sample within a tooth on lead levels. Sci Total Environ 52:239-250.

Purdy RE, Smith JR, Ding Y, et al. 1997. Lead-induced hypertension is not associated with altered vascular reactivity in vitro. Am J Hypertens 10:997-1003.

Quarterman J, Morrison JN. 1975. The effects of dietary calcium and phosphorus on the retention and excretion of lead in rats. Br J Nutr 34:351-362.

Quarterman J, Morrison E, Morrison JN, et al. 1978. Dietary protein and lead retention. Environ Res 17:68-77.

Que Hee SS. 1994. Availability of elements in leaded/unleaded automobile exhausts, a leaded paint, a soil, and some mixtures. Arch Environ Contam Toxicol 27:145-153.

Que Hee SS, Boyle JR. 1988. Simultaneous multi-elemental analysis of some environmental and biological samples by inductively coupled plasma atomic emission spectrometry. Anal Chem 60:1033-1042.

Que Hee SS, MacDonald TJ, Bornschein RL. 1985a. Blood lead by furnace-Zeeman atomic absorption spectrophotometrv. Microchem J 32:55-63.

Que Hee SS, Peace B, Clark CS, et al. 1985b. Evolution of efficient methods to sample lead sources, such as house dust and hand dust, in the homes of children. Environ Res 38:77-95.

Quintanilla-Vega B, Hoover DJ, Bal W, et al. 2000. Lead interaction with human protamine (HP2) as a mechanism of male reproductive toxicity. Chem Res Toxicol 13:594-600.

Rabinowitz MB. 1995. Relating tooth and blood lead levels in children. Bull Environ Contam Toxicol 55:853-857.

Rabinowitz MB, Bellinger D, Leviton A, et al. 1987. Pregnancy hypertension, blood pressure during labor, and blood lead levels. Hypertension 10:447-451.

Rabinowitz MB, Kopple JD, Wetherill GW. 1980. Effect of food intake on fasting gastrointestinal lead absorption in humans. Am J Clin Nutr 33:1784-1788.

Rabinowitz MB, Leviton A, Bellinger D. 1985. Home refinishing, lead paint and infant blood lead levels. Am J Public Health 75:403-404.

Rabinowitz MB, Leviton A, Bellinger D. 1989. Blood lead-tooth lead relationship among Boston children. Bull Environ Contam Toxicol 43:485-492.

Rabinowitz MB, Leviton A, Bellinger D. 1993. Relationships between serial blood lead levels and exfoliated tooth dentin lead levels: Models of tooth lead kinetics. Calcif Tissue Int 53(5):338-41.

Rabinowitz MB, Leviton A, Needleman H. 1986. Occurrence of elevated protoporphyrin levels in relation to lead burden in infants. Environ Res 39:253-257.

Rabinowitz MB, Wetherill GW, Kopple JD. 1976. Kinetic analysis of lead metabolism in healthy humans. J Clin Invest 58:260-270.

Raghavan SRV, Gonick HC. 1977. Isolation of low-molecular-weight lead-binding protein from human erythrocytes. Proc Soc Exp Biol Med 155:164-167.

Ramel C, Magnusson J. 1979. Chemical induction of nondisjunction in Drosophila. Environ Health Perspect 3:59-66.

Ratzon N, Froom P, Leikin E, et al. 2000. Effect of exposure to lead on postural control in workers. Occup Environ Med 57:201-203.

Ravnskov U. 1992. Cholesterol lowering trials in coronary heart disease: Frequency of citation and outcome. Br Med J 305:15-19.

Raymond LW, Ford MD, Coldham GJ, et al. 2002. Maternal-fetal lead poisoning in a convenience store cashier: Effects of a 15-year old bullet. J Investig Med 50(1):54A.

Reagan PL, Silbergeld EK. 1990. Establishing a health based standard for lead in residential soils. Trace Subst Environ Health 23:199-238.

Reddy KJ, Wang L, Gloss SP. 1995. Solubility and mobility of copper, zinc and lead in acidic environments. Plant Soil 171:53-58.

Reed BE, Moore RE, Cline SR. 1995. Soil flushing of a sandy loam contaminated with Pb(II), PbS04 (s), PbCo3 (3) or Pb-naphthalene: Column results. J Soil Contam 4(3):243-267.

Refowitz RM. 1984. Thyroid function and lead: No clear relationship. J Occup Med 26(8):579-583.

Reigart JR, Graber CD. 1976. Evaluation of the humoral immune response of children with low level lead exposure. Bull Environ Contam Toxicol 16:112-117.

Reimer W, Tittelbach U. 1989. Verhalten von herzfrequenz, blutdruck und systolischen zeitintervallen in ruhe und während einhandarbeit bei bleiexponierten und kontrollpersonen. Z Gesamte Hyg 35:491-492.

Rhoads GG, Ettinger AS, Weisel CP, et al. 1999. The effect of dust lead control on blood lead in toddlers: A randomized trial. Pediatrics 103(3):551-555.

Rhodes D, Spiro A, Aro A, et al. 2003. Relationship of bone and blood lead levels to psychiatric symptoms: The normative aging study. J Occup Environ Med 45:1144-1151.

Rice DC. 1984. Behavioral deficit (delayed matching to sample) in monkeys exposed from birth to low levels of lead. Toxicol Appl Pharmacol 75:337-345.

Rice DC. 1985. Chronic low-lead exposure from birth produces deficits in discrimination reversal in monkeys. Toxicol Appl Pharmacol 77:201-210.

Rice DC. 1990. Lead-induced behavioral impairment on a spatial discrimination reversal task in monkeys exposed during different periods of development. Toxicol Appl Pharmacol 106:327-333.

Rice DC. 1992. Behavioral effects of lead in monkeys tested during infancy and adulthood. Neurotoxicol Teratol 14:235-245.

Rice DC. 1993. Lead-induced changes in learning: Evidence for behavioral mechanisms from experimental animal studies. Neurotoxicology 14(2-3):167-178.

Rice DC. 1996a. Behavioral effects of lead: Commonalities between experimental and epidemiologic data. Environ Health Perspect Suppl 104:337-351.

Rice DC. 1996b. Effect of long-term lead exposure on hematology, blood biochemistry, and growth curves in monkeys. Neurotoxicology 18:221-236.

Rice DC. 1997. Effects of lifetime lead exposure in monkeys on detection of pure tones. Fundam Appl Toxicol 36(2):112-118.

Rice DC. 1998. Effects of a lifetime lead exposure on spatial and temporal visual function in monkeys. Neurotoxicology 19(6):893-902.

Rice DC, Gilbert SG. 1985. Low-level lead exposure from birth produces behavioral toxicity (DRL) in monkeys. Toxicol Appl Pharmacol 80:421-426.

Rice DC, Gilbert SG. 1990a. Lack of sensitive period for lead-induced behavioral impairment on a spatial delayed alternation task in monkeys. Toxicol Appl Pharmacol 103:364-373.

Rice DC, Gilbert SG. 1990b. Sensitive periods for lead-induced behavioral impairment (nonspatial discrimination reversal) in monkeys. Toxicol Appl Pharmacol 102:101-109.

Rice DC, Karpinski KF. 1988. Lifetime low-level lead exposure produces deficits in delayed alternation in adult monkeys. Neurotoxicol Teratol 10:207-214.

Rice DC, Willes RF. 1979. Neonatal low-level lead exposure in monkeys (Macaca fascicuiaris): Effect on two choice non-spatial form discrimination. J Environ Pathol Toxicol 2:1195-1203.

Richardt G, Federolf G, Haberman E. 1986. Affinity of heavy metal ions to intracellular Ca^2-binding proteins. Biochem Pharmacol 35:1331-1335.

Ris MD, Dietrich KN, Succop PA, et al. 2004. Early exposure to lead and neuropsychological outcome in adolescence. J Int Neuropsychol Soc 10:261-270.

Roberts TM, Hutchinson TC, Paciga J. 1974. Lead contamination around secondary smelters: Estimation of dispersal and accumulation by humans. Science 186:1120-1123.

Robins JM, Cullen MR, Connors BB, et al. 1983. Depressed thyroid indexes associated with occupational exposure to inorganic lead. Arch Intern Med 143:220-224.

Robinson GS, Baumann S, Kleinbaum D, et al. 1985. Effects of low to moderate lead exposure on brainstem auditory evoked potentials in children: Environmental health document 3. Copenhagen, Denmark: World Health Organization Regional Office for Europe, 177-182.

*Robinson GS, Keith RW, Bornschein RL, et al. 1987. Effects of environmental lead exposure on the developing auditory system as indexed by the brainstem auditory evoked potential and pure tone hearing evaluations in young children. In: Lindberg SE, Hutchinson TC., eds. International Conference on Heavy Metals in the Environment, Vol. 1, New Orleans, LA. September. Edinburgh, UK: CEP Consultants, Ltd., 223-225.

Robison SH, Cantoni O, Costa M. 1984. Analysis of metal-induced DNA lesions and DNA-repair replication in mammalian cells. Mutat Res 131:173-181.

Rodamilans M, Osaba MJ, To-Figueras J, et al. 1988. Lead toxicity on endocrine testicular function in an occupationally exposed population. Hum Toxicol 7:125-128.

Roels HA, Lauwerys R. 1987. Evaluation of dose-effect and dose-response relationships for lead exposure in different Belgian population groups (fetus, child, adult men and women). Trace Elem Med 4:80-87.

Roels HA, Balis-Jacques MN, Buchet J-P, et al. 1979. The influence of sex and of chelation therapy on erythrocyte protoporphyrin and urinary δ-aminolevulinic acid in lead-exposed workers. J Occup Med 21:527-539.

Roels HA, Buchet J, Lauwerys R, et al. 1976. Impact of air pollution by lead on the hemebiosynthetic pathway in school-age children. Arch Environ Health 31:310-316.

Roels HA, Buchet J, Lauwerys R, et al. 1980. Exposure to lead by the oral and the pulmonary routes of children living in the vicinity of a primary lead smelter. Environ Res 22:81-94.

*Roels HA, Hubermont G, Buchet J, et al. 1978. Placental transfer of lead, mercury, cadmium, and carbon monoxide in women: III. Factors influencing the accumulation of heavy metals in the placenta and the relationship between metal concentration in the placenta and in maternal and cord blood. Environ Res 16:236-247.

Roels HA, Konings J, Green S, et al. 1995. Time-integrated blood lead concentration is a valid surrogate for estimating the cumulative lead dose assessed by tibial lead measurement. Environ Res 69(2):75-82.

Roels HA, Lauwerys R, Buchet J-P, et al. 1975. Response of free erythrocyte porphyrin and urinary-delta-aminolevulinic acid in men and women moderately exposed to lead. Int Arch Arbeitsmed 34:97-108.

Roels HA, Lauwerys R, Konings J, et al. 1994. Renal function and hyperfiltration capacity in lead smelter workers with high bone lead. Occup Environ Med 51:505-512.

Rogan WJ, Dietrich KN, Ware JH, et al. 2001. The effect of chelation therapy with succimer on neuropsychological development in children exposed to lead. N Engl J Med 344(19):1421-1426.

Rogan WJ, Hogan M, Chi P. 1978. Blood pressure and lead levels in children. J Environ Pathol Toxicol 2:517-519.

Romeo R, Aprea C, Boccalon P, et al. 1996. Serum erthropoietin and blood lead concentrations. Int Arch Occup Environ Health 69:73-75.

Ronis MJJ, Aronson J, Gao GG, et al. 2001. Skeletal effects of developmental lead exposure in rats. Toxicol Sci 62:321-329.

Ronis MJJ, Badger TM, Shema SJ, et al. 1996. Reproductive toxicity and growth effects in rats exposed to lead at different periods during development. Toxicol Appl Pharmacol 136:361-371.

Ronis MJJ, Badger TM, Shema SJ, et al. 1998a. Effects on pubertal growth and reproduction in rats exposed to lead perinatally or continuously throughout development. J Toxicol Environ Health 53(4):327-341.

Ronis MJJ, Badger TM, Shema SJ, et al. 1998c. Endocrine mechanisms underlying the growth effects of developmental lead exposure in the rat. J Toxicol Environ Health 54:101-120.

Ronis MJJ, Gandy J, Badger T. 1998b. Endocrine mechanisms underlying reproductive toxicity in the developing rat chronically exposed to dietary lead. J Toxicol Environ Health 54:77-99.

Roscoe RJ, Ball W, Curran JJ, et al. 2002. Adult blood lead epidemiology and surveillance-United States, 1998-2001. MMWR Morb Mortal Wkly Rep 51(11):1-10.

Roscoe RJ, Gittleman JL, Deddens JA, et al. 1999. Blood lead levels among children of lead-exposed workers: A meta-analysis. Am J Med 36(4):475-481.

Rosen JF, Chesney RW. 1983. Circulating calcitriol concentration in health and disease. J Pediatr 103:1-17.

Rosen JF, Pounds JG. 1989. Quantitative interactions between Pb^2 and Ca^2 homeostasis in cultured osteoclastic bone cells. Toxicol Appl Pharmacol 98:530-543.

*Rosen I, Wildt K, Guilberg B, et al. 1983. Neurophysiological effects of lead exposure. Scand J Work Environ Health 9:431-441.

Rosen JF, Chesney RW, Hamstra AJ, et al. 1980. Reduction in 1,25-dihydroxyvitamin D in children with increased lead absorption. N Engl J Med 302:1128-1131.

Rosen JF, Crocetti AF, Balbi K, et al. 1993. Bone lead content assessed by L-line x-ray fluorescence in lead-exposed and non-lead-exposed suburban populations in the United States. Proc Natl Acad Sci USA 90:2789-2792.

Rosen JF, Markowitz ME, Jenks ST, et al. 1987. L-X-ray fluorescence (XRF): A rapid assessment of cortical bone lead (Pb) in Pb-toxic children. Pediatr Res 21:287A.

Rosen JF, Zarate-Salvador C, Trinidad EE. 1974. Plasma lead levels in normal and lead-intoxicated children. J Pediatr 84:45-48.

Rosenkranz HS, Poirier LA. 1979. Evaluation of the mutagenicity and DNA-modifying activity of carcinogens and noncarcinogens in microbial systems. J Natl Cancer Inst 62:873-892.

Rosenman KD, Sims A, Luo Z, et al. 2003. Occurrence of lead-related symptoms below the current Occupational Safety and Health Act allowable blood lead levels. J Occup Environ Med 45(5):546-555.

Rothenberg SJ, Rothenberg JC. 2005. Testing the dose-response specification in epidmiology: Public health and policy consequences for lead. Environ Health Perspect 113:1190-1195.

*Rothenberg SJ, Cansino S, Sepkoski C, et al. 1995. Prenatal and perinatal lead exposures alter acoustic cry parameters of neonate. Neurotoxicol Teratol 17(2):151-160.

Rothenberg SJ, Karchmer S, Schnaas L, et al. 1994a. Changes in serial blood lead levels during pregnancy. Environ Health Perspect 102(10):876-880.

Rothenberg SJ, Kondrashov V, Manalo M, et al. 2002b. Increases in hypertention and blood pressure during pregnancy with increased bone lead levels. Am J Epidemiol 156:1079-1087.

Rothenberg SJ, Manalo M, Jiang J, et al. 1999a. Blood lead level and blood pressure during pregnancy in South Central Los Angeles. Arch Environ Health 54(6):382-389.

Rothenberg SJ, Manalo M, Jiang J, et al. 1999b. Maternal blood lead level during pregnancy in South Central Los Angeles. Arch Environ Health 54(3):151-157.

Rothenberg SJ, Poblano A, Garza-Morales S. 1994b. Prenatal and perinatal low level lead exposure alters brainstem auditory evoked responses in infants. Neurotoxicology 15:695-700.

Rothenberg SJ, Poblano A, Schnaas L. 2000. Brainstem auditory evoked response at five years and prenatal and postnatal blood lead. Neurotoxicol Teratol 22:503-510.

Rothenberg SJ, Schnaas L, Cansino-Ortiz S, et al. 1989. Neurobehavioral deficits after low level lead exposure in neonates: The Mexico City pilot study. Neurotoxicol Teratol 11:85-93.

Rothenberg SJ, Schnaas L, Perroni E, et al. 1999c. Pre- and postnatal lead effect on head circumference: A case for critical periods. Neurotoxicol Teratol 21:1-11.

Rothenberg SJ, Schnaas L, Salgado-Valladares M, et al. 2002a Increased ERG a- and b-wave amplitudes in 7- to 10-year-old children resulting from prenatal lead exposure. Invest Ophthalmol Vis Sci 43(6):2036-2044.

Roy MM, Gordon CL, Beaumont LF, et al. 1997. Further experience with bone lead content measurements in residents of southern Ontario. Appl Radiat Isot 48:391-396.

RTECS. 2007. Lead. Registry of Toxic Effects on Chemical Substances. National Institute of Occupational Safety and Health. MDL Information Systems, Inc. June 8, 2007.

Ruby MV, Davis A, Kempton JH, et al. 1992. Lead bioavailability: Dissolution kinetics under simulated gastric conditions. Environ Sci Technol 26:1242-1248.

Ruby MV, Davis A, Nicholson A. 1994. In situ formation of lead phosphates in soils as a method to immobilize lead. Environ Sci Technol 28:646-654.

Ruby MV, Schoof R, Brattin W, et al. 1999. Advances in evaluating the oral bioavailability of inorganics in soil for use in human health risk assessment. Environ Sci Technol 33(21):3697-3705.

Rudolph L, Sharp DS, Samuels S, et al. 1990. Environmental and biological monitoring for lead exposure in California workplaces. Am J Public Health 80:921-934.

Ruff HA, Bijur PE, Markowitz M, et al. 1993. Declining blood lead levels and cognitive changes in moderately lead-poisoned children. JAMA 259(13):1641-1646.

*Ruff HA, Markowitz ME, Bijur PE, et al. 1996. Relationships among blood lead levels, iron deficiency, and cognitive development in two-year-old children. Environ Health Perspect 104(2):180-185.

Rummo JH, Routh DK, Rummo NJ, et al. 1979. Behavioral and neurological effects of symptomatic and asymptomatic lead exposure in children. Arch Environ Health 34:120-125.

*Ryan CM, Morrow L, Parkinson D, et al. 1987. Low level lead exposure and neuropsychological functioning in blue collar males. Int J Neurosci 36:29-39.

Ryan PB, Huet N, MacIntosh DL. 2000. Longitudinal investigation of exposure to arsenic, cadmium, and lead in drinking water. Environ Health Perspect 108(8):731-735.

Ryan PB, Scanlon KA, MacIntosh DL. 2001. Analysis of dietary intake of selected metals in the NHEXAS-Maryland investigation. Environ Health Perspect 109(2):121-128.

Ryu JE, Ziegler EE, Nelson SE, et al. 1983. Dietary intake of lead and blood lead concentration in early infancy. Am J Dis Child 137:886-891.

Sachs HK, Moel DI. 1989. Height and weight following lead poisoning in childhood. Am J Dis Child 143:820-822.

Saenger P, Markowitz ME, Rosen JF. 1984. Depressed excretion of 6β-hydroxycortisol in lead-toxic children. J Clin Endocrinol Metab 58:363-367.

Sakai T. 2000. Biomarkers of lead exposure. Ind Health 38:127-142.

Sakai T, Morita Y. 1996. δ-aminolevulinic acid in plasma or whole blood as a sensitive indicator of lead effects, and its relation to the other heme-related parameters. Int Arch Occup Environ Health 68(2):126-132.

Sakai T, Yanagihara S, Kunugi Y, et al. 1982. Relationships between distribution of lead in erythrocytes in vivo and in vitro and inhibition of ALA-D. Br J Ind Med 39:382-387.

Sakai T, Yanagihara S, Kunugi Y, et al. 1983. Mechanisms of ALA-D inhibition by lead and of its restoration by zinc and dithiothreitol. Br J Ind Med 40:61-66.

Sallmén M, Anttila A, Lindbohm M-L, et al. 1995. Time to pregnancy among women occupationally exposed to lead. J Occup Environ Med 37:931-934.

Sallmén M, Lindbohm ML, Anttila A, et al. 2000a. Time to pregnancy among the wives of men occupationally exposed to lead. Epidemiology 11:141-147.

Sallmén M, Lindbohm ML, Nurminen M. 2000b. Paternal exposure to lead and infertility. Epidemiology 11:148-152.

Samanta G, Chakraborti D. 1996. Flow injection hydride generation atomic absorption spectrometry (FI-HG-AAS) and spectrophotometric methods for determination of lead in environmental samples. Environ Technol 17(12):1327-1337.

Sandhir R, Julka D, Gill KD. 1994. Lipoperoxidative damage on lead exposure in rat brain and its implications on membrane bound enzymes. Pharmacol Toxicol 74:66-71.

Sanín LH, Gonzalez-Cossio T, Romieu I, et al. 2001. Effect of maternal lead burden on infant weight and weight gain at one month of age among breastfed infants. Pediatrics 107(55):1016-1023.

Sarasua SM, Vogt RF, Henderson LO, et al. 2000. Serum immunoglobulins and lymphocyte subset distributions in children and adults living in communities assessed for lead and cadmium exposure. J Toxicol Environ Health A 60:1-15.

Sarto F, Stella M, Acqua A. 1978. [Cytogenic studies in 20 workers occupationally exposed to lead.] Med Lav 69:172-180. (Italian)

Sata F, Araki S, Tanigawa T, et al. 1998. Changes in T cell subpopulations in lead workers. Environ Res 76(1):61-64.

Satzger RD, Clow CS, Bonnin E, et al. 1982. Determination of background levels of lead and cadmium in raw agricultural crops by using differential pulse anodic stripping voltammetry. J Assoc Off Anal Chem 65:987-991.

Sauk JJ, Smith T, Silbergeld EK, et al. 1992. Lead inhibits secretion of osteonectin/sparc without significantly altering collagen or hsp47 production in osteoblast-like ros 17/2.8 cells. Toxicol Appl Pharmacol 116(2):240-247.

Sauve S, McBride MB, Hendershot WH. 1997. Speciation of lead in contaminated soils. Environ Pollut 98(2):149-155.

Sax NI. 1984. Dangerous properties of industrial materials. 6th ed. New York, NY: Van Nostrand Reinhold Company, 2641.

Sax NI, Lewis RJ. 1987. Hawley's condensed chemical dictionary. New York, NY: Van Nostrand Reinhold Company, 687-694.

Scelfo GM, Flegal AR. 2000. Lead in calcium supplements. Environ Health Perspect 108(4):309-313.

Schalscha EB, Morales M, Pratt P. 1987. Lead and molybdenum in soils and forage near an atmospheric source. J Environ Qual 16:313-315.

Schaumberg DA, Mendes F, Balaram M, et al. 2004. Accumulated lead exposure and risk of age-related cataract in men. JAMA 292(22):2750-2754.

Schmid E, Bauchinger M, Pietruck S, et al. 1972. [Cytogenic action of lead in human peripheral lymphocytes *in vitro* and *in vivo*.] Mutat Res 16:401-406. (German)

Schmitt CJ, Brumbaugh WG. 1990. National contaminant biomonitoring program: Concentration of arsenic, cadmium, cooper, lead, mercury, selenium, and zinc in U.S. freshwater fish, 1976-1984. Arch Environ Contam Toxicol 19:731-747.

Schmitt MDC, Trippler DL, Wachtler JN, et al. 1988. Soil lead concentrations in residential Minnesota as measured by ICP AES. Water Air Soil Pollut 39:157-168.

Schnaas L, Rothenberg SJ, Flores MF. 2006. Reduced intellectual development in children with prenatal lead exposure. Environ Health Perspect 114(5):791-797.

Schnaas L, Rothenberg SJ, Perroni E, et al. 2000. Temporal pattern in the effect of postnatal blood lead level on intellectual development of young children. Neurotoxicol Teratol 22:805-810.

Schneider JS, Lee MH, Anderson DW, et al. 2001. Enriched environment during development is protective against lead-induced neurotoxicity. Brain Res 896:48-55.

Schneitzer L, Osborn HH, Bierman A, et al. 1990. Lead poisoning in adults from renovation of an older home. Ann Emerg Med 19:415-420.

Schober SE, Mirel LB, Graubard BI, et al. 2006. Blood lead levels and death from all causes, cardiovascular disease, and cancer: Results from the NHANES III mortality study. Environ Health Perspect 114(10):1538-1541.

Schroeder HA, Tipton IH. 1968. The human body burden of lead. Arch Environ Health 17:965-978.

Schroeder SR, Hawk B. 1987. Psycho-social factors, lead exposure and IQ. Monogr Am Assoc Ment Defic S:97-137.

*Schroeder SR, Hawk B, Otto DA, et al. 1985. Separating the effects of lead and social factors on IQ. Environ Res 38:144-154.

Schuhmacher M, Hernandez M, Domingo JL, et al. 1996. A longitudinal study of lead mobilization during pregnancy: Concentration in maternal and umbilical cord blood. Trace Elements and Electrolytes 13:177-181.

Schuhmacher M, Paternain JL, Domingo JL, et al. 1997. An assessment of some biomonitors indicative of occupational exposure to lead. Trace Elem Electrolytes 14(3):145-149.

Schumacher C, Brodkin CA, Alexander B, et al. 1998. Thyroid function in lead smelter workers: Absence of subacute or cumulative effects with moderate lead burdens. Int Arch Occup Environ Health 71:453-458.

Schütz A, Bergdahl IA, Ekholm A, et al. 1996. Measurement by ICP-MS of lead in plasma and whole blood of lead workers and controls. Occup Environ Med 53:736-740.

Schutz A, Skerfving S, Ranstam J, et al. 1987. Kinetics of lead in blood after the end of occupational exposure. Scand J Work Environ Health 13:221-231.

Schwanitz G, Gebhart E, Rott HD, et al. 1975. [Chromosome investigations in subjects with occupational lead exposure.] Deutsch Med Wschr 100:1007-1011. (German)

Schwanitz G, Lenhert G, Gebhart E. 1970. [Chromosome damage after occupational exposure to lead.] Deutsch Med Wschr 95:1636-1641. (German)

Schwartz J. 1988. The relationship between blood lead and blood pressure in the NHANES II survey. Environ Health Perspect 78:15-22.

Schwartz J. 1994. Low-level lead exposure and children's IQ: A meta-analysis and search for a threshold. Environ Res 65:42-55.

Schwartz J. 1995. Lead, blood pressure, and cardiovascular disease in men. Arch Environ Health 50:31-37.

Schwartz J, Otto DA. 1987. Blood lead, hearing thresholds, and neurobehavioral development in children and youth. Arch Environ Health 42:153-160.

Schwartz J, Otto DA. 1991. Lead and minor hear impairment. Arch Environ Health 46:300-305.

Schwartz BS, Stewart WF. 2000. Different associations of blood lead, meso 2,3-dimercaptosuccinic acid (DMSA)-chelatable lead, and tibial lead levels with blood pressure in 543 organolead manufacturing workers. Arch Environ Health 55:85-92.

Schwartz BS, Lee BK, Bandeen-Roche K, et al. 2005. Occupational lead exposure and longitudinal decline in neurobehavioral test scores. Epidemiology 16(1):106-113.

Schwartz BS, Lee BK, Lee GS, et al. 2000a. Associations of blood lead, dimercaptosuccinic acid-chelatable lead, and tibia lead with polymorphisms in the Vitamin D receptor and d-aminolevulinic acid dehydratase genes. Environ Health Perspect 108:949-954.

Schwartz BS, Lee BK, Lee GS, et al. 2001. Associations of blood lead, dimercaptosuccinic acid-chelatable lead, and tibia lead with neurobehavioral test scores in South Korean lead workers. Am J Epidemiol 153:453-464.

Schwartz BS, Lee B-K, Stewart W, et al. 1997a. Associations of subtypes of hemoglobin with delta-aminolevulinic acid dehydratase genotype and dimercaptosuccinic acid-chelatable lead levels. Arch Environ Health 52(2):97-103.

Schwartz BS, Lee BK, Stewart W, et al. 1997b. δ-aminolevulinic acid dehydratase genotype modifies four hour urinary lead excretion after oral administration of dimercaptosuccinic acid. Occup Environ Med 54(4):241-246.

Schwartz BS, Stewart WF, Bolla KI, et al. 2000b. Past adult lead exposure is associated with longitudinal decline in cognitive function. Neurology 55:1144-1150.

Schwartz J, Angle C, Pitchcr H. 1986. Relationship between childhood blood lead levels and stature. Pediatrics 77:281-288.

Schwartz J, Landrigan PJ, Baker EL Jr. 1990. Lead-induced anemia: Dose-response relationships and evidence for a threshold. Am J Public Health 80:165-168.

Schwartz J, Landrigan PJ, Feldman RG, et al. 1988. Threshold effect in lead-induced peripheral neuropathy. J Pediatr 112:12-17.

Scinicariello F, Murray HE, Moffett DB, et al. 2007. Lead and δ-aminolevulinic acid dehydratase polymorphism: Where does it lead? A meta-analysis. Environ Health Perspect 115(1):35-41.

Scott DR, Hemphill DC, Hoiboke LE, et al. 1976. Atomic absorption and optical emission analysis of NASN atmospheric particulate samples for lead. Environ Sci Technol 9:877-880.

Secchi GC, Erba L, Cambiaghi G. 1974. Delta-aminolevulinic acid dehydrase, activity of erythrocytes and liver tissue in man: Relationship to lead exposure. Arch Environ Health 28:130-132.

Sedman RM. 1989. The development of applied action levels for soil contact: A scenario for the exposure of humans to soil in a residential setting. Environ Health Perspect 79:291-313.

Selander S, Cramer K. 1970. Interrelationships between lead in blood, lead in urine, and ALA in urine during lead work. Br J Ind Med 27:28-39.

Selbst M, Sokas R, Hennetig F, et al. 1993. The effect of blood lead on blood pressure in children. J Envrion Pathol Toxicol Oncol 12:213-218.

Selevan SG, Landrigan PJ, Stern FB, et al. 1985. Mortality of lead smelter workers. Am J Epidemiol 122:673-683.

Selevan SG, Landrigan PJ, Stern FB, et al. 1988. Lead and hypertension in a mortality study of lead smelter workers. Environ Health Perspect 78:65-66.

Selevan SG, Rice DC, Hogan KA, et al. 2003. Blood lead concentration and delayed puberty in girls. N Engl J Med 348(16):1527-1536.

Seppalainen AM, Hernberg S, Vesanto R, et al. 1983. Early neurotoxic effects of occupational lead exposure: A prospective study. Neurotoxicology 4:181-192.

Setchell BP, Waites GMH. 1975. The blood-testis barrier. In: Creep RO, Astwood EB, Geiger SR, eds. Handbook of physiology: Endocrinology V. Washington, DC: American Physiological Society, 143-172.

Seto DSY, Freeman JM. 1964. Lead neuropathy in childhood. Am J Dis Child 107:337-342.

Shaper AG, Pocock SJ, Walker M, et al. 1981. British regional heart study: Cardiovascular risk factors in middle-aged men in 24 towns. Br Med J 283:179-186.

Sharp DS, Benowitz NL, Osterloh JD, et al. 1990. Influence of race, tobacco use, and caffeine use on the relationship between blood pressure and blood lead concentration. Am J Epidemiol 131(5):845-854.

Sharp DS, Osterloh J, Becker CE, et al. 1988. Blood pressure and blood lead concentration in bus drivers. Environ Health Perspect 78:131-137.

Sharp DS, Smith AH, Holman BL, et al. 1989. Elevated blood pressure in treated hypertensives with low-level lead accumulation. Arch Environ Health 44:18-22.

Shea EE. 1996. Lead regulation handbook. Rockville, MD: Government Institutes.

Shelton KR, Egle PM. 1982. The proteins of lead-induced intranuclear inclusion bodies. J Biol Chem 257(19):11802-11807.

Shen XM, Wu SH, Yan CH, et al. 2001. δ-Aminolevulinate dehydratase polymorphism and blood lead levels in Chinese children. Environ Res 85:185-190.

Shen XM, Yan C-H, Guo D, et al. 1998. Low-level prenatal lead exposure and neurobehavioral development of children in the first year of life: A prospective study in Shanghai. Environ Res 79:1-8.

Sherlock JC, Quinn MJ. 1986. Relationship between blood and lead concentrations and dietary lead intake in infants: The Glasgow Duplicate Diet Study 1979-1980. Food Addit Contam 3:167-176.

Sherlock JC, Ashby D, Delves HT, et al. 1984. Reduction in exposure to lead from drinking water and its effect on blood lead concentrations. Hum Toxicol 3:383-392.

Sherlock JC, Smart G, Forbes GI, et al. 1982. Assessment of lead intakes and dose-response for a population in Ayr exposed to a plumbosolvent water supply. Hum Toxicol 1:115-122.

Shiau CY, Wang JD, Chen PC. 2004. Decreased fecundity among male lead workers. Occup Environ Med 61:915-923.

Shih RA, Glass TA, Bandeen-Roche K, et al. 2006. Environmental lead exposure and cognitive function in community-dwelling older adults. Neurology 67(9):1556-1562.

*Shukla R, Bornschein RL, Dietrich KN, et al. 1987. Effects of fetal and early postnatal lead exposure on child's growth in stature--the Cincinnati lead study. In: Lindberg SE, Hutchinson TC, eds. International Conference on Heavy Metals in the Environment, Vol. 1. New Orleans, LA. Edinburgh, UK: CEP Consultants, Ltd., 210-212.

Shukla R, Bornschein RL, Dietrich KN, et al. 1989. Fetal and infant lead exposure: Effects on growth in stature. Pediatrics 84:604-612.

Shukla R, Dietrich KN, Bornschein RL, et al. 1991. Lead exposure and growth in the early preschool child: A follow-up report from the Cincinnati lead study. Pediatrics 88:886-892.

Siegel M, Forsyth B, Siegel L, et al. 1989. The effect of lead on thyroid function in children. Environ Res 49:190-196.

Silbergeld EK. 1987. Role of altered heme synthesis in chemical injury to the nervous system. Ann N Y Acad Sci 514:297-308.

Silbergeld EK. 2003. Facilitative mechanisms of lead as a carcinogen. Mutat Res 533:121-133.

Silbergeld EK, Hruska RE, Bradley D, et al. 1982. Neurotoxic aspects of porphyrinopathies: Lead and succinylacetone. Environ Res 29:459-471.

Silbergeld EK, Quintanilla-Vega B, Gandley RE. 2003. Mechanisms of male mediated developmental toxicity induced by lead. Adv Exp Med Biol 518:37-48.

Silbergeld EK, Schwartz J, Mahaffey K. 1988. Lead and osteoporosis: Mobilization of lead from bone in postmenopausal women. Environ Res 47:79-94.

Silbergeld EK, Waalkes M, Rice JM. 2000. Lead as a carcinogen: Experimental evidence and mechanisms of action. Am J Ind Med 38:316-323.

Silva PA, Hughes P, Williams S, et al. 1988. Blood lead, intelligence, reading attainment, and behavior in eleven year old children in Dunedin, New Zealand. J Child Psychol Psychiatry 29:43-52.

*Silver W, Rodriguez-Torres R. 1968. Electrocardiographic studies in children with lead poisoning. Pediatrics 41:1124-1127.

Simmon VF. 1979a. *In vitro* assays for recombinogenic activity of chemical carcinogens and related compounds with *Saccharomyces cerevisiae* D3. J Natl Cancer Inst 62:901-909.

Simmon VF. 1979b. *In vitro* mutagenicity assays of chemical carcinogens and related compounds with *Salmonella typhimurium*. J Natl Cancer Inst 62:893-899.

Simons TJB. 1985. Influence of lead ions on cation permeability in human red cell ghosts. J Membr Biol 84:61-71.

Simons TJB. 1986b. Passive transport and binding of lead by human red blood cells. J Physiol 378:267-286.

Simons TJB. 1986a. The role of anion transport in the passive movement of lead across the human red cell membrane. J Physiol 378:287-312.

Simons TJB. 1988. Active transport of lead by the calcium pump in human red cell ghosts. J Physiol 405:105-113.

Simons TJB. 1993. Lead transport and binding by human erythrocytes in vitro. Toxicol Lett 423:307-313.

Simons TJB, Pocock G. 1987. Lead enters bovine adrenal medullary cells through calcium channels. J Neurochem 48:383-389.

Singh B, Chandran V, Bandhu HK, et al. 2000a. Impact of lead exposure on pituitary-thyroid axis in humans. BioMetals 13:187-192.

Singh B, Dhawan D, Nehru B, et al. 1994. Impact of lead pollution on the status of other trace metals in blood and alterations in hepatic functions. Biol Trace Elem Res 40:21-29.

Sirover, MA, Loeb LA. 1976. Infidelity of DNA synthesis *in vitro*: Screening for potential metal mutagens or carcinogens. Science 194:1434-1436.

Six KM, Goyer RA. 1970. Experimental enhancement of lead toxicity by low dietary calcium. J Lab Clin Med 76:933-942.

Six KM, Goyer RA. 1972. The influence of iron deficiency on tissue content and toxicity of ingested lead in the rat. J Lab Clin Med 79:128-136.

Skerfving S. 1988. Biological monitoring of exposure to inorganic lead. In: Clarkson TW, Friberg L, Nordberg GF, et al., eds. Biological monitoring of toxic metals. New York, NY: Plenum Press, 169-197.

Skerfving S, Ahlgren L, Christoffersson J-O, et al. 1985. Metabolism of inorganic lead in man. Nutr Res Suppl 2:601-607.

Skerfving S, Nilsson U, Schutz A, et al. 1993. Biological monitoring of inorganic lead. Scand J Work Environ Health 19(1):59-64.

Skoczynska A, Smolik R, Jelen M. 1993. Lipid abnormalities in rats given small doses of lead. Arch Toxicol 67:200-204.

Smith GR. 1995. Lead. In: Minerals yearbook: Volume I. Metals and minerals. Reston, VA: U.S. Department of the Interior, U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/lead/380495.pdf. May 24, 2005.

Smith GR. 1998. Lead: Lead statistics and information, mineral commodity summary, 1998. U.S. Department of the Interior, U.S. Geological Survey. http://minerals.er.usgs.gov/minerals/pubs/commodity/lead/. October 11, 1998.

Smith CM, Deluca HF, Tanaka Y, et al. 1978. Stimulation of lead absorption by vitamin D administration. J Nutr 108:843-847.

Smith CM, Deluca HF, Tanaka Y, et al. 1981. Effect of lead ingestion on functions of vitamin D and its metabolites. J Nutr 111:1321-1329.

Smith CM, Wang X, Hu H, et al. 1995. A polymorphism in the δ-aminolevulinic acid dehydratase gene may modify the pharmacokinetics and toxicity of lead. Environ Health Perspect 103:248-253.

Smith D, Hernandez-Avila M, Tellez-Rojo MM, et al. 2002. The relationship between lead in plasma and whole blood in women. Environ Health Perspect 110(3):263-268.

Smith DR, Ilustre RP, Osterloh JD. 1998a. Methodological considerations for the accurate determination of lead in human plasma and serum. Am J Ind Med 33:430-438.

Smith DR, Kahng MW, Quintanilla-Vega B, et al. 1998b. High-affinity renal lead-binding proteins in environmentally-exposed humans. Toxicol Appl Pharmacol 115:39-52.

Smith D, Osterloh JD, Flegal AR. 1996. Use of endogenous, stable lead isotopes to determine release of lead from the skeleton. Environ Health Perspect 104(1):60-66.

Smith D, Woolard D, Luck ML, et al. 2000. Succimer and the reduction of tissue lead in juvenile monkeys. Toxicol Appl Pharmacol 166:230-240.

Smith FL II, Rathmell TK, Marcil GE. 1938. The early diagnosis of acute and latent plumbism. Am J Clin Pathol 8:471-508.

Smith M, Delves T, Tansdown R, et al. 1983. The effects of lead exposure on urban children: The Institute of Child Health/Southampton study. Dev Med Child Neurol 25(suppl 47):1-54.

Snyder JE, Filipov NM, Parsons PJ, et al. 2000. The efficiency of maternal transfer of lead and its influence on plasma IgE and splenic cellularity of mice. Toxicol Sci 57:87-94.

Sokas RK, Simmens S, Sophar K, et al. 1997. Lead levels in Maryland construction workers. Am J Ind Med 31:188-194.

Sokol RZ, Wang S, Wan YJY, et al. 2002. Long-term, low-dose lead exposure alters the gonadotropin-releasing hormone system in the male rat. Environ Health Perspect 110(9):871-874.

Soldin OP, Pezzullo JC, Hanak B, et al. 2003. Changing trends in the epidemiology of pediatric lead exposure: Interrelationship of blood lead and ZPP concentrations and a comparison to the US population. Ther Drug Monit 25:415-420.

Solliway BM, Schaffer A, Pratt H, et al. 1996. Effects of exposure to lead on selected biochemical and hematological variables. Pharmacol Toxicol 78:18-22.

Somashekaraiah BV, Venkaiah B, Prasad ARK. 1990. Biochemical diagnosis of occupational exposure to lead toxicity. Bull Environ Contam Toxicol 44:268-275.

Sonmez F, Donmez O, Sonmez HM, et al. 2002. Lead exposure and urinary N-acetyl B D glucosaminidase activity in adolescent workers in auto repair workshops. J Adolesc Health 30:213-216.

Sorrell M, Rosen JF, Roginskv M. 1977. Interactions of lead, calcium, vitamin D, and nutrition in lead burdened children. Arch Environ Health 32:160-164.

Sowers M, Jannausch M, Scholl T, et al. 2002a. Blood lead concentrations and pregnancy outcomes. Arch Environ Health 57(5):489-495.

Sowers M, Scholl T, Hall G, et al. 2002b. Lead in breast milk and maternal bone turnover. Am J Obstet Gynecol 187(3):770-776.

Spear TM, Svee W, Vincent JH, et al. 1998. Chemical speciation of lead dust associated with primary lead smelting. Environ Health Perspect 106(9):565-571.

Spivey GH, Baloh RW, Brown CP, et al. 1980. Subclinical effects of chronic increased lead absorption--a prospective study: III. Neurologic findings at follow-up examination. J Occup Med 22:607-612.

SRI. 2004. 2004 Directory of chemical producers. Menlo Park, CA: SRI Consulting.:787, 788, 689, 690.

Staessen JA, Buchet J-P, Ginucchio G, et al. 1996a. Public health implications of environmental exposure to cadmium and lead: An overview of epidemiological studies in Belgium. J Cardiovasc Risk 3:26-41.

Staessen JA, Bulpitt CJ, Roels H, et al. 1984. Urinary cadmium and lead concentrations and their relation to blood pressure in a population with low exposure. Br J Ind Med 41:241-248.

Staessen JA, Lauwerys RR, Buchet JP, et al. 1992. Impairment of renal function with increasing blood lead concentrations in the general population. The cadmibel study group. N Engl J Med 327(3):151-156.

Staessen JA, Lauwerys RR, Bulpitt CJ, et al. 1994. Is a positive association between lead exposure and blood pressure supported by animal experiments? Curr Opin Nephrol Hypertens 3(3):257-263.

Staessen JA, O'Brien ET, Thijs L, et al. 2000. Modern approaches to blood pressure measurement. Occup Environ Med 57:510-520.

Staessen JA, Roels H, Fagard R. 1996b. Lead exposure and conventional and ambulatory blood pressure. JAMA 275:1563-1570.

Staessen JA, Yeoman WB, Fletcher AE, et al. 1990. Blood lead concentration, renal function, and blood pressure in London civil servants. Br J Ind Med 47:442-447.

Stanek K, Manton W, Angle C, et al. 1998. Lead consumption of 18- to 36-month-old children as determined from duplicate diet collections: Nutrient intakes, blood lead levels, and effects on growth. J Am Diet Assoc 98(2):155-158.

Stark AD, Quah RF, Meigs JW, et al. 1982. The relationship of environmental lead to blood-lead levels in children. Environ Res 27:372-383.

Stauber JL, Florence TM. 1988. A comparative study of copper, lead, cadmium and zinc in human sweat and blood. Sci Total Environ 74:235-247.

Stauber JL, Florence TM, Gulson BL, et al. 1994. Percutaneous absorption of inorganic lead compounds. Sci Total Environ 145:55-70.

Steenhout A. 1982. Kinetics of lead storage in teeth and bones: An epidemiologic approach. Arch Environ Health 37(4):224-231.

Steenhout A, Pourtois M. 1981. Lead accumulation in teeth as a function of age with different exposures. Br J Ind Med 38:297-303.

Steenhout A, Pourtois M. 1987. Age-related lead kinetics in children. In: Trace elements in human health and disease, Second Nordic symposium, Odense, Denmark, August 17-21, 1987. Copenhagen, Denmark: World Health Organization, 144-147.

Steenland K, Boffetta P. 2000. Lead and cancer in humans: Where are we now? Am J Ind Med 38:295-299.

Steenland K, Selevan S, Landrigan P. 1992. The mortality of lead smelter workers: An update. Am J Public Health 82:1641-1644.

Stern AH. 1994. Derivation of a target level of lead in soil at residential sites corresponding to a *de minimis* contribution to blood lead concentration. Risk Anal 14(6):1049-1056.

Stern AH. 1996. Derivation of a target concentration of Pb in soil based on elevation of adult blood pressure. Risk Anal 16:201-210.

Sternowsky HJ, Wessolowski R. 1985. Lead and cadmium in breast milk. Arch Toxicol 57:41-45.

Stewart WF, Schwartz BS, Davatzikos C, et al. 2006. Past adult lead exposure is linked to neurodegeneration measured by brain MRI. Neurology 66:1476-1484.

Stewart WF, Schwartz BS, Simon D, et al. 1999. Neurobehavioral function and tibial and chelatable lead levels in 543 former organolead workers. Neurology 52:1610-1617.

Stewart WF, Schwartz BS, Simon D, et al. 2002. ApoE genotype, past adult lead exposure, and neurobehavioral function. Environ Health Perspect 110(5):501-505.

Stokes L, Letz R, Gerr F, et al. 1998. Neurotoxicity in young adults 20 years after childhood exposure to lead: The Bunker Hill experience. Occup Environ Med 55:507-516.

Stokinger HE. 1981. Lead. In: Clayton GD, Clayton FE, eds. Patty's industrial hygiene and toxicology. Vol. 2A: Toxicology. New York, NY: John Wiley and Sons, 1687-1728.

Stollery BT. 1996. Reaction time changes in workers exposed to lead. Neurotoxicol Teratol 18(4):477-483.

Stollery BT, Banks HA, Broadbent DE, et al. 1989. Cognitive functioning in lead workers. Br J Ind Med 46:698-707.

Stollery BT, Broadbent DE, Banks HA, et al. 1991. Short term prospective study of cognitive functioning in lead workers. Br J Ind Med 48:739-749.

Stretesky PB, Lynch MJ. 2001. The relationship between lead exposure and homicide. Arch Pediatr Adolesc Med 155:579-582.

Stuik EJ. 1974. Biological response of male and female volunteers to inorganic lead. Int Arch Arbeitsmed 33:83-97.

Stutz DR, Janusz SJ. 1988. Hazardous materials injuries: A handbook for pre-hospital care. 2nd ed. Beltsville, MD: Bradford Communications Corporation, 314-315.

Succop P, Clark S, Tseng CY, et al. 2001. Evaluation of public housing lead risk assessment data. Environ Geochem Health 23:1-15.

Sugawara E, Nakamura K, Miyake T, et al. 1991. Lipid peroxidation and concentration of flutathione in erythrocytes from workers exposed to lead. Br J Ind Med 48:239-242.

Sun LR, Suszkiw JB. 1995. Extracellular inhibition and intracellular enhancement of Ca^2 currents by Pb^2 in bovine adrenal chromaffin cells. J Neurophysiol 74:574-581.

Sun CC, Wong TT, Hwang YH, et al. 2002. Percutaneous absorption of inorganic lead compounds. Am Ind Hyg Assoc J 63:641-646.

Sun L, Hu J, Zhao Z, et al. 2003. Influence of exposure to environmental leadon serum immunoglobulin in preschool children. Environ Res 92:124-128.

Suszkiw JB. 2004. Presynaptic disruption of transmitter release by lead. Neurotoxicology 25:599-604.

Sutherland CA, Milner EF. 1990. Lead. In: Elvers B, Hawkins S, Schulz G, eds. Ullmann's encyclopedia of industrial chemistry. 5th edition. New York, NY: VCH Publishers, 193-236.

Süzen HS, Duydu Y, Aydin A, et al. 2003. Influence of the delta-aminolevulinic acid dehydratase (ALAD) polymorphism on biomarkers of lead exposure in Turkish storage battery manufacturing workers. Am J Ind Med 43:165-171.

Swenberg JA, Short B, Borghoff S, et al. 1989. The comparative pathobiology of I2-globulin nephropathy. Toxicol Appl Phamacol 97:35-46.

Symanski E, Hertz-Picciotto I. 1995. Blood lead levels in relation to menopause, smoking, and pregnancy history. Am J Epidemiol 141(11):1047-1058.

Tabuchi T, Okayama A, Ogawa Y, et al. 1989. A new HPLC fluorimetric method to monitor urinary delta-aminolevulinic acid (ALA-U) levels in workers exposed to lead. Int Arch Occup Environ Health 61:297-302.

Tachi K, Nishimae S, Saito K. 1985. Cytogenic effects of lead acetate on rat bone marrow cells. Arch Environ Health 40:144-147.

Talcott PA, Koller LD. 1983. The effect of inorganic lead and/or a polychlorinated biphenyl on the developing immune system of mice. J Toxicol Environ Health 12:337-352.

Taupeau C, Poupon J, Treton D, et al. 2003. Lead reduces messenger RNA and protein levels of cytochrome P450 aromatase and estrogen receptor beta in human ovarian granulosa cells. Biol Reprod 68:1982-1988.

Tchernitchin NN, Clavero A, Mena MA, et al. 2003. Effect of chronic exposure to lead on estrogen action in the prepubertal rat uterus. Environ Toxicol 18:268-277.

Teichmann R, Stremmel W. 1990. Iron uptake by human upper small intestine microvillous membrane vesicles. Indication for a facilitated transport mechanism mediated by a membrane iron-binding protein. J Clin Invest 86:2145-2153.

Telisman S, Cvitkovic P, Jurasovic J, et al. 2000. Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. Environ Health Perspect 108:45-53.

Téllez-Rojo MM, Bellinger DC, Arroyo-Quiroz C, et al. 2006. Longitudinal associations between blood lead concentrations lower than 10 μg/dl and neurobehavioral development in environmentally exposed children in Mexico City. Pediatrics 118(2):e323-e330.

Téllez-Rojo MM, Hernández-Avila M, Lamadrid-Figueroa H, et al. 2004. Impact of bone lead and bone resorption on plasma and whole blood lead levels during pregnancy. Am J Epidemiol 160(7):668-678.

Ter Haar GL, Aronow R. 1974. New information on lead in dirt and dust as related to the childhood lead problem. Environ Health Perspect 7:83-89.

Ter Haar GL, Bayard MA. 1971. Composition of airborne lead particles. Nature 232:553-554.

Thacker SB, Hoffman DA, Smith J, et al. 1992. Effect of low-level body burdens of lead on the mental development of children: Limitations of meta-analysis in a review of longitudinal data. Arch Environ Health 47(5):336-346.

Tharr D. 1993. Lead contamination in radiator repair shops. Appl Occup Environ Hyg 8(5):434-438.

Thatcher RW, Lester ML, McAlaster R, et al. 1982. Effects of low levels of cadmium and lead on cognitive functioning in children. Arch Environ Health 37:159-166.

Theppeang K, Schwartz BS, Lee BK, et al. 2004. Associations of patella lead with polymorphisms in the vitamin D receptor, γ-aminolevulinic acid dehydratase and endothelial nitric oxide synthase genes. J Occup Med 46:528-537.

Thier R, Bonacker D, Stoiber T, et al. 2003. Interaction of metal salts with cytoskeletal motor protein systems. Toxicol Lett 11:75-81.

Thomas KW, Pellizzari ED, Berry MR. 1999. Population-based dietary intakes and tap water concentrations for selected elements in the EPA Region V National Human Exposure Assessment Survey (NHEXAS). J Expo Anal Environ Epidemiol 9:402-413.

Thomasino JA, Zuroweste E, Brooks SM, et al. 1977. Lead, zinc and erythrocyte delta-aminolevulinic acid dehydratase: Relationships in lead toxicity. Arch Environ Health 32:244-247.

Thompson GN, Robertson EF, Fitzgerald S. 1985. Lead mobilization during pregnancy. Med J Aust 143:131.

Timchalk C, Lin Y, Weitz KK, et al. 2006. Disposition of lead (Pb) in saliva and blood of Sprague-Dawley rats following a single or repeated oral exposure to Pb-acetate. Toxicology 222(1-2):86-94.

Todd AC, Wetmur JG, Moline JM, et al. 1996. Unraveling the chronic toxicity of lead: An essential priority for environmental health. Environ Health Perspect 104(1):141-146.

Tola S, Hernberg S, Asp S, et al. 1973. Parameters indicative of absorption and biological effect in new lead exposure: A prospective study. Br J Ind Med 30:134-141.

Tomokuni K, Ichiba M. 1988. A simple method for colorimetric determination of urinary δ-aminolevulinic acid in workers exposed to lead. Sangyo Igaku 30:52-53.

Tomokuni K, Ichiba M, Hirai Y. 1988. Species difference of urinary excretion of delta-aminolevulinic acid and coproporphyrin in mice and rats exposed in lead. Toxicol Lett 41:255-259.

Tomsig JL, Suszkiw JB. 1991. Permeation of Pb^2 through calcium channels: Fura-2 measurements of voltage- and dihydrophyridine-sensitve Pb^2 entry in isolated bovine chromaffin cells. Biochim Biophys Acta 1069:197-200.

Tomsig JL, Suszkiw JB. 1995. Multisite interactions between Pb^2 and protein kinase C and its role in norepinephrine release from bovine adrenal chromaffin cells. J Neurochem 64:2667-2673.

Tong S, Baghurst P, McMichael A, et al. 1996. Lifetime exposure to environmental lead and children's intelligence at 11-13 years: The Port Pirie cohort study. BMJ 312(7046):1569-1575.

Tong S, Baghurst PA, Sawyer MG, et al. 1998. Declining blood lead levels and changes in cognitive function during childhood. JAMA 280(22):1915-1919.

Tong S, McMichael AJ, Baghurst PA. 2000. Interactions between environmental lead exposure and sociodemographic factors on cognitive development. Arch Environ Health 55(5):330-355.

*Toriumi H, Kawai M. 1981. Free erythrocyte protoporphyrin (FEP) in a general population, workers exposed to low-level lead, and organic-solvent workers. Environ Res 25:310-316.

Torres-Sánchez LE, Berkowitz G, Lopez-Carrillo L, et al. 1999. Intrauterine lead exposure and preterm birth. Environ Res 81:297-301.

Toscano CD, Guilarte TR. 2005. Lead neurotoxicity: From exposure to molecular effects. Brain Res Brain Res Rev 49(3):529-554.

Treble RG, Thompson RS. 1997. Preliminary results of a survey of lead levels in human liver tissue. Bull Environ Contam Toxicol 59:688-695.

TRI04. 2006. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. October 23, 2006.

Triebig G, Weitle D, Valentin H. 1984. Investigations on neurotoxicity of chemical substances at the workplace: V. Determination of the motor and sensory nerve conduction velocity in persons occupationally exposed to lead. Int Arch Occup Environ Health 53:189-204.

Tripathi RK, Llewellyn GC. 1990. Deterioration of air quality in firing ranges: In: A review of airborne lead exposures. Biodeterioration research 3: Mycotoxins, biotoxins, wood decay, air quality, cultural properties, general biodeterioration, and degradation. New York, NY: Wiley and Sons, 445-457.

Tsaih SW, Korrick S, Schwartz J, et al. 2004. Lead, diabetes, hypertension, and renal function: The normative aging study. Environ Health Perspect 112(11):1178-1182.

Tsao D-A, Yu H-S, Cheng J-T, et al. 2000. The change of β-adrenergic system in lead-induced hypertension. Toxicol Appl Pharmacol 163:127-133.

Tulasi SJ, Reddy PUM, Rao JV. 1992. Accumulation of lead and effects on total lipids and lipid derivatives in the freshwater fish Anabas testudineus (Bioch). Ecotoxicol Environ Safety 23:33-38.

Tuppurainen M, Wagar G, Kurppa K. 1988. Thyroid function as assessed by routine laboratory tests of workers with long-term lead exposure. Scand J Work Environ Health 14:175-180.

Turlakiewicz Z, Chmielnicka J. 1985. Diethyllead as a specific indicator of occupational exposure to tetraethyllead. Br J Ind Med 42:682-685.

Tuthill RW. 1996. Hair lead levels related to children's classroom attention-deficit behavior. Arch Environ Health 51:214-220.

Ulmer DD, Vallee BL. 1969. Effects of Lead on Biochemical Systems. In: Hemphill DD, ed. Trace substances in environmental health. University of Missouri Press, 7-27.

Ündeger U, Basaran N, Canpinar H, et al. 1996. Immune alterations in lead-exposed workers. Toxicology 109(2-3):167-172.

USAF. 1995. The fate and behavior of lead alkyls in the subsurface environment. Tyndall AFB, FL: U.S. Air Force. AL/EQ-TR-1994-0026.

USGS. 2002. Lead: Recycling-metals. U.S. Geological Survey, 62.7. http://minerals.usgs.gov/minerals/pubs/commodity/recycle/recycmyb02r.pdf. March 28, 2005.

USGS. 2003. Lead. Minerals yearbook. U.S. Geological Survey. http://minerals.usgs.gov/minerals/pubs/commodity/lead/leadmyb03.pdf. March 28, 2005.

USGS. 2004. Lead. Mineral commodity summaries. U.S. Geological Survey http://minerals.usgs.gov/minerals/pubs/commodity/lead/index.html#mcs. April 3, 2005

Vaglenov A, Carbonell E, Marcos R. 1998. Biomonitoring of workers exposed to lead. Genotoxic effects, its modulation by polyvitamin treatment and evaluation of induced radioresistance. Mutat Res 418:79-92.

Vaglenov A, Creus A, Laltchev S, et al. 2001. Occupational exposure to lead and induction of genetic damage. Environ Health Perspect 109(3):295-298.

Valciukas JA, Lilis R, Eisinger J, et al. 1978. Behavioral indicators of lead neurotoxicity: Results of a clinical field survey. Int Arch Occup Environ Health 41:217-236.

Valentino M, Governa M, Marchiseppe I, et al. 1991. Effects of lead on polymorphonuclear luekocyte (PMN) functions in occupationally exposed workers. Arch Toxicol 65:685-688.

Valverde M, Fortoul TI, Diaz-Barriga F, et al. 2002. Genotoxicity induced in CD-1 mice by inhaled lead: Differential organ response. Mutagenesis 17(1):55-61.

Van Borm W, Wouters L, Van Grieken R, et al. 1990. Lead particles in an urban atmosphere: An individual particle approach. Sci Total Environ 90:55-66.

Van Esch EJ, Kroes R. 1969. The induction of renal tumors by feeding basic lead acetate to mice and hamsters. Br J Cancer 23:765-771.

Vasilios D, Theodor S, Konstantinos S, et al. 1997. Lead concentrations in maternal and umbilical cord blood in areas with high and low air pollution. Clin Exp Obstet Gynecol 24(4):187-189.

Vaziri ND, Ding Y. 2001. Effect of lead on nitric oxide synthase expression in coronary endothelial cells: Role of superoxide. Hypertension 37:223-226.

Vaziri ND, Sica DA. 2004. Lead-induced hypertension: Role of oxidative stress. Curr Hypertens Rep 6:314-320.

Vaziri ND, Ding Y Ni Z, et al. 1997. Altered nitric oxide metabolism and increased oxygen free radical activity of lead-induced hypertension: Effect of lazaroid therapy. Kidney Int 52:1042-1046.

Vaziri ND, Ding Y, Ni Z. 1999b. Nitric oxide synthase expression in the course of lead-induced hypertension. Hypertension 34:558-562.

Vaziri ND, Ding Y, Ni Z. 2001. Compensatory up-regulation of nitric-oxide synthase isoforms in lead-induced hypertension; reversal by a superoxide dismutase-mimetic drug. J Pharmacol Exp Ther 298(2):679-685.

Vaziri ND, Liang K, Ding Y. 1999a. Increased nitric oxide inactivation by reactive oxygen species in lead-induced hypertension. Kidney Int 56:1492-1498.

Verberk MM, Willems TE, Verplanke AJ, et al. 1996. Environmental lead and renal effects in children. Arch Environ Health 51(1):83-87.

Verschoor M, Wibowo A, Herber R, et al. 1987. Influence of occupational low-level lead exposure on renal parameters. Am J Ind Med 12:341-351.

Vesper SJ, Donovan-Brand R, Paris KP, et al. 1996. Microbial removal of lead from solid media and soil. Water Air Soil Pollut 86:207-219.

Victery W, Vander AJ, Markel LK, et al. 1982a. Lead exposure begun *in utero* decreases renin and angiotensin II in adult rats. Proc Soc Exp Biol Med 170:63-67.

Victery W, Vander AJ, Mouw DR. 1979. Effect of acid-base status on renal excretion and accumulation of lead in dogs and rats. Am J Physiol 6:F398-F407.

Victery W, Vander AJ, Shulak JM, et al. 1982b. Lead, hypertension, and the renin-angiotensin system in rats. J Clin Med 99:354-362.

Vieira I, Sonnier M, Cresteil T. 1996. Developmental expression of CYP2E1 in the human liver: Hypermethylation control of gene expression during the neonatal period. Eur J Biochem 238:476-483.

*Vimpani GV, Baghurst PA, Wigg NR, et al. 1989. The Port Pirie cohort study-Cumulative lead exposure and neurodevelopmental status at age 2 years: Do HOME scores and maternal IQ reduce apparent effects of lead on Bayley mental scores? In: Smith M, Grant LD, Sors A, eds. Lead exposure and child development: An international assessment. Hingham, MA: Kluwer Academic Press, 332-344.

Vincent JH, Werner MA. 2003. Critical evaluation of historical occupational aerosol exposure records: Applications to nickel and lead. Ann Occup Hyg 47(1):49-59.

Viverette L, Mielke HW, Brisco M, et al. 1996. Environmental health in minority and other underserved populations: Benign methods for identifying lead hazards at day care centers of New Orleans. Environ Geochem Health 18(1):41-45.

Volkening J, Baumann H, Heumann KG. 1988. Atmospheric distribution of particulate lead over the Atlantic Ocean from Europe to Antarctica. Atmos Environ 22:1169-1174.

*Voors AW, Johnson WD, Shuman MS. 1982. Additive statistical effects of cadmium and lead on heart related disease in a North Carolina autopsy series. Arch Environ Health 37:98-102.

Vupputuri S, He J, Muntner P, et al. 2003. Blood lead level is associated with elevated blood pressure in blacks. Hypertension 41:463-468.

Vural N, Duydu Y. 1995. Biological, monitoring of lead in workers exposed to tetraethyllead. Sci Total Environ 171:183-187.

Vyskocil A, Panci J, Tusl M, et al. 1989. Dose-related proximal tubular dysfunction in male rats chronically exposed to lead. J Appl Toxicol 9:395-400.

Waalkes MP, Klaassen CD. 1985. Concentration of metallothionein in major organs of rats after administration of various metals. Fund Appl Toxicol 5:473-477.

Waalkes MP, Diwan BA, Ward JM, et al. 1995. Renal tubular tumors and atypical hyperplasias in B6C3F1 mice. Cancer Res 55:5265-5271.

Waalkes MP, Harvey MJ, Klaassen CD. 1984. Relative in vitro affinity of hepatic metallothionein for metals. Toxicol Lett 20:33-39.

Wada O, Yano Y, Ono T, et al. 1973. The diagnosis of different degrees of lead absorption in special references to choice and evaluation of various parameters indicative of an increased lead absorption. Ind Health 11:55-67.

Wadi SA, Ahmad G. 1999. Effects of lead on the male reproductive system in mice. J Toxicol Environ Health A 56:513-521.

Wang EX, Bormann FH, Benoit G. 1995. Evidence of complete retention of atmospheric lead in the soils of northern hardwood forested ecosystems. Environ Sci Technol 29:735-739.

Wang L, Xu SE, Zhang GD, et al. 1989. Study of lead absorption and its effect on children's development. Biomed Environ Sci 2:325-330.

*Ward NI, Watson R, Brvce-Smith D. 1987. Placental element levels in relation to fetal development for obstetrically normal births: A study of 37 elements: Evidence for the effects of cadmium, lead, and zinc on fetal growth and for smoking as a source of cadmium. Int J Biosoc Res 9:63-81.

Wasserman GA, Factor-Litvak P, Liu X, et al. 2003. The relationship between blood lead, bone lead and child intelligence. Neuropsychol Dev Cogn C Child Neuropsychol 9(1):22-34.

Wasserman G, Graziano JH, Factor-Litvak P, et al. 1992. Independent effects of lead exposure and iron deficiency anemia on developmental outcome at age 2 years. J Pediatr 121(3):695-703.

Wasserman GA, Graziano JH, Factor-Litvack P, et al. 1994. Consequences of lead exposure and iron supplementation on childhood development at age 4 years. Neurotoxicol Teratol 16:233-240.

Wasserman GA, Liu X, Lolacono NJ, et al. 1997. Lead exposure and intelligence in 7-year-old children: The Yugoslavia prospective study. Environ Health Perspect 105(9):956-962.

Wasserman GA, Liu X, Popovac D, et al. 2000a. The Yugoslavia prospective lead study: Contributions of prenatal and postnatal lead exposure to early intelligence. Neurotoxicol Teratol 22:811-818.

Wasserman GA, Staghezza-Jaramillo B, Shrout P, et al. 1998. The effect of lead exposure on behavior problems in preschool children. Am J Public Health 88(3):481-486.

Watanabe H, Hu H, Rotnitzky A. 1994. Correlates of bone and blood lead levels in carpenters. Am J Ind Med 26:255-264.

Watson GE, Davis BA, Raubertas RF, et al. 1997. Influence of maternal lead ingestion on caries in rat pups. Nat Med 3(9):1024-1025.

Watson WS, Hume R, Moore MR. 1980. Oral absorption of lead and iron. Lancet 2:236-237.

Watson WS, Morrison J, Bethel MIF, et al. 1986. Food iron and lead absorption in humans. Am J Clin Nutr 44:248-256.

Watts SW, Chai S, Webb RC. 1995. Lead acetate-induced contraction in rabbit mesenteric artery: Interaction with calcium and protein kinase C. Toxicology 99:55-65.

Waxman HS, Rabinowitz M. 1966. Control of reticulocyte polyribosome content and hemoglobin synthesis by heme. Biochim Biophys Acta 129:369-379.

Weaver VM, Jaar BG, Schwartz BS, et al. 2005a. Associations among lead dose biomarkers, uric acid, and renal function in Korean lead workers. Environ Health Perspect 113(1):36-42.

Weaver VM, Lee BK, Ahn KD, et al. 2003a. Associations of lead biomarkers with renal function in Korean lead workers. Occup Environ Med 60:551-562.

Weaver VM, Lee BK, Todd AC, et al. 2005b. Associations of patella lead and other lead biomarkers with renal function in lead workers. J Occup Environ Med 47(3):235-243.

Weaver VM, Schwartz BS, Ahu KD, et al. 2003b. Associations of renal function with polymorphisms in the gamma-aminolevulinic acid dehydratase, vitamin D receptor, and nitric oxide synthase genes in Korean lead workers. Environ Health Perspect 111(13):1613-1619.

Wedeen RP. 1988. Bone lead, hypertension, and lead nephropathy. Environ Health Perspect 78:57-60.

Wedeen RP. 1990. *In vivo* tibial XFR measurement of bone lead. Arch Environ Health 45(2):69-71.

Wedeen RP. 1992. Removing lead from bone: Clinical implications of bone lead stores. Neurotoxicology 13:843-852.

Wedeen RP, Maesaka JK, Weiner B, et al. 1975. Occupational lead nephropathy. Am J Med 59:630-641.

Wedeen RP, Mallik DK. Batuman V. 1979. Detection and treatment of occupational lead nephropathy. Arch Intern Med 139:53-57.

Weis CP, LaVelle JM. 1991. Characteristics to consider when choosing an animal model for the study of lead bioavailability. Chem Speciat Bioavail 3:113-119.

Weisel C, Demak M, Marcus S, et al. 1991. Soft plastic bread packaging: Lead content and reuse by families. Am J Public Health 81(6):756-758.

Weiss ST, Munoz A, Stein A, et al. 1986. The relationship of blood lead to blood pressure in longitudinal study of working men. Am J Epidemiol 123:800-808.

Weiss ST, Munoz A, Stein A, et al. 1988. The relationship of blood lead to systolic blood pressure in a longitudinal study of policemen. Environ Health Perspect 78:53-56.

Weisskopf MG, Wright RO, Schwartz J, et al. 2004. Cumulative lead exposure and prospective change in cognition among elderly men: The VA Normative Aging Study. Am J Epidemiol 160(12):1184-1193.

Weitzman M, Aschengrau A, Bellinger D, et al. 1993. Lead-contaminated soil abatement and urban children's blood lead levels. JAMA 269(13):1647-1654.

Wells AC, Venn JB, Heard MJ. 1975. Deposition in the lung and uptake to blood of motor exhaust labelled with 203Pb. Inhaled Particles IV. Proceedings of a Symposium of the British Occupational Hygiene Society. Oxford, England: Pergamon Press, 175–189.

West JR, Smith HW, Chasis H. 1948. Glomerular filtration rate, effective renal blood flow, and maximal tubular excretory capacity in infancy. J Pediatr 32:10-18.

Wetmur JG, Lehnert G, Desnick RJ. 1991. The δ-aminolevulinate dehydratase polymorphism: Higher blood lead levels in lead workers and environmentally exposed children with 1-2 and 2-2 isozymes. Environ Res 56:109-119.

Whelan EA, Piacitelli GM, Gerwel B, et al. 1997. Elevated blood lead levels in children of construction workers. Am J Public Health 87(8):1352-1355.

White PD, Van Leeuwen P, Davis BD, et al. 1998. The conceptual structure of the integrated exposure uptake biokinetic model for lead in children. Environ Health Perspect 106:1513-1530.

White RF, Diamond R, Proctor S, et al. 1993. Residual cognitive deficits 50 years after lead poisoning during childhood. Br J Ind Med 50:613-622.

WHO. 1977. United Nations Environmental Programme: Lead: Environmental Health Criteria 3. Geneva, Switzerland: World Health Organization, 112.

WHO. 1995. Environmental transport, distribution and transformation. Geneva, Switzerland: World Health Organization, 60-65.

WHO. 2000. Air quality guidelines. 2nd edition. Geneva, Switzerland: World Health Organization. http://www.euro.who.int/air/Activities/20050104_1. February 15, 2005.

WHO. 2004. Guidelines for drinking-water quality. 3rd edition. Geneva, Switzerland: World Health Organization. http://www.who.int/water_sanitation_health/dwq/gdwq3/en/. February 15, 2005.

Wibberley DG, Khera AK, Edwards JH, et al. 1977. Lead levels in human placentae from normal and malformed births. J Med Genet 14:339-345.

Widdowson EM, Dickerson JWT. 1964. Chemical composition of the body. In: Comar CL, Bronner F, eds. Mineral metabolism: An advanced treatise. Volume II: The elements Part A. New York, NY: Academic Press.

Wielopolski L, Ellis K, Vaswani A, et al. 1986. *In vivo* bone lead measurements: A rapid monitoring method for cumulative lead exposure. Am J Ind Med 9:221-226.

*Wigg NR, Vimpani GV, McMichael AJ, et al. 1988. Port Pirie cohort study: Childhood blood lead and neuropsychological development at age two years. J Epidemiol Community Health 42:213-219.

Wildt K, Berlin M, Isberg PE. 1987. Monitoring of zinc protoporphyrin levels in blood following occupational lead exposure. Am J Ind Med 12:385-398.

Wildt K, Eliasson R, Berlin M. 1983. Effects of occupational exposure to lead on sperm and semen. In: Clarkson TW, Nordberg GF, Sager PR, eds. Reproductive and developmental toxicity of metals. Proceedings of a Joint Meeting, Rochester, NY. New York, NY: Plenum Press, 279-300.

Wilhelm M, Lombeck I, Hafner D, et al. 1989. Hair lead levels in young children from the F.R.G. J Trace Elem Electrolytes Health Dis 3:165-170.

Willems MI, Deschepper GG, Wibowo AAE, et al. 1982. Absence of an effect of lead acetate on sperm morphology, sister chromatid exchange or on micronuclei formation in rabbits. Arch Toxicol 50:149-157.

Williamson AM, Teo RKC. 1986. Neurobehavioral effects of occupational exposure to lead. Br J Ind Med 43:374-380.

Willoughby RA, MacDonald E, McSherry BJ, et al. 1972. Lead and zinc poisoning and the interaction between Pb and Zn poisoning in the foal. Can J Comp Med 36:348-359.

Winneke G, Kraemer U. 1984. Neuropsychological affects of lead in children: Interactions with social background variables. Neuropsychobiology 11:195-202.

Winneke G, Altmann L, Kramer U, et al. 1994. Neurobehavioral and neurophysiological observations in six year old children with low lead levels in East and West Germany. Neurotoxicology 15(3):705-713.

*Winneke G, Beginn U, Ewert T, et al. 1985a. Comparing the effects of perinatal and later childhood lead exposure on neurophysiological outcome. Environ Res 38:155-167.

*Winneke G, Brockhaus A, Collet W, et al. 1985b. Predictive value of different markers of lead-exposure for neuropsychological performance. In: Lekkas TD, ed. International Conference on Heavy Metals in the Environment, Athens, Greece. September, Vol. 1. Edinburgh, United Kingdom: CEP Consultants, Ltd., 44-47.

Winneke G, Brockhous A, Ewers U, et al. 1990. Results from the European multicenter study on lead neurotoxicity in children: Implications for risk assessment. Neurotoxicol Teratol 12:553-559.

Winneke G, Lilienthal H, Kramer U. 1996. The neurobehavioural toxicology and teratology of lead. Arch Toxicol Suppl 18:57-70.

Wisconsin Department of Health and Family Services. 2002. Lead arsenate pesticides. Madison, WI: Department of Health and Family Services.

Witzmann FA, Fultz CD, Grant RA, et al. 1999. Regional protein alterations in rat kidneys induced by lead exposure. Electrophoresis 20:943-951.

*Wolf AW, Ernhart CB, White CS. 1985. Intrauterine lead exposure and early development. In: Lekkas TD, ed. International conference: Heavy metals in the environment, Athens, Greece, Vol. 2. Edinburgh, UK: CEP Consultants, Ltd., 153-155.

Wolf AW, Jimenez E, Lozoff B. 1994. No evidence of developmental III effects of low-level lead exposure in a developing country. Develop Behav Pediatr 15(4):224-231.

Wolf C, Wallnöfer A, Waldhor T, et al. 1995. Effect of lead on blood pressure in occupationally nonexposed men. Am J Ind Med 27:897-903.

Wolff MS. 1983. Occupationally derived chemicals in breast milk. Am J Ind Med 4:259-281.

Wolnik KA, Fricke FL, Capar SG, et al. 1983a. Elements in major raw agricultural crops in the United States. 1. Cadmium and lead in lettuce, peanuts, potatoes, soybeans, sweet corn, and wheat. J Agric Food Chem 31:1240-1244.

Wolnik KA, Fricke FL, Capar SG, et al. 1983b. Elements in major raw agricultural crops in the United States. 3. Cadmium, lead, and eleven other elements in carrots, field corn, onions, rice, spinach, and tomatoes. J Agric Food Chem 33:807-811.

Wong O, Harris F. 2000. Cancer mortality study of employees at lead battery plants and lead smelters, 1947-1995. Am J Ind Med 38:255-270.

Woźniak K, Blasiak J. 2003. In vitro genotoxicity of lead acetate: Induction of single and double DNA strand breaks and DNA-protein cross-links. Mutat Res 535:127-139.

Wright LS, Kornguth SE, Oberley TD. 1998. Effects of lead on glutathione S-transferase expression in rat kidney: A dose-response study. Toxicol Sci 46:254-259.

Wright RO, Hu H, Silverman EK, et al. 2003a. Apolipoprotein E genotype predicts 24-month bayley scales infant development score. Pediatr Res 54(6):819-825.

Wright RO, Silverman EK, Schwartz J, et al. 2004. Association between hemochromatosis genotype and lead exposure among elderly men: The normative aging study. Environ Health Perspect 112(6):746-750.

Wright RO, Tsaih SW, Schwartz J, et al. 2003b. Association between iron deficiency and blood lead level in a longitudinal analysis of children followed in an urban primary care clinic. J Pediatr 142:9-14.

Wright RO, Tsaih SW, Schwartz J, et al. 2003c. Lead exposure biomarkers and mini-mental status exam scores in older men. Epidemiology 14(6):713-718.

Wu FY, Chang PW, Wu CC, et al. 2002. Correlations of blood lead with DNA-protein cross-links and sister chromatid exchanges in lead workers. Cancer Epidemiol Biomarkers Prev 11:287-290.

Wu MT, Kelsey K, Schwartz J. 2003a. A δ-aminolevulinic acid dehydratase (ALAD) polymorphism may modify the relationship of low-level lead exposure to uricemia and renal function: The Normative Aging Study. Environ Health Perspect 111(3):335-340.

Wu T, Buck GM, Mendola P. 2003b. Blood lead levels and sexual maturation in U.S. girls: The Third National Health and Nutrition Examination Survey, 1988-1994. Environ Health Perspect 111(5):737-741.

Wu T, Yang K-C, Wang C-M. 1996. Lead poisoning caused by contaminated Cordyceps, a Chinese herbal medicine: Two case reports. Sci Total Environ 182:193-195.

Xian X. 1989. Response of kidney bean to concentration and chemical form of cadmium, zinc, and lead in polluted soils. Environ Pollut 57:127-137.

Xie Y, Chiba M, Shinohara A, et al. 1998. Studies on lead-binding protein and interaction between lead and selenium in the human erythrocytes. Ind Health 36:234-239.

Xu GB, Yu CP. 1986. Effects of age on deposition of inhaled aerosols in the human lung. Aerosol Sci Technol 5:349-357.

Xu Y, Liang Y. 1997. Combined nickel and phosphate modifier for lead determination in water by electrothermal atomic absorption spectrometry. J Anal Atom Spectrom 12(4):471-474.

Yankel AJ, von Lindern IH, Walter SD. 1977. The Silver Valley lead study: The relationship of childhood lead poisoning and environmental exposure. J Air Pollut Contr Assoc 27:763-767.

Yassin AS, Martonik JF, Davidson JL. 2004. Blood lead levels in U.S. workers, 1988-1994. J Occup Environ Med 46:720-728.

Yeh JH, Chang YC, Wang JD. 1995. Combined electroneurographic and electromyographic studies in lead workers. Occup Environ Med 52(6):415-419.

Yip R, Norris TN, Anderson AS. 1981. Iron status of children with elevated blood lead concentrations. J Pediatr 98:922-925.

Yokoyama K, Araki S, Murata K, et al. 1997. Subclinical vestibulo-cerebellar, anterior cerebellar lobe and spinocerebellar effects in lead workers in relation to concurrent and past exposure. Neurotoxicology 18(2):371-380.

Yokoyama K, Araki S, Yamashita K, et al. 2002. Subclinical cerebellar anterior lobe, vestibulo-cerebellar and spinocerebellar afferent effects in young female lead workers in China: Computerized posturography with sway frequency analysis and brainstem auditory evoked potentials. Ind Health 40:245-253.

Yu CC, Lin JL, Lin-Tan DT. 2004. Environmental exposure to lead and progression of chronic renal diseases: A four-year prospective longitudinal study. J Am Soc Nephrol 15:1016-1022.

Zaragoza L, Hogan K. 1998. The integrated exposure uptake biokinetic model for lead in children: Independent validation and verification. Environ Health Perspect 106(6):1551-1556.

Zawia NH, Crumpton T, Brydie M, et al. 2000. Disruption of the zinc finger domain: A common target that underlies many of the effects of lead. Neurotoxicology 21(6):1069-1080.

Zelikoff JT, Li JH, Hartwig A, et al. 1988. Genetic toxicology of lead compounds. Carcinogenesis 9:1727-1732.

Zhang W, Zhang GG, He HZ, et al. 1994. Early health effects and biological monitoring in persons occupationally exposed to tetraethyllead. Int Arch Occup Environ Health 65:395-399.

Zhang Z-W, Shimbo S, Ochi N, et al. 1997. Determination of lead and cadmium in food and blood by inductively coupled plasma mass spectrometry: A comparison with graphite furnace atomic absorption spectrometry. Sci Total Environ 205(2-3):179-187.

Ziegler EE, Edwards BB, Jensen RL, et al. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

Zimmerman-Tanselia C, Campara P, D'Andrea F, et al. 1983. Psychological and physical complaints of subjects with low exposure to lead. Hum Toxicol 2:615-623.

Zollinger HU. 1953. [Kidney adenomas and carcinomas in rats caused by chronic lead poisoning and their relationship to corresponding human neoplasms.] Virchows Arch A Pathol Anat 323:694-710. (German)

Zou C, Zhao Z, Tang L, et al. 2003. The effect of lead on brainstem auditory evoked potentials in children. Chin Med J 116(4):565-568.

10. 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 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)—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—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—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 that 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 of people that 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.

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

Immunological Effects—Functional changes in the immune response.

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.

***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 that 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 that 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 (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that 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 OR of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

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—The dynamic behavior of a material in the body, used to predict 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—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, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that 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—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, such 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) concentration 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 causal 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 group.

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 minutes continually. No more than four excursions are allowed per day, and there must be at least 60 minutes between exposure periods. The daily Threshold Limit Value-Time Weighted Average (TLV-TWA) may not be exceeded.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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 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 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis, 3 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 100-fold 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 and Environmental Medicine, expert panel peer reviews, and agency-wide 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 and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

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

Relevance to Public Health

This chapter 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 chapter covers end points in the same order that they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, and 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 chapter.

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 Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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.

MRLs 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, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "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 that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive end point 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 end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (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 levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See Sample LSE Table 3-1 (page B-6)

(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. Typically when sufficient data exist, 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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) 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 two "18r" data points in sample Figure 3-1).

(5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "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 regimens 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 “Chemical x” via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.

(8) NOAEL. A 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 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 end point 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 9 of the profile.

(11) CEL. A 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Sample Figure 3-1 (page B-7)

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 acute and intermediate 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, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. 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 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL 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

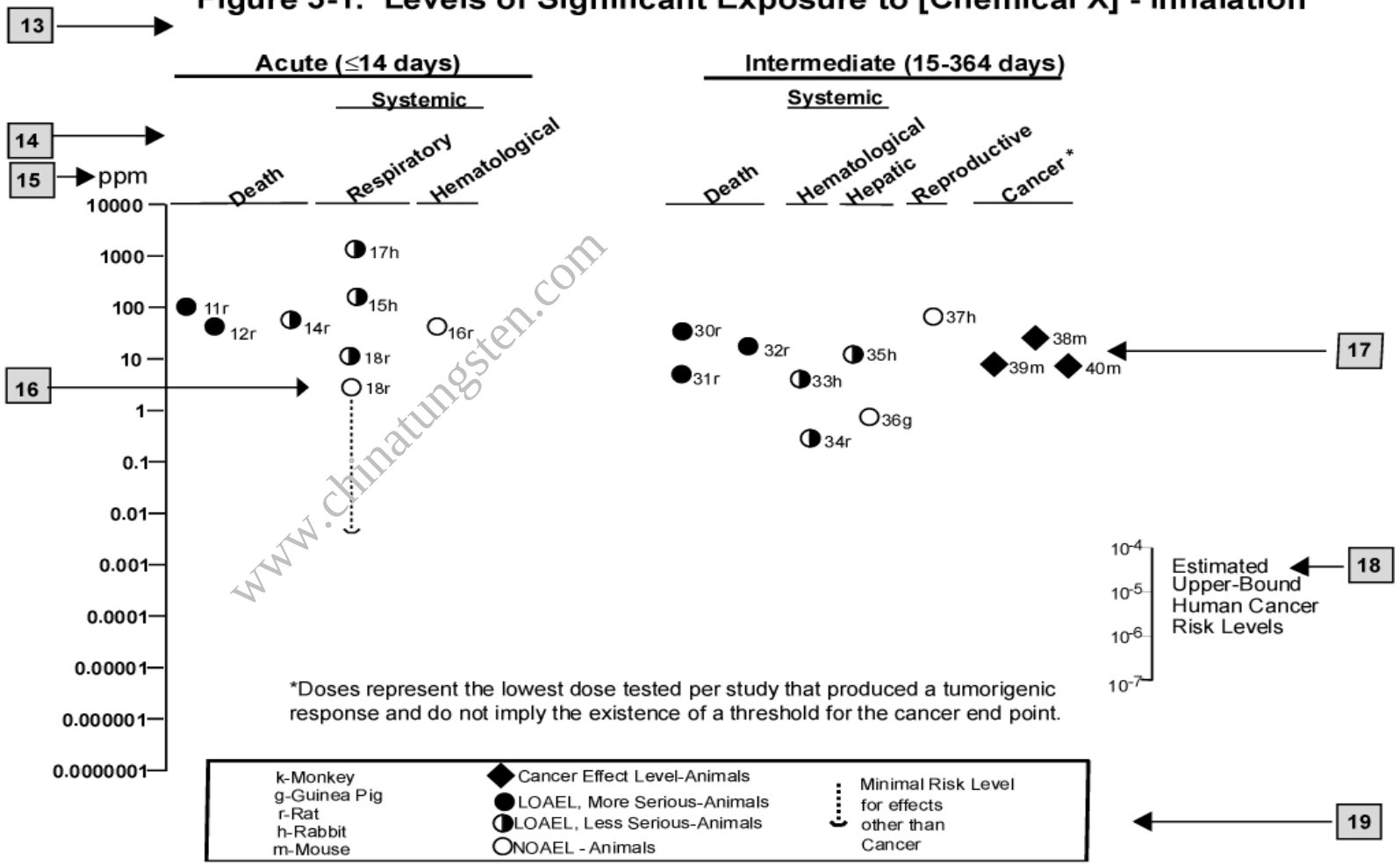
1 → **Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
4 → CHRONIC EXPOSURE							
Cancer					11		
					↓		
38	Rat	18 mo 5 d/wk 7 hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

12 → [a] The number corresponds to entries in Figure 3-1.
[b] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of $5x10^{-3}$ 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).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
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
BMD	benchmark dose
BMR	benchmark response
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
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
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/Intergovernmental 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
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
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_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
MA	*trans,trans*-muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
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
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
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
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
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
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized 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 carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

>	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

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APPENDIX D. 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 PbBs 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 PbBs 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

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

[1]The weight of evidence suggests that PbBs 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).

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 (Baltrop 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 1990; 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 µg Pb/kg		
Mixed	0.002–0.016	Review of the literature	Reagan and Silbergeld 1990
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 µg/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 PbBs 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 PbBs, and the actual PbBs 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 µg/m^3	Eldred and Cahill 1994
Indoor Air	0.03–0.06 µg/m^3 (0.3 x outdoor concentration)	EPA 1986
Food	5 µg/day	Bolger et al. 1991
Water	4 µg/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 (µg/m^3)	0.06-0.2	0.06-0.2	0.06-0.2
Water (µg/L)	1	1	1
Food (µg/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 (µg/dL)	**B** contribution to PbB (µg/dL)	**C** contribution to PbB (µg/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 (µg/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 PbBs 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 PbBs 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 PbBs. 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 PbBs.

Pharmacokinetic models have been developed that attempt to relate environmental levels to PbBs (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 PbBs 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 PbBs. 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.

References

Abadin HG, Wheeler JS. 1993. Guidance for risk assessment of exposure to lead: A site-specific, multi-media approach. In: Hazardous waste and public health: International congress on the health effects of hazardous waste. Princeton, NJ: Princeton Scientific Publishing Company, Inc., 477-485.

Angle CR, Marcus A, Cheng I-H, McIntire MS. 1984. Omaha childhood blood lead and environmental lead: A linear total exposure model. Environ Res 35:160-170.

ATSDR. 1992. Public health assessment guidance manual. US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Atlanta, GA.

ATSDR. 1993. Toxicological profile for lead. Atlanta, GA: US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

ATSDR. 1995. Multisite lead and cadmium exposure study with biological markers incorporated. Atlanta, GA: US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

ATSDR. 1996a. 1995 CERCLA priority list of hazardous substances that will be the subject of toxicological profiles and support document. Atlanta, GA: US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry.

ATSDR. 1996b. Minimal risk levels for priority substances and guidance for derivation; republication. Federal Register, Vol. 61, No. 125, June 27, 1996.

Aungst BJ, Dolce JA, Fung H-L. 1981. The effect of dose on the disposition of lead in rats after intravenous and oral administration. Toxicol Appl Pharmacol 61:48-57.

Azar A, Snee RD, Habibi K. 1975. An epidemiologic approach to community air lead exposure using personal air samplers. In: Griffin TB, Knelson JH, eds. Lead. Stuttgart, West Germany: Georg Thieme Publishers, 254-290.

Baker EL, Hayes CG, Landrigan PH, et al. 1977. A nationwide survey of heavy metal absorption in children living near primary copper, lead, and zinc smelters. Am J Epidemiol 106(4):261-273.

Barltrop D, Strehlow CD, Thorton I, et al. 1974. Significance of high soil lead concentrations for childhood lead burdens. Environ Health Perspect 7:75-82.

Barltrop D, Meek F. 1979. Effect of particle size on lead absorption from the gut. Arch Environ Health 34:280-285.

Bolger PM, Carrington CD, Capar SG, Adams MA. 1991. Reductions in dietary lead exposure in the United States. Chemical Speciation and Bioavailability 3(3/4):31-36.

Brewer GJ, Hill GM, Dick RD, et al. 1985. Interactions of trace elements: Clinical significance. J Am Coll Nutr 4:33-38.

Brunekreef BD. 1984. The relationship between air lead and blood lead in children: A critical review. Sci Total Environ 38:79-123.

Cerklewski FL, Forbes RM. 1976. Influence of dietary zinc on lead toxicity in the rat. J Nutr 106:689-696.

Chaney RL, Mielke HW, Sterrett SB. 1989. Speciation, mobility and bioavailability of soil lead. Environ Geochem Health 9[Suppl]:105-129.

CDC. 1991. Preventing lead poisoning in young children. Atlanta, GA: US Department of Health and Human Services, Public Health Service, Centers for Disease Control.

CDC. 1997. Screening young children for lead poisoning: Guidance for state and local public health officials-DRAFT. Atlanta, GA: US Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention.

Cools A, Salle HJA, Verberk MM, et al. 1976. Biochemical response of male volunteers ingesting inorganic lead for 49 days. Int Arch Occup Environ Health 38:129-139.

Davis MJ. 1990. Risk assessment of the developmental neurotoxicity of lead. Neurotoxicology 11:285-292.

De Rosa CT, Choudhury H, Peirano WB. 1991. An integrated exposure/pharmacokinetic based approach to the assessment of complex exposures: Lead: A case study. Toxicol Ind Health 7(4):231-247.

Duggan MJ, Inskip MJ. 1985. Childhood exposure to lead in surface dust and soil: A community health problem. Public Health Rev 13:1-54.

Eldred RA, Cahill TA. 1994. Trends in elemental concentrations of fine particles at remote sites in the United Sates of America. Atmos Environ 28:1009-1019.

EPA. 1986. Air quality criteria for lead. Research Triangle Park, NC: US Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. EPA 600/8-83-028F.

EPA. 1991. Maximum contaminant level goals and national primary drinking water regulations for lead and copper. Federal Register 56:26461-26564.

EPA. 1990. Uptake of lead from formula and food by infants: Reanalysis of the Ryu et al. data. Draft final report. US Environmental Protection Agency, Office of Pesticides and Toxic Substances Exposure Evaluation Division, Office of Toxic Substances.

EPA. 1994. Guidance manual for integrated exposure uptake biokinetic model for lead in children. US Environmental Protection Agency, Office of Solid Waste and Emergency Response. EPA/540/R-93/081.

Goyer RA. 1986. Toxic effect of metals. In: Klaassen CD, et al., eds. Casarett and Doull's Toxicology: The basic science of poisons. 3rd ed. New York, NY: Macmillan Publishing Co, 582-588, 598-605.

Griffin TB, Coulston F, Golberg L, et al. 1975. Clinical studies on men continuously exposed to airborne particulate lead. In: Griffin TB, Knelson JG, eds. Lead. Stuttgart, West Germany: Georg Thieme Publisher, 221-240.

Grobler SR, Rossouw RJ, Kotze D. 1988. Effect of airborne lead on the blood lead levels of rats. S Afr J Sci 84:260-262.

Gulson BL, Davis JJ, Mizon KJ, Korsch MJ, Law AJ. 1994. Lead bioavailability in the environment of children: Blood lead levels in children can be elevated in a mining community. Arch Environ Health 49(5):326-331.

Haeger-Aronsen B, Schutz A, Abdulla M. 1976. Antagonistic effect *in vivo* of zinc on inhibition of δ-aminolevulinic acid dehydratase by lead. Arch Environ Health 31(4):215-220.

Heard MJ, Chamberlain AC. 1982. Effect of minerals and food on uptake of lead from the gastrointestinal tract in humans. Hum Toxicol 1:441-415.

Hemphill CP, Ruby MV, Beck BD, Davis A, Bergstrom PD. 1991. The bioavailability of lead in mining wastes: physical/chemical considerations. Chem Speciation and Bioavailability 3(3/4):135-148.

Hodgkins DG, Robins TG, Hinkamp DL, et al. 1992. A longitudinal study of the relation of lead in blood to lead in air concentrations among battery workers. Br J Ind Med 49:241-248.

James HM, Hilburn ME, Blair JA. 1985. Effects of meals and meal times on uptake of lead from the gastrointestinal tract in humans. Hum Toxicol 4:401-407.

Johnson NE, Tenuta K. 1979. Diets and lead blood levels of children who practice pica. Environ Res 18:369-376.

Lacey RF, Moore MR, Richards WN. 1985. Lead in water, infant diet and blood: The Glasgow duplicate diet stud. Sci Total Environ 41:235-257.

Laxen DP, Raab GM, Fulton M. 1987. Children's blood lead and exposure to lead in household dust and water--a basis for an environmental standard for lead in dust. Sci Total Environ 66:235-244.

Leggett RW. 1993. An age-specific kinetic model of lead metabolism in humans. Environ Health Perspect 101:598-616.

Mahaffey KR, Rosen JF, Chesney RW, et al. 1982. Association between age, blood lead concentration, and serum 1,25-dihydroxycholecalciferol levels in children. Am J Clin Nutr 35:1327-1331.

Morrow PE, Beiter H, Amato F, Gibb FR. 1980. Pulmonary retention of lead: An experimental study in man. Environ Res 21:373-384.

Mumtaz MM, Cibulas W, De Rosa CT. 1995. An integrated framework to identify significant human exposures (SHELs). Chemosphere 31(1):2485-2498.

Mushak P. 1991. Gastro-intestinal absorption of lead in children and adults: Overview of biological and biophysico-chemical aspects. Chem Speciation and Bioavailability 3(3/4):87-104.

O'Flaherty EJ. 1995. Physiologically based models for bone-seeking elements. V Lead absorption and disposition in childhood. Toxicol Appl Pharmacol 131:297-308.

Pocock SJ, Shaper AG, Walker M, et al. 1983. Effects of tap water lead, water hardness, alcohol, and cigarettes on blood lead concentrations. J Epidemiot Communitv Health 37:1-7.

Rabinowitz MB, Wetherill GW, Kopple JD. 1976. Kinetic analysis of lead metabolism in healthy humans. J Clin Invest 58:260-270.

Reagan PL, Silbergeld EK. 1990. Establishing a health based standard for lead in residential soils. Trace Subst Environ Health 23:199-238.

Roberts TM, Hutchinson TC, Paciga J. 1974. Lead contamination around secondary smelters: Estimation of dispersal and accumulation by humans. Science 186:1120-1123.

Roels HA, Buchet J-P, Lauwerys RR, et al. 1980. Exposure to lead by the oral and the pulmonary routes of children living in the vicinity of a primary lead smelter. Environ Res 22:81-94.

Ryu JE, Ziegler EE, Nelson SE, Fomon SJ. 1983. Dietary intake of lead and blood lead concentration in early infancy. Am J Dis Child 137:886-891.

Shacklette HT and Boerngen JG. 1972. Elemental composition of surficial materials in the conterminous United States. Washington DC: US Department of the Interior, Geological Survey; Geological Survey professional paper no. 1270.

Sherlock JC, Smart G, Forbes GI, et al. 1982. Assessment of lead intakes and dose-response for a population in Ayr exposed to a plumbosolvent water supply. Human Toxicol 1:115-122.

Sorrell M. Rosen JF, Roginsky M. 1977. Interactions of lead, calcium, vitamin D, and nutrition in lead burdened children. Arch Environ Health 32:160-164.

Stark AD, Quah RF, Meigs JW, et al. 1982. The relationship of environmental lead to blood-lead levels in children. Environ Res 27:372-383.

Steele MJ, Beck BD, Murphy BL, Strauss HS. 1990. Assessing the contribution from lead in mining wastes to blood lead. Regul Toxicol Pharmacol 11:158-190.

Stern AH. 1996. Derivation of a target concentration of Pb in soil based on elevation of adult blood pressure. Risk Analysis 16:201-210.

Stuik EJ. 1974. Biological response of male and female volunteers to inorganic lead. Int Arch Arbeitsmed 33:83-97.

Xintaras C. 1992. Analysis paper: Impact of lead-contaminated soil on public health. US Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry. Atlanta, GA.

Yankel AJ, von Lindern IH, Walter SD. 1977. The Silver Valley lead study: The relationship of childhood lead poisoning and environmental exposure. J Air Pollut Contr Assoc 27:763-767.

Ziegler EE, Edwards BB, Jensen RL, Mahaffey KR, Fomon SJ. 1978. Absorption and retention of lead by infants. Pediatr Res 12:29-34.

APPENDIX E. INDEX