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7. INTEGRATIVE SYNTHESIS: MULTIMEDIA LEAD EXPOSURE, HUMAN HEALTH EFFECTS, AND ECOSYSTEM EFFECTS

7.1 INTRODUCTION

This integrative synthesis is structured to provide a coherent framework to support the assessment of multimedia exposures, human health risks, and ecological effects associated with ambient airborne lead (Pb) in the United States. The main goal of the chapter is to integrate newly available scientific information with key findings and conclusions from the 1986 Air Quality Criteria Document (Pb AQCD) and its associated Addendum (U.S. Environmental Protection Agency, 1986a,b), and their 1990 Supplement (U.S. Environmental Protection Agency, 1990), to address issues central to the EPA's assessment of evidence needed to support the current ongoing periodic review of the Pb NAAQS. The integrated assessment of key findings and conclusions provided here and elsewhere in this document provides key inputs to further analyses of such findings and their policy implications as delineated in a Lead Staff Paper prepared by EPA's Office of Air Quality Planning and Standards (OAQPS). The analyses provided in that Staff Paper aim to "bridge the gap" between scientific assessments in this criteria document and judgments required of the EPA administrator in evaluating whether to retain or, possibly, to revise the current primary and/or secondary Pb NAAQS.

7.1.1 Historical Background

In 1971, U.S. EPA promulgated national ambient air quality standards for several major "criteria" pollutants (see Federal Register, 1971), but did not include Pb among them at that time. Later, on October 5, 1978, the EPA promulgated primary and secondary Pb NAAQS under Section 109 of the CAA (43 FR 46258), as announced in the Federal Register (1979). Identical primary and secondary Pb standards were then established as: 1.5 $\mu g/m^3$ as a calendar quarterly average (maximum arithmetic mean averaged over 90 days). Those standards were based on scientific assessments in EPA's original *Air Quality Criteria for Lead* (U.S. Environmental Protection Agency, 1977) or "1977 Pb AQCD."

In 1986, the EPA published a revised Pb AQCD (U.S. Environmental Protection Agency, 1986a), which assessed newly available scientific information on health and welfare effects associated with exposure to various concentrations of Pb in ambient air, based on literature published through 1985. That 1986 document mainly assessed the health and welfare effects of Pb, but other scientific data were also discussed in order to provide a better understanding of the pollutant in the environment. Thus, the 1986 Pb AQCD included chapters that discussed the atmospheric chemistry and physics of the pollutant; analytical approaches; environmental concentrations; human exposure and dosimetry; physiological, toxicological, clinical, and epidemiological aspects of Pb health effects; and Pb effects on ecosystems. An Addendum to the 1986 Pb AQCD was also published along with it (U.S. Environmental Protection Agency, 1986b). Then, a Supplement to the 1986 Pb AQCD/Addendum was published by EPA in 1990 (U.S. Environmental Protection Agency, 1990a). That 1990 Supplement evaluated still newer information emerging in the published literature concerning (a) Pb effects on blood pressure and other cardiovascular endpoints and (b) the effects of Pb exposure during pregnancy or during the early postnatal period on birth outcomes and/or on the neonatal physical and neuropsychological development of infants and children.

The evaluations in the 1986 Pb AQCD/Addendum and the 1990 Supplement provided scientific inputs to support decision-making regarding CAA-mandated periodic review and, as appropriate, revision of the Pb NAAQS; and they were drawn upon in preparation of an associated OAQPS Lead Staff Paper (U.S. Environmental Protection Agency, 1990b). Based on the scientific assessment in the 1986 Pb AQCD/Addendum and the 1990 Supplement, as well as associated exposure/risk analyses, the 1990 Staff Paper recommended that the Administrator consider options for revision of the Pb NAAQS to a level in the range of 0.5 to 0.75 $\mu g/m^3$ (30-day arithmetic mean). After consideration of those evaluations, EPA chose not to propose revision of the Pb NAAQS. At the time, as part of a broad, integrated U.S. EPA Strategy for Reducing Lead Exposures (U.S. Environmental Protection Agency, 1991), the Agency focused efforts on regulatory and remedial clean-up actions aimed at reducing Pb exposures from a variety of non-air sources judged to pose more significant public health risks to U.S. populations than remaining air emission sources. By 1990, average ambient air Pb levels had dropped to 0.15 to 0.25 $\mu g/m^3$ across U.S. urban areas due to the phasedown of Pb in gasoline.

7.1.2 Chapter Organization

The ensuing chapter sections collectively address the following topics: (1) ambient airborne lead compounds, sources, emissions, and air quality; (2) ambient Pb exposures pathways and dosimetric considerations; (3) epidemiologic and toxicologic evidence for associations between Pb exposure of human populations and various health effects, demonstrating a broad array of pathophysiologic responses of humans and animals to acute and chronic Pb exposures; (4) characterization of applicable dose-response relationships for various types of Pb-exposure effects; (5) persistence of various key types of Pb effects; (6) delineation of factors that enhance or lessen susceptibility or vulnerability to Pb health effects; (7) the identification of susceptible and vulnerable human population groups likely at increased risk for Pb-related health effects; and (8) delineation of ecological effects of Pb.

7.2 OVERVIEW OF MULTIMEDIA LEAD, SOURCES, EMISSIONS, AND CONCENTRATIONS IN THE UNITED STATES

Lead has been observed in measurable quantities in nearly every environmental medium all over the world. Human exposure to Pb occurs through several routes, as shown in Figure 7-1. This is a simplified diagram of the various routes of exposure through the different environmental media, with a focus on the ambient air. The multimedia aspects of Pb exposure can be seen in that Pb emissions to the air contribute to Pb concentrations in water, soil, and dusts; Pb in soil and dust also can make important contributions to Pb concentrations in ambient air. The relative contributions of Pb from different media and different sources on human exposure depend on factors such as the proximity of major sources to the residence and workplace of the individual, the condition of the residence (especially the presence and condition of lead-based paint) and whether the residence is in an urban, suburban, or rural location. This section briefly summarizes available evidence concerning multimedia Pb sources and exposure pathways, with main emphasis on pathways involving airborne Pb components.

7.2.1 Sources of Lead Emissions into Ambient Air

In ambient air, Pb occurs mainly as a component of organometallic compounds and various salts or other compounds (as summarized in Chapter 2, Section 2.1) rather than as

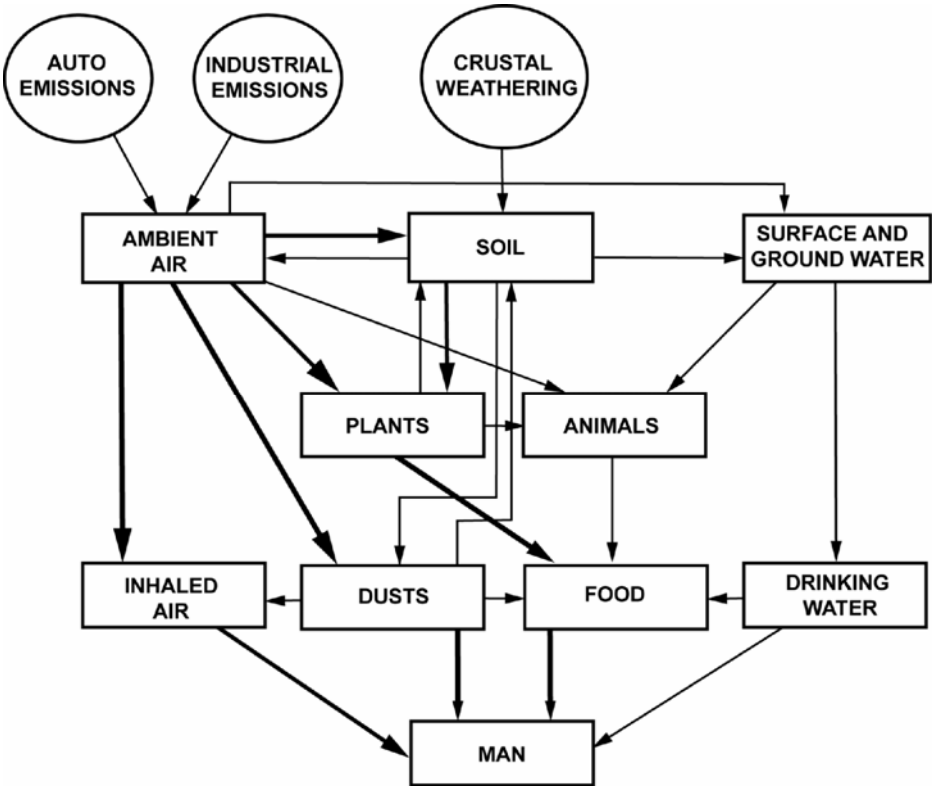

Figure 7-1. Principal pathways of lead from the environment to human consumption. Heavy arrows are those pathways discussed in greatest detail in this chapter.

elemental Pb because, at ambient atmospheric temperatures, elemental Pb deposits to surfaces or forms a component of atmospheric aerosol. Those salts and covalently bound Pb compounds that are of significance in the environment include: sulfates ($PbSO_4$); chlorides ($PbCl_2$); carbonates ($PbCO_3$, $Pb(HCO_3)_2$); hydroxides ($Pb(OH)_2$); nitrates ($Pb(NO_3)_2$); phosphates ($PbPO_4$, $Pb(HPO_4)_2$); oxides (PbO, Pb_3O_4), silicates, and PbS. With the exception of the covalently-bound sulfide and oxide, these compounds are derived from acids (or the related anions) that are common in the environment, such as sulfuric acid (H_2SO_4), nitric acid (HNO_3), carbonic acid (H_2CO_3, an acid that forms when CO_2 dissolves in water), and phosphoric acid (H_3PO_4). Lead salts, once formed, tend to be only slightly soluble in neutral solutions, but are quite soluble in the presence of acid. Another form of Pb-containing compounds is the tetravalent Pb (IV) organometallic compounds, such as the well-known fuel additives, tetramethyllead (TML) and tetraethyllead (TEL).

Natural sources of Pb emissions to the air include volcanoes, sea-salt spray, biogenic sources, forest fires, and wind-blown soil (in areas not affected by anthropogenic sources). There is significant variability in Pb emissions from these sources, but it has been estimated that they contribute 10 to 20 thousand tons per year in annual emissions of Pb, worldwide (see Chapter 2, Section 2.2.1). In addition to the typically relatively limited inputs of natural sources to ambient air, Pb emitted into the air from a wide variety of anthropogenic sources can contribute to human exposure via a number of often interlinking multimedia exposure pathways, as illustrated in Figure 7-1 and discussed below.

Historically, mobile sources constituted a major source of Pb emissions into the ambient air, due to the use of leaded gasoline (Section 2.2.4). Although its phase down began in 1974, some Pb was still added to gasoline in the United States as an anti-knock additive at the time of 1986 Lead AQCD/Addendum. Accordingly, airborne Pb concentrations nationwide have fallen dramatically over the past 20 years; and this represents one of the most important public and environmental health successes in history. Remaining mobile source-related emissions of Pb include brake wear, resuspended road dust, and emissions from vehicles that continue to use leaded gasoline (e.g., some types of race cars and aircraft).

The dramatic decreases in Pb emissions to U.S. ambient air during recent decades, including the notable decreases in Pb emissions from mobile sources, are shown in Figure 7-2. Nationwide, ambient air Pb emissions fell 98% between 1970 and 2002 (U.S. Environmental Protection Agency, 2003), primarily due to elimination of alkyl lead additives to automotive gasoline. The decreasing contributions of mobile sources to ambient airborne Pb have been documented by National Emissions Inventory data for Pb emissions from various sources for the United States in 1990 and 2002 (see Table 2-8). In 1990, mobile sources still constituted the largest single source of U.S. Pb emissions, even though substantial reductions in airborne Pb had already occurred due to the phasedown of Pb in gasoline. However, the emissions inventory data from 2002 show that, while mobile sources continue to make some contributions to Pb emissions, industrial sources now play a much more significant proportional role (as can be seen in Table 2-8).

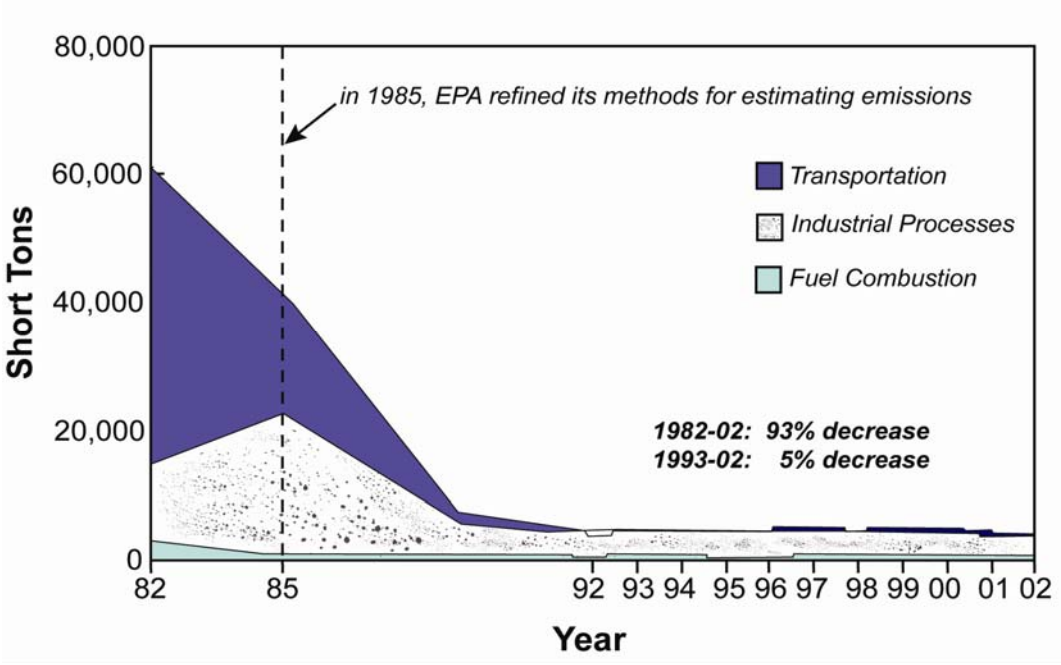

Figure 7-2. Trends in U.S. air lead emissions during the 1982 to 2002 period.

Source: U.S. Environmental Protection Agency (2003).

As discussed in Section 2.2.2, the largest Pb emitters into the ambient air are now in the manufacturing sector, which includes iron and steel foundries, primary and secondary smelters, Pb-acid battery plants, Pb-alloy production facilities, and other, mainly, stationary sources of Pb emissions to the air. Combustion sources are also a substantial source of Pb emissions in the United States. Such sources include energy generation, through coal and fuel oil combustion, or wood combustion and hazardous or solid waste incineration. Other stationary sources of airborne Pb emissions include smelters for other metals, such as copper or nickel, Pb-acid battery manufacturing, cement manufacturing and mining or processing of Pb.

One observation that can be drawn from the data on trends in Pb emissions is that currently the occurrence of airborne Pb concentrations in the United States is influenced heavily by localized industrial or other stationary sources of Pb, in contrast to the situation a few decades ago when elevated U.S. ambient air Pb concentrations were widespread mainly as a result of leaded fuel use.

7.2.2 Transport and Secondary Dispersal of Atmospheric Lead

Lead can be transported in the atmosphere and undergo secondary dispersal via the deposition and resuspension of particles containing Pb, as discussed in Section 2.3.2 of Chapter 2. Dry deposition is the process by which pollutants are removed from the atmosphere in the absence of precipitation. The size of depositing particles is arguably the most important factor affecting dry deposition rates. For very small particles, Brownian motion is the dominant mechanism that transports particles through the viscous sublayer that borders surfaces. For large particles, sedimentation is the most important process governing particle deposition. For intermediate particles, impaction and interception largely determine deposition rates. The highest extent of uncertainty applies to deposition velocities for the intermediate sized particles. As an example, in one study, although most of the airborne Pb mass was associated with submicron particles, only about 0.5% of the Pb particle mass undergoing dry deposition in Chicago was <2.5 μm in diameter. Also, more than 90% of Pb particle mass that undergoes dry deposition is in an insoluble chemical form. Overall, dry deposition velocities for Pb are in the range of 0.05 to 1.3 cm/s.

Wet deposition is the process by which airborne pollutants are scavenged by precipitation and removed from the atmosphere. The size of particles can also influence wet deposition rates. Large particles are scavenged more efficiently. Lead, which is found in particles primarily in the submicron size range, does not undergo wet deposition as easily as many of the crustal elements.

The resuspension of soil-bound Pb particles and contaminated road dust is a significant source of airborne Pb. The main sources of resuspension are typically wind and vehicular traffic, although resuspension through other mechanical processes, e.g., construction, pedestrian traffic, agricultural operations, and even raindrop impaction, is possible. In general, mechanical stresses are more effective than the wind in resuspending particles.

Understanding the physics of resuspension from natural winds requires analyzing the wind stresses on individual particles, including frictional drag, form drag, gravitation, and the Bernoulli effect. Although this analysis can be accurate on a small scale, predicting resuspension on a large scale generally focuses on empirical data for continual soil movement due to three processes: saltation, surface creep, and suspension. Saltation is the process by which particles in the 100 to 500 μm size range bounce or jump close to the surface. The low angle at which these particles strike the surface transfers momentum to smaller particles, allowing them to be

suspended into the atmosphere. Depending on soil conditions, saltation can be responsible for moving 50 to 75% of surface particles. Surface creep is the rolling or sliding motion of particles induced by wind stress or momentum exchanged from other moving particles. This generally applies to large particles 500 to 1000 μm in diameter and moves 5 to 25% of soil by weight. Suspension is the process that actually ejects particles into the air. This affects particles ≤100 μm in diameter and moves 3 to 40% of soil by weight. Resuspension may occur as a series of events. Short episodes of high windspeeds, dry conditions, and other factors conducive to resuspension may dominate annual averages of upward flux.

Soil-Pb concentrations vary significantly throughout urban areas, depending on proximity to roadways and stationary sources and on wind speed and direction, as noted in Section 3.2.1. Some of the highest soil-Pb concentrations are observed near major roadways. For example, surface soil-Pb concentrations measured near a major freeway in Cincinnati, OH, were between 59 ppm and 1980 ppm, levels well above background. These concentrations dropped off dramatically with soil depth. An estimated 40% of Pb from automobile exhaust was retained in the nearby soil. Lead-contaminated soils and dusts can be significant sources of Pb exposure for human populations.

Lead in soil is also highly elevated near stationary sources of Pb emissions. In particular, areas around smelters and battery disposal sites can have very high levels of soil Pb (Section 3.2.2). Concentrations of soil Pb are highly elevated near mines as well. Lead and zinc mines, in particular, typically have large deposits of Pb in nearby soil, but mines used for extracting other metals can also have Pb-contaminated soil. Blood-Pb levels are typically elevated in people living near Pb mines.

The resuspension of soil particles historically contaminated by past deposition of airborne Pb emitted from smelters and other stationary sources, as well as resulting from past combustion of leaded gasoline, represents a continuing source of current air Pb.

7.2.3 Ambient Air Lead Concentrations

There are four ambient monitoring networks that measure Pb concentrations in the United States, as discussed in Section 3.2.1 of Chapter 3. Determination of compliance with the current Pb NAAQS is based on measurements taken at Federal Reference Method (FRM) monitors, which measure Pb in total suspended particulate matter (TSP), i.e., particles up to about 30 μm in

diameter. In 2005, there were about 250 FRM sampling sites in operation across the United States.

Data on airborne Pb concentrations are also available from two other U.S. networks that measure Pb in fine particulate matter (≤2.5 μm in diameter). There are ~200 sites, primarily in U.S. urban locations, in the $PM_{2.5}$ speciation network; and there are over 100 sites in the Interagency Monitoring of Protected Visual Environments (IMPROVE) network that are located in U.S. national parks or wilderness areas. In addition, Pb concentrations are measured in PM_{10} samples collected at the National Air Toxics Trends Stations (NATTS) network of 24 U.S. sites.

As was seen for emissions of Pb, ambient air Pb concentrations have also markedly declined over the past several decades. Between 1983 and 2002, ambient air Pb concentrations measured at FRM monitors decreased by ~94%, as shown in Figure 7-3. Data from the FRM monitors and from the $PM_{2.5}$ speciation, IMPROVE and NATTS networks all show a consistent pattern of ambient air Pb concentrations, i.e., a long period of measured ambient levels substantially lower than the current Pb NAAQS, except in a few local areas. For example, Pb concentrations measured at the FRM monitors in 2000 to 2004 on average, are quite low, with the mean level ranging from 0.03 to 0.05 $\mu g/m^3$ (excluding point source-related monitors) and 0.10 to 0.22 (including point source-related monitors). However, when data from point source-oriented monitors are included, one to five U.S. locations (from among ~200 sites) had measured calendar quarterly maximum Pb levels that exceeded the NAAQS level (1.5 $\mu g/m^3$, quarterly max average) in any given year during 2000 to 2004. As for data from PM_{10} monitors in the NATTS network, the highest quarterly max Pb concentration observed was 0.039 $\mu g/m^3$ during 2002 to 2005. Using data from the $PM_{2.5}$ speciation network for 2002 to 2005, the highest quarterly max Pb concentration reported was 0.168 $\mu g/m^3$. Thus, overall, ambient air Pb concentrations in the United States are generally well below the current NAAQS level, except for a few scattered locations influenced by local sources.

7.2.4 Non-Air Environmental Lead Exposure Routes

In addition to ambient air, major non-air environmental routes for exposure to Pb include: Pb in house dust; Pb-based paint in older homes; drinking water; and Pb-contaminated food. Lead exposure can also occur at times due to other idiosyncratic sources such as calcium

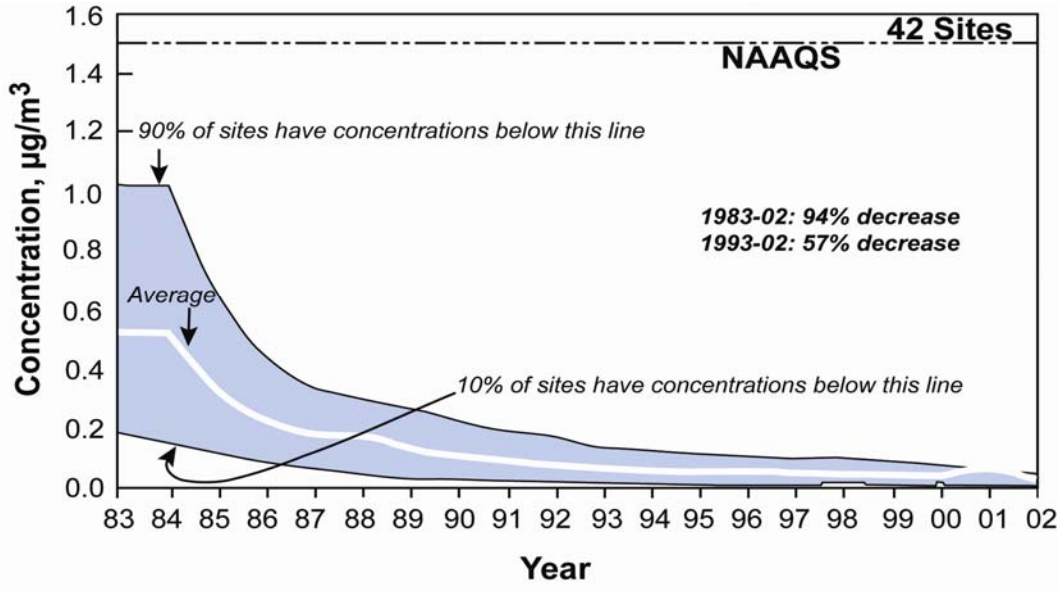

Figure 7-3. Airborne Pb concentrations measured at FRM sites, averaged across the United States for the years 1983 through 2002. The data are plotted in terms of maximum arithmetic mean averaged over a calendar quarter and are shown in relation to the Pb NAAQS of 1.5 µg/m^3

Source: U.S. Environmental Protection Agency (2003).

supplements, Pb-based glazes, certain kinds of miniblinds, hair dye, and other consumer products that can widely vary in their prevalence and the potential risk posed by them.

Given the large amount of time people spend indoors, exposure to Pb in dusts and indoor air can be significant (see Section 3.2.3). For children, dust ingested via hand-to-mouth activity may be a more important source of Pb exposure than inhalation. However, dust can be resuspended through household activities, thereby posing an inhalation risk as well. A number of different sources can contribute to Pb in housedust, both from sources outside the home and from Pb-based paint.

Throughout early childhood, floor dust Pb contamination is a source of exposure. Lead-contaminated windowsill dust becomes an additional source of Pb intake during the second year of life when children stand upright. Because of normal mouthing behaviors and increased mobility, the highest blood Pb levels are seen in children between 18 and 36 months of age. This typically is observed after a rapid rise in blood Pb levels between 6 and 12 months. Even at low concentrations, Pb in housedust can have a notable effect on children's blood Pb levels. For

example, studies discussed in Section 3.2.3 show that, at a median floor dust Pb level of 5 μg/ft^2 (54 μg/m^2), ~5% of children had blood Pb levels ≥10 μg/dL. At a floor dust Pb loading of 50 μg/ft^2 (540 μg/m^2), the percentage of children with blood Pb levels ≥10 μg/dL rose to 20%. In another study, children exposed to floor dust Pb loadings in excess of 25 μg/ft^2 (270 μg/m^2) were at eight times greater risk of having blood Pb levels ≥10 μg/dL compared to children exposed to levels below 2.5 μg/ft^2 (27 μg/m^2).

Soil Pb is a significant contributor to elevated blood-Pb levels, especially among children, in populations residing near certain Superfund sites, as discussed in Section 3.2.2. For example, Pb levels in soil collected at residences near the Tar Creek Superfund Site (a Pb mining area in northeastern Oklahoma) reflected contamination by wind-dispersed mine wastes. More than 20% of residential soil samples exceeded the EPA action level of 500 ppm, and children's blood Pb levels tended to be higher in comparison to those of children living outside the Superfund towns. In this same area, blood-Pb levels were found to be highest among African-American, Mexican-American, and poor children. Blood-Pb levels were most commonly correlated with mean floor dust Pb loading and with soil Pb, especially front yard soil. Another study found that homes at the Jasper County Superfund Site in southwestern Missouri had significantly higher soil and dust Pb levels and significantly higher blood-Pb levels than areas outside of the Superfund site. There was a strong statistical relationship observed between blood-Pb levels and soil, dust, and paint Pb concentrations.

Lead-based paint was the most widely used, dominant form of house paint for many decades, and a significant percentage of homes (especially those built before 1978) still contain Pb-based paint on some surfaces, as discussed in Section 3.5.1. As Pb-based paint degrades, it becomes incorporated into house dust, as noted earlier in this chapter. Lead-based paint poses a potential exposure risk due to ingestion of Pb-contaminated dusts via normal hand-to-mouth activities and/or pica (which are common in children) or due to inhalation during renovation or demolition projects. Lead-based paint can pose a particularly serious inhalation risk for both adults and children during renovation activities that form easily inhaled Pb particles. The ingestion and/or inhalation of Pb derived from Pb-based paint has long been one of the most common causes of clinical Pb toxicity in the United States.

As discussed in Section 3.3, most U.S. drinking water distribution systems serving more than 3,000 people typically supply drinking water that meets the EPA tap water limit of

0.015 mg/L (15 ppb) set in 1991. Of 18 major U.S. cities illustrated in Table 3-11 of Chapter 3 as exceeding the EPA water Pb Action Level in the early 1990s, 14 had decreased their 90th percentile tap water concentrations to below the 15-ppb Action Level during recent monitoring periods (since the year 2000). On the other hand, with the introduction of chloramine as an alternative water treatment used in some cities across the United States, some increases in tap water-Pb concentrations have been detected in some municipal water supplies, raising concern about possible resultant increases in blood-Pb levels among affected water-use populations.

Very little Pb in drinking water comes from public water utility supplies per se, versus from leaded solder in plumbing or Pb in plumbing fixtures in buildings attached to utility distribution lines. Thus, Pb in drinking water occurs primarily as a result of corrosion from Pb pipes, Pb-based solder, or brass or bronze fixtures within a residence, as noted in Chapter 3. However, Pb in drinking water, although generally found at low concentrations in the United States, has been linked to elevated blood Pb concentrations in general population groups. In one U.S. prospective study, for example, children exposed to water with Pb concentrations >5 ppb had blood Pb levels ~1.0 µg/dL higher than children with water Pb levels <5 ppb (Lanphear et al., 2002). In another study of mothers and infants in Glasgow, Scotland, tap water was the main correlate of elevated maternal blood Pb levels (Watt et al., 1996). Thus, under certain conditions, water may not be a trivial source of Pb exposure in some locations.

Although marked reductions of Pb in U.S. market basket food supplies have occurred during the past several decades, Pb-contaminated food still can be an important route of Pb exposure (see Section 3.4). Several recent studies in the U.S. and Australia indicate that daily dietary Pb intake is in the range of 2 to 10 µg/day (see section 3.4). Data from FDA's 1994-1996 Total Diet Studies showed that, since 1982-1984, daily intakes of lead from food dropped 96 percent in 2- to 5-year-olds (from 30 micrograms a day to 1.3) and nearly 93 percent in adults (from 38 micrograms a day to 2.5) (see: http://www.cfsan.fda.gov/~dms/fdalead.html). Lastly, some U.S. population groups that frequently consume canned foods imported from non-U.S. countries that still allow use of lead-soldered cans may be at distinctly greater risk for exposure to Pb via dietary intake and consequent higher blood-Pb concentration.

7.3 LEAD TOXICOKINETICS AND MEASUREMENT/MODELING OF LEAD EXPOSURE IMPACTS ON INTERNAL TISSUE LEAD

Understanding the relationships between human exposure to Pb in external media (air, food, water, soil/dust) and internal Pb burden in blood and other body tissues is a key issue of much importance in carrying out risk assessments that evaluate the potential risk for adverse health effects to occur in response to various Pb exposure scenarios. Use of biomarkers to index Pb exposures is predicated on knowledge concerning Pb toxickinetics. Blood-Pb concentrations have long been the most widely used biomarker by which to index Pb exposures in children and adults (as discussed extensively in the 1977 Pb AQCD and the 1986 Pb AQCD/Addendum). At the time of the 1986 Pb AQCD, it was recognized that Pb distributed to and accumulated in several bone compartments which exhibited differing mobility profiles. It was also recognized that a larger fraction of total body burden of Pb is found in the bones of adults relative to children. The possibility of bone-Pb serving as a source of long-term internal Pb exposure was considered. New studies that have since been published on the kinetics of Pb movement into and out of bone demonstrate the importance of bone-Pb stores as a source of Pb to the blood in retired lead workers and during pregnancy, as discussed in Chapter 4 of this document. Additional information regarding Pb absorption, distribution, and elimination in humans is also discussed in Chapter 4, and some of the most important points regarding these and other aspects related to Pb toxickinetics are summarized below.

7.3.1 Biokinetics of Lead Uptake and Internal Distribution

Humans are exposed to Pb mainly by ingestion and inhalation. The absorption of Pb is affected by factors such as an individual's age and diet, as well as chemical and physical properties of the ingested or inhaled Pb, as discussed in Section 4.2.1. Lead absorption appears to be increased by both iron and calcium deficiency. Fasting also increases the absorption of Pb from ingested soil. Lead absorption in humans may be a capacity limited process, such that the fraction of ingested Pb that is absorbed may decrease with increasing rate of Pb intake. The available studies to date, however, do not provide a firm basis for discerning whether the gastrointestinal absorption of Pb is limited by dose. The size of ingested Pb particles also affects absorption, with absorption decreasing as particle size increases.

In general, the Pb burden in the body may be viewed as being divided between a dominant slow compartment (bone) and a smaller fast compartment (soft tissues). This distribution of Pb in the body and factors affecting the exchange of Pb between bone and blood are discussed in detail in Sections 4.2.2, 4.3.1, and 4.3.2. In human adults, more than 90% of the total Pb body burden is found in the bones, whereas bone Pb accounts for ~70% of the body burden in children. The highest soft tissue concentrations in adults also occur in liver and kidney cortex. Lead in blood is exchanged between both of these compartments. The contribution of bone Pb to blood Pb changes with the duration and intensity of the Pb exposure, age, and various physiological variables (e.g., nutritional status, pregnancy, menopause).

As also discussed in Chapter 4, Pb accumulates in bone regions having the most active calcification at the time of exposure. Lead accumulation is thought to occur predominantly in trabecular bone during childhood and in both cortical and trabecular bone in adulthood. Lead concentrations in bone increase with age throughout life, indicative of a relatively slow turnover of Pb in adult bone. Lead content in some bones (i.e., mid femur and pelvic bone) increases into adulthood, plateaus at middle age, and then decreases at older ages. This decrease is most pronounced in postmenopausal females and may be due to osteoporosis and the release of Pb from resorbed bone to blood. Lead in adult bone can serve to maintain blood-Pb levels long after external exposure has ceased. During pregnancy, bone Pb can also serve as a Pb source with the resorption of maternal bone for production of the fetal skeleton, and maternal bone Pb can continue postnatally to serve as a source of Pb exposure to the offspring via maternal lactation/breastfeeding (see Section 4.3.2.5).

In contrast to Pb in bone, which accumulates with continued exposure in adulthood, Pb concentrations in soft tissues (e.g., liver and kidney) are relatively constant in adults, reflecting a faster turnover of lead in soft tissue relative to bone (as discussed in Chapter 4). It is also noted that Pb in soft tissues exists predominantly bound to protein (see Section 5.11). High affinity cytosolic Pb-binding proteins (PbBPs) have been identified in rat kidney and brain. Other high-affinity Pb-binding proteins 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.

Lead in blood is found primarily (~99%) in the red blood cells. As discussed in Sections 4.2.2 and 4.3.1, δ-aminolevulinic acid dehydratase (ALAD) is the primary Pb-binding ligand in erythrocytes. Lead binding to ALAD is saturable; the binding capacity has been

estimated to be ~850 µg/dL red blood cells (or ~340 µg/dL whole blood), with an apparent dissociation constant of ~1.5 µg/L. It has been suggested that the small fraction of Pb in plasma (<0.3%) may be the more biologically labile and toxicologically active fraction of circulating Pb. Several authors have proposed that Pb released from the skeleton was preferentially partitioned into serum compared with red cells. About 40 to 75% of Pb in the plasma is bound to proteins, of which albumin appears to be the dominant ligand. Lead in serum not bound to protein exists largely as complexes with low molecular weight sulfhydryl compounds (e.g., cysteine, homocysteine) and other ligands.

7.3.2 Selection of Blood-Pb Concentration as Key Index of Pb Exposure

Blood-Pb concentration is extensively used in epidemiologic studies as an index of exposure and body burden mainly due to the feasibility of incorporating its measurement into human studies relative to other potential dose indicators, e.g., lead in kidney, plasma, urine, or bone. Section 4.3.1 considers the use of blood Pb as a marker of Pb exposure and body burden, and the contribution of bone Pb to the blood is specifically discussed in Section 4.3.2.4. A single blood-Pb measurement may not distinguish between a history of long-term lower level Pb exposure from a history that includes higher acute exposures, as discussed by Mushak (1998). An additional complication is that the relationship between Pb intake and blood-Pb concentration is curvilinear; that is, the increment in blood-Pb concentration per unit of Pb intake decreases with increasing blood-Pb concentration, both in children and in adults. In general, higher blood Pb concentrations can be interpreted as indicating higher exposures (or lead uptakes); however, they do not necessarily predict higher overall body burdens. Similar blood-Pb concentrations in two individuals (or populations) do not necessarily translate to similar body burdens or similar exposure histories. The disparity in the kinetics of blood Pb and cumulative body burden may have important implications for the interpretation of blood-Pb concentration measurements in some epidemiology studies, depending on the health outcome being evaluated.

Bone Pb, as also indicated in Chapter 4, has begun to be accorded increasing attention as another potentially useful marker for Pb exposure. It is thought that bone-Pb measurements likely constitute a better indication of overall past cumulative Pb exposure history than do blood Pb concentrations, which are more strongly influenced by recent Pb exposures. Approaches to measurement of bone Pb in living human or animal subjects are discussed in Section 4.3.2.2 and

mainly involve different x-ray techniques that have undergone extensive intercomparison testing and refinements during the past decade or so. Still, in contrast to blood-Pb concentrations, bone-Pb measurements have not yet gained widespread use in epidemiologic studies as a key biomarker for Pb exposure.

In addition to blood Pb and/or bone Pb, concentrations of Pb in hair and urine have at times also been used as biomarkers of Pb exposure (see Sections 4.3.4 and 4.3.5). However, an empirical basis for interpreting hair lead measures in terms of body burden or exposure has not been firmly established. As discussed in Chapter 4, hair Pb measurements are subject to error due to contamination of the hair surface with environmental Pb and contaminants in artificial hair treatments (e.g., dyeing, bleaching, permanents) and, as such, are a relatively poor predictor of blood-Pb concentration, particularly at low blood-Pb levels < ~10 to 12 μg/dL. Spontaneous urine-Pb excretion also provides little reliable information, unless adjusted to account for unmeasured variability in urine flow rate. Analogous to blood-Pb concentration measurements, spontaneous urinary Pb excretion measured in an individual at a single point in time mainly reflects the recent exposure history. As a result, spontaneous urinary-Pb measurement may serve as a feasible surrogate for plasma-Pb concentration, and may be useful for exploring dose-response relationships for effect outcomes that may be more strongly associated with plasma-Pb level than overall Pb body burden. On the other hand, measurement of notably increased urinary Pb excretion in response to Succimer or other approved chelant challenge has proven to be reliable in both pediatric clinical and occupational settings as reflecting a history of excessive Pb exposure.

7.3.3 Trends in U.S. Blood Lead Levels

As discussed in Section 4.3.1.3, blood-Pb concentrations in the U.S. general population have been monitored over the past three decades via the National Health and Nutrition Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention. Data from the most recent survey (NHANES IV, Centers for Disease Control, 2005) are shown in Tables 7-1 and 7-2. For survey years 2001-2002, the geometric mean blood-Pb level for ages >1 year (n = 8,945) was 1.45 μg/dL (95% CI: 1.39, 1.52); with the geometric mean in males (n = 4,339) being 1.78 μg/dL (95% CI: 1.71, 1.86) and in females (n = 4,606) being 1.19 μg/dL (95% CI: 1.14, 1.25). Blood-Pb concentrations in the U.S. general population have decreased

Table 7-1. Blood Lead Concentrations in United States by Age, NHANES IV (1999–2002)

Age	1–5 years		6–11 years		12–19 years		≥20 years	
Survey Period	*1999–2000*	*2001–2002*	*1999–2000*	*2001–2002*	*1999–2000*	*2001–2002*	*1999–2000*	*2001–2002*
N	723	898	909	1,044	2,135	2,231	4,207	4,772
Blood Lead (µg/dL)[a]	2.23 (1.96, 2.53)	1.70 (1.55, 1.87)	1.51 (1.36, 1.66)	1.25 (1.14, 1.36)	1.10 (1.04, 1.17)	0.94 (0.90, 0.99)	1.75 (1.68, 1.81)	1.56 (1.49, 1.62)

[a]Blood lead concentrations presented are geometric means (95% CI).

Table 7-2. Blood Lead Concentrations in United States by Gender, NHANES IV (1999–2002)

Gender	Males		Females	
Survey Period	1999–2000	2001–2002	1999–2000	2001–2002
n	3,913	4,339	4,057	4,606
Blood Lead (µg/dL)[a]	2.01 (1.93, 2.09)	1.78 (1.71, 1.86)	1.37 (1.32, 1.43)	1.19 (1.14, 1.25)

[a]Blood lead concentrations presented are geometric means (95% CI).

over the past three decades as regulations regarding leaded fuels, leaded paint, and lead-containing plumbing materials have decreased Pb exposure among the general population. Changes in average blood-Pb concentrations among U.S. children over time are shown in Figure 7-4.

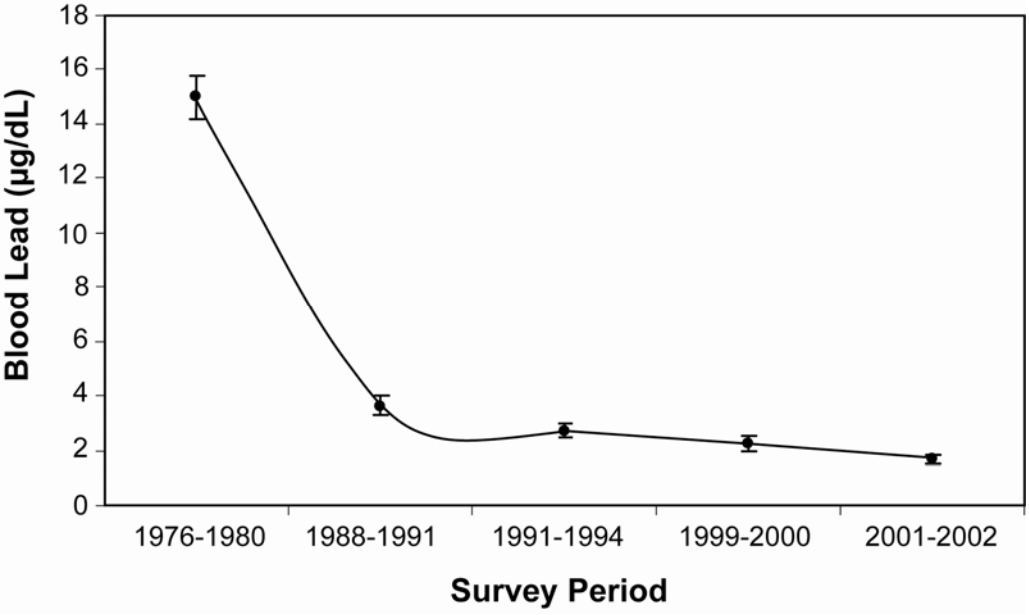

Figure 7-4. Blood lead concentrations in U.S. children, 1-5 years of age. Shown are geometric means and 95% confidence intervals as reported from the NHANES II (1976–1980) and NHANES III Phase 1 (1988–1991; Pirkle et al., 1994); NHANES III Phase 2 (1991–1994; Pirkle et al., 1998); and NHANES IV (1999-2000, 2001-2002; Centers for Disease Control, 2005).

Blood Pb concentrations can vary considerably as a function of age, physiological state (e.g., pregnancy, lactation, menopause), and numerous other factors that affect exposure to Pb. The NHANES data provide estimates for average blood lead concentrations in various demographic strata of the U.S. population. NHANES III Phase 2 samples were collected during 1991 to 1994. Geometric mean blood-Pb concentrations of U.S. adults, ages 20 to 49 years, estimated from the NHANES III Phase 2, were 2.1 µg/dL (95% CI, 2.0, 2.2). Among adults, blood-Pb concentrations were highest in the strata that included ages 70 years and older

(3.4 μg/dL; 95% CI, 3.3, 3.6). The geometric mean blood-Pb concentration of children, ages 1 to 5 years, was 2.7 (95% CI, 2.5, 3.0) for the 1991 to 1994 survey period; however, the mean varied with socioeconomic status and other demographic characteristics that have been linked to lead exposure (e.g., age of housing). Central estimates from the NHANES III Phase 2 (1991 to 1994), when compared to those from NHANES III Phase 1 (1988 to 1991) and the NHANES II (1976 to 1980), indicate a clear downward temporal trend in U.S. blood-Pb concentrations over the past 20 years or so. It should be noted, however, that blood-Pb levels have been declining at differential rates for various general subpopulations, as a function of income, race, and certain other demographic indicators such as age of housing. Also, substantial caution should be exercised with regard to use of NHANES data for risk assessment purposes, in that the nationally-representative NHANES quantitative results (e.g., national mean blood-Pb levels or strata-classified national mean blood-Pb values) vary with regard to how reflective they may be of specific regions or communities.

7.3.4 Approaches to Predictive Estimation of Pb-Exposure Impacts on Distribution to Internal Tissues

As indicated in Chapter 4, a key issue of much importance in carrying out lead risk assessments that evaluate the potential likelihood of Pb-induced health effects is the estimation of external Pb-exposure impacts on internal Pb tissue concentrations. This includes estimation of typical Pb exposure impacts on internal distribution of Pb to blood and bone (as key biomarkers of Pb exposure), as well as to other "soft tissue" target organs (e.g., brain, kidney, etc.). Earlier criteria assessments in the 1977 and 1986 Pb AQCDs extensively discussed then available slope factor and/or other regression models of external Pb exposure impacts on blood-Pb concentrations in human adults and children. The older slope factor analyses discussed in the 1977 and 1986 Pb AQCDs noted that at relatively low air-Pb concentrations ($\leq$2 μg/m^3), pediatric blood-Pb levels generally increase by ~2 μg/dL per each 1 μg/m^3 increment in air-Pb concentration. Further refinements in regression modeling of Pb impacts on blood or bone Pb are discussed in Chapter 4.

Several new studies discussed in Chapter 4 have investigated relationships between Pb exposure and blood Pb in children (see Section 4.4.2). These studies support the concept that contact with Pb in surface dust (interior and exterior) is a major contributor to Pb intake in

children. In one meta-analysis, the most common exposure pathway to emerge as notably influencing blood-Pb concentration was exterior soil, operating through its effect on interior dust Pb and hand Pb. Using a structural equation model, other analyses also found that the exposure pathway component that was most influential on blood Pb was interior dust Pb loading, directly or through its influence on hand Pb. Both soil and paint Pb influenced interior dust Pb. However, interior and exterior paints were more significant contributors to childrens' blood-Pb levels in urban (heavily paint-impacted) areas than at western U.S. extractive (mining/smelting) industry sites, and dust Pb was more significantly linked to soil Pb than paint Pb at such western sites. Still, these and other studies of populations near active sources of air emissions (e.g., smelters, etc.), substantiate the effect of airborne Pb and resuspended soil Pb on interior dust and blood Pb.

Both exterior soil and paint Pb contribute to interior dust Pb levels. It has been estimated that for every 1000 ppm increase in soil-Pb concentration, pediatric blood-Pb levels generally increase by ~1 to 5 μg/dL in exposed infants and children <6 years old. All ingested lead is not absorbed to the same extent, in that intake of soil-Pb with low bioaccessibility or bioavailability characteristics can yield distinctly lower-than-typical blood-Pb increments. Factors such as an individual's age and diet, as well as chemical and physical properties of Pb, affect absorption, e.g. absorption is increased by fasting and dietary iron or calcium deficiencies.

Additional information on Pb biokinetics, bone mineral metabolism, and Pb exposures has led to refinements and expansions of earlier modeling efforts. In particular, there are three pharmacokinetic models that are currently being used or considered for broad application in Pb risk assessment: (1) the Integrated Exposure Uptake BioKinetic (IEUBK) model for Pb in children developed by EPA (U.S. Environmental Protection Agency, 1994a,b; White et al., 1998); (2) the Leggett model, which also simulates Pb kinetics from birth through adulthood (Leggett, 1993); and (3) the O'Flaherty model, which simulates Pb kinetics from birth through adulthood (O'Flaherty, 1993, 1995). The above three models have been individually evaluated to varying degrees, against empirical physiological data on animals and humans and data on blood-Pb concentrations in individuals and/or populations (U.S. Environmental Protection Agency, 1994a,b; Leggett, 1993; O'Flaherty, 1993). In evaluating models for use in risk assessment, exposure data collected at hazardous waste sites have mainly 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.

Exposure-biokinetics models both illustrate exposure-blood-body burden relationships and provide a means for making predictions about these relationships that can be experimentally or epidemiologically tested. The EPA IEUBK model for Pb has gained widespread use for risk assessment purposes in the United States, and it is currently clearly the model of choice in evaluating mutimedia Pb exposure impacts on blood-Pb levels and distribution of Pb to bone and other tissues in young children <7 years old. The EPA All Ages Lead Model (AALM), now under development, aims to extend beyond IEUBK capabilities to model external Pb exposure impacts (including over many years) on internal Pb distribution not only in young children, but also in older children, adolescents, young adults, and other adults well into older years (up to 90 years of age). The AALM essentially uses adaptations of IEUBK exposure module features, coupled with adaptations of IEUBK biokinetics components (for young children) and of Leggett model biokinetics components (for older children and adults). However, the AALM has not yet undergone sufficient development and validation for it to be recommended for general risk assessment use.

7.4 LEAD-INDUCED TOXICITY: INTEGRATION OF TOXICOLOGIC AND EPIDEMIOLOGIC EVIDENCE

7.4.1 Introduction

As discussed in the previous two chapters (Chapters 5 and 6) dealing with the toxicology and epidemiology of Pb-induced health effects, Pb has been shown to exert a broad array of deleterious effects on multiple organ systems via widely diverse mechanisms of action. Truly remarkable progress has been made during the past several decades with regard to (a) more fully delineating over time the wide variety of pathophysiologic effects associated with Pb exposure of human population groups and laboratory animals and (b) the characterization of applicable exposure durations and dose-response relationships for the induction of the multifaceted Pb effects. This progress has been well documented by the previous Pb NAAQS criteria reviews carried out by EPA in the late 1970s and during the 1980s, as well as being well reflected by previous chapters of this document.

The 1977 Pb AQCD (U.S. Environmental Protection Agency, 1977) that provided key scientific bases for the setting in 1978 of the current Pb NAAQS included discussion of both: (a) historical literature accumulated during several preceding decades that established lead encephalopathy and other signs and symptoms of persisting severe central and/or peripheral nervous system damage, as well as renal and hepatic damage, and anemia as typifying the classic syndrome of acute and/or chronic high-level lead poisoning among human pediatric and /or adult population groups, and (b) evaluation of then newly-emerging evidence for more subtle and difficult-to-detect "subclinical" Pb effects on IQ, other neurological endpoints, and moderate blood hemoglobin deficits or other erythropoietic indicators of heme synthesis impairment, which collectively were judged to constitute an array of adverse Pb health effects associated with lead exposures indexed by blood Pb concentrations ranging down to ~30 μg/dL. The next Pb NAAQS criteria review during the 1980's, as contained in the 1986 Pb AQCD/Addendum and its 1990 Supplement (U.S. Environmental Protection Agency, 1986a, b, 1990) documented further rapid advances in Pb health effects research that provided (a) increasingly stronger evidence that substantiated still lower fetal and/or postnatal Pb-exposure levels (indexed by blood-Pb levels extending to as low as 10 to 15 μg/dL or, possibly, below) as being associated with slowed physical and neurobehavioral development, lower IQ, impaired learning, and/or other indicators of adverse neurological impacts and (b) other pathophysiological effects of Pb on cardiovascular function, immune system components, calcium and vitamin D metabolism, and other selected health endpoints.

Newly available scientific information published since the 1986 Pb AQCD/Addendum and the 1990 Supplement, as assessed in previous chapters of this document, further expands our understanding of a wide array of Pb-induced health effects, underlying mechanisms, and factors that enhance or lessen susceptibility to Pb effects. Very importantly, the newly available toxicologic and epidemiologic information, as integrated below, includes assessment of new evidence substantiating risks of deleterious effects on certain health endpoints being induced by distinctly lower than previously demonstrated Pb exposures indexed by blood-Pb levels extending well below 10 μg/dL in children and/or adults.

The ensuing subsections provide concise summarization and integrative synthesis of the most salient health-related findings and conclusions derived from the current criteria assessment. This includes discussion of new evidence concerning Pb-induced (a) effects on neurobehavioral

development and other indicators of nervous system effects; (b) cardiovascular effects; (c) heme synthesis effects; (d) renal effects; (e) immune system functions; (f) effects on calcium and vitamin D metabolism; (g) inter-relationships to bone and teeth formation and demineralization; (h) effects on reproduction and other neuroendocrine effects; and (i) genotoxicity and carcinogenic effects.

Of much importance is the characterization of applicable dose-response relationships for various health endpoints used as indicators of deleterious lead effects, especially at blood-Pb levels below 10 µg/dL. Tables 7-3 and 7-4 highlight the most important such effects observed in children and adults, respectively, as discussed in the following subsections. As evident from the ensuing discussions, neurotoxic effects in children and cardiovascular effects in adults are among those best substantiated as occurring at blood-Pb concentrations >10 µg/dL; and these are currently clearly of greatest potential public health concern. They are, therefore, accorded the most attention in what follows.

7.4.2 Neurotoxic Effects

The neurotoxic effects of Pb exposure are among those most studied and most extensively documented among human population groups. Also, extensive experimental laboratory animal evidence has been generated that (a) substantiates well the plausibility of the epidemiologic findings observed in human children and adults and (b) expands our understanding of likely mechanisms underlying the neurotoxic effects. Two major issues are important in considering the concordance of human and animal results: (1) comparability of blood Pb levels (or other internal dose markers) among species; and (2) comparability of neurobehavioral tests for animals and humans.

Animal models are extremely important in the characterization of Pb neurotoxicity because exposures can be controlled to address questions about sensitive periods of exposure. Unlike typical human exposures reported in epidemiology studies, Pb dosing to animals can be stopped at any time to address questions about the reversibility and persistence of neurotoxic effects. Also, with animals, dosing can be varied to include very low doses to examine effects seen with more current pediatric exposures. Animal models, especially inbred strains of rodents, can lessen the effects of the critical confounder of parental cognitive ability, which parallels

Table 7-3. Summary of Lowest Observed Effect Levels for Key Lead-Induced Health Effects in Children

Lowest Observed Effect Blood Lead Level	Neurological Effects	Hematological Effects	Immune Effects
30 µg/dL		Increased urinary δ-aminolevulinic acid	
15 µg/dL	Behavioral disturbances (e.g., inattention, delinquency) Altered electrophysiological responses	Erythrocyte protoporphyrin (EP) elevation	
10 µg/dL	Effects on neuromotor function CNS cognitive effects (e.g., IQ deficits)	Inhibition of δ-aminolevulinic acid dehydratase (ALAD) Pyrimidine-5′-nuclotidase (Py5N) activity inhibition	Effects on humoral (↑ serum IgE) and cell-mediated (↓ T-cell abundance) immunity
5 µg/dL	(???)	(???)	
0 µg/dL			

Note: Arrows depict cases where weight of overall evidence strongly substantiates likely occurrence of type of effect in association with blood-Pb concentrations in range of 5-10 µg/dL, or possibly lower, as implied by (???). Although no evident threshold has yet been clearly established for such effects, the existence of such at still lower blood-Pb levels cannot be ruled out based on available data.

Source: Adapted/updated from Table 1-17 of U.S. Environmental Protection Agency (1986a).

Table 7-4. Summary of Lowest Observed Effect Levels for Key Lead-Induced Health Effects in Adults

Lowest Observed Effect Blood Lead Level	Neurological Effects	Hematological Effects	Cardiovascular Effects	Renal Effects
30 µg/dL	Peripheral sensory nerve impairment	Erythrocyte protoporphyrin (EP) elevation in males		Impaired Renal Tubular Function
20 µg/dL	Cognitive impairment			
15 µg/dL	Postural sway	Erythrocyte protoporphyrin (EP) elevation in females		
		Increased urinary δ-aminolevulinic acid		
10 µg/dL		Inhibition of δ-aminolevulinic acid dehydratase (ALAD)	Elevated blood pressure	
5 µg/dL			(???)	Elevated serum creatine (↓ creatine clearance)
0 µg/dL				

Note: Arrows depict cases where weight of overall evidence strongly substantiates likely occurrence of type of effect in association with blood-Pb concentrations in range of 5-10 µg/dL, or possibly lower, as implied by (???). Although no evident threshold has yet been clearly established with for such effects, the existence of such at still lower blood-Pb levels cannot be ruled out based on available data.

Source: Adapted/updated from Table 1-16 of U.S. Environmental Protection Agency (1986a).

human IQ. Also eliminated in controlled animal exposures are the confounders of SES and nutrition.

In a review, Davis et al. (1990) state that little effort has been directed toward making direct comparisons of human and animal dose-response relationships because of the abundance of human exposure-effect data. The 1986 Pb AQCD also reported that there is some uncertainty in extrapolating from animals to humans because blood-Pb levels may not be directly comparable. Both rats and monkeys may require higher Pb exposure levels than humans to achieve a comparable blood-Pb level. It was further recognized by Davis et al (1990) that, due to inadequate numbers of subjects and the resulting lack of statistical power, it may not be possible to detect subtle Pb-induced neurotoxic effects in both epidemiological and experimental studies.

As discussed in the 1986 Pb AQCD, questions have also been raised regarding the comparability between neurobehavioral effects in animals and effects on human behavior and cognitive function. One major difficulty is the lack of standardized methodologies or a consistent operational definition by which to compare behavioral endpoints. In addition, behavior is difficult to compare meaningfully across species, because behavioral analogies do not necessarily demonstrate behavioral homologies. Davis et al. (1990) examined the comparative neurotoxicity of Pb in humans and animals and noted that a problem in comparing behavior and identifying behavioral similarities is that behavior is not a phenomenological given, but an event or series of events that must be represented by abstracting of one or more of its features. They further state that it is important of be mindful of "the degree to which the model faithfully reflects the mechanisms underlying its referent."

In assessing the comparability of measures of cognitive function in humans and animals, Sharbaugh et al. (2003) also state that of ultimate importance is finding sensitive homologous or parallel neurobehavioral tests in humans and animals. Homologous tests are those for which the same procedure is followed in humans and the animal species. Examples of homologous tests include Bayley Scales of Infant Development II, which tests a number of behavioral and reflect tasks, and the visual recognition memory test. Both tests are performed in human infants and nonhuman primates. Parallel tests are those that are conducted in a different manner in humans and animals, but for which it is believed that the same cognitive function is being measured, e.g., tests of learning, recognition memory, and long-term memory in humans and rodents.

Generally measures of cognitive function for humans and nonhuman primates are homologous, while those with rodents are parallel (Sharbaugh et al., 2003).

The most widely used measure of cognitive function in epidemiologic studies is the intelligence quotient or IQ score. An IQ score is a global measure reflecting the integration of numerous behavioral processes. There is no direct parallel to IQ tests for nonhuman primates or rodents. However, in animals a wide variety of tests that assess attention, learning, and memory suggests that Pb exposure results in a global deficit in functioning, just as it is indicated by decrements in IQ scores in children (Rice, 1996).

Examination of the effect of Pb on behavioral processes in human and experimental animals needs to focus beyond IQ, as noted by Cory-Slechta (1996). One strategy would be to use the same behavioral baselines in human studies that have revealed Pb-related deficits in cognitive functions in experimental animal studies, particularly those such as discrimination learning, reversal learning, repeated learning of response sequences, and concurrent schedule transitions. Rice (1996) concurs with this view and states further that the use of IQ has proven to be a sensitive indicator of Pb exposure, but that using more specific tests could provide even greater sensitivity. In the following sections, the epidemiologic and toxicologic evidence of Pb-induced effects on global as well as specific neurobehavioral outcomes are integrated and discussed.

7.4.2.1 Neurocognitive Ability

Global Measures of Cognitive Function – Intelligence Testing and Academic Achievement

Lead effects on human neurocognitive ability have been assessed in epidemiologic studies largely by use of age-appropriate, standardized IQ tests (as discussed in Section 6.2.3 of Chapter 6). Assessment of intelligence in infants and young children has been performed using a number of scales, including the various Bayley Scales of Infant Development and the McCarthy Scales of Children's Abilities. Most studies used the Weschler Intelligence Scales for Children-Revised (WISC-R) in older children. As discussed by Rice (1996), it is generally recognized that early tests of intelligence such as the Bayley scales do not measure the same functions as tests used at school age such as the WISC-R and have little predictive validity for individual children (though the Bayley scales may have better predictive power for low-functioning children). Regardless, numerous well-conducted longitudinal cohort and cross-sectional studies

that evaluated various study populations in several different countries have consistently found Pb-related IQ deficits from infancy through at least early school age.

For example, in the largest available new cross-sectional study, Lanphear et al. (2000) examined the relationship between blood Pb concentrations and cognitive deficits in a nationally representative sample of 4,853 U.S. children aged 6 to 16 years children (geometric mean blood Pb of 1.9 μg/dL) who participated in NHANES III, with 97.9% of the children having blood-Pb concentrations <10 μg/dL. Two subtests of the WISC-R, Block Design (a measure of visual-spatial skills) and Digit Span (a measure of short-term and working memory) were administered; and numerous potential confounders were assessed in the multivariable analyses. Although no data on maternal IQ or direct observations of caretaking quality in the home were available, other variables such as the poverty index ratio and education level of the primary caregiver likely served as adequate surrogate measures of these important potential confounders. In multivariate analyses, a significant covariate-adjusted relationship was found between blood-Pb level and scores on both WISC-R subtest for all children as well as among those with blood-Pb levels <10 μg/dL. Blood-Pb concentration was also significantly associated with Block Design when the multivariate analysis was restricted to children with blood Pb levels <7.5 μg/dL.

Other recent studies of the association of Pb with IQ in children with low Pb exposures have consistently observed effects at blood-Pb concentrations below 10 μg/dL (as discussed in Section 6.2.3 of Chapter 6). Most notably, a large international pooled analysis of 1,333 children from seven different cohorts by Lanphear et al. (2005) estimated a decline of 6.2 points (95% CI: 3.8, 8.6) in full scale IQ for an increase in concurrent blood-Pb level from 1 to 10 μg/dL. A common observation among some of these studies of low-level Pb exposure is a non-linear dose-response relationship between blood Pb and neurodevelopmental outcomes. Although this may seem at odds with certain fundamental toxicological concepts, it is possible that the initial neurodevelopmental lesions at lower Pb levels may be disrupting different biological mechanisms (e.g., early developmental processes in the central nervous system) than the more severe effects of high exposures that result in symptomatic poisoning and frank mental retardation. One ad hoc explanation may be that the predominant mechanism at very low blood-Pb levels is rapidly saturated and that a different, less-rapidly-saturated process, becomes predominant at blood-Pb levels greater than 10 μg/dL.

Another global measure of cognitive function is academic achievement. Compared to the vast number of studies assessing the blood Pb-IQ relationship in children, there are relatively little data available on the relationship between Pb exposure and objective measures of academic achievement. These studies focused on the effect of Pb on school performance, including reading, math, spelling, and handwriting (see Section 6.2.4).

Lanphear et al. (2000) examined the relationship between blood-Pb levels and a standardized measure of academic achievement among 4,853 NHANES III children, aged 6 to 16 years (geometric mean blood-Pb of 1.9 μg/dL). Subjects were administered the Arithmetic and Reading subtests of the Wide Range Achievement Test-Revised (WRAT-R). Multiple linear regression revealed significant Pb-related decrements in Arithmetic and Reading scores. In analyses stratified by blood-Pb levels, statistically significant inverse relationships between blood-Pb levels and performance for both Reading and Arithmetic subtests were found for children with concurrent blood-Pb concentrations <5 μg/dL. However, possible attribution of the observed associations of decrements in WRAT-R scores to earlier (but unmeasured) likely somewhat higher peak blood-Pb concentrations cannot be ruled out.

Several other epidemiologic studies observed inverse associations between exposure to Pb and academic achievement, for the endpoints noted above as well as class rankings and high school graduation rates. Two studies specifically examined the effects of blood-Pb levels <10 μg/dL on academic achievement. One study examined 533 girls aged 6 to 12 years (mean blood Pb level of 8.1 μg/dL) in Riyadh, Saudi Arabia and observed that, in a subset of students with blood-Pb levels <10 μg/dL, class rank percentile was statistically significantly associated with blood-Pb levels (Al-Saleh et al., 2001). In another study in Torreón, Mexico, a significant inverse relationship was found between blood-Pb concentrations and math and vocabulary scores in 594 second graders (mean blood Pb of 11.4 μg/dL). In segmented regression analyses, slopes for blood Pb associations with vocabulary and math scores were significantly steeper below 10 μg/dL than above (Téllez-Rojo et al., 2006). Associations between Pb exposure and academic achievement observed in the above-noted studies were significant even after adjusting for IQ, suggesting that Pb-sensitive neuropsychological processing and learning factors not reflected by global intelligence indices might contribute to reduced performance on academic tasks.

Specific Cognitive Abilities – Learning, Memory, and Attention

In addition to IQ and academic achievement, epidemiologic studies have evaluated Pb effects on specific cognitive abilities, e.g., attention, executive functions, language, memory, learning, and visuospatial processing. Results from these studies are most comparable to those experimental animal studies examining Pb effects on learning ability, memory, and attention.

Executive functions refer to an individual's ability to regulate attention and engage several related higher order cognitive processes such as strategic planning, control of impulses, organized search, flexibility of thought and action, and self-monitoring of one's own behavior. In some earlier studies, as assessed in the 1986 Pb AQCD/Addendum and/or 1990 Supplement, Pb exposure was associated with higher frequency of negative ratings by teachers and/or parents on behaviors such as inattentiveness, impulsivity, distractibility, and lack of persistence on assigned tasks, as well as slowed psychomotor responses and more errors on simple, serial, and choice reaction time tasks. More recent studies (see Section 6.2.5) have observed inverse relationships between exposure to Pb and attentional behaviors and executive function, even in cohorts where more than 80% of the children had blood-Pb levels <10 μg/dL. These associations were observed across a wide range of age groups, from children 4-5 years to 19-20 years of age. Higher blood-Pb levels were also associated with impaired memory and visual-spatial skills.

Whether the domains of executive functions, attention, memory, or visual-motor integration per se are specifically sensitive to Pb is unknown, as there is rarely a one-to-one correspondence between performance on a focused neuropsychological test and an underlying neuropsychological process. For example, a low score on the visual-motor integration test may reflect singular or multiple neurobehavioral deficits, e.g., difficulties with graphomotor control, visual perception, behavioral monitoring (impulsivity), and/or planning (executive functions). Early Pb exposure may be associated with poorer performance on executive/regulatory functions that are thought to depend on the frontal or prefrontal brain regions. The prefrontal cortex is highly innervated by neuronal projections from the midbrain and has the highest concentration of dopamine of all cortical areas. The dopamine system, which plays a key role in cognitive abilities mediated by the prefrontal cortex, is particularly sensitive to Pb, based on data from studies of rodents and nonhuman primates (see Section 5.3). These animal toxicology findings

provide strong biological plausibility in support of the concept that Pb may impact one or more of these specific cognitive functions in humans.

Results from fixed interval (FI) studies in 4 species of laboratory animal models at environmentally relevant doses (as shown in Figure 5-3.5) clearly demonstrate that Pb induces increased response rates. The increased response rates are mostly due to shortened time to initiate responding in the interval and more rapid response once the responding begins. This pattern of effects has been compared to young human males diagnosed with Attention Deficit/Hyperactivity Disorder (ADHD), and it is thought that increases in response rates found in animal models parallel increases in impulsivity in self-control paradigms (as noted by Cory-Slecta, 2003a).

As noted in Section 5.3.5, NMDAR function and ontogeny are affected by Pb exposure. Functional NMDARs are necessary for spatial learning and memory, as tested by the Morris water maze. Several studies that evaluated Pb effects with this learning paradigm have shown that chronic exposure to 250 ppm Pb affected long-term memory. The effect of Pb on memory is not clearly understood. In some studies, memory impairment was found at blood Pb levels of 10 μg/dL, whereas numerous other studies found no Pb-induced effects on short term memory. This parallels findings from most cross-sectional and prospective epidemiological studies, which generally did not detect low-level Pb exposure effects on memory.

Studies of early developmental cognitive ability in monkeys postnatally exposed to Pb (see Section 5.3.5) have used the Early Infant Behavioral Scale, which is modeled after the Brazelton Neonatal Behavioral Assessment. The monkeys displayed both decreased visual attentiveness and increased agitation. Other epidemiologic studies using the Brazelton scale have shown analogous results for human infants.

7.4.2.2 Behavior, Mood, and Social Conduct

Investigating associations between Pb exposure and behavior, mood, and social conduct of children has been an emerging area of research (see Section 6.2.6). Early studies indicated linkages between lower-level Pb toxicity and behavioral problems (e.g., aggression, attentional problems, and hyperactivity) in children. Blood-Pb and tooth-Pb levels have been associated with behavioral features of ADHD, including distractibility, poor organization, lacking persistence in completing tasks, and daydreaming, in various cohorts of children with a wide

range of Pb exposures. In the Port Pirie, Australia cohort study, the relationship between Pb exposure and emotional and behavioral problems at ages 11 to 13 years were examined after stratifying the data set by gender. Stronger associations with Pb were observed for externalizing behavior problems in boys compared to girls. In contrast, greater internalizing behavior problems were observed for girls than in boys.

The relationship between Pb exposure and delinquent and criminal behavior also has been addressed in several investigations. Studies linking attention deficits, aggressive and disruptive behaviors, and poor self-regulation with Pb have raised the prospect that early exposure may result in an increased likelihood of engaging in antisocial behaviors in later life. In two prospective cohort studies conducted in Pittsburgh (Needleman et al., 1996) and Cincinnati (Dietrich et al. 2001), elevated Pb levels were associated with several measures of behavioral disturbance and delinquent behavior. It was also observed that bone-Pb levels in adjudicated delinquents were significantly higher than in non-delinquent community control subjects in Pittsburgh and surrounding Allegheny County, PA environs. In a Philadelphia survey of 987 African-American youths, a history of Pb poisoning was among the most significant predictors of delinquency and adult criminality in males (Denno, 1990).

These results indicate that Pb may play a role in the epigenesis of behavioral problems in inner-city children independent of other social and biomedical cofactors. The particular biological mechanisms that may underlie Pb's effects on aggression, impulsivity, and poor self-regulation are not yet well understood. However, Pb impacts many brain sites and processes involved in impulse control (Lidsky and Schneider, 2003). Also, the increased risk of delinquency may indirectly be a consequence of attentional problems and academic under-achievement among children who suffered higher Pb exposures during their formative years (as noted by Needleman et al., 2002).

Lead has been shown to affect reactivity to the environment and social behavior in both rodents and nonhuman primates at blood-Pb levels of 15 to 40 μg/dL, though the literature has some conflicting studies (see Section 5.3.5). In general, most studies show a Pb-induced enhancement of social investigation and exploratory behavior. Aggression was increased in hamsters, but not in rats, though the latter did display increased behavioral reactivity to stimuli. Early postnatal testing of Pb-exposed rhesus monkeys has shown lowered muscle tonus, greater agitation, and decreased visual attentiveness. Chronically exposed rhesus monkeys exhibited Pb-

induced disruption of social play and increased self-stimulation and fearful behavior that persisted for months after exposure ended. Thus, no clear pattern is yet apparent in the experimental literature examining aggression that parallels the epidemiologic findings of Pb-induced increases in aggression and delinquent behavior among humans. However, the findings of increased reactivity to stimuli, impulsivity, and attention dysfunction found in both Pb-exposed animals and humans may underlie some of the behavioral and emotional problems observed epidemiologically.

7.4.2.3 Neurophysiologic Outcomes

Electrophysiological evaluations have been conducted on Pb-exposed children in attempts to obtain a more direct measure of the toxicant's impact on the nervous system (as discussed in Section 6.2.9). Much of this work was conducted by Otto and colleagues during the 1980s and demonstrated effects of Pb on neurosensory functioning (auditory and visual evoked potentials) within a broad range of exposures. Associations between Pb exposure and brainstem auditory evoked responses were less consistent.

Epidemiologic studies of the effect of Pb on sensory acuity have focused on hearing thresholds and features of auditory processing in Pb-exposed children. Schwartz and Otto (1987) observed significant Pb-associated elevations in pure-tone hearing thresholds at various frequencies within the range of human speech among over 4,500 4 to 19 year old subjects in NHANES II. These findings were replicated in a sample of ~3,000 subjects (6 to 19 years old) in the Hispanic Health and Nutrition Examination Survey (HHANES) (Schwartz and Otto, 1991), including at blood-Pb levels <10 µg/dL.

Dietrich et al. (1992) assessed the relationship between scores on a test of central auditory processing (SCAN) and blood-Pb concentrations in 215 children 5 years of age drawn from the Cincinnati Lead Study. Higher prenatal, neonatal, and postnatal blood-Pb concentrations were associated with more incorrect identification of common monosyllabic words presented under conditions of filtering (muffling). In another study, conducted in Poland, a significant association between concurrent blood-Pb levels and increased hearing thresholds was also observed among 155 children 4 to 14 years of age (median blood Pb of 7.2 µg/dL) (Osman et al., 1999). This relationship remained statistically significant when restricted to children with blood-Pb levels <10 µg/dL. The supportive evidence of a relationship between Pb exposure and

auditory processing suggests that Pb-related deficits in hearing and auditory processing may be one plausible mechanism by which an increased Pb burden might impede a child's learning (Bellinger, 1995).

Animal studies have shown Pb-induced deficits in both auditory and visual acuity, which may contribute to the cognitive deficits associated with Pb exposure. Blood Pb levels as low as 33 μg/dL in nonhuman primates impair auditory function by increasing latencies in brainstem auditory evoked potentials and elevating hearing thresholds. Blood-Pb levels of 19 μg/dL in rats have been found to cause selective effects on rod and bipolar cells, resulting in decreased maximal ERG amplitude, decreased ERG sensitivity, and increased mean ERG latency. In a review of Pb-induced auditory and visual dysfunction, Otto and Fox (1993) point to the structural, biophysical, and photochemical similarities of rods in rats, monkeys and humans and suggest that undetected visual or auditory deficits may profoundly impact both sensory motor and mental development in children.

In recent epidemiologic studies of Pb-exposed children (see Section 6.2.9), the methods of Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) have been applied. Several studies compared subjects with elevated blood-Pb levels (blood Pb $\geq$23 μg/dL) to control subjects (blood Pb <10 μg/dL). Although all of the participants had normal MRI examinations, the Pb-exposed subjects exhibited a significant reduction in N-acetylaspartate: creatine and phosphocreatine ratios in frontal gray matter compared to controls. Similarly, reduced peak values of N-acetylaspartate, choline, and creatine were found in all four brain regions in Pb-exposed children relative to control subjects. The reduced brain N-acetylaspartate levels observed in cases may be related to decreased neuronal density or neuronal loss. Also, reduced choline signal may indicate decreased cell membrane turnover or myelin alterations that can lead to central nervous system hypertrophy, while lower creatine may indicate reduced neuronal cell viability.

Using functional MRI (fMRI), a subsample of 48 young adults (aged 20-23 years) from the Cincinnati Lead Study performed an integrated verb generation/finger tapping paradigm (Cecil et al. 2005; Yuan et al., 2006). Higher childhood average blood-Pb levels were significantly associated with reduced activation in Broca's area, a recognized region of speech production in the left hemisphere, and increased activation in the right temporal lobe, the homologue of Wernicke's area (an area associated with speech production) in the left

hemisphere. This suggests that elevated childhood Pb exposure may influence neural substrates underlying semantic language function in normal language areas, with concomitant recruitment of contra-lateral regions causing a dose-dependent atypical organization of language function.

7.4.2.4 Neuromotor Function and Vocalization

Only a few recent epidemiologic studies have evaluated neuromotor deficits as an outcome of early Pb exposure (see Section 6.2.8). In the Cincinnati Lead Study cohort, blood-Pb levels, both neonatal and postnatal, were significantly associated with poorer scores on measures of bilateral coordination, visual-motor control, upper-limb speed and dexterity, fine motor composite from the Bruininks-Oseretsky scales, and postural stability in children 6 years of age (Dietrich et al. 1993b). In general, the strongest and most consistent relationships were observed with concurrent blood-Pb levels (mean 10.1 μg/dL). At 16 years of age, 78-month postnatal blood-Pb levels were significantly associated with poorer fine-motor skills, as indexed by covariate-adjusted factor scores derived from a factor analysis of a comprehensive neuropsychological battery. Variables loading highly on the fine-motor component came from grooved pegboard and finger tapping tasks. In the Yugloslavian Prospective Study, lifetime average blood-Pb concentration through 54 months of age was associated with poorer fine motor and visual motor function, but was unrelated to gross motor function (Wasserman et al., 2000a).

Another recent study examined the effect of multiple exposures (including Pb, mercury, and PCBs) on neuromotor functions in 110 preschool Inuit children residing in Canada (Després et al., 2005). Significant associations that were found only for blood-Pb concentrations (mean of 5.0 μg/dL) were those associated with increased reaction time, sway oscillations, alternating arm movements, and action tremor. Even after eliminating children with blood-Pb levels >10 μg/dL (10% of cohort) from the analyses, results generally remained consistent, suggesting that neuromotor effects of Pb occurred at blood Pb levels <10 μg/dL.

Changes in vocalization are a potential biomarker for Pb exposure. That is, analyses of acoustical cries in babies showed that percent nasalization decreased progressively over cord blood-Pb ranging from 4 to 40 μg/dL and that the number of cries was inversely related to cord blood-Pb. These data may parallel Pb-induced changes in vocalization seen in developing rats (see Section 5.3.5).

Earlier studies showed developmental lags in gross activity in rats with blood-Pb levels as low as 14 μg/dl, but other studies have found often contradictory results. More recent nonhuman primate studies showed either no effects or subtle motor impairments, increased durations of activity, failures to habituate, increased agitation, and fear. Rodent studies showed either no effects or increases in locomotor activity and changes in vocalization patterns. Thus, no clear pattern of Pb-induced effects on motor activity has yet emerged, though many studies do point to an increase in activity, as seen with epidemiologic findings. However, Cory-Slechta (1989), in discussing behavioral endpoints in Pb neurotoxicity, suggests that motor activity has little correspondence with more complex functions important for human populations.

7.4.2.5 Neurochemical Alterations

Examination of Pb-induced biochemical alterations of the nervous system has largely been limited to laboratory animal toxicologic studies. Although the linkage of neurochemical alterations in animal to human neurobehavioral function is somewhat speculative, these studies do provide some insight into possible neurochemical mediators of Pb neurotoxicity.

As summarized in Section 5.3.2, it has long been well known that Pb^{2+} acts as a Ca^{2+} mimetic. This affects neurotransmitter release in a dose-dependent fashion at glutamatergic, cholinergic, and dopaminergic synapses. Glutamate, acetylcholine and dopamine systems play very important roles in both cognitive function and brain development in both laboratory animals and in humans. Extensive research has focused on chronic Pb exposure effects on NMDA receptors. Much of the data point to an inhibition of NMDAR and changes in the ontogeny of receptor subunit expression, though full characterization of the effects on specific subunits is not available.

Considerable research has also focused on interactions of Pb^{2+} and Ca-dependent kinases and phosphodiesterases. Lead alters the activity of many of these enzymes, which results in changes in CREB, the transcription factor that controls expression of genes involved in learning, memory, and synaptic plasticity. Protein kinase C (PKC) is also a Pb target, though the Pb effects on PKC in the intact animal have not been fully characterized. Thus, possible relationships of Pb effects on this pathway to human cognitive function effects are not yet clear.

7.4.2.6 Assessment of Dose-Response Relationships for Neurotoxic Effects of Lead Exposure

An important consideration in assessing potential public health impacts associated with Pb exposure is whether concentration-response relationships are linear across the full exposure range or, rather, shows nonlinearity. Also of interest is whether any thresholds can be discerned for various types of health effects associated with Pb exposure. The 1986 AQCD/Addendum and 1990 Supplement concluded that neurotoxic effects were related to blood Pb levels of 10 to 15 μg/dL and possibly lower. Since then, the U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) have also lowered their definition of an elevated blood Pb concentration to 10 μg/dL (CDC, 1991; WHO, 1995). Average blood-Pb levels in U.S. children ages 1 to 5 years decreased from 15 μg/dL in 1976-1980 to ~3 μg/dL in 1991-1994 (CDC, 2000; Pirkle et al., 1998), allowing more recent studies to examine the effects of low level Pb exposure on the neurodevelopment of children (as discussed in Section 6.2.3).

Several recent epidemiologic studies have observed significant Pb-induced IQ decrements in children with blood Pb levels <10 μg/dL (e.g., Canfield et al., 2003a; Lanphear et al., 2005) and, in some cases, possibly below 5 μg/dL (Bellinger and Needleman, 2003; Téllez-Rojo et al., 2006). The most compelling evidence for effects below 10 μg/dL, as well as a nonlinear relationship between blood Pb levels and IQ, comes from the international pooled analysis of seven prospective cohort studies (n = 1,333) by Lanphear et al. (2005). The slope for Pb effects on IQ was steeper at lower blood-Pb levels, as indicated by the cubic spline function, the log-linear model, and the piece-wise linear model. The shape of the spline function indicated that the steepest declines in IQ were at blood-Pb concentrations <10 μg/dL. Based on stratified analyses using two cut points, a maximal blood-Pb of 7.5 and 10 μg/dL, the effect estimate for children with maximal blood-Pb levels <7.5 μg/dL was significantly greater than for those with a maximal blood-Pb ≥7.5 μg/dL. Similar results were seen at the cut point of 10 μg/dL. Thus, recent epidemiologic evidence is highly indicative of Pb-induced neurocognitive deficits in children at blood Pb levels below 10 μg/dL and, possibly, as low as 5 μg/dL.

In addition to IQ, significant associations were observed at low blood-Pb levels for other neurotoxicity endpoints. In the large NHANES III study, children aged 6 to 16 years with concurrent blood Pb <5 μg/dL exhibited significant Pb-related decrements in Arithmetic and Reading scores (Lanphear et al., 2000), but the possibility of earlier somewhat higher peaks in

blood-Pb levels of the same children around 2.5 years of age cannot be ruled out. Inverse relationships between exposure to Pb and attentional behaviors and executive function were also observed in cohorts where >80% of the children had blood Pb levels <10 μg/dL (Canfield et al., 2003b; Stiles and Bellinger, 1993). Other studies have found significant Pb-induced impairments of neuromotor function (Després et al., 2005) and hearing (Osman et al., 1999; Schwartz and Otto, 1987, 1991) in children with blood-Pb levels <10 μg/dL. Collectively, these studies most clearly indicate that Pb is associated with various neurodevelopmental endpoints in children at blood-Pb levels as low as 5 to 10 μg/dL. However, the shape of the concentration-response curve has not been as extensively examined in these studies; thus, there is still some question as to whether, for endpoints other than IQ, larger effects per incremental dose occur at blood Pb levels <10 μg/dL.

As stated in Section 5.3.7, there is little if any evidence from experimental animal studies that allow for any clear delineation at this time of a threshold for neurotoxic effects of Pb. Neurobehavioral changes have been reported in rodent studies at blood-Pb levels of ~10 μg/dL, whereas neurochemical and neurophysiological changes have been reported at blood Pb levels of ~15 μg/dL. However, these levels do not necessarily indicate a threshold for such effects but, rather, may only reflect the levels of exposure that have been studied to date. Also, other information, discussed in Chapter 4, suggests that blood-Pb concentrations in some animal models (e.g., the rat or other rodents) may be more comparable to somewhat lower blood-Pb levels seen in humans with more or less similar exposure conditions. Thus, blood-Pb levels associated with neurobehavioral effects appear to be reasonably parallel between humans at blood-Pb concentrations and animals; and such effects appear likely to occur in humans ranging down at least to 5-10 μg/dL, or possibly lower (although the possibility of a threshold for such neurotoxic effects cannot be ruled out at lower blood-Pb concentrations).

Lead appears to exhibit a curvilinear, or U-shaped, dose-effect relationship for a number of toxicological endpoints. This effect is not unique to Pb, but occurs with other toxicants (e.g., mercury chloride, chlordane, toluene, chlorpyrifos) as well, as reviewed by Calabrese (2005). In the case of Pb, this nonlinear dose-effect relationship occurs in the pattern of glutamate release (Section 5.3.2), in the capacity for long term potentiation (LTP; Section 5.3.3), and in conditioned operant responses (Section 5.3.5). The 1986 AQCD also reported U-shaped dose-effect relationships for maze performance, discrimination learning, auditory evoked

potential, and locomotor activity. Davis and Svendsgaard (1990) reviewed U-shaped dose-response curves and their implications for Pb risk assessment. An important implication is the uncertainty created in identification of thresholds and "no-observed-effect-levels" (NOELS). As a nonlinear relationship is observed between IQ and low blood Pb levels in humans, as well as in new toxicologic studies wherein neurotransmitter release and LTP show this same relationship, it is plausible that these nonlinear cognitive outcomes may be due, in part, to nonlinear mechanisms underlying these observed Pb neurotoxic effects.

7.4.2.7 Susceptibility and Vulnerability to Neurotoxic Effects from Lead Exposure

Several factors have emerged as likely affecting the relative likelihood that humans or laboratory animals may experience Pb-induced neurotoxic effects under particular Pb exposure conditions. Among the more important factors identified thus far are: age; gene-environment interactions; gender; and socioeconomic status.

Age

Identifying discrete periods of development when the fetus or child is particularly susceptible to Pb's effects on neurodevelopment is difficult as (1) age strongly predicts the period of peak exposure (around 18-27 months when there is maximum hand-to-mouth activity), making it difficult to distinguish whether greater neurotoxic effects resulted from increased exposure or enhanced susceptibility at a particular age; and (2) despite changes in actual blood Pb levels, children tend to maintain their relative rank order with regard to neurodevlopment indicators through time, limiting the ability to examine critical periods of development.

One notable epidemiologic study has observed the strongest associations between IQ at school age and academic achievement and blood Pb concentrations at 2 years of age (Bellinger, et al., 1992). An understanding of human neurodevelopmental biology supports the notion that the first 3 years of life represent a particularly vulnerable period. Maximal ingestion of Pb often coincides with this same period of time when major events are occurring in the development of the human central nervous system, including some neurogenesis, rapid dendritic and axonal outgrowth, synaptogenesis, synaptic pruning, and programmed cell death (see Nolte, 1993).

However, the human central nervous system continues to mature and be vulnerable to neurotoxicants throughout the lifespan (Selevan et al., 2000, Weiss, 2000, Rice and Barone,

2000). Several prospective studies of children with both high and low Pb exposures found concurrent or lifetime average blood-Pb levels to be more strongly associated than other earlier blood-Pb measures with school age IQ and other measures of neurodevelopment (Canfield et al., 2003a; Dietrich et al., 1993a,b; Tong et al., 1996; Wasserman et al., 2000b). Using data from the Treatment of Lead-Exposed Children (TLC) study, Chen et al. (2005) examined whether cross-sectional associations observed in school age children 84-90 months of age represented residual effects from 2 years of age or "new" effects emerging among these children. Concurrent blood-Pb concentration always had the strongest association with IQ. The strength of the cross-sectional associations increased over time, despite lower blood-Pb concentrations in older children. Adjustment for prior IQ did not fundamentally change the strength of the association with concurrent blood-Pb level. These results suggest that Pb exposure continues to be toxic to children as they reach school age, but does not support an interpretation that all of the damage occurred by the time the child reaches 2 to 3 years of age. Examination of the toxicologic evidence may be especially enlightening on this topic, given the difficulties involved in assessing any periods of particularly increased susceptibility to Pb neurodevelopmental health effects in the epidemiologic setting.

Cory-Slechta (1989) has reviewed age considerations in the neurotoxicology of Pb and concluded that: (1) though the presumed critical exposure period is prenatal and neonatal, vulnerability extends well beyond this period in both rodents and humans; (2) for some neurobehavioral endpoints (such as schedule-controlled behavior), the developmental period of exposure can be relatively unimportant, whereas the body burden of Pb is more critical; (3) enhanced vulnerability to Pb may also occur in later life, as ageing processes induce degenerative changes in various organ systems; and (4) age-related shifts occur in the toxicokinetics of Pb, such that Pb can be redistributed to brain and liver from bone during later phases of life beyond the time of earlier Pb exposures.

Gene-Environment Interactions

A few recent epidemiologic studies have examined susceptibility to Pb health effects as related to genetic polymorphisms associated with Pb biokinetics and/or neurotransmitter metabolism and function (as discussed in Section 6.2.10). Genetic polymorphisms in certain genes have been implicated as influencing the absorption, retention and toxicokinetics of Pb in

humans. Although the ALAD gene has been the most studied, as of yet, the consequences of different alleles for susceptibility to the neurodevelopmental consequences of Pb exposure in children are unclear. For example, ALAD2 polymorphism has been implicated in influencing vulnerability by raising blood Pb levels or by decreasing them by maintaining Pb in a sequestered state in the bloodstream. Suggestive but limited evidence appears to indicate that adolescents with the ALAD2 polymorphism tended to have lower dentin-Pb levels and performed better in areas of attention and executive functioning when compared to subjects with the ALAD1 polymorphism.

Another gene of interest is the vitamin D receptor or VDR gene, which is involved in calcium absorption through the gut. The variant VDR alleles may modify Pb concentrations in bone and the rate of resorption and excretion of Pb over time. The relationship between the VDR Fok1 polymorphism and blood Pb concentrations was evaluated in 275 children enrolled in the Rochester Longitudinal Study. A significant interaction was found between floor dust-Pb loading and VDR-Fok1 genotypes on blood Pb concentration, with the FF genotypes (a marker for increased calcium absorption) having the highest adjusted mean blood Pb concentrations at 2 years of age compared to children with Ff or ff genotypes. High prevalence of FF genotypes in African American children, compared to non-African American children, may partially explain higher blood Pb concentrations often observed in African American children. There have been no studies to indicate which, if any, of the VDR polymorphisms are associated with increased vulnerability to the neurodevelopmental toxicity of Pb. Animal toxicology studies have yet to identify any role of genetic polymorphism in ALAD or VDR in affecting Pb toxicity.

Tiffany-Castiglioni et al. (2005), in an overview of genetic polymorphisms relating to mechanisms of neurotoxicity, state that an understanding of the relationship among ALAD polymorphisms, blood Pb levels, and Pb neurotoxicity is difficult at this time. They further note that, though urinary ALA is a good marker for Pb exposure, it may not correlate with neuronal damage. There is a similar lack of information using animal models to characterize genetic polymorphisms of the VDR and hemochromatosis genes.

Gender

Most surveys find that boys have higher blood-Pb levels than girls; yet the data are less clear with regard to gender-related differences in Pb-associated neurodevelopmental effects. As

discussed in Section 6.2.10, a greater male vulnerability was seen in the Cincinnati Lead Study at various assessments from birth to adolescence. Also, data from a cross-sectional study in England showed more pronounced Pb-IQ deficit associations for boys at 6 years of age. However, in a study of 764 children in Taiwan, the relationship between Pb exposure and IQ scores was much stronger in girls; and, in the Port Pirie, Australia cohort study, Pb effects on cognition were significantly stronger in girls at ages 2, 4, 7, and 11-13 years.

In the Cincinnati Lead Study (see Section 6.2.3.1), an extensive neuropsychological battery administered to 15-17 year old subjects examined executive functions, attention, memory, achievement, verbal abilities, visuoconstructional skills, and fine-motor coordination as key endpoints. About 30% of the subjects had blood-Pb concentrations $\geq$25 µg/dL during the first 5 years of life, and 80% of the cohort had at least one blood Pb $\geq$15 µg/dL. A strong "executive functions" factor did not emerge from a factor analysis of scores. However, the analysis, following covariate-adjustment, revealed strong associations between Pb exposure and the attention factor for males. This gender interaction suggests that neuromechanisms sub-serving attention were affected by Pb in this cohort for boys but not for girls. This is not surprising, given the heightened vulnerability of males for a wide range of developmental perturbations. A substantial gender difference (greater incidence among boys) in the incidence of Attention Deficit/Hyperactivity Disorder (ADHD) is well established, and one could speculate that early exposure to Pb exacerbates a latent potential for such problems.

The Port Pirie, Australia cohort study examined relationships between Pb exposure and emotional and behavioral problems at ages 11-13 years after stratifying the data set by gender. Stronger associations with Pb were observed for externalizing behavior problems in boys versus girls; but greater internalizing behavior problems were found for girls.

Early laboratory animal Pb toxicology studies did not evaluate gender differences in responses to chronic or acute Pb exposure, with the exception of several that showed differences in social investigatory behavior and nonsocial activity. Some studies pointed to greater social investigatory behavior in males compared to females. More recent work by Cory-Slechta and colleagues (Section 5.3.1.7) has shown greater synergistic effects of Pb and stress in female rats, coupled with permanently elevated corticosterone levels. Also, maternal Pb exposure and restraint stress caused greater changes in operant behavior and stress responses in female

offspring. These studies point to clear gender differences in response to Pb and suggest possible hypothalamic-pituitary-adrenal axis-modulated effects of Pb on CNS function.

Socioeconomic Status

Epidemiologic studies have shown that Pb exposure is typically higher among low socioeconomic status (SES) children compared to other U.S. children. Chronic stress and consequent increased levels of glucocorticoids are also associated with low SES. Cory-Slechta et al. (2004) have pointed out that both elevated glucocorticoids and Pb can cause similar behavioral changes and that both impact the mesocorticolimbic systems of the brain. As discussed in Section 5.3.7, their data indicate a potential mechanism whereby Pb exposure enhances susceptibility to cognitive deficits and disease states.

7.4.2.8 Persistence/Reversibility of Neurotoxic Effects from Lead Exposure

Much of the classic Pb poisoning literature substantiates well the persistence of serious neurological damage resulting from extremely high Pb exposures. The persistence of more subtle, but important, neurotoxic effects of lower level Pb exposure has been accorded much attention during the past decade or so. Much of the pertinent human and animal data seem to suggest that the neurotoxic effects of Pb may not generally be reversible. As noted in Chapter 6, excessive accumulation of Pb in childhood has latent and/or persistent adverse health effects on both the peripheral and central nervous systems of human adults assessed 19-29 years later. Also, chelation studies in humans and animals (summarized in AX6-X and AX5-3.6) show that chelation decreases total body Pb burden, but does not necessarily exert evident effects on Pb-induced cognitive deficits. For example, the extensive multi-center TLC study summarized by Rogan et al. (2001) indicates that medical interventions involving chelation therapy (e.g., Succimer use) do not seem to fully reverse cognitive deficits associated with early Pb exposure. Also, nonhuman primate studies evaluated the persistence of effects by limiting the Pb exposures to the first year of life, as discussed in the 1986 AQCD and more recently (see Section 5.3.5). In these monkeys, deficits in performance of both spatial discrimination tasks and delayed spatial alternation were seen up to 8 years post exposure, when blood Pb had dropped to control levels. In one study, however, the Pb-treated monkeys performed better than control subjects at 4 years of age. In addition, a few studies discussed in the 1986 Pb AQCD and some more recent studies

have suggested possible reversibility of observed Pb-induced learning deficits. Such studies suggest that reversibility depends on the age of the organism at the time of exposure, the exposure duration, dosage, and other exposure parameters. Also, several animal studies (Section 5.3.5) demonstrate that environmental enrichment during development can help to protect against cognitive effects of low-level Pb exposures.

Davis et al. (1990), however, sound a cautionary note with regard to the interpretation of neurobehavioral data in light of compensatory capacities of the nervous system. They note that compensatory capacities may become overwhelmed with aging, concurrent disease state, stress due to socioeconomic status, or other stressors. It may be only then, possibly decades following earlier Pb exposure, that some Pb-induced neurobehavioral effects become obvious.

7.4.2.9 Summary of Toxicologic and Epidemiologic Evidence of Lead-Induced Neurotoxicity

Findings from numerous experimental studies of rats and of nonhuman primates, as discussed in Chapter 5, parallel the observed human neurocognitive deficits and the processes responsible for them. Learning and other higher order cognitive processes show the greatest similarities in Pb-induced deficits between humans and experimental animals. Deficits in cognition are due the combined and overlapping effects of Pb-induced perseveration, inability to inhibit responding, inability to adapt to changing behavioral requirements, aversion to delays, and distractibility. Higher level neurocognitive functions are affected in both animals and humans at very low exposure levels ($\leq$10 µg/dL), more so than simple cognitive functions. For example, the discrimination reversal paradigm is a more sensitive indicator of Pb-induced learning impairment than simple discrimination. Many studies suggest that most Pb-induced cognitive deficits are very persistent and that animals remain vulnerable to the effect of Pb throughout development. Some studies, however, suggest that environmental enrichment during early development may confer some offsetting protection against Pb-induced cognitive effects or that other factors (e.g., short-lived exposure duration/low concentration) may, at times, induce detectable but transient cognitive deficits. Also, more evidence is emerging that substantiates Pb-induced attentional deficits, which may contribute to persisting cognitive dysfunction, poorer academic performance, and/or maladaptive anti-social behavior patterns (e.g., delinquency).

Other behavioral endpoints (e.g. social behavior, aggression, and locomotor activity) evaluated in animal studies in relation to Pb exposure did not clearly indicate Pb-induced impairments. This may be due to the lack of effect with low-level Pb exposure or to variables (e.g., nutrition, age, gender, and strain) possibly not well controlled for experimentally.

7.4.3 Cardiovascular Effects

Epidemiologic studies that have examined the effects of blood-Pb levels on blood pressure have generally found positive associations, even after controlling for confounding factors such as tobacco smoking, exercise, body weight, alcohol consumption, and socioeconomic status (discussed in Section 6.5.2). Recent meta-analyses of these studies have reported robust, statistically-significant, though small effect-size, associations between blood-Pb concentrations and blood pressure. For example, the meta-analysis of Nawrot et al. (2002) indicated that a doubling of blood Pb corresponded to a 1 mm Hg increase in systolic blood pressure. Although this magnitude of increase is not clinically meaningful for an individual, a population shift of 1 mm Hg is important. The majority of the more recent studies employing bone-Pb level have also found a strong association between long-term Pb exposure and arterial pressure. Since the residence time of Pb in blood is relatively short but very long in bone, the latter observations have provided compelling evidence for the positive relationship between Pb exposure and a subsequent rise in arterial pressure in human adults.

Numerous experimental animal studies have shown that exposure to low levels of Pb for extended periods results in an eventual onset of arterial hypertension (HTN) that persists long after the cessation of Pb exposure in genetically normal animals. Many studies have been conducted to explore the mechanisms by which chronic Pb exposure may cause HTN. Most of these studies have examined various blood-pressure regulatory and vasoactive systems in animal models of Pb-induced HTN. A number of studies have also utilized in vitro cell culture systems such as endothelial and vascular smooth muscle cells to gain insight into molecular mechanisms implicated in this process. Key findings have emerged from the newly available in vivo and in vitro studies of mechanisms including the following several important points.

During the past decade, several studies have shown that Pb exposure causes oxidative stress, particularly in the kidney and cardiovascular tissues, as well as in cultured endothelial and vascular smooth muscle cells (VSMC), as noted in Section 5.5.2.1. The in vivo studies have

further shown that Pb-induced oxidative stress is, at least in part, responsible for associated hypertension (HTN) in experimental animals. Khalil-Manesh et al. (1994) were among the first to suggest that oxidative stress may be involved in the pathogenesis of lead-induced HTN. Gonick et al. (1997) later provided evidence for the occurrence of oxidative stress and compensatory up regulation of NOS isotypes in the kidney of animals with lead-induced HTN. Studies carried out with antioxidants, e.g., lazaroid compound, resulted in a significant alleviation of oxidative stress, improved NO availability, and a marked attenuation of HTN without affecting blood Pb concentration, further demonstrating that Pb-induced HTN is associated with diminished NO availability and that the latter was mediated by oxidative stress (Vaziri et al., 1997).

Numerous in vivo and in vitro studies on Pb-induced HTN, using endothelial and VSMC with or without intervention by antioxidant therapeutics, suggest a role of oxidative stress and NO in the pathogenesis of lead-induced HTN in the rat.

These observations provided compelling evidence that Pb-induced HTN causes oxidative stress, which, in turn, promotes functional NO deficiency via ROS-mediated NO inactivation. The latter, in turn, participates in the development and maintenance of HTN and cardiovascular abnormalities. Also, the formation of the highly cytotoxic reactive nitrogen species peroxynitrite ($ONOO^-$) from the NO-ROS interaction and the associated nitrosative stress could potentially contribute to long-term cardiovascular, renal, and neurological consequences of Pb exposure.

Higher plasma levels of lipid peroxides in uncontrolled essential hypertension as compared to normal controls suggested that free radicals are involved in the pathobiology of human essential hypertension. Angiotensin II, a potent vasoconstrictor, was found to stimulate free radical generation in normal leukocytes. This increase in free radical generation was thought to inactivate NO, and possibly prostacyclin, which can lead to an increase in peripheral vascular resistance and hypertension.

In spite of such a wide range of experimental investigations into the cardiovascular effects of Pb in animal studies, it is still not clear as to why low, but not high, levels of Pb exposure cause HTN in experimental animals.

7.4.4 Heme Synthesis and Blood Effects

Lead exposure has long been recognized to be associated with disruption of heme synthesis in both human children and adults. With extreme Pb exposure leading to blood-Pb levels >30 μg/dL, Pb-induced heme synthesis interference leads to notable reductions in hemoglobin synthesis and, at blood-Pb ≥40 μg/dL, to frank anemia (a classic clinical sign of severe Pb poisoning).

Other indications of disruption of heme synthesis are readily detectable at distinctly lower blood-Pb concentrations, but mainly tend to serve as highly useful biomarkers of Pb exposure. Elevated blood-Pb concentrations of ~20–30 μg/dL, for example, are sufficient to halve erythrocyte ALAD activity and sufficiently inhibit ferrochelatase so as to double erythrocyte protoporphyrin (EP) levels. Erythrocyte ALAD activity ratio (the ratio of activated/non-activated enzyme activity) has been shown to be a sensitive, dose-responsive measure of Pb exposure, regardless of the mode of Pb administration. Competitive enzyme kinetic analyses in RBCs from both humans and cynomolgus monkeys indicated similar inhibition profiles by Pb. Decreased ALAD activity in rat RBCs have been reported at blood Pb levels of 10 μg/dL.

The effects of various metals, including Pb, on RBC porphobilinogen synthase (PBG-S) have been studied using human RBC hemolysate (see Section 5.2.3). Effects on the enzyme were found to depend on the affinity of the metal for thiol groups at its active sites. Additional studies utilizing rabbit erythrocyte PBG-S indicate that Pb acts as a potent effector of this enzyme both in vitro and in vivo. Increased erythrocyte protoporphyrin levels seen at blood-Pb concentrations ≥15 μg/dL represent another widely used biomarker of Pb exposure.

Comparison of pyrimidine-5′-nucleotidase (P5N) and deoxypyramidine-5-nucleotidase levels in the RBC of Pb-exposed workers and matched controls also showed significantly lower levels of P5N in Pb-exposed workers. Similar observations were reported for neonatal rat RBCs, with the low levels of nucleotides being hypothesized to be due to inhibition of P5N activity by Pb, as the depression in enzyme activity was correlated with blood-Pb levels (see Section 5.2.5).

7.4.5 Renal System Effects

The nephrotoxic effects of Pb are mediated by alterations in the glomerular filtration rate (GFR). A battery of tests used to screen both environmentally- and occupationally-exposed individuals often include: (1) measures of glomerular integrity, (2) tubular absorption and

secretion, (3) measure of tubular integrity, (4) measure of glomerular and distal tubular function, (5) glomerular structural proteins, and (6) measure of distal tubular function. Numerous new epidemiologic studies discussed in Chapter 6 provide important new findings on associations between Pb exposure and impacts on renal function (see Section 6.4).

Of particular importance are new analyses of associations between blood-Pb and renal outcomes in 15,211 adult subjects in the NHANES III study (conducted during 1988-1994). Dichotomous renal outcome measures analyzed included elevated serum creatinine and chronic kidney disease. Mean blood-Pb level was 4.2 µg/dL among the 4,813 hypertensives and 3.3 µg/dL in normotensives, with prevalence of elevated serum creatinine being higher among hypertensives than nonhypertensives but prevalence of chronic kidney disease being similar. The authors noted that (1) the associations were strong, dose-dependent and consistent before and after adjustment (e.g., for age, race, and gender) and (2) higher blood Pb was associated in nonhypertensives with higher prevalence of chronic kidney disease in diabetics. This study is notable for sample size, comprehensive adjustment for other renal risk factors, and the fact that the study population is representative of the general U.S. population. In another study of 820 women (ages 53-64 years) in Sweden, significant negative associations were seen between blood Pb (mean blood Pb of 2.2 µg/dL) and both glomerular filtration rate (GFR) and creatinine clearance, an association that was apparent over the entire dose range. This study also had the additional advantage of blood and urinary cadmium assessment.

The above studies and other general population studies constitute some of the most important types of research on Pb renal effects during the past 20 years, as discussed in Section 6.4.4.1. Overall, a number of strengths are present in this body of literature. These include study design with longitudinal data in some studies; large populations in both the United States and Europe; comprehensive assessment of Pb dose (including use of bone Pb as a measure of cumulative Pb body burden in some studies); and statistical approaches using a range of exposure and outcome measures, while adjusting for numerous renal risk factors. Associations between Pb exposure and worse renal function were observed in most of the general population studies.

Residual confounding and reverse causality have both been proposed as alternative explanations for the reported associations between Pb and renal dysfunction. As discussed in Section 6.5, increased blood pressure has been associated with Pb exposure in general

populations. Adjustment for hypertension or blood pressure, although typical in Pb-renal studies, carries the risk of underestimating the actual slope of the association between Pb dose and renal dysfunction. Given the careful adjustment for confounding in the Pb-renal general population literature, it is thought that residual confounding is not a likely explanation for the observed Pb-renal dysfunction associations. Reverse causality, i.e. attributing increased Pb dose to reduced Pb excretion as a consequence of renal insufficiency, is another possible explanation posed to explain such associations. However, by examining temporal relationships between Pb dose and renal function in longitudinal studies, it has been convincingly shown that Pb dose predicts decline in renal function. Other evidence against possible reverse causality is the positive impact of Pb chelation on renal function (see Section 6.4.4.3), although the possibility of a direct beneficial effect of chelating agents on renal function cannot be ruled out.

Increased risk for nephrotoxicity has been observed at the lowest Pb exposure levels studied epidemiologically to date. More specifically, the newly available general population studies have shown associations between blood Pb and indicators of renal function impairment at blood-Pb levels extending below 10 μg/dL, with nephrotic effects having been reported among some adults with mean concurrent blood-Pb levels as low as ~2 to 4 μg/dL. However, the data available to date are not sufficient to determine whether nephrotoxicity is related more to such current blood-Pb levels, higher levels from past exposures, or both. An association between cumulative Pb dose (indexed by mean tibia Pb of 21.5 μg/g bone mineral) and longitudinal decline in renal function has been observed as well. Blood Pb levels <10 μg/dL have also been associated with altered creatinine clearance, as noted in Chapter 6 (Figure 6.4-1). Slopes ranged from 0.2 to −1.8 mL/min change in creatinine clearance per each μg/dL increase in blood Pb.

Animal toxicology studies reported that both low and high dose Pb-treated animals showed a "hyperfiltration" phenomenon during the first 3 months of Pb exposure. This finding could be invoked as a partial explanation for late changes of glomerulosclerosis seen in high-Pb dose animals but cannot explain the lack of glomerular changes in the low-dose animals. These results support observations by several investigators in humans, leading some to argue that Pb nephropathy should be added to diabetic nephropathy as diseases that lead to early hyperfiltration. Also, animal toxicology studies that evaluated biochemical alterations in Pb-induced renal toxicity suggest a role for oxidative stress and involvement of NO, with a significant increase in nitrotyrosine and substantial fall in urinary excretion of NO_x.

A few animal toxicology studies that evaluated the effect of coexposure to other metals indicated that cadmium increases Pb in blood when both are given, but diminishes Pb in liver and kidney. Selenium, an antioxidant, improves both parameters, as does thiamine or L-lysine plus zinc. Iron deficiency increases intestinal absorption of Pb and the Pb content of soft tissues and bone. Aluminum decreases kidney Pb content and serum creatinine in Pb-intoxicated animals. Age also has an effect on Pb retention. There is higher Pb retention at a very young age but lower bone and kidney Pb at old age, attributed in part to increased bone resorption and decreased bone accretion and kidney Pb.

The above findings appear to indicate likely associations between some indicators of altered kidney function (e.g., increased creatinine clearance) at relatively low blood-Pb levels among the general population. However, the potential public health significance of such findings is difficult to discern just yet. This is especially true in light of difficulties in resolving discrepancies between these newly reported findings in the general population studies versus observation among the more than 10,000 occupationally-exposed workers studied, of notable Pb effects on renal tubular function only when blood-Pb exceeds distinctly higher levels (e.g., >30-40 μg/dL).

7.4.6 Lead-Associated Immune Outcomes

The effects of Pb exposure on the immune system of animals are described in Section 5.9 and are summarized in Figure 5.9.2. These include the targeting of T cells and macrophages by Pb. Lead-induced alterations center on an increased inflammatory profile for macrophages (i.e. elevated tumor necrosis factor-alpha, oxygen radical, and prostaglandin production) and a skewing of the T cell response away from T helper 1 (Th1)-dependent functions toward T helper 2 (Th2)-dependent functions. The resulting immune changes include an increased production of Th2 cytokines (e.g. IL-4, IL-10) and certain immunoglobulins [e.g., immunoglobulin E (IgE)]. Concomitantly, there is a decrease in Th1-associated cytokines (interferon gamma and IL-12) and in Th1-functions, e.g., the delayed type hypersensitivity (DTH) response. Significant age-related differences in immunotoxic sensitivity to Pb (based on blood-Pb concentrations) approximate an order of magnitude difference in sensitivity between the perinatal period and adulthood (see Table 5-9.5). Importantly, immune changes are associated with blood-Pb levels well below 10 μg/dL following gestational or perinatal

exposures (see Table 5-9.4). However, major immune cellular alterations are not a hallmark of low-level Pb exposure, despite significant Pb-induced shifts in immune function. This lack of major immune cell population changes becomes important for interpretation of human epidemiologic results.

Human epidemiologic immune evaluations are hampered by the reality that the most informative sources of functionally-reactive immune cells (e.g. those responding to antigens in the lymphoid organs and local lymph nodes) are not available for routine human sampling. This can be important in considerations of early-life associated immunotoxicity where functional assessment of immune changes appear to be particularly important, as noted by Dietert and Piepenbrink (2006). Instead, circulating lymphocytes and serum or plasma immunoglobulin levels in humans must serve as easily accessible surrogates for a more comprehensive determination of immune status. Despite this inherent limitation, the animal and human data for Pb-induced immune alterations are in general agreement, including the association of blood-Pb levels below 10 μg/dL with significant neonatal/juvenile immune alterations.

The sentinel result suggesting that low-level Pb exposure produces similar immune changes among animals and humans is the positive association of blood-Pb levels with IgE level. This association has been observed at blood-Pb levels <10 μg/dL following early life exposure in both humans (Section 5.9.3.2) and animals (Section 5.9.3). Other animal studies also support this by showing low-level Pb-induced increases in neonatal/juvenile IL-4, the hallmark cytokine modulating IgE production. Similarly, in the adult human, a positive association between blood-Pb level and IgE level has been reported for occupationally-exposed workers. It is not surprising that human epidemiologic results showed less consistent changes in other immunoglobulins, since Th biasing would be expected to produce shifts among immunoglobulin G (IgG) subclasses without necessarily changing overall IgG concentrations, consistent with results in the rat.

It should be noted that, prior to 1992, no human epidemiology study involving Pb reported comparisons of IgE levels. Also, since IgE is a minor immunglobulin component of human serum, several studies since 1992 did not include IgE quantitation in the evaluation. The animal data suggest that IgE (as well as the supporting cytokine, IL-4) are among the most sensitive parameters for modulation following low-level Pb exposure. Thus, in retrospect, those human studies that did not evaluate IgE levels may have focused on Pb-insensitive immune parameters.

Cell-mediated immunity in animals evaluated by the Th-dependent DTH reaction in most animal studies (see Section 5.9.4) showed that this measure was particularly sensitive to Pb-induced immunosuppression. In humans, the primary surrogate for cell-mediated immunity was a non-functional measure of circulating leukocyte populations. Despite this difficulty in evaluation, a majority of studies (see Table 6-8.2) that quantitated T, Th, Tc, and B cells reported decreases in either T or Th cells relative to an increase in circulating B cells. This is consistent with the profile described in the animal studies, where Th promotion of cell mediated immune function is impaired by Pb exposure while humoral immunity remained either unchanged or displayed increased IgE production.

Numerous animal studies reported that Pb produced elevated levels of TNF-alpha, superoxide anion and prostaglandins while depressing production of nitric oxide by macrophages (see Section 5.9.6). To the extent the same endpoints have been examined, the results are similar between animals and humans. One study has reported that in vitro-activated monocytes from Pb-exposed children were depressed in nitric oxide production, contrasting with a positive association between blood-Pb level and production of superoxide anion. Based on these results, the pattern of Pb-induced changes in major macrophage metabolites appears to be similar between the animal experimental and human epidemiological data.

Comparison of the human and animal studies is quite feasible and is limited only by the number of studies that incorporated comparable immune endpoints. In retrospect, several prior human epidemiological studies measured endpoints that appear to be Pb-insensitive based on the most recent animal data. Of the studies that evaluated similar parameters, the results are strikingly in agreement.

7.4.7 Reproduction and Development Effects

The majority of the experimental animal studies of Pb effects on reproduction and development examined effects due to inorganic forms of Pb, with very little being known about reproductive and developmental effects of organic Pb compounds.

Timing of exposure has been found to be critical to Pb-induced male reproductive toxicity in rats. Studies conducted in nonhuman primates support the importance of exposure timing and indicate that the adverse effects of Pb on male reproduction are dependent upon age (i.e., developmental stage at time of exposure) and duration of exposure. Numerous more recent

studies conducted in experimental animals support the earlier findings that Pb exposure during early development can delay the onset of male puberty and alter reproductive function later in life (see Section 5.4.2.1).

Other recent research supports the conclusion that mechanisms for endocrine disruption in males involve Pb acting at multiple sites along the hypothalamic-pituitary-gonadal (HPG) axis. However, variable findings regarding specific types of Pb effects have been attributed to complex mechanisms involved in hormone regulation and the multiple sites of action for Pb. It has been suggested that differences in results among studies may, in part, be attributed to an adaptive mechanism in the hypothalamic-pituitary-gonadal axis that may render the expression of some toxic effects dependent on dose and exposure duration (see Section 5.4.2). Thus, adaptive or multiple effects on the HPG axis having different dose-duration-response relationships may explain apparent inconsistencies among reported Pb effects on circulating testosterone levels, sperm count, and sperm production.

A possible mode of action for Pb-induced testicular injury is oxidative stress (as discussed in Section 5.4.2.4). Pb-induced oxygen free radical generation has been suggested as a plausible mechanism of testicular injury in primates. This oxygen radical hypothesis is supported by studies conducted in rodents; and the oxidative stress hypothesis is supported by observations of increases in the percentage of apoptotic cells in the testes of rodents in response to Pb exposure.

Several modes of action for Pb-induced, endocrine disruption-mediated, alterations in female reproduction have also been proposed, as discussed in Section 5.4.3. These include changes in hormone synthesis or metabolism at the enzyme level and changes in hormone receptor levels. In addition, Pb may alter sex hormone release and imprinting during early development. The latter effects would be consistent with observations of persistent changes in estrogen receptor levels in the uterus and altered ovarian LH function in Pb-exposed animals.

A persistent effect of maternal Pb exposure (blood Pb 30 to 40 μg/dL) has been seen on corticosteroid levels in adult offspring (as discussed in Section 5.4.6). Both male and female offspring born to dams exposed to Pb exhibited elevated corticosteroid levels as adults. In female offspring, the Pb effect was potentiated when maternal Pb exposure occurred in combination with environmental stress (administered as restraint). The interplay between Pb and stress hormones is consistent with other animal toxicologic findings wherein neonatal exposure

to Pb (blood Pb 70 µg/dL) decreased cold-water swimming endurance (a standard test for stress endurance).

The literature provides convincing support for Pb-induced impairment of postnatal growth, as discussed in Section 5.4.5. Although some early studies ascribed the reduction in postnatal growth to reduced food consumption (suggesting an effect of Pb on satiety mechanisms), more recent studies report impaired growth unrelated to changes in food consumption. These and other findings suggest that Pb exposure may impair growth through a mechanism that involves a suppressed pituitary response to hypothalamic stimulation. The mechanism may involve Pb-induced reduction in plasma concentrations of IGF_1.

7.4.8 Bone and Teeth Effects

Lead is readily taken up and stored in the bone of experimental animals, where it can potentially manifest toxic effects that result in stunted skeletal growth. In experiments reported since the 1986 Pb AQCD (see Section 5.8.3), uptake and retention of Pb were determined in bone from rats exposed to plain water or water containing Pb-acetate (41.7 to 166.6 mg/L) for 12 to 16 weeks. After 4 weeks, the skeletal Pb in animals receiving the lowest dose was almost 5 times higher than in control animals (5.9 versus 1.2 µg Pb/g bone, respectively). Lead levels in bones from animals receiving 83.3 mg/L and 166.6 mg/L were dose-dependently higher (at 11.7 and 17.0 µg Pb/g bone, respectively) after 4 weeks of exposure.

Results from several new animal studies have also yielded evidence for Pb exposure adversely affecting bone growth and density, which may be potentially manifested through Pb interference with growth and hormonal factors as well as toxic effects directly on bone. One of the studies suggested Pb was mediating its effect through 1,25-$(OH_2)D_3$, rather than via a direct action on the Calbindin-D protein.

The fact that Pb exposure has been associated with altered bone metabolism and decreased growth and skeletal development is suggestive of potential Pb perturbation of one or more endocrine factors, e.g., growth hormone. However, overall, available rat studies suggest that differences in growth seen with Pb exposure may not necessarily be due to alterations in secretion of growth hormone. Rather, effects on calcium uptake and/or metabolism may be more crucial, as suggested by the results of several in vitro studies. The results suggest that the calcium-ATPases of intracellular stores are potentially poisoned by Pb entering the cells.

An invaluable method to explore the kinetics of Pb transfer from bone to blood has been developed and evaluated within the last decade (see Section 5.8.6). The method uses recent administration of sequential doses of Pb mixes enriched in stable isotopes (^{204}Pb, ^{206}Pb, and ^{207}Pb) to female cynomolgus monkeys that were earlier chronically administered a common Pb isotope mix (1,300 to 1,500 µg Pb/kg body weight/day for ≥10 years). The stable isotope mixes serve as a marker of recent exogenous Pb exposure, whereas the chronically administered common Pb serves as a marker of endogenous (principally bone) Pb. It was found that administration of the first isotope label allows measurement of the contribution of historic bone stores to blood Pb. Exposure to subsequent isotopic labels allows measurement of contributions from historic bone Pb stores and the recently administered enriched isotopes that incorporated into bone. In general, the contribution from historic bone Pb (common Pb) to blood Pb level was relatively constant (~20%), but was augmented by spikes in total blood Pb due to current administration of the stable isotopes (blood Pb ranged from 31.2 to 62.3 µg/100 g).

Using the above sequential stable isotope administration method, another study examined flux of Pb from maternal bone during pregnancy of 5 female cynomolgus monkeys previously exposed to common Pb (~1,100 to1,300 µg Pb/kg body weight) for about 14 years. In general, Pb levels in maternal blood (as high as 65 µg/100 g) attributable to Pb from mobilized bone dropped 29 to 56% below prepregnancy baseline levels during the first trimester of pregnancy. This was ascribed to the known increase in maternal fluid volume, specific organ enlargement (e.g., mammary glands, uterus, placenta), and increased metabolic activity that occurs during pregnancy. During the two later trimesters, when there is a rapid growth in the fetal skeleton and compensatory demand for calcium from the maternal blood, the Pb levels increased up to 44% over pre-pregnancy levels. Blood-Pb levels in the fetus generally corresponded to those found in the mothers, both in total Pb concentration and in the proportion of Pb attributable to each isotopic signature dose. From 7 to 25% of the Pb found in fetal bone originated from maternal bone, with the balance derived from oral dosing of the mothers with isotope during pregnancy. Of interest, in offspring from a low Pb exposure control monkey (blood Pb <5 µg/100 g) ~39% of Pb found in fetal bone was of maternal origin, suggesting enhanced transfer and retention of Pb under low Pb conditions.

These studies show that Pb stored in bone is mobilized during pregnancy and lactation, exposing both mother and fetus/nursing infant to potentially toxic blood/milk Pb levels. Also of

much concern, a significant proportion of Pb transferred from the mother is incorporated into the offspring's developing skeletal system, where it can serve as a continuing source of toxic exposure. The latter study illustrates the utility of sequentially administered stable isotopes in pregnancy; however, its use may also be applicable in studies of lactation, menopause, osteoporosis, and other disease states where mobilization of bone and release of Pb stores occurs. Further, given that isotopic ratios of common Pbs vary by location and source of exposure, when humans migrate from one area and source of exposure to another, it is possible to document changes in mobilized Pb, especially during times of metabolic stress.

During pregnancy, transfer of Pb from mother to offspring has been documented. Still, other available evidence also suggests that a more significant transfer from mother to offspring occurs during lactation, when the Pb concentration in mother's milk can be several times higher than corresponding blood-Pb levels.

7.4.9 Hepatic and Gastrointestinal System Effects

A large body of experimental animal toxicology database reviewed in this document indicated hepatotoxic effects, including liver hyperplasia, at very high dose Pb exposures. Based on the limited data available in these toxicology studies on blood-Pb levels, inhibition of liver heme synthesis and inhibition of liver ALAD was reported at 15-20 μg/dL, whereas alterations in liver cholesterol metabolism and induction of hepatic oxidative stress was observed at 20-30 μg/dL.

Studies of hepatic enzyme levels in serum suggest that liver injury may be present in lead workers; however, associations specifically with Pb exposures were not evident. Also, children exposed to relatively high Pb levels (blood-Pb >30 μg/dL) exhibit depressed levels of circulating 1,25-dihydroxy vitamin D (1,25-OH-D). However, associations between serum vitamin D status and blood Pb were not evident in a study of calcium-replete children who had average lifetime blood-Pb concentrations <25 μg/dL.

Investigations into the potential molecular mechanisms involved in these alterations suggest induction of gene expression for CYP51 (Lanosterol 14α-demethylase), an essential enzyme for cholesterol biosynthesis, in Pb-nitrate-induced liver hyperplasia, although other cytochrome P450 enzymes involved in drug metabolism have been reported as being suppressed. The induction of the cytokines interleukin-1α and TNF-α in rat liver prior to the induction of the

genes for these synthesis enzymes suggested that Pb-nitrate-induced cholesterol synthesis is independent of sterol homeostasis regulation.

The effect of low-concentration Pb-acetate (0.1%) on the jejunal ultrastructure has been studied in young male rats. The villi of jejunum of rats exposed to Pb for 30 days had a rough appearance on the surface, which could be associated with a distortion of glycocalyx layer. Areas of extensive degenerative lesions were also observed on the surface of most villi on the 60th day of exposure. All intestinal epithelial cells exhibited various degrees of glycocalyx disturbance, indicating that pronounced toxic effects of Pb were related to modifications of the biochemical properties of the surface coat of the cells.

7.4.10 Genotoxicity and Carcinogenicity

One study has investigated the carcinogenicity of a series of chromate compounds, i.e., Pb-chromate and several Pb-chromate-based compounds. The authors indicated that in this design, Pb-chromate was not carcinogenic, but that 4 of the Pb chromate compounds did induce a very rare tumor in the mice. The remaining five studies focused on Pb-acetate. In most studies, this compound was administered in drinking water at concentrations from 0.5 to 4000 ppm, but one study considered effects from a subcutaneous (SC) injection both in mice and in rats. Consistent with the findings in the 1986 Pb AQCD, Pb not only induced renal tumors, but also induced other tumors (e.g. pituitary, thyroid, testicular), although the possible effect on mammary tumors is difficult to interpret.

Overall, the above studies confirm that Pb is an animal carcinogen and extend our understanding of mechanisms involved to include a role for metallothionein. Specifically, the recent data show that metallothionein may participate in Pb inclusion bodies and, thus, serves to prevent or reduce Pb-induced tumorigenesis. Much more work is needed to determine the potential exacerbating or ameliorating roles of calcium and selenium and to determine what role Pb-induced immunomodulation may play in the promotion of tumors.

The data currently seem to indicate that Pb can induce anchorage independence in human cells, but its ability to induce neoplastic transformation of human cells is uncertain. Further study of different Pb compounds and the full assessment of their neoplastic potential (i.e., including studies of the ability of treated cells to form tumors in experimental animal models) are needed before definitive conclusions can be drawn.

All together, animal cell culture studies suggest that Pb ions alone cannot transform rodent cells; however, they may be co-carcinogenic or promote the carcinogenicity of other compounds such as chromate.

The proliferative effects of various Pb salts (i.e., Pb-acetate, Pb-chloride, Pb-monoxide, Pb-sulfate), have been evaluated, using liver-derived REL cells. All the Pb compounds tested showed dose- and time-dependent effects on the proliferation of REL cells. Unlike other tumor promoters, Pb compounds did not exhibit effects on cell junctional coupling. Liver hyperplasia induced by Pb-nitrate has been shown to demonstrate sexual dimorphism in all phases of the proliferation as well as in apoptosis.

Investigations of cell cycle-dependent expression of proto-oncogenes in Pb-nitrate (10 μM/100 g body wt)-induced liver cell proliferation showed that peak DNA synthesis occurred at 36 h after a single injection of Pb-nitrate. In addition to DNA synthesis, Pb-induced expression of c-fos, c-myc, and c-Ha-ras oncogenes was also observed in rat liver tissue. Additional studies by the same group reported that Pb-nitrate-induced liver hyperplasia involved an increased expression of c-jun in the absence of c-fos expression.

Differential activation of various PKC isoforms, down regulation of PKC-α, and marked activation of PKC-ϵ in Pb-nitrate-mediated liver hyperplasia suggested the involvement of these PKC enzymes in DNA synthesis and related signal transduction pathways.

The majority of studies on genotoxicity of Pb compounds in animal models focused on mice. Lead was administered by intraperitoneal (IP) or intravenous (IV) injection. Several endpoints were considered, including chromosome aberrations, SCE, micronucleus formation, and DNA strand breaks. Overall, the results are ambiguous, due in part to study design and the various endpoints considered. The results for SCE are consistently positive.

The potential mutagenicity of Pb compounds in rodent cells was evaluated by using three mutagenesis systems: mutagenesis at the HPRT locus, the gpt locus, and mutations in sodium-potassium ATPase. The results are highly variable and may be specific to the Pb compound considered in each case. In particular, Pb-chromate and Pb-acetate appear to be nonmutagenic. Lead acetate was positive but only at highly cytotoxic concentrations. By contrast, Pb-chloride and Pb-sulfate appeared to be mutagenic at relatively nontoxic concentrations. Insufficient data exist at this point to conclude whether or not Pb is mutagenic in animal cells.

Both Pb-chromate and Pb-nitrate induced DNA-protein crosslinks in cultured mammalian cells. These data suggest that Pb is genotoxic in this manner; however, it is thought that the Pb -chromate-induced DNA-protein crosslinks result from the chromate.

It is plausible that through this mechanism, Pb may act as a co-carcinogen by affecting the metabolism of other chemicals or possibly as a direct carcinogen by enhancing endogenously-induced damage. However, no studies have directly shown that such Pb effects are linked to cancer or alter the potency of another chemical; and, thus, it remains only a plausible hypothesis.

Pb has been classified by IARC as a probable human carcinogen. This is based mainly on a judgment that there is sufficient animal evidence. This classification is consistent with the National Toxicology Program's Report on Carcinogens Review Committee which recommended that Pb and Pb compounds be considered "reasonably anticipated to be human carcinogens." Ten rat bioassays and one mouse assay have shown statistically significant increases in renal tumors with dietary and subcutaneous exposure to several soluble Pb salts. Animal assays provide reproducible results in several laboratories and in multiple rat strains, with some evidence of multiple tumor sites. Also, short-term studies show that Pb affects gene expression. Thus, although the human evidence is inadequate according to EPA's Guidelines for Carcinogen Risk Assessment (U.S. Environmental Protection Agency, 2005), Pb is likely classifiable under those guidelines as a probable human carcinogen based on the available animal data.

7.5 KEY LOW-LEVEL LEAD EXPOSURE HEALTH EFFECTS AND POTENTIAL PUBLIC HEALTH IMPLICATIONS

Numerous new studies that have become available since the 1986 Pb AQCD and the 1990 Supplement provide extensive new data on health effects of Pb across a wide exposure range, including information on concentration-response relationships for key health effects that have been observed at blood Pb levels below 10 µg/dL. Of particular interest for present purposes is the identification of lowest observed effect levels for those Pb-induced effects that are clearly associated with blood Pb <10µg/dL in children and/or adults and are of likely public health concern.

Recent studies have strengthened the consensus that the developing nervous system is the organ system that is probably most sensitive to Pb toxicity in children. Based on new findings,

notable neurobehavioral deficits appear to occur at distinctly lower levels of exposure than had been previously documented. The discussion in Section 7.5.1 below focuses on the functional form of these observed relationships and their potential public health implications, starting with blood-Pb/IQ relationships. Probably the most clearly established other Pb effects of concern are cardiovascular effects, with several well-conducted new studies providing strong evidence that elevations in blood Pb levels (even at <10 μg/dL) are significantly associated with increased systolic and diastolic blood pressure in adults (as discussed in Sections 6.5 and 6.10.8.2).

7.5.1 Concentration-Response Relationships for Neurotoxicity Effects

Newly accumulating data validate well the statement made in the 1996 AQCD/Addendum and the 1990 Supplement that adverse effects occur at blood Pb levels of 10 to 15 μg/dL or "possibly lower." In a recent study of 6 to 16 year old children in the NHANES III survey, concentration-related deficits in reading and arithmetic scores were found even when analyses were restricted to children with concurrent blood Pb levels below 5 μg/dL (Lanphear et al., 2000), although these analyses were limited by the fact that direct adjustments could not be made for certain important potential confounding factors (i.e., maternal IQ or caretaking quality in the home) whose inclusion in regression models often notably reduces the size of the Pb coefficient. Canfield et al. (2003a) applied semi-parametric models with penalized splines to their data, essentially allowing the data to reveal the functional form that best described them. These analyses showed that the IQ decline per μg/dL increase in blood Pb was greater below 10 μg/dL than it was above 10 μg/dL. The estimated slope of the IQ decline per μg/dL was greatest among children for whom the maximum blood Pb level measured over the course of the study never exceeded 10 μg/dL. Also, a similarly steeper slope was seen at lower than at higher blood Pb levels in a re-analysis of the Boston prospective study (Bellinger and Needleman, 2003).

Identifying the functional form that best fits a particular set of data and that presumably represents the best description of the pertinent underlying concentration-response relationship is clearly important. The linear model (Figure 7-5), as the name implies, is linear over the entire range of the exposure data. For certain tests, the assumption is made that the residuals (observed – predicted response) are normally distributed with constant variance, but violations of this assumption in the presence of heteroscedasticity have no real effect on the estimation and

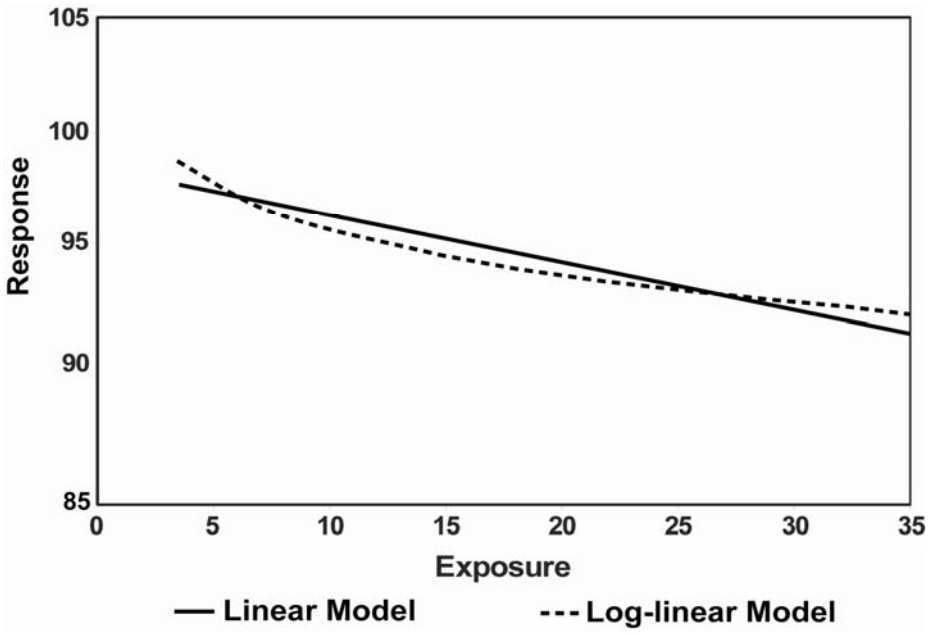

Figure 7-5. Comparison of a linear and log-linear model to describe the relationship between exposure and response.

minimal effect on the tests of significance. If heteroscedasticity is present but all other conditions are met, the regression model still yields unbiased estimators, but the standard errors can be larger than when remedial efforts such as using weighted regression are employed. The use of regression requires no assumption concerning the distribution of the independent variable (i.e., Pb exposure marker).

However, when the form of the heteroscedasticity is an increase in variance with blood Pb level and when the data are lognormally distributed or otherwise skewed, there are possibly a large number of influential data points at high blood Pb where the data are least reliable. In this case, a log transformation of blood-Pb values may result in more precise estimation of the slope parameter. The log-linear model is concave upwards (assuming that the estimated coefficient is negative). It approaches a linear function for very high exposure values, but approaches infinity at very low exposure values. In other words, it implies that the adverse effect of Pb is greater at lower than at higher blood-Pb levels. Blood Pb levels have been shown repeatedly to follow a lognormal distribution (Azar et al., 1975; Billick et al., 1979; Hasselblad and Nelson, 1975; Hasselblad et al., 1980; U.S. Environmental Protection Agency, 1986a; Yankel et al., 1977), but

this is not an argument for choosing the log-linear model. The choice of either log-linear or linear may be based on the Akaike's Information Criteria (Akaike, 1973), J-test (Davidson and MacKinnon, 1981), or other statistical tests if the choice is to be based on the best fitting model. Rothenberg and Rothenberg (2005) compared the linear Pb model with the log-linear Pb model for the pooled data from Lanphear et al. (2005) using the J-test. The J-test showed that the log Pb specification was still significant ($p = 0.009$) in a model that also included the linear Pb specification, indicating that the log Pb specification described the data significantly better than did the linear Pb specification. Other models have been used, such as nonparametric models, spline functions, and polynomial models, but the vast majority of the analyses have used either a linear model or a log-linear model.

Recently, Bowers and Beck (2006) note the mathematical requirement for a supralinear curve when blood Pb is lognormally distributed, IQ is normally distributed, and the correlation between these two variables is not zero. On this basis, they infer that the supralinear model arises due to these conditions rather than being a reason for these conditions. This is likely correct if the process of converting raw scores from a study to IQ points forced a normal distribution on the IQ data. Normalized standard scores are forced to be normal and may be used for a norm group, but are not used as IQ scores in these Pb epidemiologic studies (e.g., the WISC is not normalized). The usual assumption of regression analysis is that the outcome distribution is normal conditional on the predictors, unlike the assumption made by Bowers and Beck that the outcome is normally distributed. Blood Pb, social economic status and other predictors have skewed distributions and when outcome is linearly related to these predictors, the outcome distribution will be skewed. This is the case whether or not the non-normal skewness is statistically detectable. Hornung et al. (2006) provided evidence that IQ data in the pooled analysis of seven studies by Lanphear et al. (2005) were not normalized. They state that for the individual study data, a linear relationship between IQ and blood Pb provided an adequate fit over the narrower range of Pb values (≤ 10 μg/dL) associated with each study. This suggests that the linear model provides a better fit to that data than the log-linear model, which does not occur (except by chance) when the relationship is linear and the IQ data have not been normalized. When normalized and the relationship is linear, the improvement in fit of the log-linear model depends on the correlation coefficient. The linear model is but one of many

non-supralinear models for which their reasoning does not imply the lognormal model to be statistical artifact.

The segmented line model consists of joined straight line segments, where the joined points are chosen to best fit the data. The log-linear and the quadratic models have been shown in several cases to better fit the biomarker-response relationship than the linear model. However, these models are not considered practicable for extrapolation outside the range of the biomarker variable. The segmented line model is suggested as a more reasonable model for extrapolation into the low-concentration sparse-data region.

Nonlinear concentration-response relationships are not uncommon in toxicology, although many of these are claimed to be examples of hormesis, with the lowest doses of a toxicant being associated with a beneficial effect rather than a greater adverse effect. Concentration-response curves having shapes similar to the hormetic curve are sometimes referred to as U-shaped, to avoid inferring that the effect opposite to the toxic effect is beneficial. Figure 5-3.5 in Chapter 5 shows a graph where the response at lower Pb doses is opposite to the response at higher Pb doses. By itself, this curve may appear linear or even supralinear, but realizing that the response must return to 100% of control at zero dose indicates that it is U-shaped. However, this curve should be considered an example of hormesis, as increases in fixed interval response rate is not beneficial, given that they unnecessarily increase the number of responses required per reward obtained. Note that Figure 6-2.5 of the blood Pb-IQ relationship is similar to the Pb dose-fixed interval response curve shown in Figure 5-3.5, but shows no evidence of the curves being U-shaped. Although the curve in Figure 6-2.5 is nonlinear, it is monotonic, i.e., unidirectional. Only the slope changes, not the range of Pb levels. In the pooled analysis of seven studies by Lanphear et al. (2005), a steeper inverse relationship was observed between blood-Pb levels and IQ at blood-Pb levels <10 μg/dL than at blood Pb >10 μg/dL (see Figure 6-2.5, which present both the fitted cubic spline and log-linear functions).

A biological mechanism for a steeper slope at lower than at higher blood-Pb levels has not been identified. It is conceivable that the initial neurodevelopmental lesions at lower Pb levels may be disrupting different biological mechanisms than the more severe effects of high exposures that result in symptomatic poisoning or frank mental retardation (Dietrich et al. 2001). Perhaps the predominant mechanism at very low blood-Pb levels is rapidly saturated, but a different, less rapidly saturated process becomes predominant at blood-Pb levels >10 μg/dL.

As Kordas et al. (2006) states, this might help explain why, within the range of exposures not producing overt clinical effects, an increase in blood Pb beyond a certain concentration might cause less additional impairment in children's cognitive functions. However, one must take care not to interpret this as meaning that higher blood-Pb levels do not induce further toxic harm. For example, blood-Pb levels >70-80 µg/dL are still associated with encephalopathy and notable risk for fatal outcome.

The ad hoc explanation provided above for the observed nonlinear concentration-response relationship is more descriptive than explanatory, however; and specific processes that may produce this result have not yet been identified. Nevertheless, relationships of this apparent form have been seen in several data sets, indicating the need to further examine this issue. There are reasons that a supralinear model could be distorted to some degree. Austin and Hoch (2004) have shown that the use of the detection limit as a substitute values for undetected values can lead to bias of the regression slope away from zero. This can occur in multivariate regressions when there is high correlation and a high percent of non-detects. When regressions involve successively decreasing cut points of blood Pb, the percent of nondetects increases, potentially creating a supralinear relationship. An important caveat regarding efforts to specify the functional form of the concentration-response relationship is that the accuracy that can be achieved is constrained by the extent to which the biomarker of Pb concentration does, in fact, reflect the concentration at the critical target organ, the brain. The greater the misclassification, the more uncertain will be the biological relevance of the best statistical description of the concentration-response relationship.

The nonlinear concentration-response relationship observed between blood-Pb levels and IQ in recent epidemiologic studies does not preclude the presence of a threshold. Patterson et al. (1991) determined Pb concentrations in the tooth enamel, femur, and rib from buried skeletons of Pre-Columbian Southwest American Indians. They found that the mean natural body burden of adults Homo sapiens uncontaminated by technological Pb was 40 µg Pb/70 kg, which is about one-thousandth of the mean body burden of present day American adults with no occupational exposures and no record of childhood lead poisoning. This suggests that much reduced blood-Pb levels in the 1-10 µg/dL range are still orders of magnitude above pre-industrial natural levels. Thus, a threshold for Pb neurotoxic effects may exist at levels distinctly lower than the lowest exposures examined in these epidemiologic studies.

7.5.2 Persistence/Reversibility of Lead Neurotoxic Effects

Persistence or apparent "irreversibility" of effects can result from two different scenarios: (1) organic damage has occurred without adequate repair or compensatory offsets, or (2) exposure somehow persists. As Pb exposure can also derive from endogenous sources (e.g., bone), a performance deficit that remains detectable after external exposure has ended, rather than indicating irreversibility, could reflect ongoing toxicity due to Pb remaining at the critical target organ or Pb deposited at the organ post-exposure as the result of redistribution of Pb among body pools.

The persistence of effect appears to depend on the duration of exposure as well as other factors that may affect an individual's ability to recover from an insult. The likelihood of reversibility also seems to be related, at least for the adverse effects observed in certain organ systems, to both the age-at-exposure and the age-at-assessment. In occupationally-exposed adults, the central and peripheral nervous system correlates of higher Pb burdens appear to attenuate if exposure is reduced.

Data from the Treatment of Lead Exposed Children (TLC) study, a randomized controlled trial of late outcomes of children treated for Pb poisoning (baseline blood Pb of 20 to 44 μg/dL), support the hypothesis that the deficits associated with exposures of such magnitude are persistent (Dietrich et al., 2004; Rogan et al., 2001). At 36-months post-treatment and at age 7 years, no significant differences in cognition or behavior were noted between the succimer and placebo groups. Current blood Pb levels were significantly associated with cognitive performance at baseline, 36-months post-treatment, and at 7 years of age, and the regression coefficients were similar in magnitude to those estimated in observational studies (i.e., ~3 point IQ decline per 10 μg/dL increase in blood Pb), providing a linkage between the results of the observational studies and those of this experimental study. However, within-child analyses indicated that changes in developmental test scores over time were not consistently associated with changes over time in blood Pb level.

The prospective studies of childhood Pb exposure, using serial measurements of Pb biomarkers and health outcomes, provide the best opportunities available to assess the natural history of adversities associated with low-level Pb exposures. In some prospective studies, associations observed in infancy between biomarkers of prenatal Pb exposure and slowed neurodevelopment appeared to be attenuated by the time children reached preschool age. It can

be difficult to determine, however, whether this reflects actual disappearance of the effect or an increased difficulty in detecting it due to the emergence of associations between Pb biomarkers measured postnatally and neurodevelopment. It is notable, however, that in some prospective studies of children, associations between biomarkers of prenatal Pb exposure and various outcomes in middle adolescence have been reported, suggesting that the persistence of the associations might be endpoint-specific. For example, among children in Kosovo, Yugoslavia, IQ scores at the age of 8 years were inversely associated with a composite index of prenatal Pb exposure (average of mothers' blood Pb levels at midpregnancy and at delivery) (Wasserman et al., 2000b). This association was independent of changes in postnatal blood Pb levels. Or, among 15 to 17 year old inner-city children in Cincinnati, OH, maternal blood-Pb levels (ranging from 1 to ~30 μg/dL) in the first trimester were inversely related to attention and vasoconstriction (Ris et al., 2004) and positively related to the frequency of self-reported delinquent behaviors (Dietrich et al., 2001).

In most prospective cohort studies, the potential for true longitudinal analysis of the data has not been fully exploited, with the data evaluated in what is effectively a series of cross-sectional analyses. Nevertheless, the results of the prospective studies are consistent in showing that higher postnatal Pb biomarkers are associated with neurocognitive deficits that persist, in some studies, into early adulthood when the concurrent Pb exposures are generally much lower. Ongoing external exposure does not appear to be necessary to maintain the deficits, although, as noted previously, it is not possible to exclude entirely a role for ongoing endogenous exposures of the target organs resulting from the redistribution, over time, of Pb stores among different compartments. These data are consistent with those from experimental nonhuman primate studies, in which the temporal characteristics of exposure are manipulated as opposed to merely observed, as in the human studies.

One study examined the persistence of lead-related cognitive impairment using an intervention that resulted in a marked reduction in external Pb exposure (Soong et al., 1999). The cognitive abilities of exposed children (n = 32, median blood-Pb level of 15.1 μg/dL [range 7.7-31.7]) from a kindergarten located near a Pb-recycling plant in Taiwan were compared to a referent group of children (n = 35, median blood-Pb of 8.4 μg/dL [range 4.8-12.8]) from another kindergarten 5 km away from the plant. Both groups of children were comparable with respect to age, sex, birth order, sibling number, and parental education level. The exposed children were

found to have significantly lower IQ levels compared to the referent children, with a median score of 94.5 points (range 60-121) compared to 101 points (range 76-129). The next year, the school located near the Pb-recycling plant was moved an additional 2 km away. A follow-up study was conducted with 28 in each group 2½ years later. The median blood-Pb levels of the previously exposed and referent children decreased to 8.5 μg/dL (range 5.0-15.0, average decline of 6.9 μg/dL) and 7.0 μg/dL (range 4.0-11.0, average decline of 1.7 μg/dL), respectively. The average IQ scores in the previously exposed children increased by 11.7 points (SD 13.2), with a median value of 107 points (range 75-135). This value was not significantly different from the median score of the referent children, 109.5 points (range 79-132). These results indicate that IQ impairment resulting from blood-Pb elevations for a period of 1 to 3 years in 3 to 5 year old children was at least partially reversible when external Pb exposure was reduced.

Only limited data are available on factors that influence the likelihood that an association observed between an early Pb biomarker and later outcome will persist among children. In one study, the association between prenatal exposure and cognitive development in infancy and the preschool period appeared to attenuate among children living in more privileged circumstances or in whom postnatal Pb exposures were lower (Bellinger et al., 1988, 1990). These findings are consistent with those from cross-sectional epidemiologic studies showing that the effects of a given level of Pb exposure are more severe among disadvantaged children (Lansdown et al., 1986; Winneke and Kraemer, 1984) and from experimental animal studies showing that being raised in an enriched environment can reduce the apparent detrimental impact of Pb exposure on learning (Guilarte et al., 2003; Schneider et al., 2001).

7.5.3 Interindividual Variability in Susceptibility to Lead Toxicity

Although increased Pb exposure has been linked to adverse health effects in many different organ systems, scatterplots reveal tremendous variability of observed points about the best fit lines representing the concentration-response relationships. In other words, individuals for whom the Pb biomarker measured has the same value can have markedly different values on the health indicator measured. Even for neurobehavioral deficits in children, the correlation between biomarker level and test score rarely exceeds 0.2, indicating that the explained variance in the test score generally does not exceed 5%. A major challenge is therefore to decompose this

variability, to distinguish components of it that reflect error from components that reflect biological processes that determine an individual's response to Pb.

Deviation of the observed points from the fitted point can have many sources. Exposure misclassification is one source. The Pb biomarker measured might not adequately capture the Pb dose delivered to the target organ that, at the time, is most appropriate biologically. In general, the error would be expected to be non-differential, i.e., it would not introduce a systematic bias in the estimation of the concentration-response relationship. On average, such misclassification would be expected to result both in an attenuation of the slope of the concentration-response relationship and an increase in the scatter of the observations. As focus shifts to the risks associated with lower and lower levels of Pb exposure, the importance of errors introduced by poor dosimetry will assume greater importance insofar as the effects at such levels will presumably be more subtle and increasingly difficult to detect amid the noise contributed by exposure misclassification. Outcome misclassification is another source of error that is likely to contribute to apparent interindividual variability in response. This results if the indicator of the critical health effect that is measured is fallible, i.e., an imperfect measure of the target function. Such misclassification would generally be expected to be non-differential, introducing random noise rather than a systematic bias.

Another likely source of scatter in observed points is true interindividual variability in response to a given Pb dose. That is, the magnitude of individual response to Pb might depend on other characteristics of that individual. Three major categories of such effect modifying factors that might influence susceptibility to Pb toxicity are genetic polymorphisms, nutritional status, and social environmental factors. Adequate data are not available to provide a quantitative estimate of the amount of interindividual variability in susceptibility to Pb.

Influence of Genetic Polymorphisms on Risk

Genetic polymorphisms that are presumed to influence Pb toxicokinetics and/or toxicodynamics have been identified, mostly in studies of adults who were occupationally exposed to Pb. The magnitude of Pb-associated renal dysfunction appears to vary, in complex ways, with the delta-aminolevulinic acid dehydratase (ALAD) polymorphism (Chia et al., 2005, 2006). Lead workers with the ATP1A2(3′) polymorphism appear to be at increased risk of Pb-associated effects on blood pressure (Glenn et al., 2001). The slope of the association

between floor dust-Pb and blood-Pb is steeper among children with the less common variant of the vitamin D receptor (Fok 1 or B) than among children with the wild-type allele (Haynes et al., 2003). In adults, these same alleles are associated with higher blood-Pb levels and increased blood pressure (Schwartz et al., 2000a; Lee et al., 2001). Greater Pb-associated reductions in renal function have been observed in adults with a variant allele of nitric acid synthetase, although cardiovascular outcomes, such as blood pressure and hypertension do not appear to depend on the eNOS (endogenous nitric oxide synthase) allele (Weaver et al., 2003b). Adults with variants of the hemochromatosis gene (C282Y and/or H63D) have higher patella Pb levels (Wright et al., 2004). With regard to polymorphisms that modify Pb neurotoxicity, workers with the apolipoprotein E4 allele showed greater Pb-associated decreases in neurobehavioral function than did workers with the E1, E2, or E3 alleles (Stewart et al., 2002). Chia et al. (2004) speculated that the ALAD2 confers protection against Pb neurotoxicity, although Kamel et al. (2003) reported that this variant allele is associated with an increased risk of amyotrophic lateral sclerosis. This work is in its early stages and, while it promises to shed light on bases of susceptibility to Pb toxicity, firm conclusions cannot yet be drawn.

Influence of Nutritional Status on Risk

Only limited epidemiologic data are available on the role of nutritional status in modifying an individual's risk of Pb toxicity. Adjusting for severity of environmental Pb contamination, iron-deficient children appear to have higher blood-Pb levels than iron-replete children (Bradman et al., 2001). One interpretation of these data is that children experiencing the same external Pb dose can experience different internal doses. In another study of iron status, a decline in blood-Pb level was associated with improved cognitive performance in iron-sufficient but not in iron-deficient children (Ruff et al., 1996). Among the possible explanations for this finding is that iron deficiency contributes to pharmacodynamic variability, increasing the toxicity of a given Pb dose. Some evidence suggests that the intellectual deficit associated with an elevated blood-Pb level is greater among undernourished children than well-nourished children (Gardner et al., 1998).

Several studies have suggested that dietary calcium may have a protective role by decreasing absorption of Pb in the gastrointestinal tract and decreasing the mobilization of Pb from bone stores to blood, especially during periods of high metabolic activity of the bone such

as pregnancy and lactation. Lower calcium intake during pregnancy, especially the second half, appears to increase the mobilization of Pb from bone compartments (Hernandez-Avila et al., 1996). However, in other studies, calcium supplementation had no effect on bone-Pb levels in pregnant and lactating women (Rothenberg et al., 2000; Téllez-Rojo et al., 2002).

Influence of Health Status on Risk

The influence of an individual's health status on susceptibility to Pb toxicity has been demonstrated most clearly for renal outcomes. Individuals with diabetes, hypertension, and chronic renal insufficiency are at increased risk of Pb-associated declines in renal function, and indications of altered kidney function have been reported at blood Pb levels ranging somewhat below 5 µg/dL (Lin et al., 2001, 2003; Muntner et al., 2003; Tsaih et al., 2004). As noted in the previous section, children with nutritional deficiencies also appear to be more vulnerable to Pb-associated neurobehavioral deficits.

Influence of Coexposures on Risk

Epidemiologic studies do not provide an adequate basis for determining whether cigarette smoking and/or alcohol affect the nature or severity of Pb health effects. Both factors have often been included in models of both child and adult health outcomes to adjust for potential confounding. Both have also been evaluated as pertinent pathways of adult exposure. However, their possible roles as effect modifiers have not been well studied.

Although most individuals are not exposed to Pb in isolation but rather to Pb in combination with other toxicants (e.g., cadmium, arsenic, mercury, and polychlorinated biphenyls), epidemiologic studies have generally focused solely on Pb. Other toxicant exposures have sometimes been measured but are usually treated as potential confounders in the statistical analyses, with their potential as possible modifiers of Pb toxicity left unexplored (Bellinger, 2000). Thus, available epidemiologic studies do not provide an adequate basis for determining the extent to which co-exposure to other toxicants may affect the nature or severity of Pb-related health effects.

Influence of Timing of Exposure on Risk

Children

Available studies do not provide a definitive answer to the question of whether Pb-associated neurodevelopmental deficits are the result of exposure during a circumscribed critical period or of cumulative exposure. Although support can be cited for the conclusion that it is exposure within the first few postnatal years that is most important in determining long-term outcomes (Bellinger et al., 1992), other studies suggest that concurrent blood-Pb level is as predictive, or perhaps more predictive, of long-term outcomes than are early blood-Pb levels (Canfield et al., 2003a; Dietrich et al., 1993a,b; Tong et al., 1996; Wasserman et al., 2000b). Because of the complex kinetics of Pb, an accumulative toxicant, it is extremely difficult to draw strong conclusions from these observational studies about windows of heightened vulnerability in children. The high degree of intra-individual "tracking" of blood Pb levels over time, especially among children in environments providing substantial, chronic exposure opportunities (e.g., residence near a smelter or in older urban dwellings in poor repair), poses formidable obstacles to identifying the time interval during which exposure to Pb caused the health effects measured in a study. It could be that damage occurred during a circumscribed period when the critical substrate was undergoing rapid development, but that the high correlation between serial blood Pb levels impeded identification of the special significance of exposure at that time.

Under such circumstances, an index of cumulative blood Pb level or concurrent blood Pb level, which might be a good marker of overall body burden under conditions of relatively steady-state exposure, might bear the strongest association with the effect. Under these circumstances, however, it might be incorrect to conclude that it was the later exposures, incurred around the time that the effect was detected, that was responsible for producing it. While some observations in children as old as adolescence indicate that exposure biomarkers measured concurrently are the strongest predictors of late outcomes, the interpretation of these observations with regard to critical windows of vulnerability remains uncertain. Additional research will be needed to distinguish effects that reflect the influence of later Pb exposures from effects that reflect the persistent of effects resulting from exposure during some prior critical window. Resolving this issue solely on the basis of data from observational studies will be difficult due to the high intercorrelation among blood Pb measures taken at different ages.

Increasing attention is being devoted to determining the extent to which early childhood Pb exposures increases the risk of adverse effects that are only apparent at older ages (i.e., delayed or latent effects). Among young adults who lived as children in an area heavily polluted by a smelter and whose current Pb exposure was low, higher bone Pb levels were associated with higher systolic and diastolic blood pressure (Gerr et al., 2002). In adult rats, greater early exposures to Pb are associated with increased levels of amyloid protein precursor, a marker of risk for neurodegenerative disease (Basha et al., 2005).

Aging Population

Increases in blood Pb for postmenopausal women have been attributed to release of Pb from the skeleton associated with increased bone remodeling during menopause in both occupationally- and environmentally-exposed women (Garrido-Latorre et al., 2003; Popovic et al., 2005). Also, in middle-aged to elderly males from the Normative Aging Study, patella Pb accounted for the dominant portion of variance in blood Pb (Hu et al., 1996). These findings suggest that the skeleton serves as an endogenous source of Pb in the aging population.

Considerable evidence also suggests that indicators of cumulative or long-term Pb exposure are associated with adverse effects in several organ systems, including the central nervous, renal, and cardiovascular systems. Among occupationally-exposed men, higher tibia Pb levels have been associated with increased cognitive decline over repeated assessments (Schwartz et al., 2005). With regard to the renal system, increased Pb exposure may accelerate the effects of normal aging, producing a steeper age-related decline in function. Weaver et al. (2003a) observed that higher Pb exposure and dose were associated with worse renal function in older workers, but with lower blood urea nitrogen and serum creatinine in young workers.

Pregnancy

Mobilization of Pb from the skeleton also occurs during pregnancy and lactation due to increased bone remodeling to meet the calcium requirements of the developing fetus (Hertz-Picciotto et al., 2000; Manton, 1985; Silbergeld, 1991). In women who have been exposed to Pb in childhood and have accumulated large stores in their bones, there may be significant mobilization of Pb from bone to blood during late pregnancy and lactation. Lead isotope studies on immigrant women to Australia reported increases of 20% to 99% during pregnancy (Gulson

et al., 1997, 1998). Skeletal Pb contribution to blood Pb was significantly greater during the postpregnancy period than during the second and third trimesters. The highest probability of Pb toxicity for the mothers will be in postpartum while they are lactating; the infants will be particularly vulnerable during the prenatal period, especially in the last weeks of pregnancy (Manton et al., 2003). Calcium supplementation appears to provide a modest reduction in blood-Pb levels in pregnant or lactating women (Gulson et al., 2004; Hernandez-Avila et al., 2003).

A variety of adverse reproductive outcomes have been associated with higher paternal or maternal Pb exposures, including reduced fertility, spontaneous abortion, gestational hypertension, congenital malformations, fetal growth deficits, and neurobehavioral deficits in offspring. The levels of exposure at which different adverse outcomes occur vary. Increased risks of spontaneous abortion, neurobehavioral deficits in offspring and, in some studies, gestational hypertension, have been reported at pregnancy blood Pb levels below 10 μg/dL (Bellinger, 2005).

7.5.4 Potential Public Health Implications of Low-Level Lead Exposure

In studies of Pb toxicity, health endpoints have more often been continuously-distributed indices such as blood pressure or IQ. A view that the endpoints should be diagnoses rather than measured values on the underlying indices is that a change in the value of a health index that does not exceed the criterion value defining the diagnosis is therefore without consequence for an individual's health. The World Health Organization (WHO) definition of "health," is: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (World Health Organization, 1948). By this definition, even decrements in health status that are not severe enough to result in the assignment of a diagnosis might be undesirable if they reflect a decrement in an individual's well-being but are not severe enough to meet diagnostic criteria. Deficits in health indices or well-being may not be observable except in aggregate, at the population level. The American Thoracic Society discusses similar concepts of shift in population distribution and health effects (American Thoracic Society, 2000).

Sometimes, the importance of a Pb-associated change on a health index is evaluated by comparing it to the standard error of measurement of the index, i.e., the statistic that defines the range within which an individual's "true" value on the index is likely to lie. For instance the standard error of measurement for full scale IQ is 3 to 4 points, leading some to conclude that the

estimated IQ decrement of 3 points per 10 µg/dL increase in blood Pb level is "in the noise" of measurement and, therefore, meaningless. A similar claim has been made with regard to the magnitude of the association between Pb and blood pressure. The error in this argument is that the estimated decrement of 3 IQ points per 10 µg/dL applies to grouped, not individual, data. For measurement error to provide an explanation for the observation of an association that is approximately the size of the standard error of measurement, it would be necessary to postulate that the true association is null, but that, by chance or because of some bias, the measured IQ scores of the individuals with higher Pb exposures were systematically underestimated (i.e., their true IQ scores lie in the upper tails of the 95% CI for the children's observed scores) and that the measured IQ scores of the individuals with lower exposures were systematically overestimated (i.e., their true IQ scores lie in the lower tails of the 95% CI). Thus, this argument requires an assumption that the direction of measurement error is highly correlated with exposure status. The fundamental flaw is using a statistic that pertains to individual-level data to draw inferences about group-level data.

Nosology (the classification and naming of diseases) is dynamic as knowledge accrues. The total serum cholesterol level that is considered indicative of hyperlipidemia has dropped steadily over the past 40 years. Second, even within the range of health index values that are sub-diagnostic, variations on the index are significantly associated with health outcomes. For instance, even among children with birth weights greater than the cut-off used to define "low birth weight," birth weight is significantly associated with IQ at age 7 years (Matte et al., 2001). Third, exposure-related changes on a health index can be markers or indicators of other changes that are likely to have occurred whose significance is more certain. For instance, slower completion of a commonly-used neuropsychological test, the Grooved Pegboard, is associated with poorer handwriting, and reduced ability to copy a drawing is associated with a greater risk of a need for remedial school services (Bellinger, 2004).

The critical distinction between population and individual risk, an issue pertinent to many questions in chronic disease epidemiology, has often been blurred in discussions of the public health implications of Pb-associated decrements in health. In regard to neurodevelopment, although a two- or three-point decline in IQ might not be consequential for an individual, it is important to recognize that this figure represents the central tendency of the distribution of declines among individuals. Thus, some individuals might manifest declines that are much

greater in magnitude, while others manifest no decline at all, reflecting interindividual differences in vulnerability. Moreover, the import of a decline for an individual's well-being is likely to vary depending on the portion of the IQ distribution. For an individual functioning in the low range due to the influence of developmental risk factors other than Pb, a Pb-associated decline of several points might be sufficient to drop that individual into the range associated with increase risk of educational, vocational, and social failure.

The point estimate indicating a modest mean change on a health index at the individual level can have substantial implications at the population level. For example, although an increase of a few mmHg in blood pressure might not be of concern for an individual's well-being, the same increase in the population mean might be associated with substantial increases in the percentages of individuals with values that are sufficiently extreme that they exceed the criteria used to diagnose hypertension (Rose and Day, 1990). In other words, the mean value conveys substantial information about the percentage of individuals with clinically relevant, extreme values of the indicator. Moreover, interventions that shift the population mean, in a beneficial direction, by an amount that is without clinical consequence for an individual have been shown to produce substantial decreases in the percentage of individuals with values that are clinically significant (Bellinger, 2004). The following subsections discuss quantitatively Pb-related effects of a population level change in IQ and blood pressure.

Effects of Lead on Intelligence

The outcome most often examined to investigate the neurotoxic effects of Pb is IQ. Although the definition of "intelligence" is quite abstract, IQ remains a useful outcome measure as it is correlated with important measures of life success, such as academic achievement, earnings, and social status (Bellinger, 2003; Weiss, 2000). Several studies reported quantitative relationships between full scale IQ and current blood-Pb levels for children aged 5 to 11 years old. The estimated relationships as reported by the authors are summarized in Table 7-5, organized by the type of model used in the analysis.

The curves over a range of blood Pb levels from the 10th percentile to the 90th percentile are shown in Figure 7-6. The curves are restricted to that range because log-linear curves become very steep at the lower end of the blood Pb levels, and this may be an artifact of the model chosen. The percentiles are estimated using various methods and are only approximate

Table 7-5. Summary of Studies with Quantitative Relationships for IQ and Blood Lead

Reference	Study Location	n	Model Used	Estimated Slope (IQ points/µg/dL) – Blood Lead 10th to 90th Percentile	Estimated Slope (IQ points/µg/dL) – Blood Lead <10 µg/dL[a]
Bellinger et al. (1992)	Boston, Massachusetts	148	Linear	−0.5	−1.6
Dietrich et al. (1993a)	Cincinnati, Ohio	253	Linear	−0.3	−0.3
Ernhart et al. (1989)	Cleveland, Ohio	242	Linear	−0.1	NA
Kordas et al. (2006)	Torreón, Mexico	589	Linear	−0.5	−1.1
Wasserman et al. (1997)	Kosovo, Yugoslavia	309	Linear	−0.2	NA
Canfield et al. (2003a)	Rochester, New York	172	Quadratic	−0.7	−0.8
Al-Saleh et al. (2001)	Riyadh, Saudi Arabia	533	Log-linear	−0.6	−0.6
Baghurst et al. (1992)	Port Pirie, South Australia	494	Log-linear	−0.2	−0.4
Lanphear et al. (2005)[b]	International Pooled Analysis	1,333	Log-linear	−0.2	−0.5
Schnaas et al. (2006)	Mexico City, Mexico	150	Log-linear	−0.4	−0.6
Téllez-Rojo et al. (2006)	Mexico City, Mexico	294	Log-linear	−1.0	−1.0

[a] The slope for blood lead levels <10 µg/dL were estimated from the 10th percentile to 10 µg/dL. See Table 6-2.2 for additional details on how data for blood lead levels <10 µg/dL were analyzed in the individual studies.

[b] The pooled analysis by Lanphear et al. (2005) included data from seven individual studies, including Baghurst et al. (1992), Bellinger et al. (1992), Canfield et al. (2003a), Dietrich et al. (1993a), Ernhart et al. (1989), and Wasserman et al. (1997).

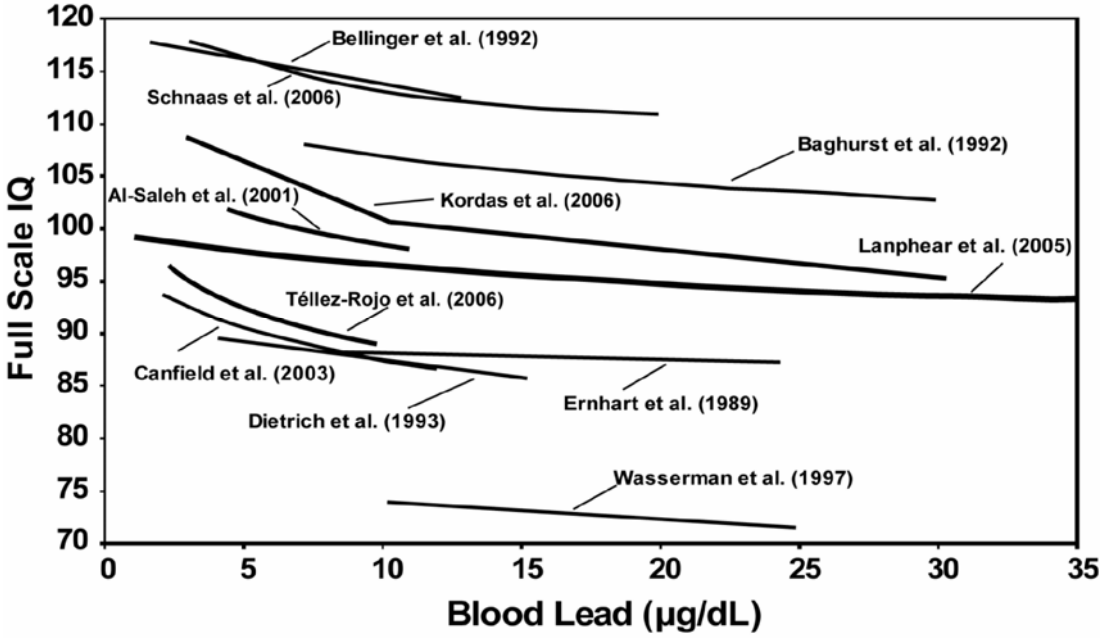

Figure 7-6. Concentration-response relationships of IQ to blood lead for the individual studies and the pooled analysis by Lanphear et al. (2005).

values. Studies which estimated a linear relationship are shown as reported, and similarly for the log-linear relationships. Note that these are not forest plots of slopes or hazard ratios—they are the actual estimated relationships.

The pooled analysis by Lanphear et al. (2005) included the studies of Baghurst et al. (1992), Bellinger et al. (1992), Canfield et al. (2003a), Dietrich et al. (1993a), Ernhart et al. (1989) and Wasserman et al. (1997). That pooled analysis also included the Mexico City study of Schnaas et al. (2000). The results from Schnaas et al. (2000) are not included in Table 7-5 or Figure 7-6 because the authors did not provide regression coefficients in their paper, thus the concentration-response relationship was not estimable.

Several conclusions can be drawn from these graphs. First, note that the overall IQ levels are quite different. This results from different populations and from different applications of the IQ tests. Second, all studies showed a decreasing IQ score as the blood-Pb level increased. It is the slope of the studies that is relevant, not the actual IQ scores. Third, for studies with lower blood-Pb levels, the slopes appear to be steeper. This is the reason that many authors choose to use the log-linear model. However, for those studies where the blood-Pb levels were generally high, the log-linear and linear models are almost identical. Thus, it is not surprising

that some authors chose a linear model instead of a log-linear model. The curves in Figure 7-6 do not show evidence of a no-effect threshold because the slopes increase as the blood-Pb levels become smaller. The observed mean adjusted IQ levels (for blood Pb <5, 5-10, 10-15, 15-20, and >20 µg/dL) reported by Lanphear et al. (2005) also show no evidence of a threshold, as seen in Figure 7-7.

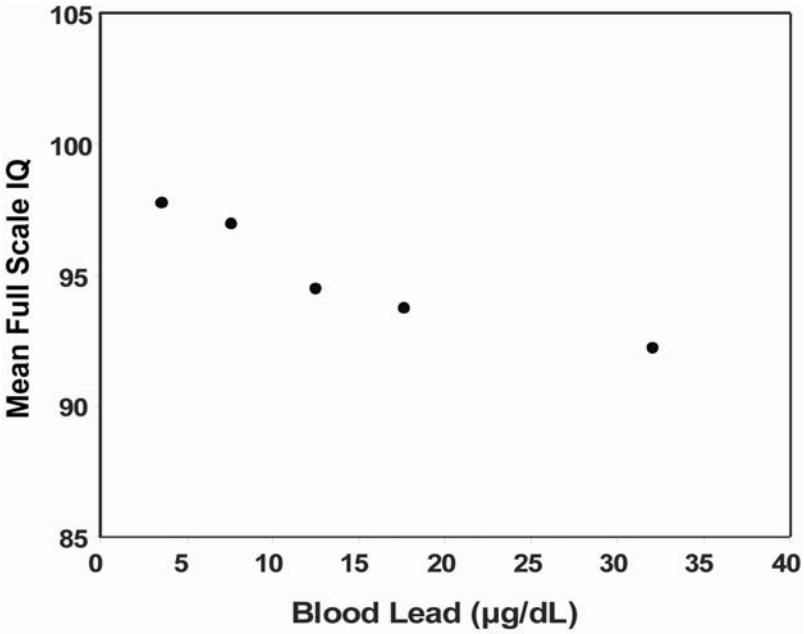

Figure 7-7. Mean blood lead levels adjusted for HOME score, maternal education, maternal IQ, and birth weight from the pooled analysis of seven studies by Lanphear et al. (2005). Mean adjusted IQ levels at blood lead levels of <5, 5 to 10, 10 to 15, 15 to 20, and >20 µg/dL are shown.

Weiss (1990) predicted, on purely statistical grounds, that a downward shift of five points in mean IQ, if the amount of dispersion in the distribution remained the same, should be accompanied by a doubling of the numbers of individuals with scores two or more standard deviations below the mean and a reduction by half of the number of individuals with scores two or more standard deviations above the mean. With respect to Pb, the general accuracy of this prediction has been empirically demonstrated in two different datasets by Needleman et al. (1982) and Bellinger (2004). An illustrative example is provided below, and it shows further

evidence of the change in percentages of individuals with IQ <80 or <70 points and >120 or >130 points after restricting the analysis to those with blood-Pb levels <10 µg/dL.

The slope of −0.9 points/µg/dL was used in these calculations. This slope is the median value from the estimated slopes for blood-Pb levels <10 µg/dL presented in Table 7-5. Studies that did not specifically conduct analyses to examine effects at blood-Pb levels <10 µg/dL (Baghurst et al., 1992; Dietrich et al., 1993a; Ernhart et al., 1989; Schnaas et al., 2006; Wasserman et al., 1997) were not considered.

A nonexposed population was assumed to have a standard mean IQ of 100 and standard deviation of 15 at a blood-Pb exposure of 0 µg/dL. The fraction of the population that would have an IQ <80 or <70 as a function of blood-Pb level was then calculated. The results are shown in Figure 7-8A. The fraction of the population with an IQ level less than 80 more than doubles from 9% with no Pb exposure to 23% with a blood-Pb level of 10 µg/dL. The fraction with an IQ level below 70, a level often requiring community support to live (World Health Organization, 1992) increases from a little over 2% with no Pb exposure to about 8% with a blood-Pb level of 10 µg/dL.

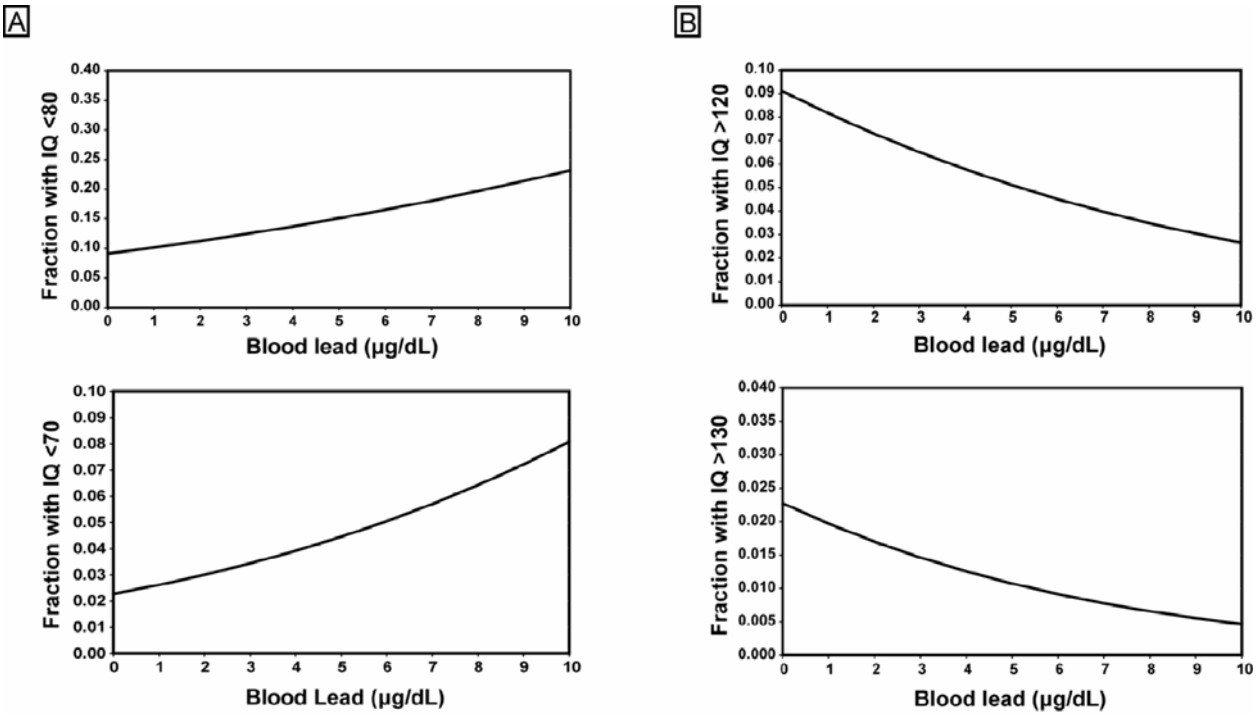

Figure 7-8. Effect of blood lead on fraction of population with IQ levels <80 or <70 points (A) and IQ levels >120 or >130 points (B).

The Pb-related decrements in IQ are manifested fairly uniformly across the range of IQ scores (Needleman et al., 1982). Thus, a shift in the mean value of a health indicator has substantial importance for both extremes of the distribution. In the case of Pb, a downward shift in the mean IQ value is not associated only with a substantial increase in the percentage of individuals achieving very low scores, but also with substantial decreases in percentages achieving very high scores. Based on the study by Bellinger et al. (1987) examining intelligence test scores of Pb-exposed children, Weiss (1988) discussed the shift of the population distribution of IQ from a mean of 100 and a standard deviation of 15 to a mean of 95, a 5% reduction. When the mean IQ level is 100, 2.3% of the individuals in a given population would score above 130. However, with the population distribution shift and the resulting mean decline in IQ, only 0.99% of the individuals would score above 130. Weiss states that the implication of such a loss transcends the current circumscribed definitions of risk. Similar results were observed using the slope of −0.9 points/ μg/dL to examine the effects on the percentage of individuals with an IQ >120 or >130 points at blood Pb levels <10 μg/dL (Figure 7-8B). The fraction of individuals with an IQ >120 decreased from about 9% with no Pb exposure to less than 3% at a blood Pb level of 10 μg/dL. The fraction of individuals with an IQ >130 points decreased from 2.25% to 0.5% with a blood Pb level change from 0 to 10 μg/dL.

Cardiovascular Effects of Lead

In human epidemiology studies investigating the cardiovascular effects of Pb, blood pressure has been examined most frequently, as discussed in Section 6.10.8 of Chapter 6. Results from the Framingham Heart Study show that higher levels of blood pressure, even within the nonhypertensive range, impose increased rates of cardiovascular disease (Kannel, 2000a,b). A continuous graded increase in cardiovascular risk is observed as blood pressure increases, with no evidence of a threshold value. Most events arise not in the most severe cases, but mainly in those with high normal blood pressure (i.e., mild hypertension). This view is further supported by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (Chobanian et al., 2003). Kannel (2000b) states that reducing even moderate elevation in blood pressure is likely to be beneficial.

Kannel (2000a) emphasized that systolic blood pressure exerts a strong influence on more serious cardiovascular events, as it is the prime causal function of hypertension and its adverse

cardiovascular sequelae. Cardiovascular events include coronary disease, stroke, peripheral artery disease, and cardiac failure. Risk ratios are larger for cardiac failure and stroke, but coronary disease (i.e., myocardial infarction, angina pectonis, sudden death) is the most common and most lethal sequela of hypertension (Kannel, 1996). Kannel (2000a) notes that the Framingham Heart Study has recognized that elevated blood pressure tends to occur alongside other major risk factors of cardiovascular disease such as glucose intolerance, dyslipidemia, abdominal obesity, and left ventricular hypertrophy, among others. If a cluster of multiple risk factors is present, the hazard is formidable for coronary disease and stroke.

No single critical level for blood pressure is evident. The risk appears to be simply proportional from the lowest to the highest level recorded. In the Multiple Risk Factor Intervention Trial (MRFIT), Neaton et al. (1995) confirmed a continuing and graded influence of systolic blood pressure on cardiovascular disease mortality extending down into the range of <140 mm Hg. The Prospective Studies Collaboration (2002) meta-analysis of 61 prospective studies relates blood pressure to vascular mortality without indication of a threshold down to 115/75 mm Hg. The absence of a demonstrable safe or critical level of blood pressure suggests using the range of blood pressure rather than discrete categories such as hypertension.

Many studies have provided evidence for a relationship between blood Pb and systolic blood pressure. In particular, the meta-analysis of Nawrot et al. (2002) indicated that a doubling of the blood Pb corresponded to a 1 mm Hg increase in systolic blood pressure. As noted earlier, although this magnitude of increase in systolic blood pressure is not particularly meaningful clinically for any given individual, a population shift of 1 mm Hg is important.

The Framingham Heart Study results (Kannel, 2000a) were used to estimate a typical population distribution of systolic blood pressure values (Figure 7-9). The distribution of systolic blood pressure values was approximated well by a lognormal distribution for both women and men ($p \geq 0.4$). The relationship between systolic blood pressure and the risk of cardiovascular events was also given by Kannel (2000a), as shown in Figure 7-10.

To estimate population risk, it was assumed that the effect of blood Pb on blood pressure was to shift the entire distribution by the amount given by Nawrot et al. (2002). For each shift in the distribution, the entire distribution was integrated out over the risk given in Figure 7-10. The result estimated was the expected number of cardiovascular events per 1,000 person years, and this was plotted for blood-Pb levels ranging from 5 to 15 μg/dL for both women and men. The

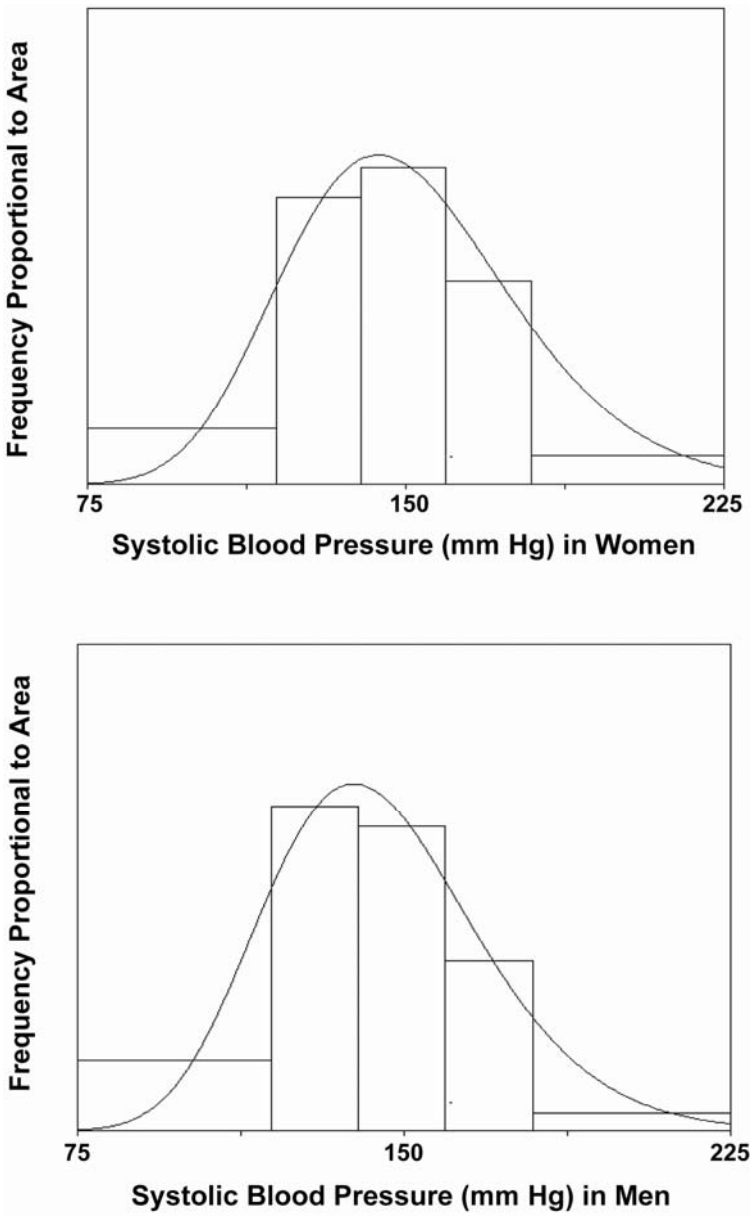

Figure 7-9. Distribution of systolic blood pressure in women and men aged 35 to 64 years from the Framingham Heart Study (Kannel, 2000a).

1 results are shown in Figure 7-11. Although the effects are modest, they translate into a large
2 number of events for a moderate population size. For example, a decrease in blood Pb from
3 10 to 5 µg/dL results in an annual decrease of 27 events per 100,000 women and 39 events per
4 100,000 men.
5

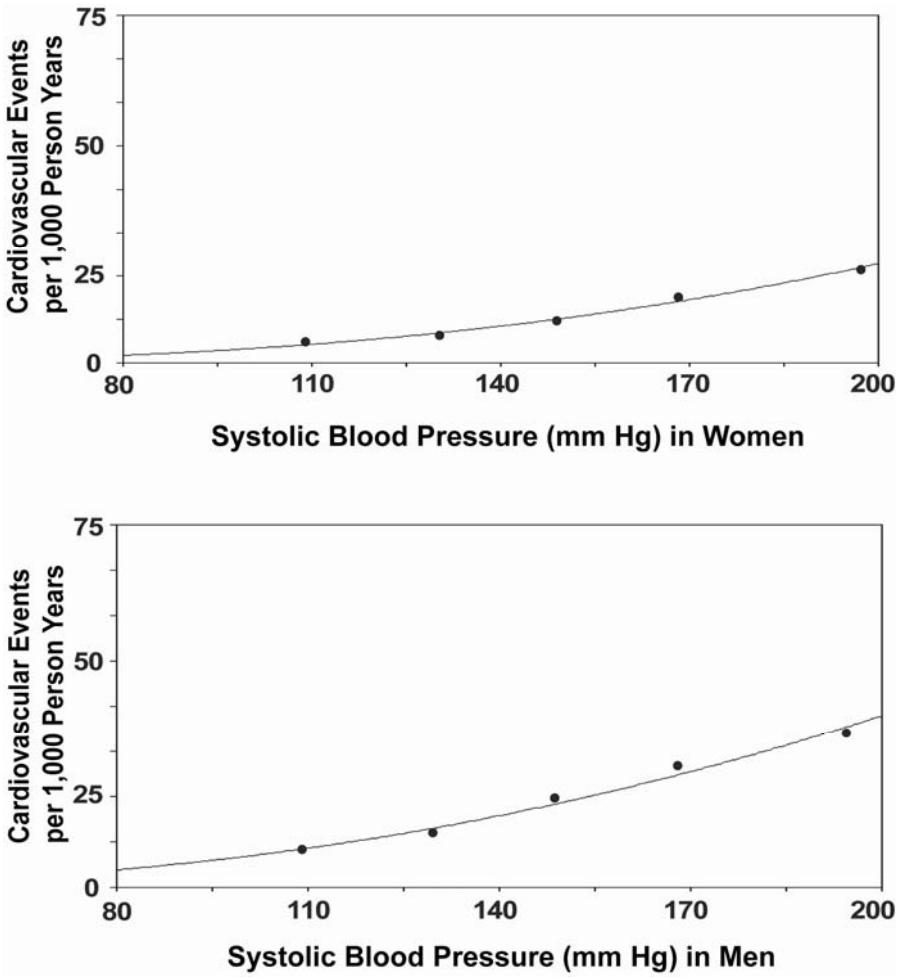

Figure 7-10. Relationship of serious cardiovascular events (coronary disease, stroke, peripheral artery disease, cardiac failure) to systolic blood pressure in women and men aged 35 to 64 years from the Framingham Heart Study (Kannel, 2000a).

In order to relate the effects of blood Pb levels to air Pb concentrations, an estimate of the relationship of air Pb to blood Pb in adults is necessary. One such estimate, as an example, can be derived from the Azar et al. (1975) study, which used personal monitors to estimate air Pb exposure in 149 adults (as discussed in Chapter 11 of the 1986 Pb AQCD). In that study, the estimated slope at an air Pb concentration of 1.0 $\mu g/m^3$ was a 2.57 µg/dL increase in blood Pb per 1 $\mu g/m^3$ increase in air Pb. Based on this slope estimate, a 0.25 $\mu g/m^3$ decrease in air Pb would lead to a 0.64 µg/dL decrease in blood Pb levels. Using both the relationship between blood-Pb levels and blood pressure (i.e., a doubling of the blood-Pb corresponds to a 1 mm Hg

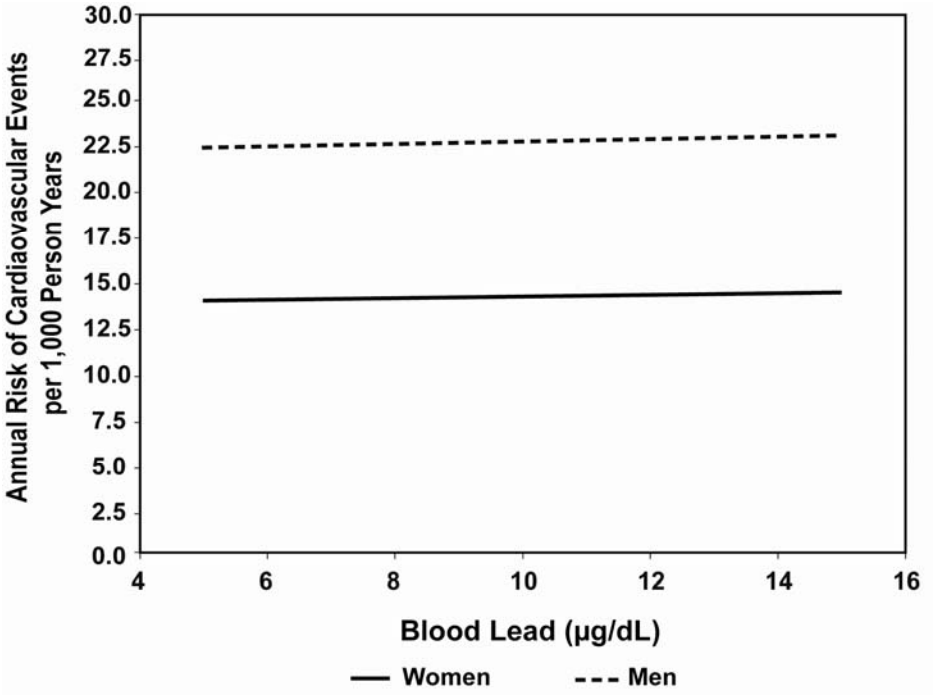

Figure 7-11. Effect of blood lead on expected annual risk of cardiovascular events per 1,000 person-years.

increase in systolic blood pressure) and the relationship between blood pressure and cardiovascular events, a decrease of 0.64 µg/dL in blood Pb from 5 µg/dL to 4.36 µg/dL would be projected to lead to an annual decrease of 5 cardiovascular events per 100,000 for women and 8 events per 100,000 for men. For a city of 3 million people (about the size of Chicago) this would translate to about 150 fewer events (e.g., heart attacks, strokes) for women and 240 fewer events for men, respectively. For a city of 10 million people (about the size of New York City) the estimated fewer serious cardiovascular events annually would be 500 and 800, respectively, for women and men.

Renal Effects of Lead

The potential clinical relevance of Pb renal effects for chronic kidney disease has recently been examined. Chronic kidney disease is an important risk factor for cardiac disease and other causes of mortality and morbidity. Increasing blood lead from the 5th to the 95th percentile (3.5 µg/dL) has the same adverse impact on glomerular filtration as increases in age and body

mass index (both known renal risk factors) among the general population. Further, a 10-fold increase in blood Pb (e.g., from 1 to 10 μg/dL) causes a 22.5% decrease in creatinine clearance in populations at high risk for Pb exposure. The biomedical significance of such altered creatinine clearance remains to be more fully elucidated, however, given observations in occupationally exposed groups of more notable renal dysfunction signs only at substantially higher blood-Pb levels (≤30-40 μg/dL).

A Pb-induced small downward shift in renal function among a general population may not alone result in chronic kidney disease in identifiable individuals; however, the segment of the population with the lowest renal reserve may be put at increased risk for chronic kidney disease when Pb exposure is combined with one or more other renal risk factors. Effect estimates in susceptible populations, such as those with diabetes, hypertension, or chronic renal insufficiency from non-Pb related causes, are likely to be higher. Lead exposure in populations that are also at increased risk for obesity, diabetes, and hypertension represent groups likely to be the most impacted by Pb. Frequently both risk factors are present in the same lower socioeconomic status groups.

Implications of Lead-Induced Immune System Effects

Disease implications associated with Pb-induced immune changes seen in animals are likely to include an increased risk of allergic diseases, atopic manifestations and possibly later-life autoimmunity as well as a reduced capacity to combat certain viral infections and cancers. Diseases associated with hyperinflammation would also be of concern. A recent mechanistic study in the mouse produced two major findings (see Section 5.9.8): (1) it confirmed the capacity of Pb to induce a Th2 bias, increasing allergic disease concerns; and (2) it showed that Pb exposure elevates immune reaction against neoantigens, thereby increasing the risk of autoimmune reactions.

7.5.5 Summary of Key Findings and Conclusions Derived from Lead Health Studies

The remarkable progress that has been made since the mid-1980s in understanding the effects of Pb on health can be gauged by noting the changes that have occurred over time in the questions investigators have addressed. In the 1980s, the question of interest was often,

"Does low-level lead exposure affect health?" The questions asked in recent studies have more often focused on details of the associations, including the shapes of concentration-response relationships, especially at levels well within the range of general population exposures, biological and socioenvironmental factors that either increase or decrease an individual's risk, the prognoses associated with Pb-associated effects, the efficacy of interventions to reduce adverse effects, and so on. In fact, "low-level," a term long-used to describe exposures that are not sufficiently high to produce clinical signs and symptoms, is increasingly being recognized as a descriptor that has little biological meaning and is interpretable only in a specific historical context. What was considered "low" in the 1980s is an order of magnitude higher than the current mean level in the U.S. population, and the current mean remains perhaps as much as two orders of magnitude above "natural" background levels in humans. The current CDC screening guideline for children of 10 µg/dL is not a "bright line" separating toxicity from safety, but merely a risk management tool. There is no level of Pb exposure that can yet be clearly identified, with confidence, as being "risk free." Recent studies of Pb neurotoxicity in infants have observed effects at population average blood-Pb levels of only 1 or 2 µg/dL and some cardiovascular, renal, and immune outcomes have been reported at blood-Pb levels below 5 µg/dL. Public health interventions have resulted in declines, over the last 25 years, of more than 90% in the mean blood-Pb level within all age and gender subgroups of the U.S. population, substantially decreasing the numbers of individuals at risk for Pb-induced toxicities.

7.6 KEY LEAD ECOSYSTEM EFFECTS AND POTENTIAL IMPLICATIONS

7.6.1 Terrestrial Ecosystems

Surface soils across the United States are enriched in lead (Pb) relative to levels expected from natural (geogenic) inputs. While some of this Pb contamination is attributable to paint, salvage yards, shooting ranges, and the use of Pb arsenate as a pesticide in localized areas, Pb contamination of surface soils is essentially ubiquitous because of atmospheric pollution associated with waste incineration, metal smelting and production, the combustion of fossil fuels, and past widespread use of leaded gasoline. However, lead inputs to terrestrial ecosystems in the United States have declined dramatically in the past 30 years, due to the almost complete

elimination of alkyl-lead additives in gasoline in North America. Also, emissions from smelters have declined as older plants have been shut down or fitted with improved emissions controls.

Most terrestrial ecosystems in North America remain sinks for Pb, despite reductions in atmospheric Pb deposition of more than 95% during the past several decades. Lead released from forest floor soils in the past has been largely immobilized in mineral soils (see Section 8.1). The amount of Pb that has leached into the mineral soil has been estimated to range from 20 to 90% of past total anthropogenic Pb deposition, depending on forest type, climate, and litter cycling. While inputs of Pb to ecosystems are currently low, Pb export from watersheds via groundwater and streams appears to be substantially lower, Pb concentrations in waters draining natural terrestrial ecosystems always having been reported as low (generally less than 1 ng/L), even at moderately polluted sites. Therefore, even at current low input levels, U.S. watersheds are accumulating industrial Pb. However, burial/movement of lead over time down into lower soil/sediment layers also tends to sequestor it away from more biologically active parts of the watershed (unless later disturbed or redistributed, e.g., by flooding, dredging, etc.).

Metal Speciation for Plants

When considering the bioavailability of a metal to plants from soils and sediments, it is generally assumed that both the kinetic rate of supply and the speciation of the metal to either the root or shoot are highly important. In soils and sediments, generally only a small volume of water is in contact with the chemical form; and, although the proportion of the concentration of a metal in this pore water to the bulk soil/sediment concentration is small, it is this phase that is directly available to plants. Therefore, pore water chemistry, i.e., metal concentration as simple inorganic species, organic complexes, or colloid complexes, is most important. Tools currently used for metal speciation for plants include (1) in situ measurements using selective electrodes; (2) in situ collection techniques using diffusive equilibrium thin films (DET) and diffusive gradient thin films (DGT) followed by laboratory analyses; and (3) equilibrium models (e.g., SOILCHEM) (see Section 8.1.1 and AX8.1.1.2).

Lead Speciation in Solid Phases

Lead can enter terrestrial ecosystems through natural rock weathering and by a variety of anthropogenic pathways. During the hydrolysis and oxidation of Pb-containing minerals,

divalent Pb (Pb^{2+}) is released to the soil solution, where it is rapidly fixed by organic matter and secondary mineral phases. The geochemical form of natural Pb in terrestrial ecosystems is strongly controlled by soil type (see AX8.1.2.1). In contrast, anthropogenically-introduced Pb has a variety of different geochemical forms, depending on the specific source. While Pb in soils from battery reclamation areas can be in the form of $PbSO_4$ or $PbSiO_3$, Pb in soils from shooting ranges and paint spills is commonly found as PbO and a variety of Pb carbonates. Atmospherically-delivered Pb from fossil fuel combustion is typically introduced into terrestrial ecosystems as Pb-sulfur compounds and Pb oxides. After deposition, most all Pb species are likely transformed. Although the specific factors that control the speciation of anthropogenic Pb in soils are not well understood, there are many studies that have partitioned Pb into its different geochemical phases. A thorough understanding of Pb speciation is critical in order to predict potential mobility and bioavailability.

Selective chemical extractions and synchrotron-based X-ray studies have shown that industrial Pb can be strongly sequestered by organic matter and secondary minerals such as clays and oxides of Al, Fe, and Mn. More recent X-ray studies have further demonstrated the importance of biomineralization of Pb in soils by bacteria and nematodes.

Lead Solid-Solution Partitioning

The concentration of Pb species dissolved in soil solution is probably controlled by some combination of (a) Pb mineral solubility equilibria; (b) adsorption reactions of dissolved Pb phases on inorganic surfaces (e.g., oxides of Al, Fe, Si, Mn, etc., clay minerals); and (c) adsorption reactions of dissolved Pb phases on soil organic matter. Dissolved Pb phases in soil solution can be some combination of Pb^{2+} and its hydrolysis species, Pb bound to dissolved organic matter, and Pb complexes with inorganic ligands such as Cl^- and SO_4^{2-}. Alkaline soils typically have solutions supersaturated with respect to $PbCO_3$, $Pb_3(CO_3)_2(OH)_2$, $Pb(OH)_2$, $Pb_3(PO_4)_2$, $Pb_5(PO_4)_3(OH)$, and $Pb_4O(PO_4)_2$. Pb phosphate minerals in particular, are very insoluble, and calculations based on thermodynamic data predict that these phases will control dissolved Pb in soil solution under a variety of conditions. However, certain chelating agents, such as dissolved organic matter can prevent the precipitation of Pb minerals (see AX8.1.2.1).

Soil solution dissolved organic matter content and pH typically have a very strong positive and negative correlation, respectively, with the concentration of dissolved Pb species. In

the case of adsorption phenomena, the partitioning of Pb^{2+} to the solid phase is also controlled by total metal loading: high Pb loadings will result in a lower fraction partitioned to the solid phase. It has been found that only a fraction of the total Pb in solution was actually Pb^{2+} in soils treated with leaf compost. The fraction of Pb^{2+} to total dissolved Pb ranged from <1 to 60%, depending on pH and the availability of Pb-binding ligands. In acidic soils, Al species can compete for sites on natural organic matter and inhibit Pb binding to surfaces.

Tracing the Fate of Atmospherically Delivered Lead

Radiogenic Pb isotopes offer a powerful tool for separating anthropogenic Pb from natural Pb derived from mineral weathering (see AX8.1.2.2). This is particularly useful for studying Pb in mineral soil, where geogenic Pb often dominates. The ore bodies from which anthropogenic Pb are typically derived are usually enriched in ^{207}Pb relative to ^{206}Pb and ^{208}Pb when compared with Pb found in granite rocks. Uranium-238 series ^{210}Pb also provides a tool for tracing atmospherically delivered Pb in soils. Fallout ^{210}Pb is deposited onto forests via wet and dry deposition, similar to anthropogenic Pb deposition in forests and is thusly useful as a tracer for non-native Pb in soils. ^{210}Pb is convenient to use for calculating the residence time of Pb in soil layers because its atmospheric and soil fluxes can be assumed to be in steady-state at undisturbed sites.

Researchers assessing the fate of atmospheric Pb in soils have also relied on repeated sampling of soils and vegetation for total Pb. This technique works best when anthropogenic Pb accounts for the vast majority of total Pb in a particular reservoir. Evans et al. (2005), for example, have noted that surface soils sampled relatively recently demonstrate that the upper soil horizons (O + A horizons) have been retaining most of the anthropogenic Pb burden introduced to the systems during the 20^{th} century, and others have suggested that vertical movement of organic particles dominated Pb transport in the soil profile (see AX8.1.2.2).

Uptake into Plants and Invertebrates

Recent work supports previous conclusions that the form of metal tested, and its speciation in soil, influence uptake and toxicity to plants and invertebrates. The oxide Pb form is less toxic than the chloride or acetate forms, which are less toxic than the nitrate form of Pb. However, these results must be interpreted with caution, as the counterion (e.g., the nitrate ion)

may be contributing to the observed toxicity (see AX8.1.3.1). Most lead is taken up by plants via the symplastic route (through cell membranes) and remains in the roots, with little translocation to shoots, leaves, or other plant parts. Different species of plants and invertebrates accumulate different amounts of lead.

Detoxification in Plants and Invertebrates

Lead may be deposited in root cell walls as a detoxification mechanism, and this may be regulated by calcium precipitates in the cell wall. The oxalate content in root and root exudates may reduce the bioavailability of Pb in soil, and constitute an important tolerance mechanism. Other hypotheses put forward recently include (a) the presence of sulfur ligands and (b) the sequestration of Pb in old leaves as detoxification mechanisms. Lead detoxification has not been studied extensively in invertebrates. Glutathione detoxification enzymes were measured in two species of spider; and Pb may be stored in waste nodules in earthworms or as pyromorphite in nematodes.

Physiological Effects

The effects on heme synthesis, as measured by 5-aminolaevulinic acid dehydratase (ALAD) activity and protoporphyrin concentration, primarily, were well-documented in the 1986 AQCD (U.S. Environmental Protection Agency, 1986) and continue to be studied in birds and mammals. However, Henny et al. (1991) caution that changes in ALAD and other enzyme parameters are not always related to adverse effects, but may simply indicate exposure. Other effects on plasma enzymes that may damage other organs have been reported (see AX8.1.3.3). Lead also may cause lipid peroxidation which may be alleviated by Vitamin E, although Pb poisoning may still result. Also, changes in fatty acid production have been reported, which may influence immune response and bone formation.

Response Modification

Genetics, biological factors, physical/environmental factors, nutritional factors, and interactions with other pollutants can all modify terrestrial organism response to Pb (see AX8.1.3.4). Some species are more sensitive to Pb than others. For example, Fisher 344 rats were found to be more sensitive to Pb than Sprague-Dawley rats. Also, younger animals are more sensitive than older animals, and females generally more so than males. Too, monogastric

animals are more sensitive than ruminants, insectivorous mammals may be more exposed to Pb than herbivores, and higher tropic-level consumers may be less exposed than lower trophic-level organisms. Nutritionally-deficient diets (including low calcium) cause increased uptake of Pb and greater toxicity in birds. Data on effects of Pb interactions with other metals vary, depending on the endpoint measured, the tissue analyzed, the animal species, and the metal combination.

Mycorrhizal fungi may ameliorate Pb toxicity until a threshold is surpassed, which may explain why some studies show increased uptake into plants while others show no difference or less uptake. Lower soil pH generally increases Pb uptake into plants and soil invertebrates. However, calcium content, organic matter content, and cation exchange capacity of soils also can significantly influence Pb uptake into plants and invertebrates (see AX8.1.3.4).

Primary Producers

Effects of lead on terrestrial plants include decreased photosynthetic and transpiration rates, and decreased growth and yield. The phytotoxicity of lead is considered to be relatively low, and there are few reports of phytotoxicity from Pb exposure under field conditions. Data on phytotoxicity were recently reviewed for development of ecological soil screening levels (Eco-SSL) (U.S. Environmental Protection Agency, 2005b). Many of the toxicity data presented in U.S. Environmental Protection Agency (2005b) are lower than those discussed in the 1986 Pb AQCD (U.S. Environmental Protection Agency, 1986), although both documents acknowledge that toxicity is observed over a wide range of concentrations of Pb in soil (tens to thousands of mg/kg soil). This may be due to many factors, such as the soil conditions (e.g., pH, organic matter) and differences in bioavailability of the Pb in spiked soils, perhaps due to lack of equilibration of the Pb solution with the soil after spiking. Most phytotoxicity data continue to be developed for agricultural plant species (i.e., vegetable and grain crops). Few data are available for trees or native herbaceous plants, although two of the five ecotoxicological endpoints used to develop the Eco-SSL were for trees and two were for clover.

Consumers

Lead effects on avian and mammalian consumers include decreased reproduction, growth, and survival, as well as effects on development and behavior. Only relatively few field effects

data exist for consumers, except from sites with multiple contaminants, for which it is difficult to attribute toxicity specifically to Pb. Much of the avian and mammalian toxicity data recently reviewed for the development of Eco-SSLs (U.S. Environmental Protection Agency, 2005b) are lower than those discussed in the 1986 Pb AQCD, although EPA (U.S. Environmental Protection Agency, 2005b) recognizes that toxicity is observed over a wide range of doses (<1 to >1,000 mg Pb/kg bw-day). Most toxicity data for birds are derived from chicken and quail studies, and most data for mammals are derived from laboratory rat and mouse studies. Data derived for other species would contribute to increased understanding of Pb toxicity, particularly for wildlife species with different gut physiologies. In addition, data derived using environmentally-realistic exposures, such as from Pb-contaminated soil and food may be recommended. Finally, data derived from inhalation exposures that evaluate endpoints such as survival, growth, and reproduction would enhance understanding the implications of airborne releases of Pb.

Decomposers

Lead effects on soil invertebrates include decreased survival, growth and reproduction. Effects on microorganisms include changes in nitrogen mineralization and in enzyme activities. Recent data on Pb toxicity to soil invertebrates and microorganisms are consistent with those reported in the 1986 Pb AQCD, with toxicity generally observed at concentrations of 100's to 1,000's of mg Pb/kg soil. Studies on microbial processes may be influenced significantly by soil parameters, and the significance of the test results is not clear.

Ecological Soil Screening Levels (Eco-SSLs)

Eco-SSLs are concentrations of contaminants in soils developed by U.S. EPA for use in the screening level assessments at Superfund sites to identify those contaminants needing further investigation, and also to identify those contaminants that are not of potential ecological concern and do not need to be considered in the subsequent analyses. The Eco-SSLs are intentionally conservative in order to provide confidence that contaminants which could present an unacceptable risk are not screened out early in the evaluation process. That is, at or below these levels, adverse effects are considered unlikely. Due to conservative modeling assumptions (e.g., metal exists in most toxic form or highly bioavailable form, high food ingestion rate, high soil ingestion rate) which are common to screening processes, several Eco-SSLs are derived below

the average background soil concentration for a particular contaminant. The Pb Eco-SSLs for terrestrial plants, birds, mammals, and soil invertebrates are 120 mg/kg, 11 mg/kg, 56 mg/kg, and 1700 mg/kg, respectively. (For additional information see Annex Section AX8.1.4).

Effects of Lead on Natural Terrestrial Ecosystems

Few significant effects of Pb pollution have been observed at sites that are not near point sources of Pb. At present, industrial point sources such as smelter sites represent the greatest Pb-related threat to the maintenance of sustainable, healthy, diverse, and high-functioning terrestrial ecosystems in the United States. However, assessing the risks specifically associated with Pb is difficult because these sites also experience elevated concentrations of other metals and because of effects related to SO_2 emissions. Terrestrial ecosystems may respond to stress in a variety of ways, including reductions in the vigor and/or growth of vegetation, reductions in biodiversity, and effects on energy flow and biogeochemical cycling.

Influence of Acidification

Like most metals, the solubility of Pb is increased at lower pH, suggesting that enhanced mobility of Pb should be found in ecosystems under acidification stress. However, reductions in pH may also cause a decrease in the solubility of dissolved organic matter (DOM), due to the protonation of carboxylic functional groups. Because of the importance of complexation with organic matter to Pb mobility in soils, lower DOM concentrations resulting from acidification may offset the increased solubility of the metal. The increased mobility was only observed in very acidic soils, those with pH <4.5 (see AX8.1.5.1). Acidification also may enhance Pb export to drainage water in very sandy soils that have limited ability to retain organic matter.

Influence of Forest Harvesting

Forest harvesting represents a severe disruption of the organic matter cycle in forest ecosystems. However, observations from clear-cut sites in the United States and Europe indicate that forest harvesting causes little or no mobilization or loss of Pb from forest soils. The principal risk associated with forest harvesting is the loss of Pb in particulate form to drainage waters through erosion (see AX8.1.5.1).

Influence of Land Use and Industry

Changes in land use represent potentially significant changes in the cycling of organic matter in terrestrial ecosystems. Conversion of pasture and croplands to woodlands changes the nature and quantity of organic matter inputs to the soil. The introduction of industrial activity may have consequences for organic matter cycling, and subsequently, Pb mobilization. In one rare long-term study of polluted soils, loss of soil carbon was found to induce the mobilization and loss of Pb from terrestrial ecosystems. However, it is worth noting that the decline in soil Pb was considerably smaller than the decline in organic carbon. This suggests that Pb mobilized during organic matter decomposition can resorb to remaining organic matter or perhaps to alternate binding sites (e.g., Fe and Mn oxides).

Effects Observed Around Industrial Point Sources

The effects of Pb exposure on natural ecosystems are confounded by the fact that Pb exposure cannot be decoupled from other factors that may also effect the ecosystem under consideration. Principal among these factors are other trace metals and acidic deposition. Emissions of Pb from smelting and other industrial activities are accompanied by other trace metals (e.g., Zn, Cu, Cd) and sulfur dioxide (SO_2) that may cause toxic effects independently or in concert with Pb.

Natural terrestrial ecosystems near smelters, mines, and other industrial plants have exhibited a variety of effects related to ecosystem structure and function. These effects include decreases in species diversity, changes in floral and faunal community composition, and decreasing vigor of terrestrial vegetation (see AX8.1.5.2). Subsequent to the effects on vegetation, wind and erosion may remove litter and humus, leaving bare mineral soil, a nearly sterile environment in which very little energy transfer takes place. In a rare case, metal pollution around a Pb-Zn smelter near Bristol, England has not resulted in the loss of oak woodlands within 3 km of the smelter, despite significant accumulation of Pb, Cd, Cu, and Zn in soils and vegetation. However, the high metal concentrations have favored the growth of metal-tolerant species in the woodland (see AX8.1.5.2). The effects of Pb on terrestrial ecosystems near smelters and other industrial sites decrease downwind from the Pb source. Several studies using the soil Pb burden as an indicator have shown that much of the contamination occurs within a radius of 20 to 50 km around the emission source.

Influence of Climate Change

Atmospheric Pb is not likely to contribute significantly to global climate change. The potential linkages between climate-related stress and Pb cycling are poorly understood. Climate effects related to alterations in organic matter cycling may influence Pb migration. For example, an increase in temperature leading to increased rates of organic matter decomposition could lead to temporary increases in DOM concentrations and smaller steady-state pools of soil organic matter. There also is some evidence for recent increases in the frequency of soil freezing events in the northeastern United States. Soil freezing occurs when soils have little or no snow cover to insulate them from cold temperatures and results in an increased release of nitrate and DOC from the O horizons of forest soils. Increased fluctuations in precipitation may induce more frequent flooding, potentially increasing inputs of Pb and other metals to floodplain soils. All of these factors could result in increased concentrations of Pb in waters draining terrestrial ecosystems.

Influence on Energy Flow and Biogeochemical Cycling

Lead can have a significant effect on energy flow in terrestrial ecosystems. In terrestrial ecosystems, energy flow is closely linked to the carbon cycle. The principal input of energy to terrestrial ecosystems is through photosynthesis, in which CO_2 is converted to biomass carbon. Because of this link between photosynthesis and energy flow, any effect that Pb has on the structure and function of terrestrial ecosystems influences the flow of energy into the ecosystem. At some sites severely affected by metal pollution, death of vegetation can occur, dramatically reducing the input of carbon to the ecosystem (see AX8.1.5.3).

Lead influences energy transfer within terrestrial ecosystems, which begins with the decomposition of litter and other detrital material by soil bacteria and fungi, and cascades through the various components of the detrital food web. Numerous investigators have documented significant declines in litter decomposition rates and/or the rate of carbon respiration in acid- and metal-contaminated soils or soils treated with Pb (see AX8.1.5.3). The resulting accumulation of organic matter on the soil surface can be dramatic. Lower decomposition rates in polluted ecosystems are the result of the inhibition of soil bacteria and fungi and its effects on microbial community structure (see AX8.1.5.3). Decreases in carbon respiration have been observed. Lead and other metals also inhibit the mineralization of nitrogen from soil organic matter and nitrification, resulting in lower nitrogen availability to plants. This suggests that the

inhibitory effect of Pb and other metals is broad-based, and not specific to any particular metabolic pathway. Because the mobility of Pb in soils is closely tied to organic matter cycling, decomposition processes are central to the biogeochemical cycle of Pb.

7.6.2 Aquatic Ecosystems

Sediment Quality Benchmarks and Bioavailability

There are a number of factors in sediment that can influence lead bioavailability to benthic (sediment) organisms. Although sediment quality criteria have not been formally adopted, the EPA has published an equilibrium partitioning procedure for developing sediment criteria for metals (U.S. Environmental Protection Agency 2005c). Equilibrium partitioning (EqP) theory predicts that metals partition in sediment between acid volatile sulfide, pore water, benthic organisms, and other sediment phases, such as organic carbon. Using this theory, sediment toxicity and organism mortality can be more reliably predicted by accounting for both the site-specific organic carbon and AVS concentrations.

Speciation of Lead in Aquatic Ecosystems

The speciation of Pb in the aquatic environment is controlled by many factors, such as pH, salinity, sorption, and biotransformation processes. Lead is typically present in acidic aquatic environments as $PbSO_4$, $PbCl_4$, ionic Pb, cationic forms of Pb hydroxide, and ordinary hydroxide $Pb(OH)_2$. In alkaline, waters common Pb species include anionic forms of Pb carbonate $Pb(CO_3)$ and hydroxide $Pb(OH)_2$. In freshwaters, Pb typically forms strong complexes with inorganic OH^- and CO_3^{2-} and weak complexes with Cl^-. The primary form of Pb in freshwaters at low pH ($\leq$6.5) is predominantly Pb^{2+}; and less abundant inorganic forms include $Pb(HCO)_3$, $Pb(SO_4)_2^{2-}$, PbCl, $PbCO_3$, and $Pb_2(OH)_2CO_3$. At higher pH ($\geq$7.5) Pb forms hydroxide complexes ($PbOH^+$, $Pb(OH)_2$, $Pb(OH)_3^-$, $Pb(OH)_4^{2-}$). Lead speciation in seawater is a function of chloride concentration and the primary species are $PbCl^{3-} > PbCO_3 > PbCl_2 > PbCl^+$ > and $Pb(OH)^+$ (see AX8.2.2.1).

Lead sorption to suspended or bed sediments or suspended organic matter typically increases with increasing pH, increasing amounts of iron or manganese; and with the polarity of component particulate matter (e.g., clays). Adsorption decreases with water hardness. At higher pH, Pb precipitates as $Pb(OH)^+$ and $PbHCO_3^+$ into bed sediments. Conversely, at low pH, Pb is

negatively sorbed, i.e., repelled from the adsorbent surface (see AX8.2.2.1). Also, Pb may be remobilized from sediment due to a decrease in metal concentration in the solution phase, complexation with chelating agents (e.g., EDTA), and changing redox conditions. Changes in water chemistry (e.g., reduced pH or ionic composition) can cause sediment Pb to become re-mobilized and potentially bioavailable to aquatic organisms. Methylation may result in Pb remobilization, its reintroduction into the aqueous environmental compartment, and its subsequent release into the atmosphere. However, methylation is not a significant environmental pathway controlling Pb fate in the aquatic environment.

Lead Concentrations in United States Surface Waters

Nationwide U.S. data for Pb in surface waters, from 1991 onward, were compiled using the United States Geological Survey's (USGS) National Water-Quality Assessment (NAWQA) database. Data were compiled from locations categorized as "ambient" or "natural." Ambient refers to data collected from all sampling locations, while natural refers to data collected from sampling locations categorized as forest, rangeland, or reference. Summary statistics for surface water, sediment (bulk, <63 um), and fish tissue (whole body and liver) are summarized in Table 7-6. Overall, atmospheric sources of Pb have generally decreased as regulations have removed Pb from gasoline and other products; however, elevated Pb concentrations remain at sites near ongoing sources, such as near mining wastes or wastewater effluents.

Lead concentrations in lakes and oceans were generally found to be much lower than those measured in the lotic waters assessed by NAWQA. Surface water concentrations of dissolved Pb measured in Hall Lake, Washington in 1990 ranged from 2.1 to 1015.3 ng/L, and the average surface water dissolved Pb concentrations measured in the Great Lakes (Superior, Erie, and Ontario) between 1991 and 1993 were 3.2, 6.0, and 9.9 ng/L, respectively. Pb concentrations ranged from 3.2 to 11 ng/L across all three lakes. Similarly, 101 surface water total Pb concentrations measured at the Hawaii Ocean Time-series (HOT) station ALOHA between 1998 and 2002 ranged from 5 to 11 ng/kg. Based on the fact that Pb is predominately found in the dissolved form in the open ocean (<90%), dissolved Pb concentrations measured at these locations would likely have been even lower than the total Pb concentrations reported.

In addition to directly measuring Pb concentrations in various aquatic compartments, it is useful to study the vertical distribution of Pb. Sediment profiling and core dating is a method

Table 7-6. Summary of Lead Concentrations in United States Surface Water, Sediment, and Fish Tissue

	Surface Water – Dissolved (µg/L)		Sediment – Bulk, <63 µm (µg/g dry wt.)		Fish Tissue (µg/g dry wt.)			
					Whole Organism		Liver	
Statistic	**Ambient**	**Natural**	**Ambient**	**Natural**	**Ambient**	**Natural**	**Ambient**	**Natural**
n	3,445	430	1,466	258	332	93	559	83
%ND	86	88	0.48	1.2	39	51	71	89
Min	0.04	0.04	0.50	0.50	0.08	0.08	0.01	0.01
Mean	0.66	0.52	120	109	1.03	0.95	0.36	0.28
95th %ile	1.10	0.50	200	162	1.06	1.26	3.24	2.50
Max	29.78	8.40	12,000	12,000	22.6	22.6	12.7	3.37

%ND = Percentage not detected

used to determine the extent of accumulation of atmospheric Pb and provides information on potential anthropogenic sources. Sediment concentration profiles are typically coupled with lead isotopic analysis. The isotope fingerprinting method utilizes measurements of the abundance of common lead isotopes (^{204}Pb, ^{206}Pb, ^{207}Pb, ^{208}Pb) to distinguish between natural Pb over geologic time and potential anthropogenic sources. Studies of sediment profiles have suggested that observed increases in Pb concentrations in the upper sediment layer are concomitant with increases in anthropogenic inputs. Isotopic ratios have been used to link increases in sediment concentrations with specific anthropogenic sources and to estimate historic records of Pb fluxes to surface waters and sediments (see AX8.2.2.3).

Lead Uptake

Lead can bioaccumulate in the tissues of aquatic organisms through ingestion of food and water, and adsorption from water, and can subsequently lead to adverse effects if exposed to sufficiently high concentrations. The accumulation of Pb is influenced by pH and decreasing pH favors bioavailability and bioaccumulation. Organisms that bioaccumulate Pb with little excretion must partition the metal such that it has limited bioavailability, otherwise toxicity will occur if a sufficiently high concentration is reached (see AX8.2.3.1).

Resistance Mechanisms

Aquatic organisms have various methods to resist the toxic effects of metals such as Pb. Mechanisms of resistance vary among aquatic biota and may include detoxification and avoidance responses. Detoxification processes can include translocation, excretion, chelation, adsorption, and vacuolar storage and deposition. For example, protists and plants produce intracellular polypeptides that form complexes with Pb. Some macrophytes and wetland plants have developed translocation strategies for tolerance and detoxification. Various aquatic invertebrates may sequester Pb in the exoskeleton or have developed specialized excretion processes. Fish scales and mucous may chelate Pb in the water column and potentially reduce Pb uptake (see AX8.2.3.2).

Avoidance responses are actions performed to evade a perceived threat. Some aquatic organisms have been shown to be quite adept at avoiding Pb in aquatic systems, while others seem incapable of detecting its presence. Snails have been shown to be sensitive to Pb, and avoid it at high concentrations. Conversely, anuran (frog and toad) species lack an avoidance response up to 1000 µg Pb/L. Fish avoidance of chemical toxicants has been well established and is a dominant sublethal response in polluted waters. However, studies examining avoidance behavior of Pb in fish are lacking (see AX8.2.3.2).

Physiological Effects of Lead

Physiological effects of Pb on aquatic biota can occur at the biochemical, cellular and tissue levels of organization. Lead has been shown to affect brain receptors in fish and serum enzyme activity (e.g., EROD and ALAD) in fish and amphibians. Studies examining Pb effects on fish blood chemistry have indicated alterations from acute and chronic exposures ranging from 100 to 10,000 µg/L. Lead exposure has also been shown to negatively affect the growth of aquatic invertebrates (see AX8.2.3.3).

Factors that Modify Organism Response to Lead

There are several factors that may modify responses of aquatic organisms to Pb exposure. These may include the size or age of an organism, genetics, environmental factors (e.g., pH, salinity), nutrition, and the presence of other contaminants. Lead accumulation in living organisms is controlled, in part, by metabolic rates and by the physiological conditions of an

organism. Relationships between age, size and Pb body burden in aquatic invertebrates and fish are variable and depend on many environmental variables (e.g., exposure). For example, examination of Pb exposure (up to 100 µg/L) in aquatic invertebrates showed little relationship between body size and Pb accumulation (MacLean et al., 1996; Canli and Furness, 1993) while Pb accumulation and fish size were positively correlated (Douben, 1989; Köck et al., 1996).

The genetics of an organism and/or population may alter the response to Pb exposure through one of two processes: (1) a contaminant may influence selection, by selecting for certain phenotypes that enable populations to better cope with the chemical, or (2) a contaminant can be genotoxic, meaning it can produce alterations in nucleic acids at sublethal exposure concentrations, resulting in changes in hereditary characteristics or DNA inactivation. Genetic selection has been observed in aquatic organisms due to lead tolerance. Because tolerant individuals have a selective advantage over vulnerable individuals in polluted environments, the frequency of tolerance genes will increase in exposed populations over time. Several studies have shown that heavy metals can alter population gene pools resulting in decreased genetic diversity. Laboratory studies have shown that Pb exposure at 10 mg Pb^{2+}/mL of blood Pb to chromosomal aberrations in some aquatic organisms. Low level (50 µg/L) Pb exposure in water over four weeks resulted in DNA strand breakage in the freshwater mussel *Anodonta grandis*. More recently, similar results (increase in the frequency of chromosomal aberrations and DNA damage in kidney cell cultures) were observed in fish (*Hoplias malabaricus*) fed Pb-contaminated food over 18, 41, and 64 days (see AX8.2.3.4).

Environmental factors can alter the availability, uptake and toxicity of Pb to aquatic organisms. A study of the influence of abiotic variables, including dissolved organic carbon (DOC) on Pb concentrations in freshwater isopods found that, as DOC concentrations increased, BCFs decreased in *P. meridianus* and *A. aquaticus*, indicating that DOC acts to inhibit the availability of Pb to these isopods. Schwartz et al. (2004) collected natural organic matter (NOM) from several aquatic sites across Canada and investigated the effects of NOM on Pb toxicity in rainbow trout (*Oncorhynchus mykiss*). The results showed that NOM in test water almost always increased LT_{50} (time to reach 50% mortality), and optically dark NOM tended to decrease Pb toxicity more than did optically light NOM in rainbow trout. Studies generally agree that the toxicity of Pb decreases as pH increases. As pH decreases, Pb becomes more soluble and more readily bioavailable to aquatic organisms (Weber, 1993). Acute and chronic

toxicity of Pb increases with decreasing water hardness, as Pb becomes more soluble and bioavailable to aquatic organisms (Horne and Dunson, 1995c; Borgmann et al., 2005). There is some evidence that water hardness and pH work together to increase or decrease Pb toxicity (see AX8.2.3.4).

High Ca^{2+} concentrations have been shown to protect against the toxic effects of Pb. Ca^{2+} affects the permeability and integrity of cell membranes and intracellular contents. As Ca^{2+} concentrations decrease, the passive flux of ions (e.g., lead) and water increases. Finally, increasing salinity was found to decrease Pb toxicity. The reduction in toxicity was attributed to increased complexation of Pb^{2+} with Cl^- ions (see AX8.2.3.4).

Also, nutrients (e.g., nitrate, carbonate) have been shown to affect Pb toxicity in some aquatic organisms. A study of blue-green algae (*Synechococcus aeruginosus*) exposed to 200 mg Pb/L indicated that additional nitrogen, phosphates, and some carbon sources (including sodium acetate, citric acid and sodium carbonate) all protected the algae from Pb toxicity. The protective mechanism is still not clear. One hypothesis was that nutrients were able to reverse toxic effects. The second hypothesis was that nutrients directly interacted with Pb, in some way sequestering the metal so as to inhibit its metabolic interaction with the organism (see AX8.2.3.4).

Interactions with Other Pollutants

Predicting the response of organisms to mixtures of chemicals is a daunting task. Antagonism, synergism, and additivity are potential responses that can occur following exposure to multiple contaminants. When two or more metals compete for the same binding sites or interfere with transport through cell walls or membranes, the interaction is termed less than strictly additive or antagonistic. Antagonistic interactions can reduce metal bioavailability when metals are present in combination, and may lead to reduced potential for toxicity. There are a number of elements (Ca^{2+}, Cd^{2+}, Mg^{2+}, Na^+ and Cl^-) that act in an antagonistic fashion with Pb (see AX8.2.3.4). For example, Pb is a well-known antagonist to Ca^{2+}, an essential element required for many physiological processes in most organisms.

Synergism occurs when the interaction of two or more metals causes an effect that is greater than the effect observed from the individual metals themselves. Synergism is likely the result of increased bioavailability of one or more of the metal ions due to the presence of other

metals. Synergistic interactions have been observed with Pb and other metals (Cd, Cu, Ni, Zn) (see discussion in AX8.2.3.4).

The combined effects of two or more metals may result in additivity when the observed effects are greater than that observed with individual metals but equivalent to a summation of the effects from multiple metals (see AX8.2.3.4). The two most commonly reported Pb-element interactions are between Pb and calcium and Pb and zinc. Both calcium and zinc are essential elements in organisms, and the interaction of Pb with these ions can lead to adverse effects both by increased Pb uptake and by a decrease in Ca and Zn required for normal metabolic functions.

Effects of Lead on Primary Producers

Several studies have been conducted since the 1986 Pb AQCD on the toxicity of Pb to primary producers. Effects on algal growth (*Chlorella vulgaris*, *Closterium acerosum*, *Pediastrum simplex*, *Scenedesmus quadricauda*), ranging from minimal to complete inhibition, have been reported at Pb concentrations between 100 and 200,000 μg/L. The toxicity of Pb to aquatic plant growth has been studied using *Spirodela polyrhiza*, *Azolla pinnata*, and *Lemna gibba*. Test durations ranged from 4 to 25 days and test concentrations ranged between 49.7 and 500,000 μg/L. Research on aquatic plants has been focused on Pb effects on aquatic plant growth, chlorophyll and protein content (see AX8.2.4.2).

Algae and aquatic plants have a wide range in sensitivity to the effects of Pb in water. Both groups of primary producers experience EC_{50} values for growth inhibition between ~1,000 and >100,000 μg/L (see AX8.2.4.2). Exposure to Pb in combination with other metals is generally less toxic to growth than exposure to Pb alone. Studies have shown that Pb adversely affects the metabolic processes of nitrate uptake, nitrogen fixation, ammonium uptake, and carbon fixation. Lead in combination with nickel or chromium produced synergistic effects for nitrate uptake, nitrogenase activities, ammonium uptake, and carbon fixation.

Effects of Lead on Consumers

The 1986 Pb AQCD (U.S. Environmental Protection Agency, 1986a) reported that hematological and neurological responses are the most commonly reported Pb effects on aquatic vertebrates. These effects include red blood cell destruction and inhibition of the enzyme ALAD, required for hemoglobin synthesis. The lowest reported exposure concentration causing

either hematological or neurological effects was 8 μg Pb/L (U.S. Environmental Protection Agency, 1986a).

More recent literature on the toxicity of lead to fish and aquatic invertebrates has been summarized by Eisler (2000). Exposure of invertebrates to Pb can lead to adverse effects on reproduction, growth, survival, and metabolism. Water-borne Pb is highly toxic to aquatic organisms, with toxicity varying, depending on the species and life stage tested, duration of exposure, the form of Pb tested, and water quality characteristics (see AX8.2.4.1). Among the species tested, aquatic invertebrates, such as amphipods and water fleas, were the most sensitive to Pb effects, with adverse effects being reported at water Pb concentrations ranging from 0.45 to 8000 μg/L. Freshwater fish demonstrated adverse effects at concentrations ranging from 10 to >5400 μg/L, generally depending upon water quality parameters (e.g., pH, hardness, salinity). Amphibians tend to be relatively tolerant of Pb, but may exhibit decreased enzyme activity (e.g., ALAD reduction) and changes in behavior (e.g., hypoxia response behavior). Lead tends to be more toxic in longer-term exposures, with chronic toxicity thresholds for reproduction in water fleas ranging as low as 30 μg/L.

Effects of Lead on Natural Aquatic Ecosystems

Recent studies on exposure to Pb in laboratory studies and simulated ecosystems indicate that Pb may alter species competitive behaviors, predator-prey interactions, and contaminant avoidance behaviors. Alteration of these interactions may have negative effects on species abundance and community structure (see AX8.2.5.2). For example, reduced avoidance behaviors have been observed at Pb concentrations ranging from 0.3 to 1.0 mg/L. The feeding behaviors of competitive species in some aquatic organisms are also influenced by the presence of Pb. Lead (6 to 80 mg/L) has also been found to reduce primary productivity and increase respiration in an algal community; and laboratory microcosm studies found reduced species abundance and diversity in protozoan communities exposed to 0.02 to 1 mg Pb/L. Lastly, numerous field studies have associated the presence or bioaccumulation of Pb with reductions in species abundance, richness, or diversity, particularly in benthic macroinvertebrate communities. In natural aquatic ecosystems, Pb is often found coexisting with other metals or other stressors. Thus, understanding the effects of Pb in natural systems is challenging given that observed effects may be due to cumulative toxicity from multiple stressors.

The effects of Pb have primarily been studied in relation to point source pollution rather than area-wide atmospheric deposition. Thus, the effects of atmospheric Pb on aquatic ecological condition remain to be defined. There is a paucity of data in the general literature that explores Pb effects in conjunction with all or several of the various components of ecological condition as defined by the EPA (Young and Sanzone, 2002). However, numerous studies are available that associate the presence of Pb with effects on biotic conditions.

7.6.3 Application of Critical Loads to Terrestrial and Aquatic Ecosystems

For the purpose of this section, critical loads are defined as threshold deposition rates of air pollutant that current knowledge indicates will not cause long-term adverse effects to ecosystem structure and function (see Section 8.3.1). A combinatorial application of critical limit and critical load allows one to assess current risk while simultaneously estimating future risk from exposure to a chemical. Figure 7-12 shows that four combinations of critical load and limit exceedance or non-exceedance are possible for a given ecosystem (Figure 1 of De Vries et al. [2004]). For example, if a current risk is indicated by an exceedance of the critical limit for Pb due to historical Pb deposition, but current inputs of Pb to the ecosystem are below the critical load (lower left corner), the critical load model predicts that Pb concentrations will fall below the critical limit at some point in the future if Pb deposition is maintained at the present level. If current soil concentrations are below the critical limit (upper right corner), inputs greater than the critical load will not result in exceedance of the critical limit for some period of time, but continued exceedance of a critical load will eventually lead to an exceedance of the critical limit. The time until a critical limit is exceeded (critical time) can also be predicted using the critical load model. This requires knowledge of current concentrations, the critical load, and predicted deposition rates. Critical times may be useful for setting priorities between ecosystems with critical load exceedances or between different chemicals.

Calculation of Critical Loads

This section summarizes various methods used to calculate critical loads (De Vries et al., 2001, 2002, 2004; Groenenberg et al., 2002), with an emphasis on the most recent material.

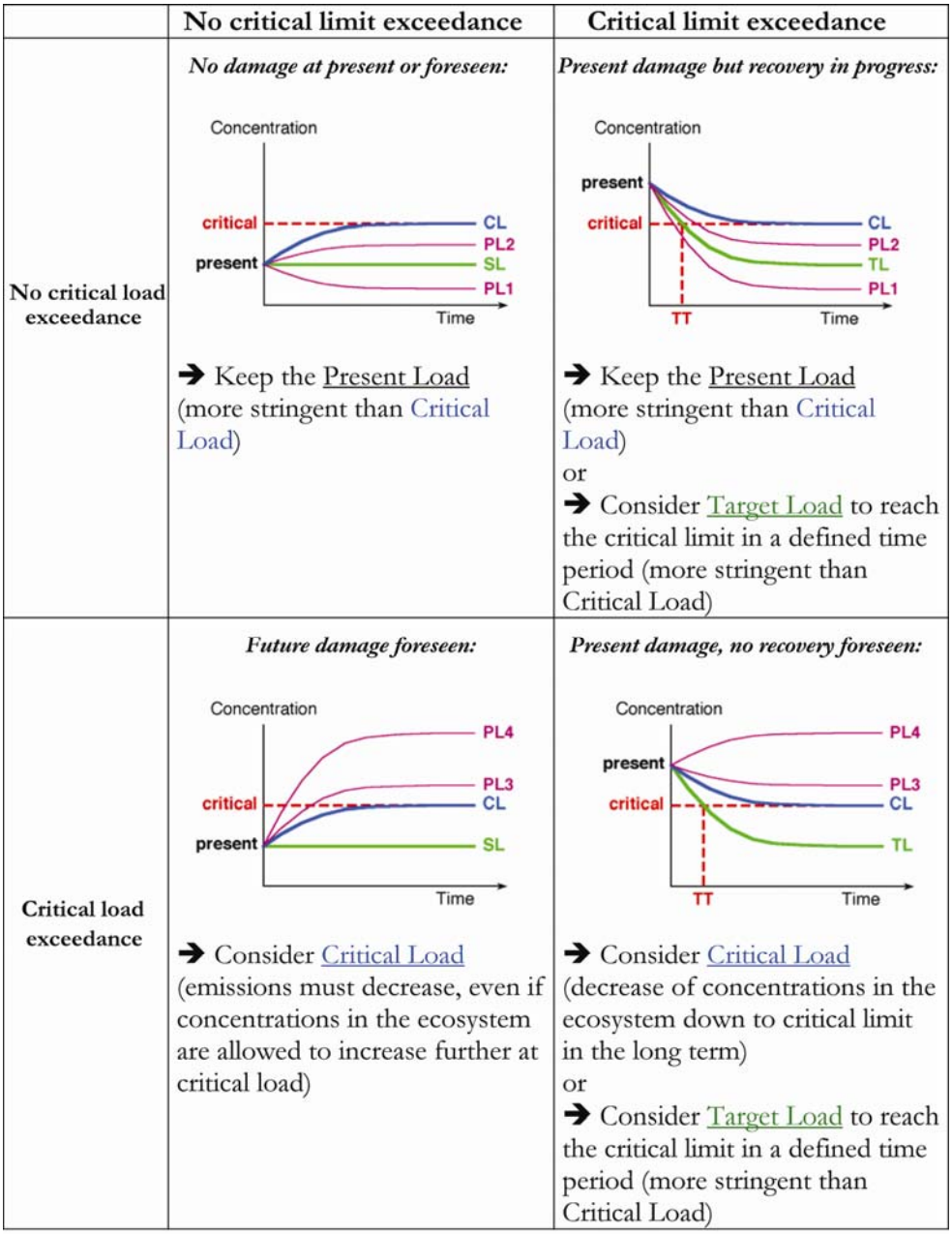

Figure 7-12. The predicted development of metal concentrations in ecosystems for four cases of exceedance or non-exceedance of critical limits and critical loads, respectively.

Source: Taken from DeVries et al. (2004).

Critical Limits

To determine the critical limit, effects-based criteria for the major ecological endpoints should be developed for the ecosystem of concern. Criteria may be developed for any receptor that is exposed to the chemical of concern deposited in the ecosystem. In terrestrial ecosystems, possible ecological endpoints include effects from direct contact of invertebrates or plants with soil and ingestion of plants by herbivores. Effects-based criteria for use in defining the critical limit should be derived from ecotoxicological data appropriate to the most sensitive endpoint (De Vries et al., 2004). Regardless of the selected endpoint, the critical limit should be defined as a concentration in the medium that receives the depositional load, typically soil in terrestrial ecosystems and surface water in aquatic ecosystems. To derive these values, uptake and/or food- chain modeling may be necessary.

Criteria for Pb vary widely and can be the largest source of uncertainty in a critical load calculation. One reason for the wide range in estimates of effects criteria is that Pb speciation is often not taken into account. This can result in variation in estimates of concentration for total Pb that is associated with adverse effects, since the fraction of Pb available to cause a toxic effect depends on chemical factors such as the pH or organic matter content. To develop effects-based criteria applicable to media with a pH or organic matter content different from the test medium, it is more appropriate to develop criteria based on the free concentration of Pb rather than the total Pb concentration.

Models

Critical loads for heavy metals are typically calculated using a steady state model that ignores internal metal cycling and keeps the calculations as simple as possible (De Vries et al., 2004). The critical load is equal to the atmospheric input flux, which equals the sum of the output fluxes from the system minus the other input fluxes (e.g., weathering) when the concentration of Pb is at the critical limit. The input flux of heavy metals via weathering is sometimes neglected, because quantitative estimates are highly uncertain, and weathering is generally thought to be a relatively minor process (see Section 8.3.4.2).

Critical Loads in Terrestrial Ecosystems

Critical loads for Pb have been calculated using simple mass balance, dynamic, and probabilistic models for forested and agricultural land in Europe and Canada in a handful of preliminary studies. The methods and model assumptions used to calculate critical loads vary widely between these studies and little attempt has been made to validate the models that were used, so it is not known how much various simplifying assumptions affect the results.

In spite of the variation in methods and model assumptions used to calculate critical loads for Pb, some general conclusions may be drawn. The critical limit is the most important value for determining the value of the critical load. Wide variations in available effects levels makes this parameter one of the most important sources of uncertainty when calculating critical loads in terrestrial ecosystems. Spatial variations in critical loads for Pb are largely controlled by net runoff. Weathering and uptake by harvestable vegetation were less important. The time to reach steady state is several hundred years in the two studies that used dynamic models to determine critical loads.

Critical Loads in Aquatic Ecosystems

Doyle et al. (2003) modeled critical loads in surface water bodies assuming complete mixing with dilution water entering from the terrestrial catchment area. Loss of metal was also assumed to occur through downstream flushing and burial in sediment. Transfer of metal to sediment was modeled as a first-order process dependant on the dissolved concentration and pH. The inputs to the model included the following: water body area, terrestrial catchment area, water body depth, sediment accumulation rate, thickness of biologically active sediment, net precipitation, and water pH. The fist-order rate constant for transfer to sediment was correlated with pH. The model reached steady state within a few years. Transfer of Pb from the terrestrial catchment to the water body was neglected, because the time to steady state could be on the order of 10,000 years if the model included this source of Pb. However, the authors cited a separate calculation that indicated that neglect of transfer of Pb from the catchment may lead to a 5-fold underestimation of Pb concentrations in the surface water. These results indicate that Pb run-off from soil is more important than direct atmospheric deposition to the surface water bodies considered in this study. Due to the long times required to achieve steady state, the critical load methodology may not be appropriate for Pb in aquatic systems.

Limitations and Uncertainties

The largest sources of uncertainty identified in studies of critical loads for Pb include the following: (1) steady-state assumption; (2) derivation of the critical limit; (3) Pb speciation; and (4) soil runoff as an input to aquatic ecosystems

The critical load is calculated for steady state conditions, but the time for Pb to reach steady-state concentrations can be as long as several centuries. Thus, dynamic models are often used to predict Pb concentrations over shorter time frames. Dynamic modeling requires additional knowledge about current concentrations in the considered ecosystem. For regulatory purposes, use of dynamic modeling requires that a target time be set in order to calculate a critical load.

Speciation strongly influences the toxicity of Pb in soil and water and partitioning between dissolved and solid phases determines the concentration of Pb in soil drainage water, but it has not been taken into account in most of the critical load calculations for Pb performed to date. Recent guidance for heavy metals has begun to emphasize the importance of speciation to critical load calculations and suggest methods to calculate speciation (De Vries et al., 2004). To this end, Lofts et al. (2004) developed critical limit functions for several metals, including Pb, that take into account the effects of pH, organic matter, and the protective effects of cations on speciation.

Runoff of Pb from soil may be the major source of Pb into aquatic systems. However, little attempt has been made to include this source into critical load calculations for aquatic systems due to the complexity of including this source in the critical load models.

Preliminary efforts to calculate critical loads for Pb in terrestrial and aquatic ecosystems have so far relied on a variety of calculation methods and model assumptions. Efforts are ongoing to refine and standardize methods for the calculation of critical loads for heavy metals which are valid in the context of CLPTRP. At this time, the methods and models commonly used for the calculation of critical loads have not been validated for Pb. Many of the methods neglect the speciation of Pb when estimating critical limits, the uptake of Pb into plants, and the outflux of Pb in drainage water, limiting the utility of current models.

Future efforts should focus on fully incorporating the role of Pb speciation into critical load models, and validating the assumptions used by the models.

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