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1 **7. INTEGRATIVE SYNTHESIS: MULTIMEDIA LEAD**
2 **EXPOSURE, HUMAN HEALTH EFFECTS, AND**
3 **ECOSYSTEM EFFECTS**

4
5
6 **7.1 INTRODUCTION**

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

21
22 **7.1.1 Historical Background**

23 In 1971, U.S. EPA promulgated national ambient air quality standards for several major
24 “criteria” pollutants (see Federal Register, 1971), but did not include Pb among them at that time.
25 Later, on October 5, 1978, the EPA promulgated primary and secondary Pb NAAQS under
26 Section 109 of the CAA (43 FR 46258), as announced in the Federal Register (1979). Identical
27 primary and secondary Pb standards were then established as: 1.5 µg/m³ as a calendar quarterly
28 average (maximum arithmetic mean averaged over 90 days). Those standards were based on
29 scientific assessments in EPA’s original *Air Quality Criteria for Lead* (U.S. Environmental
30 Protection Agency, 1977) or “1977 Pb AQCD.”

1 In 1986, the EPA published a revised Pb AQCD (U.S. Environmental Protection Agency,
2 1986a), which assessed newly available scientific information on health and welfare effects
3 associated with exposure to various concentrations of Pb in ambient air, based on literature
4 published through 1985. That 1986 document mainly assessed the health and welfare effects of
5 Pb, but other scientific data were also discussed in order to provide a better understanding of the
6 pollutant in the environment. Thus, the 1986 Pb AQCD included chapters that discussed the
7 atmospheric chemistry and physics of the pollutant; analytical approaches; environmental
8 concentrations; human exposure and dosimetry; physiological, toxicological, clinical, and
9 epidemiological aspects of Pb health effects; and Pb effects on ecosystems. An Addendum to the
10 1986 Pb AQCD was also published along with it (U.S. Environmental Protection Agency,
11 1986b). Then, a Supplement to the 1986 Pb AQCD/Addendum was published by EPA in 1990
12 (U.S. Environmental Protection Agency, 1990a). That 1990 Supplement evaluated still newer
13 information emerging in the published literature concerning (a) Pb effects on blood pressure and
14 other cardiovascular endpoints and (b) the effects of Pb exposure during pregnancy or during the
15 early postnatal period on birth outcomes and/or on the neonatal physical and neuropsychological
16 development of infants and children.

17 The evaluations in the 1986 Pb AQCD/Addendum and the 1990 Supplement provided
18 scientific inputs to support decision-making regarding CAA-mandated periodic review and, as
19 appropriate, revision of the Pb NAAQS; and they were drawn upon in preparation of an
20 associated OAQPS Lead Staff Paper (U.S. Environmental Protection Agency, 1990b). Based on
21 the scientific assessment in the 1986 Pb AQCD/Addendum and the 1990 Supplement, as well as
22 associated exposure/risk analyses, the 1990 Staff Paper recommended that the Administrator
23 consider options for revision of the Pb NAAQS to a level in the range of 0.5 to 0.75 $\mu\text{g}/\text{m}^3$
24 (30-day arithmetic mean). After consideration of those evaluations, EPA chose not to propose
25 revision of the Pb NAAQS. At the time, as part of a broad, integrated U.S. EPA Strategy for
26 Reducing Lead Exposures (U.S. Environmental Protection Agency, 1991), the Agency focused
27 efforts on regulatory and remedial clean-up actions aimed at reducing Pb exposures from a
28 variety of non-air sources judged to pose more significant public health risks to U.S. populations
29 than remaining air emission sources. By 1990, average ambient air Pb levels had dropped to
30 0.15 to 0.25 $\mu\text{g}/\text{m}^3$ across U.S. urban areas due to the phasedown of Pb in gasoline.

31

1 **7.1.2 Chapter Organization**

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

12
13

14 **7.2 OVERVIEW OF MULTIMEDIA LEAD, SOURCES, EMISSIONS,**
15 **AND CONCENTRATIONS IN THE UNITED STATES**

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

28

29 **7.2.1 Sources of Lead Emissions into Ambient Air**

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

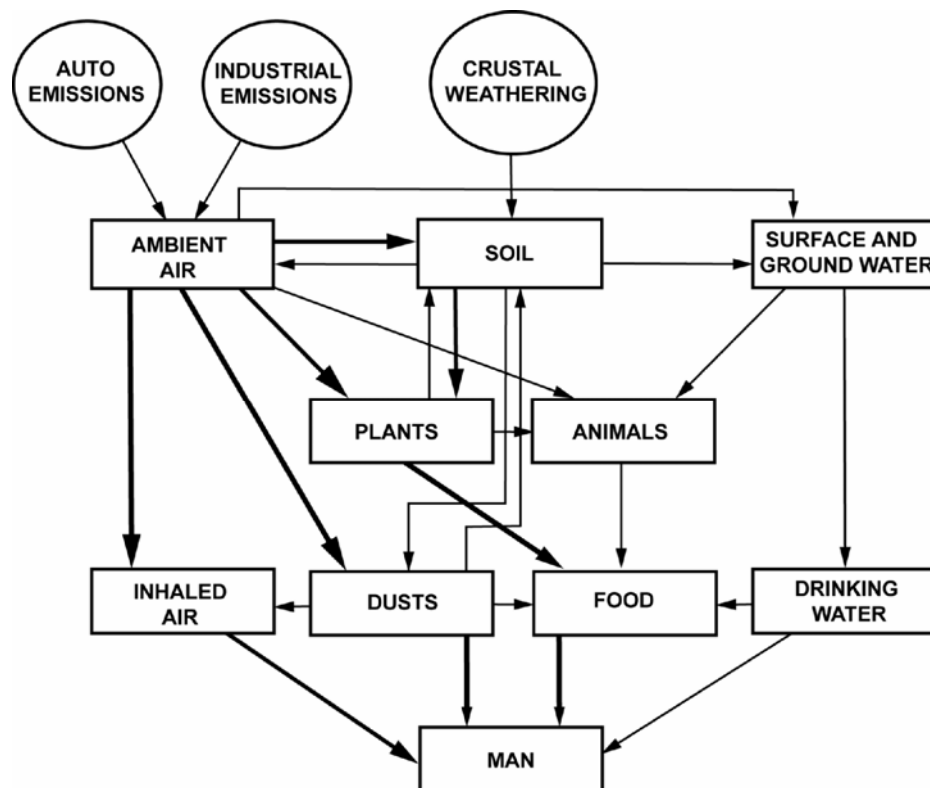


Figure 7-1. Principal pathways of lead from the environment to human consumption. Heavy arrows are those pathways discussed in greatest detail in this chapter.

1 elemental Pb because, at ambient atmospheric temperatures, elemental Pb deposits to surfaces or
 2 forms a component of atmospheric aerosol. Those salts and covalently bound Pb compounds
 3 that are of significance in the environment include: sulfates (PbSO_4); chlorides (PbCl_2);
 4 carbonates (PbCO_3 , $\text{Pb}(\text{HCO}_3)_2$); hydroxides ($\text{Pb}(\text{OH})_2$); nitrates ($\text{Pb}(\text{NO}_3)_2$); phosphates
 5 (PbPO_4 , $\text{Pb}(\text{HPO}_4)_2$); oxides (PbO , Pb_3O_4), silicates, and PbS. With the exception of the
 6 covalently-bound sulfide and oxide, these compounds are derived from acids (or the related
 7 anions) that are common in the environment, such as sulfuric acid (H_2SO_4), nitric acid (HNO_3),
 8 carbonic acid (H_2CO_3 , an acid that forms when CO_2 dissolves in water), and phosphoric acid
 9 (H_3PO_4). Lead salts, once formed, tend to be only slightly soluble in neutral solutions, but are
 10 quite soluble in the presence of acid. Another form of Pb-containing compounds is the
 11 tetravalent Pb (IV) organometallic compounds, such as the well-known fuel additives,
 12 tetramethyllead (TML) and tetraethyllead (TEL).

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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).

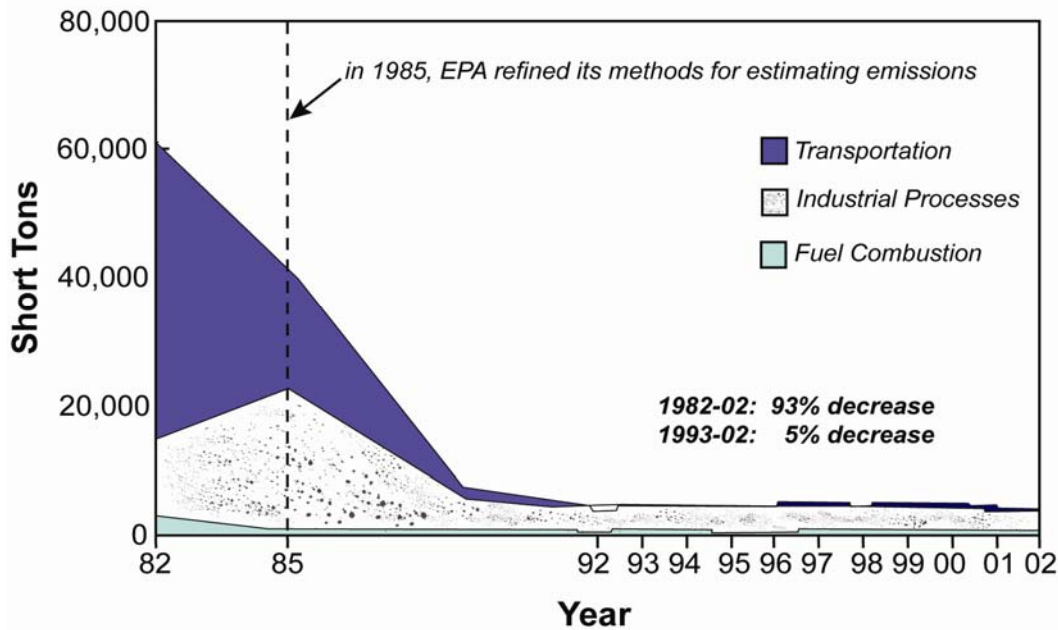


Figure 7-2. Trends in U.S. air lead emissions during the 1982 to 2002 period.

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

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

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

14

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 $<2.5 \mu\text{m}$ 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

1 suspended into the atmosphere. Depending on soil conditions, saltation can be responsible for
2 moving 50 to 75% of surface particles. Surface creep is the rolling or sliding motion of particles
3 induced by wind stress or momentum exchanged from other moving particles. This generally
4 applies to large particles 500 to 1000 μm in diameter and moves 5 to 25% of soil by weight.
5 Suspension is the process that actually ejects particles into the air. This affects particles
6 $\leq 100 \mu\text{m}$ in diameter and moves 3 to 40% of soil by weight. Resuspension may occur as a series
7 of events. Short episodes of high windspeeds, dry conditions, and other factors conducive to
8 resuspension may dominate annual averages of upward flux.

9 Soil-Pb concentrations vary significantly throughout urban areas, depending on proximity
10 to roadways and stationary sources and on wind speed and direction, as noted in Section 3.2.1.
11 Some of the highest soil-Pb concentrations are observed near major roadways. For example,
12 surface soil-Pb concentrations measured near a major freeway in Cincinnati, OH, were between
13 59 ppm and 1980 ppm, levels well above background. These concentrations dropped off
14 dramatically with soil depth. An estimated 40% of Pb from automobile exhaust was retained in
15 the nearby soil. Lead-contaminated soils and dusts can be significant sources of Pb exposure for
16 human populations.

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

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

27 **7.2.3 Ambient Air Lead Concentrations**

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

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

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

9 As was seen for emissions of Pb, ambient air Pb concentrations have also markedly
10 declined over the past several decades. Between 1983 and 2002, ambient air Pb concentrations
11 measured at FRM monitors decreased by $\sim 94\%$, as shown in Figure 7-3. Data from the FRM
12 monitors and from the $\text{PM}_{2.5}$ speciation, IMPROVE and NATTS networks all show a consistent
13 pattern of ambient air Pb concentrations, i.e., a long period of measured ambient levels
14 substantially lower than the current Pb NAAQS, except in a few local areas. For example, Pb
15 concentrations measured at the FRM monitors in 2000 to 2004 on average, are quite low, with
16 the mean level ranging from 0.03 to $0.05 \mu\text{g}/\text{m}^3$ (excluding point source-related monitors) and
17 0.10 to 0.22 (including point source-related monitors). However, when data from point source-
18 oriented monitors are included, one to five U.S. locations (from among ~ 200 sites) had measured
19 calendar quarterly maximum Pb levels that exceeded the NAAQS level ($1.5 \mu\text{g}/\text{m}^3$, quarterly
20 max average) in any given year during 2000 to 2004. As for data from PM_{10} monitors in the
21 NATTS network, the highest quarterly max Pb concentration observed was $0.039 \mu\text{g}/\text{m}^3$ during
22 2002 to 2005. Using data from the $\text{PM}_{2.5}$ speciation network for 2002 to 2005, the highest
23 quarterly max Pb concentration reported was $0.168 \mu\text{g}/\text{m}^3$. Thus, overall, ambient air Pb
24 concentrations in the United States are generally well below the current NAAQS level, except
25 for a few scattered locations influenced by local sources.

26

27 **7.2.4 Non-Air Environmental Lead Exposure Routes**

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

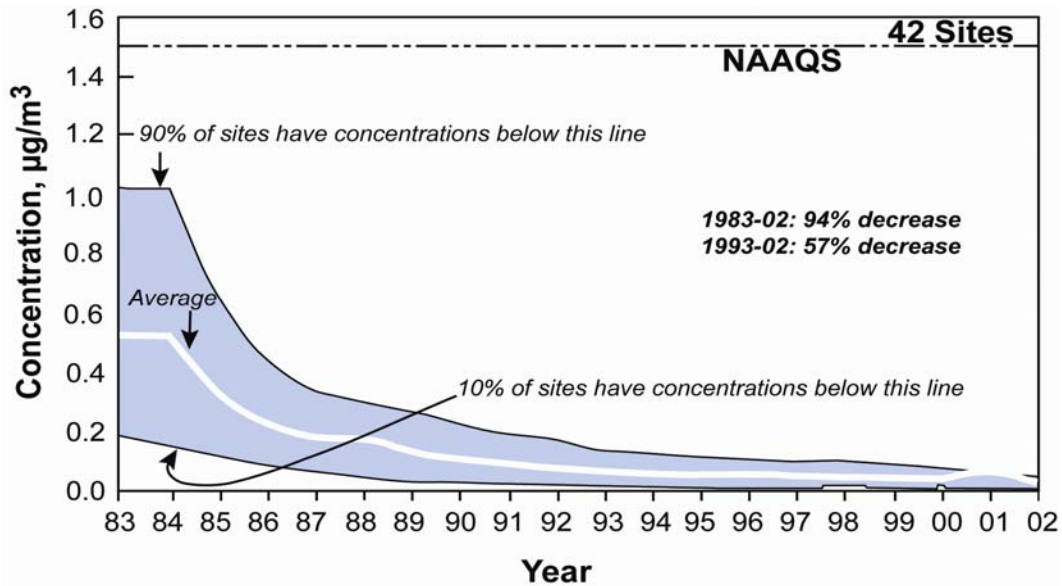


Figure 7-3. Airborne Pb concentrations measured at FRM sites, averaged across the United States for the years 1983 through 2002. The data are plotted in terms of maximum arithmetic mean averaged over a calendar quarter and are shown in relation to the Pb NAAQS of 1.5 µg/m³

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

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

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

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

1 example, studies discussed in Section 3.2.3 show that, at a median floor dust Pb level of 5 $\mu\text{g}/\text{ft}^2$
2 (54 $\mu\text{g}/\text{m}^2$), ~5% of children had blood Pb levels $\geq 10 \mu\text{g}/\text{dL}$. At a floor dust Pb loading of
3 50 $\mu\text{g}/\text{ft}^2$ (540 $\mu\text{g}/\text{m}^2$), the percentage of children with blood Pb levels $\geq 10 \mu\text{g}/\text{dL}$ rose to 20%.
4 In another study, children exposed to floor dust Pb loadings in excess of 25 $\mu\text{g}/\text{ft}^2$ (270 $\mu\text{g}/\text{m}^2$)
5 were at eight times greater risk of having blood Pb levels $\geq 10 \mu\text{g}/\text{dL}$ compared to children
6 exposed to levels below 2.5 $\mu\text{g}/\text{ft}^2$ (27 $\mu\text{g}/\text{m}^2$).

7 Soil Pb is a significant contributor to elevated blood-Pb levels, especially among children,
8 in populations residing near certain Superfund sites, as discussed in Section 3.2.2. For example,
9 Pb levels in soil collected at residences near the Tar Creek Superfund Site (a Pb mining area in
10 northeastern Oklahoma) reflected contamination by wind-dispersed mine wastes. More than
11 20% of residential soil samples exceeded the EPA action level of 500 ppm, and children's blood
12 Pb levels tended to be higher in comparison to those of children living outside the Superfund
13 towns. In this same area, blood-Pb levels were found to be highest among African-American,
14 Mexican-American, and poor children. Blood-Pb levels were most commonly correlated with
15 mean floor dust Pb loading and with soil Pb, especially front yard soil. Another study found that
16 homes at the Jasper County Superfund Site in southwestern Missouri had significantly higher
17 soil and dust Pb levels and significantly higher blood-Pb levels than areas outside of the
18 Superfund site. There was a strong statistical relationship observed between blood-Pb levels and
19 soil, dust, and paint Pb concentrations.

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

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

1 0.015 mg/L (15 ppb) set in 1991. Of 18 major U.S. cities illustrated in Table 3-11 of Chapter 3
2 as exceeding the EPA water Pb Action Level in the early 1990s, 14 had decreased their 90th
3 percentile tap water concentrations to below the 15-ppb Action Level during recent monitoring
4 periods (since the year 2000). On the other hand, with the introduction of chloramine as an
5 alternative water treatment used in some cities across the United States, some increases in tap
6 water-Pb concentrations have been detected in some municipal water supplies, raising concern
7 about possible resultant increases in blood-Pb levels among affected water-use populations.

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

19 Although marked reductions of Pb in U.S. market basket food supplies have occurred
20 during the past several decades, Pb-contaminated food still can be an important route of Pb
21 exposure (see Section 3.4). Several recent studies in the U.S. and Australia indicate that daily
22 dietary Pb intake is in the range of 2 to 10 µg/day (see section 3.4). Data from FDA's 1994-1996
23 Total Diet Studies showed that, since 1982-1984, daily intakes of lead from food dropped
24 96 percent in 2- to 5-year-olds (from 30 micrograms a day to 1.3) and nearly 93 percent in adults
25 (from 38 micrograms a day to 2.5) (see: <http://www.cfsan.fda.gov/~dms/fdalead.html>). Lastly,
26 some U.S. population groups that frequently consume canned foods imported from non-U.S.
27 countries that still allow use of lead-soldered cans may be at distinctly greater risk for exposure
28 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 toxicokinetics. 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 toxicokinetics 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.

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

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

22 In contrast to Pb in bone, which accumulates with continued exposure in adulthood, Pb
23 concentrations in soft tissues (e.g., liver and kidney) are relatively constant in adults, reflecting a
24 faster turnover of lead in soft tissue relative to bone (as discussed in Chapter 4). It is also noted
25 that Pb in soft tissues exists predominantly bound to protein (see Section 5.11). High affinity
26 cytosolic Pb-binding proteins (PbBPs) have been identified in rat kidney and brain. Other high-
27 affinity Pb-binding proteins have been isolated in human kidney, two of which have been
28 identified as a 5 kD peptide, thymosin 4, and a 9 kD peptide, acyl-CoA binding protein.

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

1 estimated to be ~850 µg/dL red blood cells (or ~340 µg/dL whole blood), with an apparent
2 dissociation constant of ~1.5 µg/L. It has been suggested that the small fraction of Pb in plasma
3 (<0.3%) may be the more biologically labile and toxicologically active fraction of circulating Pb.
4 Several authors have proposed that Pb released from the skeleton was preferentially partitioned
5 into serum compared with red cells. About 40 to 75% of Pb in the plasma is bound to proteins,
6 of which albumin appears to be the dominant ligand. Lead in serum not bound to protein exists
7 largely as complexes with low molecular weight sulfhydryl compounds (e.g., cysteine,
8 homocysteine) and other ligands.
9

10 **7.3.2 Selection of Blood-Pb Concentration as Key Index of Pb Exposure**

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

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

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

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

22

23 **7.3.3 Trends in U.S. Blood Lead Levels**

24 As discussed in Section 4.3.1.3, blood-Pb concentrations in the U.S. general population
25 have been monitored over the past three decades via the National Health and Nutrition
26 Examination Survey (NHANES) conducted by the Centers for Disease Control and Prevention.
27 Data from the most recent survey (NHANES IV, Centers for Disease Control, 2005) are shown
28 in Tables 7-1 and 7-2. For survey years 2001-2002, the geometric mean blood-Pb level for ages
29 >1 year ($n = 8,945$) was $1.45 \mu\text{g/dL}$ (95% CI: 1.39, 1.52); with the geometric mean in males
30 ($n = 4,339$) being $1.78 \mu\text{g/dL}$ (95% CI: 1.71, 1.86) and in females ($n = 4,606$) being $1.19 \mu\text{g/dL}$
31 (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 | | |
|---------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| | <i>Survey Period</i> | <i>1999–2000</i> | <i>2001–2002</i> | <i>1999–2000</i> | <i>2001–2002</i> | <i>1999–2000</i> | <i>2001–2002</i> | <i>1999–2000</i> | <i>2001–2002</i> |
| 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) |

^aBlood 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 | | |
|---------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| | <i>Survey Period</i> | <i>1999–2000</i> | <i>2001–2002</i> | <i>1999–2000</i> | <i>2001–2002</i> |
| 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) |

^aBlood lead concentrations presented are geometric means (95% CI).

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

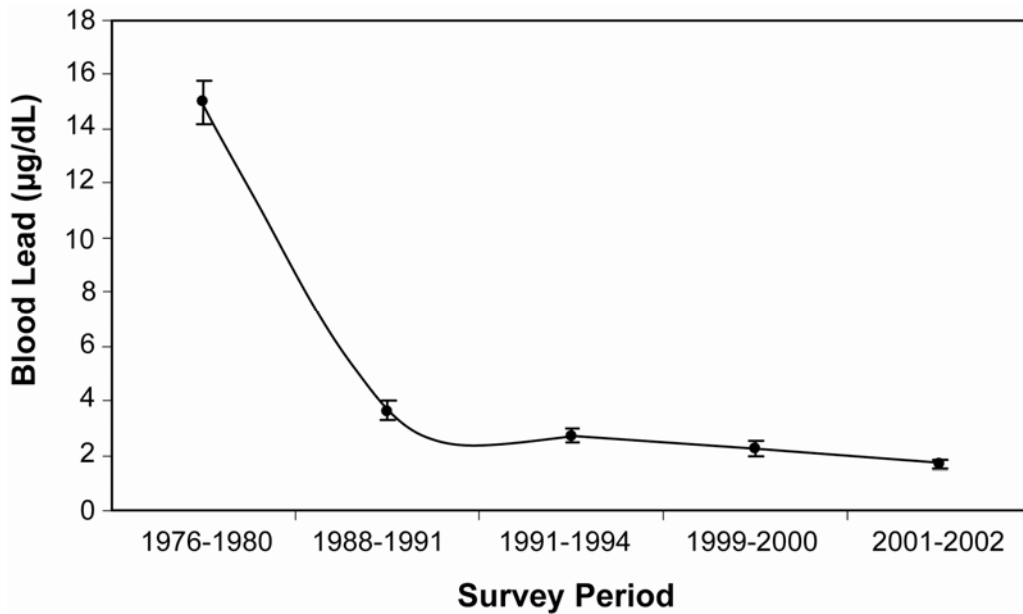


Figure 7-4. Blood lead concentrations in U.S. children, 1-5 years of age. Shown are geometric means and 95% confidence intervals as reported from the NHANES II (1976–1980) and NHANES III Phase 1 (1988–1991; Pirkle et al., 1994); NHANES III Phase 2 (1991–1994; Pirkle et al., 1998); and NHANES IV (1999–2000,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

5 Blood Pb concentrations can vary considerably as a function of age, physiological state
6 (e.g., pregnancy, lactation, menopause), and numerous other factors that affect exposure to Pb.
7 The NHANES data provide estimates for average blood lead concentrations in various
8 demographic strata of the U.S. population. NHANES III Phase 2 samples were collected during
9 1991 to 1994. Geometric mean blood-Pb concentrations of U.S. adults, ages 20 to 49 years,
10 estimated from the NHANES III Phase 2, were 2.1 µg/dL (95% CI, 2.0, 2.2). Among adults,
11 blood-Pb concentrations were highest in the strata that included ages 70 years and older

1 (3.4 µg/dL; 95% CI, 3.3, 3.6). The geometric mean blood-Pb concentration of children, ages 1 to
2 5 years, was 2.7 (95% CI, 2.5, 3.0) for the 1991 to 1994 survey period; however, the mean varied
3 with socioeconomic status and other demographic characteristics that have been linked to lead
4 exposure (e.g., age of housing). Central estimates from the NHANES III Phase 2 (1991 to
5 1994), when compared to those from NHANES III Phase 1 (1988 to 1991) and the NHANES II
6 (1976 to 1980), indicate a clear downward temporal trend in U.S. blood-Pb concentrations over
7 the past 20 years or so. It should be noted, however, that blood-Pb levels have been declining at
8 differential rates for various general subpopulations, as a function of income, race, and certain
9 other demographic indicators such as age of housing. Also, substantial caution should be
10 exercised with regard to use of NHANES data for risk assessment purposes, in that the
11 nationally-representative NHANES quantitative results (e.g., national mean blood-Pb levels or
12 strata-classified national mean blood-Pb values) vary with regard to how reflective they may be
13 of specific regions or communities.

14

15 **7.3.4 Approaches to Predictive Estimation of Pb-Exposure Impacts on** 16 **Distribution to Internal Tissues**

17 As indicated in Chapter 4, a key issue of much importance in carrying out lead risk
18 assessments that evaluate the potential likelihood of Pb-induced health effects is the estimation
19 of external Pb-exposure impacts on internal Pb tissue concentrations. This includes estimation of
20 typical Pb exposure impacts on internal distribution of Pb to blood and bone (as key biomarkers
21 of Pb exposure), as well as to other “soft tissue” target organs (e.g., brain, kidney, etc.). Earlier
22 criteria assessments in the 1977 and 1986 Pb AQCDs extensively discussed then available slope
23 factor and/or other regression models of external Pb exposure impacts on blood-Pb
24 concentrations in human adults and children. The older slope factor analyses discussed in the
25 1977 and 1986 Pb AQCDs noted that at relatively low air-Pb concentrations ($\leq 2 \mu\text{g}/\text{m}^3$),
26 pediatric blood-Pb levels generally increase by $\sim 2 \mu\text{g}/\text{dL}$ per each $1 \mu\text{g}/\text{m}^3$ increment in air-Pb
27 concentration. Further refinements in regression modeling of Pb impacts on blood or bone Pb
28 are discussed in Chapter 4.

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

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

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

19 Additional information on Pb biokinetics, bone mineral metabolism, and Pb exposures has
20 led to refinements and expansions of earlier modeling efforts. In particular, there are three
21 pharmacokinetic models that are currently being used or considered for broad application in Pb
22 risk assessment: (1) the Integrated Exposure Uptake BioKinetic (IEUBK) model for Pb in
23 children developed by EPA (U.S. Environmental Protection Agency, 1994a,b; White et al.,
24 1998); (2) the Leggett model, which also simulates Pb kinetics from birth through adulthood
25 (Leggett, 1993); and (3) the O'Flaherty model, which simulates Pb kinetics from birth through
26 adulthood (O'Flaherty, 1993, 1995). The above three models have been individually evaluated
27 to varying degrees, against empirical physiological data on animals and humans and data on
28 blood-Pb concentrations in individuals and/or populations (U.S. Environmental Protection
29 Agency, 1994a,b; Leggett, 1993; O'Flaherty, 1993). In evaluating models for use in risk
30 assessment, exposure data collected at hazardous waste sites have mainly been used to drive

1 model simulations (Bowers and Mattuck, 2001; Hogan et al., 1998). The exposure module in the
2 IEUBK model makes this type of evaluation feasible.

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

17
18

19 **7.4 LEAD-INDUCED TOXICITY: INTEGRATION OF TOXICOLOGIC** 20 **AND EPIDEMIOLOGIC EVIDENCE**

21 **7.4.1 Introduction**

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

1 The 1977 Pb AQCD (U.S. Environmental Protection Agency, 1977) that provided key
2 scientific bases for the setting in 1978 of the current Pb NAAQS included discussion of both:
3 (a) historical literature accumulated during several preceding decades that established lead
4 encephalopathy and other signs and symptoms of persisting severe central and/or peripheral
5 nervous system damage, as well as renal and hepatic damage, and anemia as typifying the classic
6 syndrome of acute and/or chronic high-level lead poisoning among human pediatric and /or adult
7 population groups, and (b) evaluation of then newly-emerging evidence for more subtle and
8 difficult-to-detect “subclinical” Pb effects on IQ, other neurological endpoints, and moderate
9 blood hemoglobin deficits or other erythropoietic indicators of heme synthesis impairment,
10 which collectively were judged to constitute an array of adverse Pb health effects associated with
11 lead exposures indexed by blood Pb concentrations ranging down to ~30 µg/dL. The next Pb
12 NAAQS criteria review during the 1980's, as contained in the 1986 Pb AQCD/Addendum and its
13 1990 Supplement (U.S. Environmental Protection Agency, 1986a, b, 1990) documented further
14 rapid advances in Pb health effects research that provided (a) increasingly stronger evidence that
15 substantiated still lower fetal and/or postnatal Pb-exposure levels (indexed by blood-Pb levels
16 extending to as low as 10 to 15 µg/dL or, possibly, below) as being associated with slowed
17 physical and neurobehavioral development, lower IQ, impaired learning, and/or other indicators
18 of adverse neurological impacts and (b) other pathophysiological effects of Pb on cardiovascular
19 function, immune system components, calcium and vitamin D metabolism, and other selected
20 health endpoints.

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

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

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

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

15 **7.4.2 Neurotoxic Effects**

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

24 Animal models are extremely important in the characterization of Pb neurotoxicity
25 because exposures can be controlled to address questions about sensitive periods of exposure.
26 Unlike typical human exposures reported in epidemiology studies, Pb dosing to animals can be
27 stopped at any time to address questions about the reversibility and persistence of neurotoxic
28 effects. Also, with animals, dosing can be varied to include very low doses to examine effects
29 seen with more current pediatric exposures. Animal models, especially inbred strains of rodents,
30 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'-nucleotidase (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).

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

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

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

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

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

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

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

19

20 **7.4.2.1 Neurocognitive Ability**

21 *Global Measures of Cognitive Function – Intelligence Testing and Academic Achievement*

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

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

3 For example, in the largest available new cross-sectional study, Lanphear et al. (2000)
4 examined the relationship between blood Pb concentrations and cognitive deficits in a nationally
5 representative sample of 4,853 U.S. children aged 6 to 16 years children (geometric mean blood
6 Pb of 1.9 $\mu\text{g}/\text{dL}$) who participated in NHANES III, with 97.9% of the children having blood-Pb
7 concentrations $<10 \mu\text{g}/\text{dL}$. Two subtests of the WISC-R, Block Design (a measure of visual-
8 spatial skills) and Digit Span (a measure of short-term and working memory) were administered;
9 and numerous potential confounders were assessed in the multivariable analyses. Although no
10 data on maternal IQ or direct observations of caretaking quality in the home were available, other
11 variables such as the poverty index ratio and education level of the primary caregiver likely
12 served as adequate surrogate measures of these important potential confounders. In multivariate
13 analyses, a significant covariate-adjusted relationship was found between blood-Pb level and
14 scores on both WISC-R subtest for all children as well as among those with blood-Pb levels
15 $<10 \mu\text{g}/\text{dL}$. Blood-Pb concentration was also significantly associated with Block Design when
16 the multivariate analysis was restricted to children with blood Pb levels $<7.5 \mu\text{g}/\text{dL}$.

17 Other recent studies of the association of Pb with IQ in children with low Pb exposures
18 have consistently observed effects at blood-Pb concentrations below $10 \mu\text{g}/\text{dL}$ (as discussed in
19 Section 6.2.3 of Chapter 6). Most notably, a large international pooled analysis of 1,333 children
20 from seven different cohorts by Lanphear et al. (2005) estimated a decline of 6.2 points (95% CI:
21 3.8, 8.6) in full scale IQ for an increase in concurrent blood-Pb level from 1 to $10 \mu\text{g}/\text{dL}$. A
22 common observation among some of these studies of low-level Pb exposure is a non-linear dose-
23 response relationship between blood Pb and neurodevelopmental outcomes. Although this may
24 seem at odds with certain fundamental toxicological concepts, it is possible that the initial
25 neurodevelopmental lesions at lower Pb levels may be disrupting different biological
26 mechanisms (e.g., early developmental processes in the central nervous system) than the more
27 severe effects of high exposures that result in symptomatic poisoning and frank mental
28 retardation. One ad hoc explanation may be that the predominant mechanism at very low
29 blood-Pb levels is rapidly saturated and that a different, less-rapidly-saturated process, becomes
30 predominant at blood-Pb levels greater than $10 \mu\text{g}/\text{dL}$.

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

6 Lanphear et al. (2000) examined the relationship between blood-Pb levels and a
7 standardized measure of academic achievement among 4,853 NHANES III children, aged 6 to
8 16 years (geometric mean blood-Pb of 1.9 $\mu\text{g}/\text{dL}$). Subjects were administered the Arithmetic
9 and Reading subtests of the Wide Range Achievement Test-Revised (WRAT-R). Multiple linear
10 regression revealed significant Pb-related decrements in Arithmetic and Reading scores. In
11 analyses stratified by blood-Pb levels, statistically significant inverse relationships between
12 blood-Pb levels and performance for both Reading and Arithmetic subtests were found for
13 children with concurrent blood-Pb concentrations $<5 \mu\text{g}/\text{dL}$. However, possible attribution of
14 the observed associations of decrements in WRAT-R scores to earlier (but unmeasured) likely
15 somewhat higher peak blood-Pb concentrations cannot be ruled out.

16 Several other epidemiologic studies observed inverse associations between exposure to Pb
17 and academic achievement, for the endpoints noted above as well as class rankings and high
18 school graduation rates. Two studies specifically examined the effects of blood-Pb levels
19 $<10 \mu\text{g}/\text{dL}$ on academic achievement. One study examined 533 girls aged 6 to 12 years (mean
20 blood Pb level of 8.1 $\mu\text{g}/\text{dL}$) in Riyadh, Saudi Arabia and observed that, in a subset of students
21 with blood-Pb levels $<10 \mu\text{g}/\text{dL}$, class rank percentile was statistically significantly associated
22 with blood-Pb levels (Al-Saleh et al., 2001). In another study in Torreón, Mexico, a significant
23 inverse relationship was found between blood-Pb concentrations and math and vocabulary scores
24 in 594 second graders (mean blood Pb of 11.4 $\mu\text{g}/\text{dL}$). In segmented regression analyses, slopes
25 for blood Pb associations with vocabulary and math scores were significantly steeper below 10
26 $\mu\text{g}/\text{dL}$ than above (Télliez-Rojo et al., 2006). Associations between Pb exposure and academic
27 achievement observed in the above-noted studies were significant even after adjusting for IQ,
28 suggesting that Pb-sensitive neuropsychological processing and learning factors not reflected by
29 global intelligence indices might contribute to reduced performance on academic tasks.

1 Specific Cognitive Abilities – Learning, Memory, and Attention

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

6 Executive functions refer to an individual's ability to regulate attention and engage
7 several related higher order cognitive processes such as strategic planning, control of impulses,
8 organized search, flexibility of thought and action, and self-monitoring of one's own behavior.

9 In some earlier studies, as assessed in the 1986 Pb AQCD/Addendum and/or 1990 Supplement,
10 Pb exposure was associated with higher frequency of negative ratings by teachers and/or parents
11 on behaviors such as inattentiveness, impulsivity, distractibility, and lack of persistence on
12 assigned tasks, as well as slowed psychomotor responses and more errors on simple, serial, and
13 choice reaction time tasks. More recent studies (see Section 6.2.5) have observed inverse
14 relationships between exposure to Pb and attentional behaviors and executive function, even in
15 cohorts where more than 80% of the children had blood-Pb levels <10 µg/dL. These
16 associations were observed across a wide range of age groups, from children 4-5 years to 19-20
17 years of age. Higher blood-Pb levels were also associated with impaired memory and visual-
18 spatial skills.

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

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

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

11 As noted in Section 5.3.5, NMDAR function and ontogeny are affected by Pb exposure.
12 Functional NMDARs are necessary for spatial learning and memory, as tested by the Morris
13 water maze. Several studies that evaluated Pb effects with this learning paradigm have shown
14 that chronic exposure to 250 ppm Pb affected long-term memory. The effect of Pb on memory is
15 not clearly understood. In some studies, memory impairment was found at blood Pb levels of
16 10 µg/dL, whereas numerous other studies found no Pb-induced effects on short term memory.
17 This parallels findings from most cross-sectional and prospective epidemiological studies, which
18 generally did not detect low-level Pb exposure effects on memory.

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

24 25 **7.4.2.2 Behavior, Mood, and Social Conduct**

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

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

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

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

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

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

9 **7.4.2.3 Neurophysiologic Outcomes**

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

16 Epidemiologic studies of the effect of Pb on sensory acuity have focused on hearing
17 thresholds and features of auditory processing in Pb-exposed children. Schwartz and Otto (1987)
18 observed significant Pb-associated elevations in pure-tone hearing thresholds at various
19 frequencies within the range of human speech among over 4,500 4 to 19 year old subjects in
20 NHANES II. These findings were replicated in a sample of ~3,000 subjects (6 to 19 years old)
21 in the Hispanic Health and Nutrition Examination Survey (HHANES) (Schwartz and Otto,
22 1991), including at blood-Pb levels <10 µg/dL.

23 Dietrich et al. (1992) assessed the relationship between scores on a test of central auditory
24 processing (SCAN) and blood-Pb concentrations in 215 children 5 years of age drawn from the
25 Cincinnati Lead Study. Higher prenatal, neonatal, and postnatal blood-Pb concentrations were
26 associated with more incorrect identification of common monosyllabic words presented under
27 conditions of filtering (muffling). In another study, conducted in Poland, a significant
28 association between concurrent blood-Pb levels and increased hearing thresholds was also
29 observed among 155 children 4 to 14 years of age (median blood Pb of 7.2 µg/dL) (Osman et al.,
30 1999). This relationship remained statistically significant when restricted to children with
31 blood-Pb levels <10 µg/dL. The supportive evidence of a relationship between Pb exposure and

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

4 Animal studies have shown Pb-induced deficits in both auditory and visual acuity, which
5 may contribute to the cognitive deficits associated with Pb exposure. Blood Pb levels as low as
6 33 µg/dL in nonhuman primates impair auditory function by increasing latencies in brainstem
7 auditory evoked potentials and elevating hearing thresholds. Blood-Pb levels of 19 µg/dL in rats
8 have been found to cause selective effects on rod and bipolar cells, resulting in decreased
9 maximal ERG amplitude, decreased ERG sensitivity, and increased mean ERG latency. In a
10 review of Pb-induced auditory and visual dysfunction, Otto and Fox (1993) point to the
11 structural, biophysical, and photochemical similarities of rods in rats, monkeys and humans and
12 suggest that undetected visual or auditory deficits may profoundly impact both sensory motor
13 and mental development in children.

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

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

1 hemisphere. This suggests that elevated childhood Pb exposure may influence neural substrates
2 underlying semantic language function in normal language areas, with concomitant recruitment
3 of contra-lateral regions causing a dose-dependent atypical organization of language function.
4

5 **7.4.2.4 Neuromotor Function and Vocalization**

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

19 Another recent study examined the effect of multiple exposures (including Pb, mercury,
20 and PCBs) on neuromotor functions in 110 preschool Inuit children residing in Canada (Després
21 et al., 2005). Significant associations that were found only for blood-Pb concentrations (mean of
22 5.0 $\mu\text{g}/\text{dL}$) were those associated with increased reaction time, sway oscillations, alternating arm
23 movements, and action tremor. Even after eliminating children with blood-Pb levels $>10 \mu\text{g}/\text{dL}$
24 (10% of cohort) from the analyses, results generally remained consistent, suggesting that
25 neuromotor effects of Pb occurred at blood Pb levels $<10 \mu\text{g}/\text{dL}$.

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

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

11 **7.4.2.5 Neurochemical Alterations**

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

16 As summarized in Section 5.3.2, it has long been well known that Pb²⁺ acts as a Ca²⁺
17 mimetic. This affects neurotransmitter release in a dose-dependent fashion at glutamatergic,
18 cholinergic, and dopaminergic synapses. Glutamate, acetylcholine and dopamine systems play
19 very important roles in both cognitive function and brain development in both laboratory animals
20 and in humans. Extensive research has focused on chronic Pb exposure effects on NMDA
21 receptors. Much of the data point to an inhibition of NMDAR and changes in the ontogeny of
22 receptor subunit expression, though full characterization of the effects on specific subunits is not
23 available.

24 Considerable research has also focused on interactions of Pb²⁺ and Ca-dependent kinases
25 and phosphodiesterases. Lead alters the activity of many of these enzymes, which results in
26 changes in CREB, the transcription factor that controls expression of genes involved in learning,
27 memory, and synaptic plasticity. Protein kinase C (PKC) is also a Pb target, though the Pb
28 effects on PKC in the intact animal have not been fully characterized. Thus, possible
29 relationships of Pb effects on this pathway to human cognitive function effects are not yet clear.

1 **7.4.2.6 Assessment of Dose-Response Relationships for Neurotoxic Effects of** 2 **Lead Exposure**

3 An important consideration in assessing potential public health impacts associated with
4 Pb exposure is whether concentration-response relationships are linear across the full exposure
5 range or, rather, shows nonlinearity. Also of interest is whether any thresholds can be discerned
6 for various types of health effects associated with Pb exposure. The 1986 AQCD/Addendum
7 and 1990 Supplement concluded that neurotoxic effects were related to blood Pb levels of 10 to
8 15 µg/dL and possibly lower. Since then, the U.S. Centers for Disease Control and Prevention
9 (CDC) and the World Health Organization (WHO) have also lowered their definition of an
10 elevated blood Pb concentration to 10 µg/dL (CDC, 1991; WHO, 1995). Average blood-Pb
11 levels in U.S. children ages 1 to 5 years decreased from 15 µg/dL in 1976-1980 to ~3 µg/dL in
12 1991-1994 (CDC, 2000; Pirkle et al., 1998), allowing more recent studies to examine the effects
13 of low level Pb exposure on the neurodevelopment of children (as discussed in Section 6.2.3).

14 Several recent epidemiologic studies have observed significant Pb-induced IQ decrements
15 in children with blood Pb levels <10 µg/dL (e.g., Canfield et al., 2003a; Lanphear et al., 2005)
16 and, in some cases, possibly below 5 µg/dL (Bellinger and Needleman, 2003; Téllez-Rojo et al.,
17 2006). The most compelling evidence for effects below 10 µg/dL, as well as a nonlinear
18 relationship between blood Pb levels and IQ, comes from the international pooled analysis of
19 seven prospective cohort studies (n = 1,333) by Lanphear et al. (2005). The slope for Pb effects
20 on IQ was steeper at lower blood-Pb levels, as indicated by the cubic spline function, the log-
21 linear model, and the piece-wise linear model. The shape of the spline function indicated that the
22 steepest declines in IQ were at blood-Pb concentrations <10 µg/dL. Based on stratified analyses
23 using two cut points, a maximal blood-Pb of 7.5 and 10 µg/dL, the effect estimate for children
24 with maximal blood-Pb levels <7.5 µg/dL was significantly greater than for those with a
25 maximal blood-Pb ≥7.5 µg/dL. Similar results were seen at the cut point of 10 µg/dL. Thus,
26 recent epidemiologic evidence is highly indicative of Pb-induced neurocognitive deficits
27 in children at blood Pb levels below 10 µg/dL and, possibly, as low as 5 µg/dL.

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

1 blood-Pb levels of the same children around 2.5 years of age cannot be ruled out. Inverse
2 relationships between exposure to Pb and attentional behaviors and executive function were also
3 observed in cohorts where >80% of the children had blood Pb levels <10 µg/dL (Canfield et al.,
4 2003b; Stiles and Bellinger, 1993). Other studies have found significant Pb-induced
5 impairments of neuromotor function (Després et al., 2005) and hearing (Osman et al., 1999;
6 Schwartz and Otto, 1987, 1991) in children with blood-Pb levels <10 µg/dL. Collectively, these
7 studies most clearly indicate that Pb is associated with various neurodevelopmental endpoints in
8 children at blood-Pb levels as low as 5 to 10 µg/dL. However, the shape of the concentration-
9 response curve has not been as extensively examined in these studies; thus, there is still some
10 question as to whether, for endpoints other than IQ, larger effects per incremental dose occur at
11 blood Pb levels <10 µg/dL.

12 As stated in Section 5.3.7, there is little if any evidence from experimental animal studies
13 that allow for any clear delineation at this time of a threshold for neurotoxic effects of Pb.
14 Neurobehavioral changes have been reported in rodent studies at blood-Pb levels of ~10 µg/dL,
15 whereas neurochemical and neurophysiological changes have been reported at blood Pb levels of
16 ~15 µg/dL. However, these levels do not necessarily indicate a threshold for such effects but,
17 rather, may only reflect the levels of exposure that have been studied to date. Also, other
18 information, discussed in Chapter 4, suggests that blood-Pb concentrations in some animal
19 models (e.g., the rat or other rodents) may be more comparable to somewhat lower blood-Pb
20 levels seen in humans with more or less similar exposure conditions. Thus, blood-Pb levels
21 associated with neurobehavioral effects appear to be reasonably parallel between humans at
22 blood-Pb concentrations and animals; and such effects appear likely to occur in humans ranging
23 down at least to 5-10 µg/dL, or possibly lower (although the possibility of a threshold for such
24 neurotoxic effects cannot be ruled out at lower blood-Pb concentrations).

25 Lead appears to exhibit a curvilinear, or U-shaped, dose-effect relationship for a number
26 of toxicological endpoints. This effect is not unique to Pb, but occurs with other toxicants
27 (e.g., mercury chloride, chlordane, toluene, chlorpyrifos) as well, as reviewed by Calabrese
28 (2005). In the case of Pb, this nonlinear dose-effect relationship occurs in the pattern of
29 glutamate release (Section 5.3.2), in the capacity for long term potentiation (LTP; Section 5.3.3),
30 and in conditioned operant responses (Section 5.3.5). The 1986 AQCD also reported U-shaped
31 dose-effect relationships for maze performance, discrimination learning, auditory evoked

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

8 9 **7.4.2.7 Susceptibility and Vulnerability to Neurotoxic Effects from Lead Exposure**

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

14 15 Age

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

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

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

1 2000). Several prospective studies of children with both high and low Pb exposures found
2 concurrent or lifetime average blood-Pb levels to be more strongly associated than other earlier
3 blood-Pb measures with school age IQ and other measures of neurodevelopment (Canfield et al.,
4 2003a; Dietrich et al., 1993a,b; Tong et al., 1996; Wasserman et al., 2000b). Using data from the
5 Treatment of Lead-Exposed Children (TLC) study, Chen et al. (2005) examined whether cross-
6 sectional associations observed in school age children 84-90 months of age represented residual
7 effects from 2 years of age or “new” effects emerging among these children. Concurrent blood-
8 Pb concentration always had the strongest association with IQ. The strength of the cross-
9 sectional associations increased over time, despite lower blood-Pb concentrations in older
10 children. Adjustment for prior IQ did not fundamentally change the strength of the association
11 with concurrent blood-Pb level. These results suggest that Pb exposure continues to be toxic to
12 children as they reach school age, but does not support an interpretation that all of the damage
13 occurred by the time the child reaches 2 to 3 years of age. Examination of the toxicologic
14 evidence may be especially enlightening on this topic, given the difficulties involved in assessing
15 any periods of particularly increased susceptibility to Pb neurodevelopmental health effects in
16 the epidemiologic setting.

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

26 27 Gene-Environment Interactions

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

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

9 Another gene of interest is the vitamin D receptor or VDR gene, which is involved in
10 calcium absorption through the gut. The variant VDR alleles may modify Pb concentrations in
11 bone and the rate of resorption and excretion of Pb over time. The relationship between the
12 VDR Fok1 polymorphism and blood Pb concentrations was evaluated in 275 children enrolled in
13 the Rochester Longitudinal Study. A significant interaction was found between floor dust-Pb
14 loading and VDR-Fok1 genotypes on blood Pb concentration, with the FF genotypes (a marker
15 for increased calcium absorption) having the highest adjusted mean blood Pb concentrations at
16 2 years of age compared to children with Ff or ff genotypes. High prevalence of FF genotypes in
17 African American children, compared to non-African American children, may partially explain
18 higher blood Pb concentrations often observed in African American children. There have been
19 no studies to indicate which, if any, of the VDR polymorphisms are associated with increased
20 vulnerability to the neurodevelopmental toxicity of Pb. Animal toxicology studies have yet to
21 identify any role of genetic polymorphism in ALAD or VDR in affecting Pb toxicity.

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

28

29 Gender

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

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

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

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

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

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

4 Socioeconomic Status

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

13 **7.4.2.8 Persistence/Reversibility of Neurotoxic Effects from Lead Exposure**

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

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

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

11 12 **7.4.2.9 Summary of Toxicologic and Epidemiologic Evidence of Lead-** 13 **Induced Neurotoxicity**

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

1 Other behavioral endpoints (e.g. social behavior, aggression, and locomotor activity)
2 evaluated in animal studies in relation to Pb exposure did not clearly indicate Pb-induced
3 impairments. This may be due to the lack of effect with low-level Pb exposure or to variables
4 (e.g., nutrition, age, gender, and strain) possibly not well controlled for experimentally.
5

6 **7.4.3 Cardiovascular Effects**

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

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

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

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

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

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

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

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

29

1 **7.4.4 Heme Synthesis and Blood Effects**

2 Lead exposure has long been recognized to be associated with disruption of heme
3 synthesis in both human children and adults. With extreme Pb exposure leading to blood-Pb
4 levels $>30 \mu\text{g/dL}$, Pb-induced heme synthesis interference leads to notable reductions in
5 hemoglobin synthesis and, at blood-Pb $\geq 40 \mu\text{g/dL}$, to frank anemia (a classic clinical sign of
6 severe Pb poisoning).

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

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

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

27

28 **7.4.5 Renal System Effects**

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

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

5 Of particular importance are new analyses of associations between blood-Pb and renal
6 outcomes in 15,211 adult subjects in the NHANES III study (conducted during 1988-1994).
7 Dichotomous renal outcome measures analyzed included elevated serum creatinine and chronic
8 kidney disease. Mean blood-Pb level was 4.2 $\mu\text{g}/\text{dL}$ among the 4,813 hypertensives and
9 3.3 $\mu\text{g}/\text{dL}$ in normotensives, with prevalence of elevated serum creatinine being higher among
10 hypertensives than nonhypertensives but prevalence of chronic kidney disease being similar.
11 The authors noted that (1) the associations were strong, dose-dependent and consistent before
12 and after adjustment (e.g., for age, race, and gender) and (2) higher blood Pb was associated in
13 nonhypertensives with higher prevalence of chronic kidney disease in diabetics. This study is
14 notable for sample size, comprehensive adjustment for other renal risk factors, and the fact that
15 the study population is representative of the general U.S. population. In another study of 820
16 women (ages 53-64 years) in Sweden, significant negative associations were seen between blood
17 Pb (mean blood Pb of 2.2 $\mu\text{g}/\text{dL}$) and both glomerular filtration rate (GFR) and creatinine
18 clearance, an association that was apparent over the entire dose range. This study also had the
19 additional advantage of blood and urinary cadmium assessment.

20 The above studies and other general population studies constitute some of the most
21 important types of research on Pb renal effects during the past 20 years, as discussed in Section
22 6.4.4.1. Overall, a number of strengths are present in this body of literature. These include study
23 design with longitudinal data in some studies; large populations in both the United States and
24 Europe; comprehensive assessment of Pb dose (including use of bone Pb as a measure of
25 cumulative Pb body burden in some studies); and statistical approaches using a range of
26 exposure and outcome measures, while adjusting for numerous renal risk factors. Associations
27 between Pb exposure and worse renal function were observed in most of the general population
28 studies.

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

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

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

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

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

9 The above findings appear to indicate likely associations between some indicators of
10 altered kidney function (e.g., increased creatinine clearance) at relatively low blood-Pb levels
11 among the general population. However, the potential public health significance of such
12 findings is difficult to discern just yet. This is especially true in light of difficulties in resolving
13 discrepancies between these newly reported findings in the general population studies versus
14 observation among the more than 10,000 occupationally-exposed workers studied, of notable Pb
15 effects on renal tubular function only when blood-Pb exceeds distinctly higher levels (e.g.,
16 >30-40 µg/dL).

18 **7.4.6 Lead-Associated Immune Outcomes**

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

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

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

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

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

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

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

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

24 **7.4.7 Reproduction and Development Effects**

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

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

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

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

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

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

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

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

3 The literature provides convincing support for Pb-induced impairment of postnatal
4 growth, as discussed in Section 5.4.5. Although some early studies ascribed the reduction in
5 postnatal growth to reduced food consumption (suggesting an effect of Pb on satiety
6 mechanisms), more recent studies report impaired growth unrelated to changes in food
7 consumption. These and other findings suggest that Pb exposure may impair growth through a
8 mechanism that involves a suppressed pituitary response to hypothalamic stimulation. The
9 mechanism may involve Pb-induced reduction in plasma concentrations of IGF₁.

11 **7.4.8 Bone and Teeth Effects**

12 Lead is readily taken up and stored in the bone of experimental animals, where it can
13 potentially manifest toxic effects that result in stunted skeletal growth. In experiments reported
14 since the 1986 Pb AQCD (see Section 5.8.3), uptake and retention of Pb were determined in
15 bone from rats exposed to plain water or water containing Pb-acetate (41.7 to 166.6 mg/L) for
16 12 to 16 weeks. After 4 weeks, the skeletal Pb in animals receiving the lowest dose was almost
17 5 times higher than in control animals (5.9 versus 1.2 µg Pb/g bone, respectively). Lead levels in
18 bones from animals receiving 83.3 mg/L and 166.6 mg/L were dose-dependently higher (at 11.7
19 and 17.0 µg Pb/g bone, respectively) after 4 weeks of exposure.

20 Results from several new animal studies have also yielded evidence for Pb exposure
21 adversely affecting bone growth and density, which may be potentially manifested through Pb
22 interference with growth and hormonal factors as well as toxic effects directly on bone. One of
23 the studies suggested Pb was mediating its effect through 1,25-(OH)₂D₃, rather than via a direct
24 action on the Calbindin-D protein.

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

1 An invaluable method to explore the kinetics of Pb transfer from bone to blood has been
2 developed and evaluated within the last decade (see Section 5.8.6). The method uses recent
3 administration of sequential doses of Pb mixes enriched in stable isotopes (^{204}Pb , ^{206}Pb , and
4 ^{207}Pb) to female cynomolgus monkeys that were earlier chronically administered a common Pb
5 isotope mix (1,300 to 1,500 $\mu\text{g Pb/kg body weight/day}$ for ≥ 10 years). The stable isotope mixes
6 serve as a marker of recent exogenous Pb exposure, whereas the chronically administered
7 common Pb serves as a marker of endogenous (principally bone) Pb. It was found that
8 administration of the first isotope label allows measurement of the contribution of historic bone
9 stores to blood Pb. Exposure to subsequent isotopic labels allows measurement of contributions
10 from historic bone Pb stores and the recently administered enriched isotopes that incorporated
11 into bone. In general, the contribution from historic bone Pb (common Pb) to blood Pb level was
12 relatively constant ($\sim 20\%$), but was augmented by spikes in total blood Pb due to current
13 administration of the stable isotopes (blood Pb ranged from 31.2 to 62.3 $\mu\text{g}/100\text{ g}$).

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

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

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

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

14 **7.4.9 Hepatic and Gastrointestinal System Effects**

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

21 Studies of hepatic enzyme levels in serum suggest that liver injury may be present in lead
22 workers; however, associations specifically with Pb exposures were not evident. Also, children
23 exposed to relatively high Pb levels (blood-Pb $>30 \mu\text{g}/\text{dL}$) exhibit depressed levels of circulating
24 1,25-dihydroxy vitamin D (1,25-OH-D). However, associations between serum vitamin D status
25 and blood Pb were not evident in a study of calcium-replete children who had average lifetime
26 blood-Pb concentrations $<25 \mu\text{g}/\text{dL}$.

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

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

3 The effect of low-concentration Pb-acetate (0.1%) on the jejunal ultrastructure has been
4 studied in young male rats. The villi of jejunum of rats exposed to Pb for 30 days had a rough
5 appearance on the surface, which could be associated with a distortion of glycocalyx layer.
6 Areas of extensive degenerative lesions were also observed on the surface of most villi on the
7 60th day of exposure. All intestinal epithelial cells exhibited various degrees of glycocalyx
8 disturbance, indicating that pronounced toxic effects of Pb were related to modifications of the
9 biochemical properties of the surface coat of the cells.

11 **7.4.10 Genotoxicity and Carcinogenicity**

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

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

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

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

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

10 Investigations of cell cycle-dependent expression of proto-oncogenes in Pb-nitrate
11 (10 μ M/100 g body wt)-induced liver cell proliferation showed that peak DNA synthesis
12 occurred at 36 h after a single injection of Pb-nitrate. In addition to DNA synthesis, Pb-induced
13 expression of c-fos, c-myc, and c-Ha-ras oncogenes was also observed in rat liver tissue.
14 Additional studies by the same group reported that Pb-nitrate-induced liver hyperplasia involved
15 an increased expression of c-jun in the absence of c-fos expression.

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

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

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

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

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

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

19 **7.5 KEY LOW-LEVEL LEAD EXPOSURE HEALTH EFFECTS AND** 20 **POTENTIAL PUBLIC HEALTH IMPLICATIONS**

21 Numerous new studies that have become available since the 1986 Pb AQCD and the
22 1990 Supplement provide extensive new data on health effects of Pb across a wide exposure
23 range, including information on concentration-response relationships for key health effects that
24 have been observed at blood Pb levels below 10 µg/dL. Of particular interest for present
25 purposes is the identification of lowest observed effect levels for those Pb-induced effects that
26 are clearly associated with blood Pb <10µg/dL in children and/or adults and are of likely public
27 health concern.

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

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

9 **7.5.1 Concentration-Response Relationships for Neurotoxicity Effects**

10 Newly accumulating data validate well the statement made in the 1996 AQCD/Addendum
11 and the 1990 Supplement that adverse effects occur at blood Pb levels of 10 to 15 µg/dL or
12 “possibly lower.” In a recent study of 6 to 16 year old children in the NHANES III survey,
13 concentration-related deficits in reading and arithmetic scores were found even when analyses
14 were restricted to children with concurrent blood Pb levels below 5 µg/dL (Lanphear
15 et al., 2000), although these analyses were limited by the fact that direct adjustments could not be
16 made for certain important potential confounding factors (i.e., maternal IQ or caretaking quality
17 in the home) whose inclusion in regression models often notably reduces the size of the Pb
18 coefficient. Canfield et al. (2003a) applied semi-parametric models with penalized splines to
19 their data, essentially allowing the data to reveal the functional form that best described them.
20 These analyses showed that the IQ decline per µg/dL increase in blood Pb was greater below
21 10 µg/dL than it was above 10 µg/dL. The estimated slope of the IQ decline per µg/dL was
22 greatest among children for whom the maximum blood Pb level measured over the course of the
23 study never exceeded 10 µg/dL. Also, a similarly steeper slope was seen at lower than at higher
24 blood Pb levels in a re-analysis of the Boston prospective study (Bellinger and Needleman,
25 2003).

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

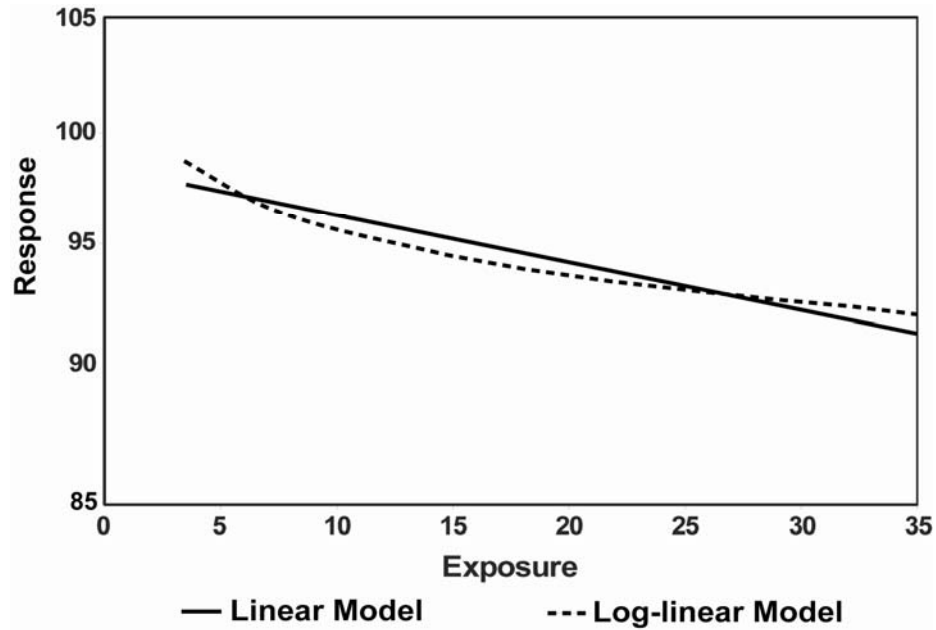


Figure 7-5. Comparison of a linear and log-linear model to describe the relationship between exposure and response.

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

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

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

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

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

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

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

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

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

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

22 The nonlinear concentration-response relationship observed between blood-Pb levels and
23 IQ in recent epidemiologic studies does not preclude the presence of a threshold. Patterson et al.
24 (1991) determined Pb concentrations in the tooth enamel, femur, and rib from buried skeletons of
25 Pre-Columbian Southwest American Indians. They found that the mean natural body burden of
26 adults *Homo sapiens* uncontaminated by technological Pb was 40 $\mu\text{g Pb}/70 \text{ kg}$, which is about
27 one-thousandth of the mean body burden of present day American adults with no occupational
28 exposures and no record of childhood lead poisoning. This suggests that much reduced blood-Pb
29 levels in the 1-10 $\mu\text{g}/\text{dL}$ range are still orders of magnitude above pre-industrial natural levels.
30 Thus, a threshold for Pb neurotoxic effects may exist at levels distinctly lower than the lowest
31 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 $\mu\text{g}/\text{dL}$), 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 $\mu\text{g}/\text{dL}$ 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

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

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

25 One study examined the persistence of lead-related cognitive impairment using an
26 intervention that resulted in a marked reduction in external Pb exposure (Soong et al., 1999).
27 The cognitive abilities of exposed children (n = 32, median blood-Pb level of 15.1 µg/dL [range
28 7.7-31.7]) from a kindergarten located near a Pb-recycling plant in Taiwan were compared to a
29 referent group of children (n = 35, median blood-Pb of 8.4 µg/dL [range 4.8-12.8]) from another
30 kindergarten 5 km away from the plant. Both groups of children were comparable with respect
31 to age, sex, birth order, sibling number, and parental education level. The exposed children were

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

12 Only limited data are available on factors that influence the likelihood that an association
13 observed between an early Pb biomarker and later outcome will persist among children. In one
14 study, the association between prenatal exposure and cognitive development in infancy and the
15 preschool period appeared to attenuate among children living in more privileged circumstances
16 or in whom postnatal Pb exposures were lower (Bellinger et al., 1988, 1990). These findings are
17 consistent with those from cross-sectional epidemiologic studies showing that the effects of a
18 given level of Pb exposure are more severe among disadvantaged children (Lansdown et al.,
19 1986; Winneke and Kraemer, 1984) and from experimental animal studies showing that being
20 raised in an enriched environment can reduce the apparent detrimental impact of Pb exposure on
21 learning (Guilarte et al., 2003; Schneider et al., 2001).

22

23 **7.5.3 Interindividual Variability in Susceptibility to Lead Toxicity**

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

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

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

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

24

25 **Influence of Genetic Polymorphisms on Risk**

26 Genetic polymorphisms that are presumed to influence Pb toxicokinetics and/or
27 toxicodynamics have been identified, mostly in studies of adults who were occupationally
28 exposed to Pb. The magnitude of Pb-associated renal dysfunction appears to vary, in complex
29 ways, with the delta-aminolevulinic acid dehydratase (ALAD) polymorphism (Chia et al., 2005,
30 2006). Lead workers with the ATP1A2(3') polymorphism appear to be at increased risk of
31 Pb-associated effects on blood pressure (Glenn et al., 2001). The slope of the association

1 between floor dust-Pb and blood-Pb is steeper among children with the less common variant of
2 the vitamin D receptor (Fok 1 or B) than among children with the wild-type allele (Haynes et al.,
3 2003). In adults, these same alleles are associated with higher blood-Pb levels and increased
4 blood pressure (Schwartz et al., 2000a; Lee et al., 2001). Greater Pb-associated reductions in
5 renal function have been observed in adults with a variant allele of nitric acid synthetase,
6 although cardiovascular outcomes, such as blood pressure and hypertension do not appear to
7 depend on the eNOS (endogenous nitric oxide synthase) allele (Weaver et al., 2003b). Adults
8 with variants of the hemochromatosis gene (C282Y and/or H63D) have higher patella Pb levels
9 (Wright et al., 2004). With regard to polymorphisms that modify Pb neurotoxicity, workers with
10 the apolipoprotein E4 allele showed greater Pb-associated decreases in neurobehavioral function
11 than did workers with the E1, E2, or E3 alleles (Stewart et al., 2002). Chia et al. (2004)
12 speculated that the ALAD2 confers protection against Pb neurotoxicity, although Kamel et al.
13 (2003) reported that this variant allele is associated with an increased risk of amyotrophic lateral
14 sclerosis. This work is in its early stages and, while it promises to shed light on bases of
15 susceptibility to Pb toxicity, firm conclusions cannot yet be drawn.

16

17 **Influence of Nutritional Status on Risk**

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

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

1 as pregnancy and lactation. Lower calcium intake during pregnancy, especially the second half,
2 appears to increase the mobilization of Pb from bone compartments (Hernandez-Avila et al.,
3 1996). However, in other studies, calcium supplementation had no effect on bone-Pb levels in
4 pregnant and lactating women (Rothenberg et al., 2000; Téllez-Rojo et al., 2002).

6 **Influence of Health Status on Risk**

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

15 **Influence of Coexposures on Risk**

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

21 Although most individuals are not exposed to Pb in isolation but rather to Pb in
22 combination with other toxicants (e.g., cadmium, arsenic, mercury, and polychlorinated
23 biphenyls), epidemiologic studies have generally focused solely on Pb. Other toxicant exposures
24 have sometimes been measured but are usually treated as potential confounders in the statistical
25 analyses, with their potential as possible modifiers of Pb toxicity left unexplored (Bellinger,
26 2000). Thus, available epidemiologic studies do not provide an adequate basis for determining
27 the extent to which co-exposure to other toxicants may affect the nature or severity of Pb-related
28 health effects.

1 **Influence of Timing of Exposure on Risk**

2 *Children*

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

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

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

9 ***Aging Population***

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

16 Considerable evidence also suggests that indicators of cumulative or long-term Pb
17 exposure are associated with adverse effects in several organ systems, including the central
18 nervous, renal, and cardiovascular systems. Among occupationally-exposed men, higher tibia Pb
19 levels have been associated with increased cognitive decline over repeated assessments
20 (Schwartz et al., 2005). With regard to the renal system, increased Pb exposure may accelerate
21 the effects of normal aging, producing a steeper age-related decline in function. Weaver et al.
22 (2003a) observed that higher Pb exposure and dose were associated with worse renal function in
23 older workers, but with lower blood urea nitrogen and serum creatinine in young workers.

25 ***Pregnancy***

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

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

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

15 **7.5.4 Potential Public Health Implications of Low-Level Lead Exposure**

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

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

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

15 Nosology (the classification and naming of diseases) is dynamic as knowledge accrues.
16 The total serum cholesterol level that is considered indicative of hyperlipidemia has dropped
17 steadily over the past 40 years. Second, even within the range of health index values that are
18 sub-diagnostic, variations on the index are significantly associated with health outcomes.
19 For instance, even among children with birth weights greater than the cut-off used to define
20 “low birth weight,” birth weight is significantly associated with IQ at age 7 years (Matte et al.,
21 2001). Third, exposure-related changes on a health index can be markers or indicators of other
22 changes that are likely to have occurred whose significance is more certain. For instance, slower
23 completion of a commonly-used neuropsychological test, the Grooved Pegboard, is associated
24 with poorer handwriting, and reduced ability to copy a drawing is associated with a greater risk
25 of a need for remedial school services (Bellinger, 2004).

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

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

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

20 **Effects of Lead on Intelligence**

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

28 The curves over a range of blood Pb levels from the 10th percentile to the 90th percentile
29 are shown in Figure 7-6. The curves are restricted to that range because log-linear curves
30 become very steep at the lower end of the blood Pb levels, and this may be an artifact of the
31 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/ $\mu\text{g}/\text{dL}$) – Blood Lead 10th to 90th Percentile | Estimated Slope (IQ points/ $\mu\text{g}/\text{dL}$) – Blood Lead <10 $\mu\text{g}/\text{dL}$ ^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 $\mu\text{g}/\text{dL}$ were estimated from the 10th percentile to 10 $\mu\text{g}/\text{dL}$. See Table 6-2.2 for additional details on how data for blood lead levels <10 $\mu\text{g}/\text{dL}$ 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).

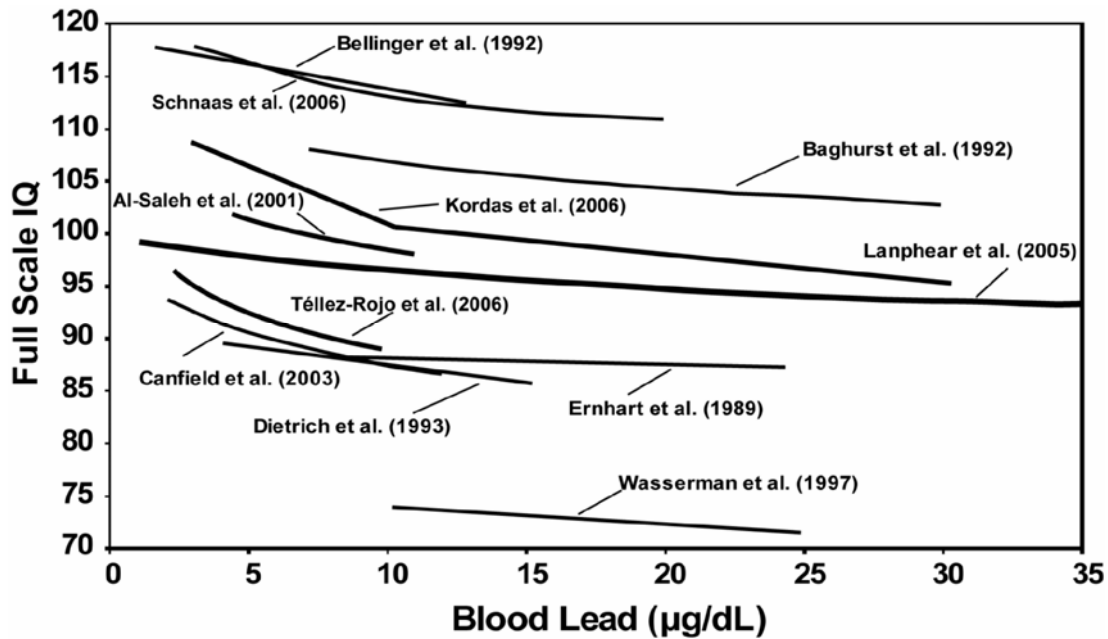


Figure 7-6. Concentration-response relationships of IQ to blood lead for the individual studies and the pooled analysis by Lanphear et al. (2005).

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

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

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

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

6
7

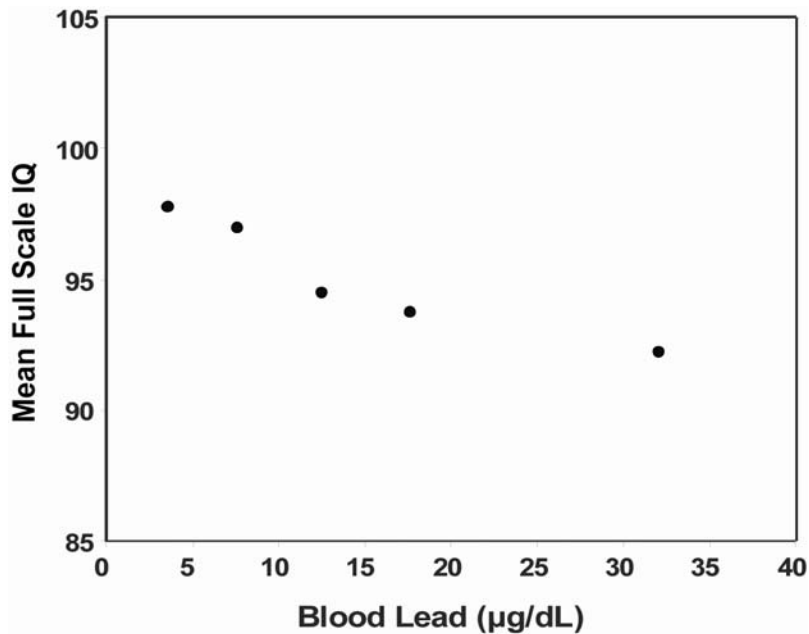


Figure 7-7. Mean blood lead levels adjusted for HOME score, maternal education, maternal IQ, and birth weight from the pooled analysis of seven studies by Lanphear et al. (2005). Mean adjusted IQ levels at blood lead levels of <5, 5 to 10, 10 to 15, 15 to 20, and >20 $\mu\text{g/dL}$ are shown.

8 Weiss (1990) predicted, on purely statistical grounds, that a downward shift of five points
9 in mean IQ, if the amount of dispersion in the distribution remained the same, should be
10 accompanied by a doubling of the numbers of individuals with scores two or more standard
11 deviations below the mean and a reduction by half of the number of individuals with scores two
12 or more standard deviations above the mean. With respect to Pb, the general accuracy of this
13 prediction has been empirically demonstrated in two different datasets by Needleman et al.
14 (1982) and Bellinger (2004). An illustrative example is provided below, and it shows further

1 evidence of the change in percentages of individuals with IQ <80 or <70 points and >120 or
2 >130 points after restricting the analysis to those with blood-Pb levels <10 $\mu\text{g}/\text{dL}$.

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

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

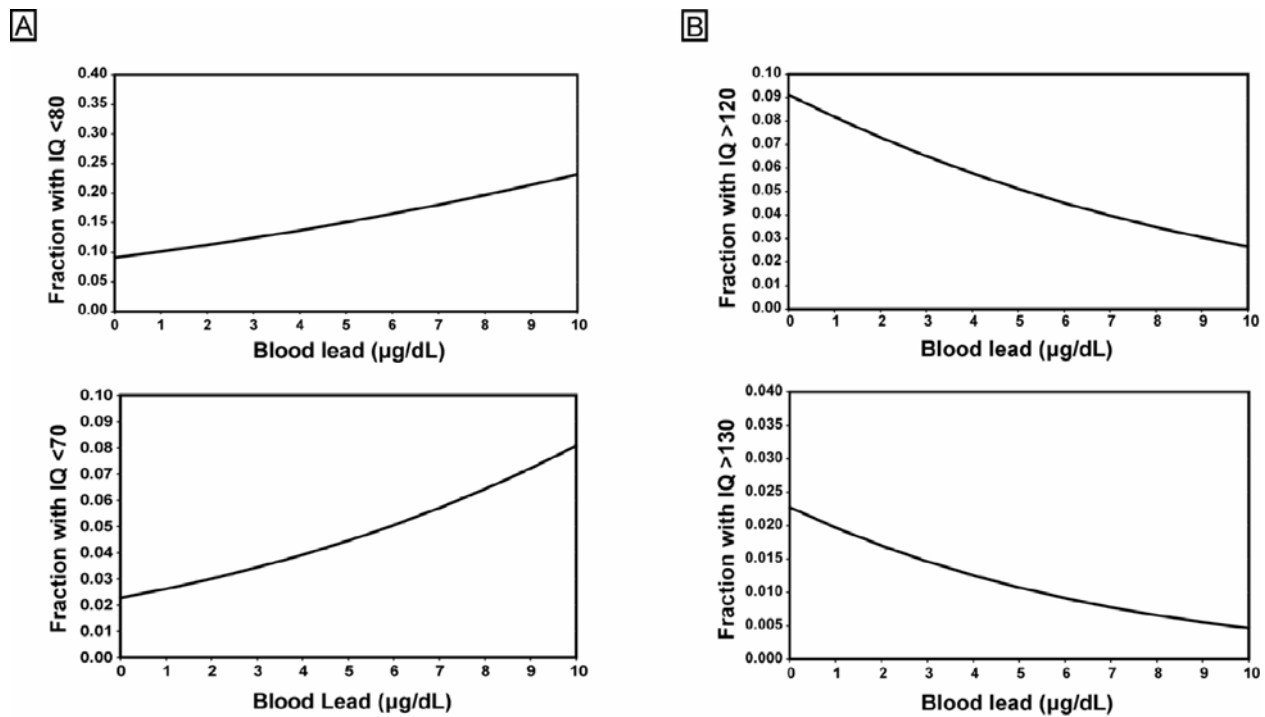


Figure 7-8. Effect of blood lead on fraction of population with IQ levels <80 or <70 points (A) and IQ levels >120 or >130 points (B).

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

18

19 **Cardiovascular Effects of Lead**

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

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

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

9 No single critical level for blood pressure is evident. The risk appears to be simply
10 proportional from the lowest to the highest level recorded. In the Multiple Risk Factor
11 Intervention Trial (MRFIT), Neaton et al. (1995) confirmed a continuing and graded influence of
12 systolic blood pressure on cardiovascular disease mortality extending down into the range of
13 <140 mm Hg. The Prospective Studies Collaboration (2002) meta-analysis of 61 prospective
14 studies relates blood pressure to vascular mortality without indication of a threshold down to
15 115/75 mm Hg. The absence of a demonstrable safe or critical level of blood pressure suggests
16 using the range of blood pressure rather than discrete categories such as hypertension.

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

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

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

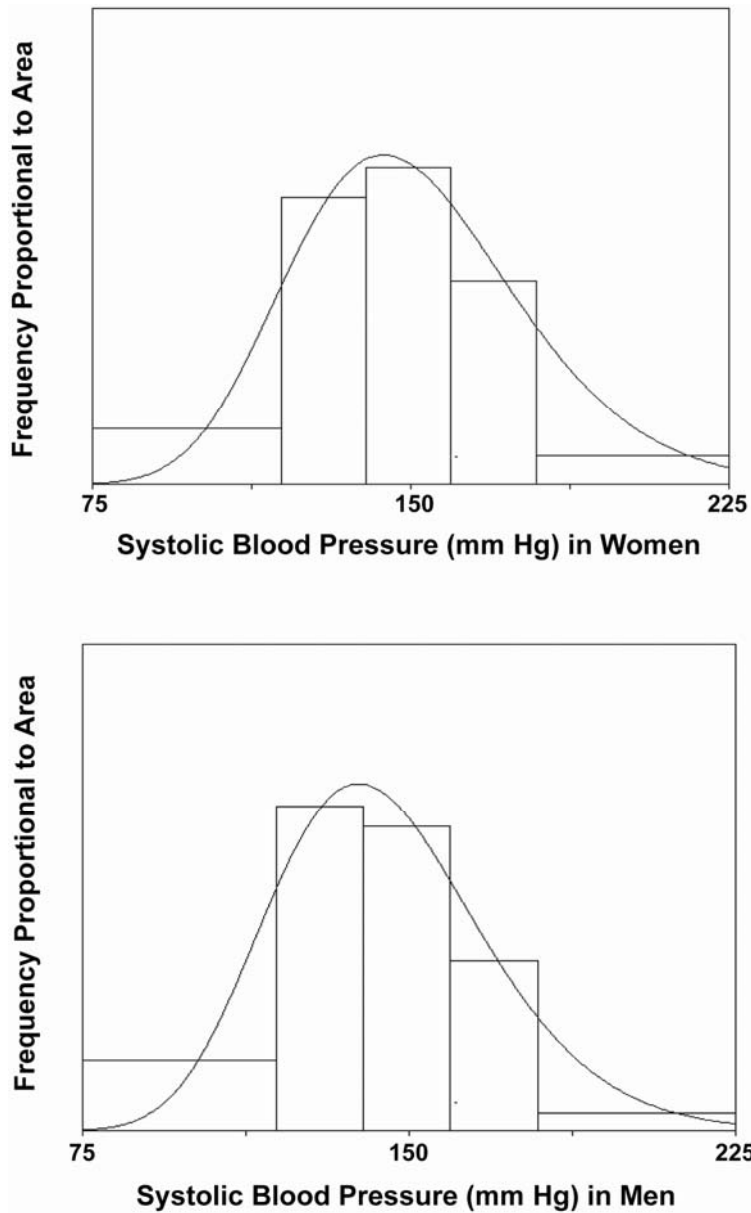


Figure 7-9. Distribution of systolic blood pressure in women and men aged 35 to 64 years from the Framingham Heart Study (Kannel, 2000a).

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 $\mu\text{g/dL}$ results in an annual decrease of 27 events per 100,000 women and 39 events per
 4 100,000 men.
 5

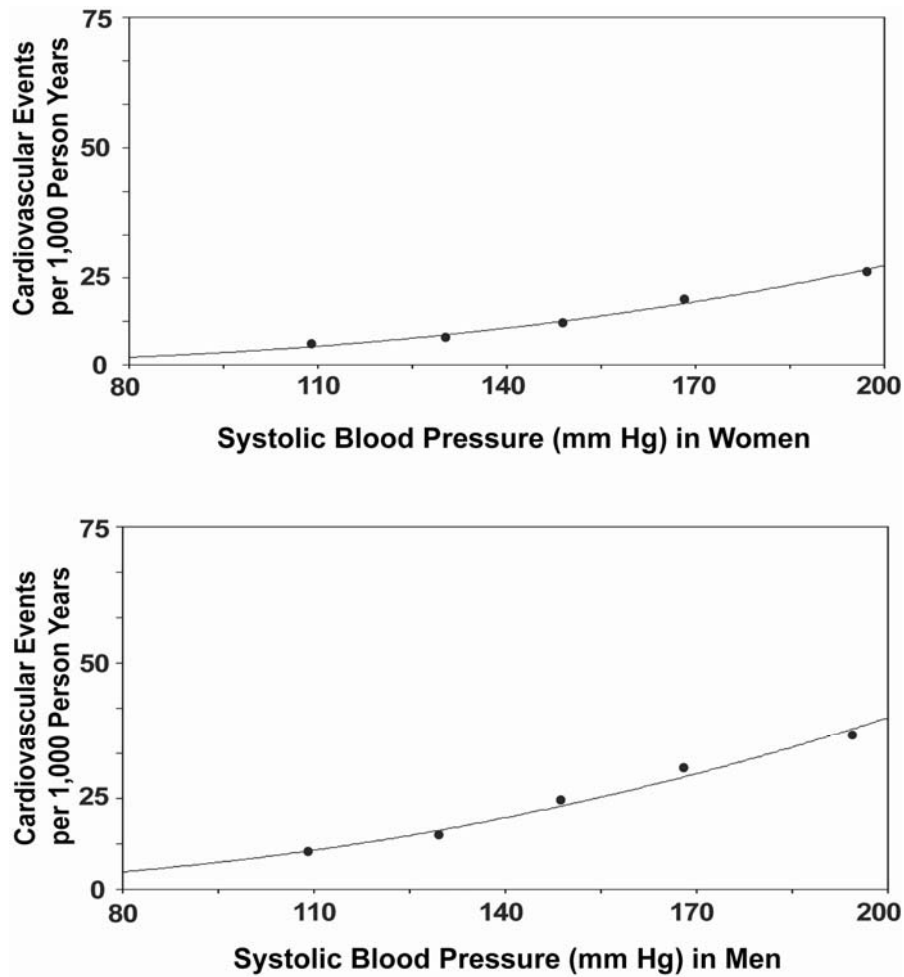


Figure 7-10. Relationship of serious cardiovascular events (coronary disease, stroke, peripheral artery disease, cardiac failure) to systolic blood pressure in women and men aged 35 to 64 years from the Framingham Heart Study (Kannel, 2000a).

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

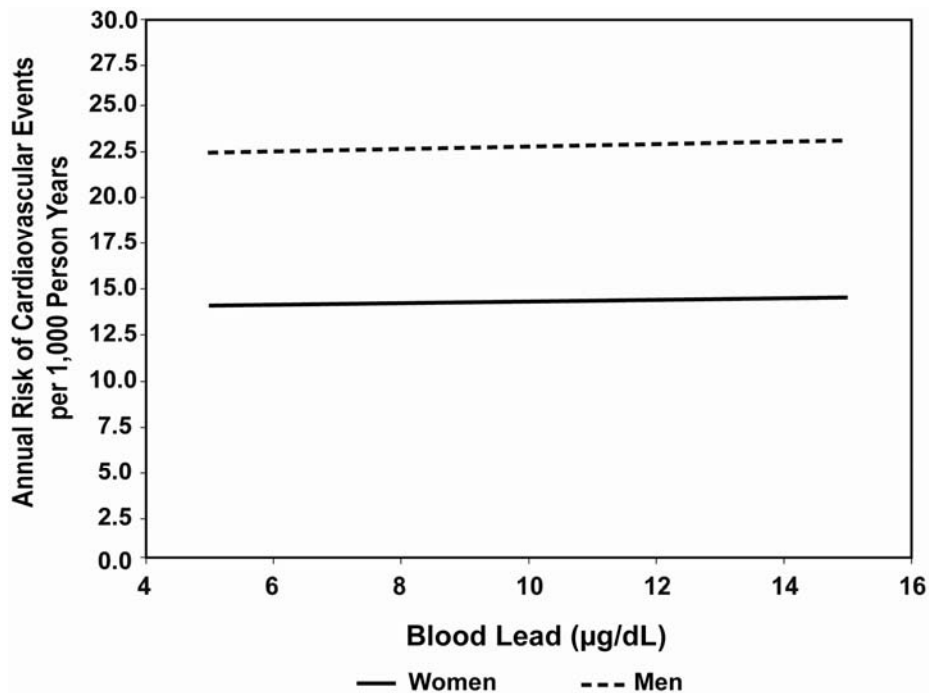


Figure 7-11. Effect of blood lead on expected annual risk of cardiovascular events per 1,000 person-years.

1 increase in systolic blood pressure) and the relationship between blood pressure and
 2 cardiovascular events, a decrease of 0.64 µg/dL in blood Pb from 5 µg/dL to 4.36 µg/dL would
 3 be projected to lead to an annual decrease of 5 cardiovascular events per 100,000 for women and
 4 8 events per 100,000 for men. For a city of 3 million people (about the size of Chicago) this
 5 would translate to about 150 fewer events (e.g., heart attacks, strokes) for women and 240 fewer
 6 events for men, respectively. For a city of 10 million people (about the size of New York City)
 7 the estimated fewer serious cardiovascular events annually would be 500 and 800, respectively,
 8 for women and men.

9

10 **Renal Effects of Lead**

11 The potential clinical relevance of Pb renal effects for chronic kidney disease has recently
 12 been examined. Chronic kidney disease is an important risk factor for cardiac disease and other
 13 causes of mortality and morbidity. Increasing blood lead from the 5th to the 95th percentile
 14 (3.5 µg/dL) has the same adverse impact on glomerular filtration as increases in age and body

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

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

16

17 **Implications of Lead-Induced Immune System Effects**

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

26

27 **7.5.5 Summary of Key Findings and Conclusions Derived from Lead** 28 **Health Studies**

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

1 “Does low-level lead exposure affect health?” The questions asked in recent studies have more
2 often focused on details of the associations, including the shapes of concentration-response
3 relationships, especially at levels well within the range of general population exposures,
4 biological and socioenvironmental factors that either increase or decrease an individual’s risk,
5 the prognoses associated with Pb-associated effects, the efficacy of interventions to reduce
6 adverse effects, and so on. In fact, “low-level,” a term long-used to describe exposures that are
7 not sufficiently high to produce clinical signs and symptoms, is increasingly being recognized as
8 a descriptor that has little biological meaning and is interpretable only in a specific historical
9 context. What was considered “low” in the 1980s is an order of magnitude higher than the
10 current mean level in the U.S. population, and the current mean remains perhaps as much as two
11 orders of magnitude above “natural” background levels in humans. The current CDC screening
12 guideline for children of 10 µg/dL is not a “bright line” separating toxicity from safety, but
13 merely a risk management tool. There is no level of Pb exposure that can yet be clearly
14 identified, with confidence, as being “risk free.” Recent studies of Pb neurotoxicity in infants
15 have observed effects at population average blood-Pb levels of only 1 or 2 µg/dL and some
16 cardiovascular, renal, and immune outcomes have been reported at blood-Pb levels below
17 5 µg/dL. Public health interventions have resulted in declines, over the last 25 years, of more
18 than 90% in the mean blood-Pb level within all age and gender subgroups of the U.S. population,
19 substantially decreasing the numbers of individuals at risk for Pb-induced toxicities.

20
21

22 **7.6 KEY LEAD ECOSYSTEM EFFECTS AND POTENTIAL** 23 **IMPLICATIONS**

24 **7.6.1 Terrestrial Ecosystems**

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

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

3 Most terrestrial ecosystems in North America remain sinks for Pb, despite reductions in
4 atmospheric Pb deposition of more than 95% during the past several decades. Lead released
5 from forest floor soils in the past has been largely immobilized in mineral soils (see Section 8.1).
6 The amount of Pb that has leached into the mineral soil has been estimated to range from 20 to
7 90% of past total anthropogenic Pb deposition, depending on forest type, climate, and litter
8 cycling. While inputs of Pb to ecosystems are currently low, Pb export from watersheds via
9 groundwater and streams appears to be substantially lower, Pb concentrations in waters draining
10 natural terrestrial ecosystems always having been reported as low (generally less than 1 ng/L),
11 even at moderately polluted sites. Therefore, even at current low input levels, U.S. watersheds
12 are accumulating industrial Pb. However, burial/movement of lead over time down into lower
13 soil/sediment layers also tends to sequester it away from more biologically active parts of the
14 watershed (unless later disturbed or redistributed, e.g., by flooding, dredging, etc.).

15

16 *Metal Speciation for Plants*

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

28

29 *Lead Speciation in Solid Phases*

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

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

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

17

18 *Lead Solid-Solution Partitioning*

19 The concentration of Pb species dissolved in soil solution is probably controlled by some
20 combination of (a) Pb mineral solubility equilibria; (b) adsorption reactions of dissolved Pb
21 phases on inorganic surfaces (e.g., oxides of Al, Fe, Si, Mn, etc., clay minerals); and (c)
22 adsorption reactions of dissolved Pb phases on soil organic matter. Dissolved Pb phases in soil
23 solution can be some combination of Pb^{2+} and its hydrolysis species, Pb bound to dissolved
24 organic matter, and Pb complexes with inorganic ligands such as Cl^- and SO_4^{2-} . Alkaline soils
25 typically have solutions supersaturated with respect to PbCO_3 , $\text{Pb}_3(\text{CO}_3)_2(\text{OH})_2$, $\text{Pb}(\text{OH})_2$,
26 $\text{Pb}_3(\text{PO}_4)_2$, $\text{Pb}_5(\text{PO}_4)_3(\text{OH})$, and $\text{Pb}_4\text{O}(\text{PO}_4)_2$. Pb phosphate minerals in particular, are very
27 insoluble, and calculations based on thermodynamic data predict that these phases will control
28 dissolved Pb in soil solution under a variety of conditions. However, certain chelating agents,
29 such as dissolved organic matter can prevent the precipitation of Pb minerals (see AX8.1.2.1).

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

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

7 8 *Tracing the Fate of Atmospherically Delivered Lead*

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

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

26 27 *Uptake into Plants and Invertebrates*

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

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

5 *Detoxification in Plants and Invertebrates*

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

14

15 *Physiological Effects*

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

25

26 *Response Modification*

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

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

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

12

13 *Primary Producers*

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

28

29 *Consumers*

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

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

13

14 *Decomposers*

15 Lead effects on soil invertebrates include decreased survival, growth and reproduction.
16 Effects on microorganisms include changes in nitrogen mineralization and in enzyme activities.
17 Recent data on Pb toxicity to soil invertebrates and microorganisms are consistent with those
18 reported in the 1986 Pb AQCD, with toxicity generally observed at concentrations of 100's to
19 1,000's of mg Pb/kg soil. Studies on microbial processes may be influenced significantly by soil
20 parameters, and the significance of the test results is not clear.

21

22 *Ecological Soil Screening Levels (Eco-SSLs)*

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

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

4 5 **Effects of Lead on Natural Terrestrial Ecosystems**

6 Few significant effects of Pb pollution have been observed at sites that are not near point
7 sources of Pb. At present, industrial point sources such as smelter sites represent the greatest Pb-
8 related threat to the maintenance of sustainable, healthy, diverse, and high-functioning terrestrial
9 ecosystems in the United States. However, assessing the risks specifically associated with Pb is
10 difficult because these sites also experience elevated concentrations of other metals and because
11 of effects related to SO₂ emissions. Terrestrial ecosystems may respond to stress in a variety of
12 ways, including reductions in the vigor and/or growth of vegetation, reductions in biodiversity,
13 and effects on energy flow and biogeochemical cycling.

14 15 *Influence of Acidification*

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

24 25 *Influence of Forest Harvesting*

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

1 *Influence of Land Use and Industry*

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

11
12 *Effects Observed Around Industrial Point Sources*

13 The effects of Pb exposure on natural ecosystems are confounded by the fact that Pb
14 exposure cannot be decoupled from other factors that may also effect the ecosystem under
15 consideration. Principal among these factors are other trace metals and acidic deposition.
16 Emissions of Pb from smelting and other industrial activities are accompanied by other trace
17 metals (e.g., Zn, Cu, Cd) and sulfur dioxide (SO₂) that may cause toxic effects independently or
18 in concert with Pb.

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

1 *Influence of Climate Change*

2 Atmospheric Pb is not likely to contribute significantly to global climate change. The
3 potential linkages between climate-related stress and Pb cycling are poorly understood. Climate
4 effects related to alterations in organic matter cycling may influence Pb migration. For example,
5 an increase in temperature leading to increased rates of organic matter decomposition could lead
6 to temporary increases in DOM concentrations and smaller steady-state pools of soil organic
7 matter. There also is some evidence for recent increases in the frequency of soil freezing events
8 in the northeastern United States. Soil freezing occurs when soils have little or no snow cover to
9 insulate them from cold temperatures and results in an increased release of nitrate and DOC from
10 the O horizons of forest soils. Increased fluctuations in precipitation may induce more frequent
11 flooding, potentially increasing inputs of Pb and other metals to floodplain soils. All of these
12 factors could result in increased concentrations of Pb in waters draining terrestrial ecosystems.
13

14 *Influence on Energy Flow and Biogeochemical Cycling*

15 Lead can have a significant effect on energy flow in terrestrial ecosystems. In terrestrial
16 ecosystems, energy flow is closely linked to the carbon cycle. The principal input of energy to
17 terrestrial ecosystems is through photosynthesis, in which CO₂ is converted to biomass carbon.
18 Because of this link between photosynthesis and energy flow, any effect that Pb has on the
19 structure and function of terrestrial ecosystems influences the flow of energy into the ecosystem.
20 At some sites severely affected by metal pollution, death of vegetation can occur, dramatically
21 reducing the input of carbon to the ecosystem (see AX8.1.5.3).

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

1 inhibitory effect of Pb and other metals is broad-based, and not specific to any particular
2 metabolic pathway. Because the mobility of Pb in soils is closely tied to organic matter cycling,
3 decomposition processes are central to the biogeochemical cycle of Pb.
4

5 **7.6.2 Aquatic Ecosystems**

6 *Sediment Quality Benchmarks and Bioavailability*

7 There are a number of factors in sediment that can influence lead bioavailability to
8 benthic (sediment) organisms. Although sediment quality criteria have not been formally
9 adopted, the EPA has published an equilibrium partitioning procedure for developing sediment
10 criteria for metals (U.S. Environmental Protection Agency 2005c). Equilibrium partitioning
11 (EqP) theory predicts that metals partition in sediment between acid volatile sulfide, pore water,
12 benthic organisms, and other sediment phases, such as organic carbon. Using this theory,
13 sediment toxicity and organism mortality can be more reliably predicted by accounting for both
14 the site-specific organic carbon and AVS concentrations.
15

16 *Speciation of Lead in Aquatic Ecosystems*

17 The speciation of Pb in the aquatic environment is controlled by many factors, such as pH,
18 salinity, sorption, and biotransformation processes. Lead is typically present in acidic aquatic
19 environments as PbSO_4 , PbCl_4 , ionic Pb, cationic forms of Pb hydroxide, and ordinary hydroxide
20 $\text{Pb}(\text{OH})_2$. In alkaline, waters common Pb species include anionic forms of Pb carbonate $\text{Pb}(\text{CO}_3)$
21 and hydroxide $\text{Pb}(\text{OH})_2$. In freshwaters, Pb typically forms strong complexes with inorganic
22 OH^- and CO_3^{2-} and weak complexes with Cl^- . The primary form of Pb in freshwaters at low pH
23 (≤ 6.5) is predominantly Pb^{2+} ; and less abundant inorganic forms include $\text{Pb}(\text{HCO}_3)_3$, $\text{Pb}(\text{SO}_4)_2^{2-}$,
24 PbCl , PbCO_3 , and $\text{Pb}_2(\text{OH})_2\text{CO}_3$. At higher pH (≥ 7.5) Pb forms hydroxide complexes (PbOH^+ ,
25 $\text{Pb}(\text{OH})_2$, $\text{Pb}(\text{OH})_3^-$, $\text{Pb}(\text{OH})_4^{2-}$). Lead speciation in seawater is a function of chloride
26 concentration and the primary species are $\text{PbCl}^{3-} > \text{PbCO}_3 > \text{PbCl}_2 > \text{PbCl}^+ > \text{Pb}(\text{OH})^+$
27 (see AX8.2.2.1).

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

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

9

10 *Lead Concentrations in United States Surface Waters*

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

20 Lead concentrations in lakes and oceans were generally found to be much lower than
21 those measured in the lotic waters assessed by NAWQA. Surface water concentrations of
22 dissolved Pb measured in Hall Lake, Washington in 1990 ranged from 2.1 to 1015.3 ng/L, and
23 the average surface water dissolved Pb concentrations measured in the Great Lakes (Superior,
24 Erie, and Ontario) between 1991 and 1993 were 3.2, 6.0, and 9.9 ng/L, respectively. Pb
25 concentrations ranged from 3.2 to 11 ng/L across all three lakes. Similarly, 101 surface water
26 total Pb concentrations measured at the Hawaii Ocean Time-series (HOT) station ALOHA
27 between 1998 and 2002 ranged from 5 to 11 ng/kg. Based on the fact that Pb is predominately
28 found in the dissolved form in the open ocean (<90%), dissolved Pb concentrations measured at
29 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

| Statistic | Surface Water – Dissolved (µg/L) | | Sediment – Bulk, <63 µm (µg/g dry wt.) | | Fish Tissue (µg/g dry wt.) | | | |
|-----------|----------------------------------|---------|--|---------|----------------------------|---------|---------|---------|
| | Ambient | Natural | Ambient | Natural | Whole Organism | | Liver | |
| | | | | | 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

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

10

11 *Lead Uptake*

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

18

1 *Resistance Mechanisms*

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

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

18

19 *Physiological Effects of Lead*

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

26

27 *Factors that Modify Organism Response to Lead*

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

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

6 The genetics of an organism and/or population may alter the response to Pb exposure
7 through one of two processes: (1) a contaminant may influence selection, by selecting for certain
8 phenotypes that enable populations to better cope with the chemical, or (2) a contaminant can be
9 genotoxic, meaning it can produce alterations in nucleic acids at sublethal exposure
10 concentrations, resulting in changes in hereditary characteristics or DNA inactivation. Genetic
11 selection has been observed in aquatic organisms due to lead tolerance. Because tolerant
12 individuals have a selective advantage over vulnerable individuals in polluted environments, the
13 frequency of tolerance genes will increase in exposed populations over time. Several studies
14 have shown that heavy metals can alter population gene pools resulting in decreased genetic
15 diversity. Laboratory studies have shown that Pb exposure at 10 mg Pb²⁺/mL of blood Pb to
16 chromosomal aberrations in some aquatic organisms. Low level (50 µg/L) Pb exposure in water
17 over four weeks resulted in DNA strand breakage in the freshwater mussel *Anodonta grandis*.
18 More recently, similar results (increase in the frequency of chromosomal aberrations and DNA
19 damage in kidney cell cultures) were observed in fish (*Hoplias malabaricus*) fed Pb-
20 contaminated food over 18, 41, and 64 days (see AX8.2.3.4).

21 Environmental factors can alter the availability, uptake and toxicity of Pb to aquatic
22 organisms. A study of the influence of abiotic variables, including dissolved organic carbon
23 (DOC) on Pb concentrations in freshwater isopods found that, as DOC concentrations increased,
24 BCFs decreased in *P. meridianus* and *A. aquaticus*, indicating that DOC acts to inhibit the
25 availability of Pb to these isopods. Schwartz et al. (2004) collected natural organic matter
26 (NOM) from several aquatic sites across Canada and investigated the effects of NOM on Pb
27 toxicity in rainbow trout (*Oncorhynchus mykiss*). The results showed that NOM in test water
28 almost always increased LT₅₀ (time to reach 50% mortality), and optically dark NOM tended to
29 decrease Pb toxicity more than did optically light NOM in rainbow trout. Studies generally
30 agree that the toxicity of Pb decreases as pH increases. As pH decreases, Pb becomes more
31 soluble and more readily bioavailable to aquatic organisms (Weber, 1993). Acute and chronic

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

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

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

18

19 *Interactions with Other Pollutants*

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

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

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

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

9

10 *Effects of Lead on Primary Producers*

11 Several studies have been conducted since the 1986 Pb AQCD on the toxicity of Pb to
12 primary producers. Effects on algal growth (*Chlorella vulgaris*, *Closterium acerosum*,
13 *Pediastrum simplex*, *Scenedesmus quadricauda*), ranging from minimal to complete inhibition,
14 have been reported at Pb concentrations between 100 and 200,000 µg/L. The toxicity of Pb to
15 aquatic plant growth has been studied using *Spirodela polyrhiza*, *Azolla pinnata*, and *Lemna*
16 *gibba*. Test durations ranged from 4 to 25 days and test concentrations ranged between 49.7 and
17 500,000 µg/L. Research on aquatic plants has been focused on Pb effects on aquatic plant
18 growth, chlorophyll and protein content (see AX8.2.4.2).

19 Algae and aquatic plants have a wide range in sensitivity to the effects of Pb in water.
20 Both groups of primary producers experience EC₅₀ values for growth inhibition between ~1,000
21 and >100,000 µg/L (see AX8.2.4.2). Exposure to Pb in combination with other metals is
22 generally less toxic to growth than exposure to Pb alone. Studies have shown that Pb adversely
23 affects the metabolic processes of nitrate uptake, nitrogen fixation, ammonium uptake, and
24 carbon fixation. Lead in combination with nickel or chromium produced synergistic effects for
25 nitrate uptake, nitrogenase activities, ammonium uptake, and carbon fixation.

26

27 *Effects of Lead on Consumers*

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

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

3 More recent literature on the toxicity of lead to fish and aquatic invertebrates has been
4 summarized by Eisler (2000). Exposure of invertebrates to Pb can lead to adverse effects on
5 reproduction, growth, survival, and metabolism. Water-borne Pb is highly toxic to aquatic
6 organisms, with toxicity varying, depending on the species and life stage tested, duration of
7 exposure, the form of Pb tested, and water quality characteristics (see AX8.2.4.1). Among the
8 species tested, aquatic invertebrates, such as amphipods and water fleas, were the most sensitive
9 to Pb effects, with adverse effects being reported at water Pb concentrations ranging from 0.45 to
10 8000 µg/L. Freshwater fish demonstrated adverse effects at concentrations ranging from 10 to
11 >5400 µg/L, generally depending upon water quality parameters (e.g., pH, hardness, salinity).
12 Amphibians tend to be relatively tolerant of Pb, but may exhibit decreased enzyme activity (e.g.,
13 ALAD reduction) and changes in behavior (e.g., hypoxia response behavior). Lead tends to be
14 more toxic in longer-term exposures, with chronic toxicity thresholds for reproduction in water
15 fleas ranging as low as 30 µg/L.

16

17 **Effects of Lead on Natural Aquatic Ecosystems**

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

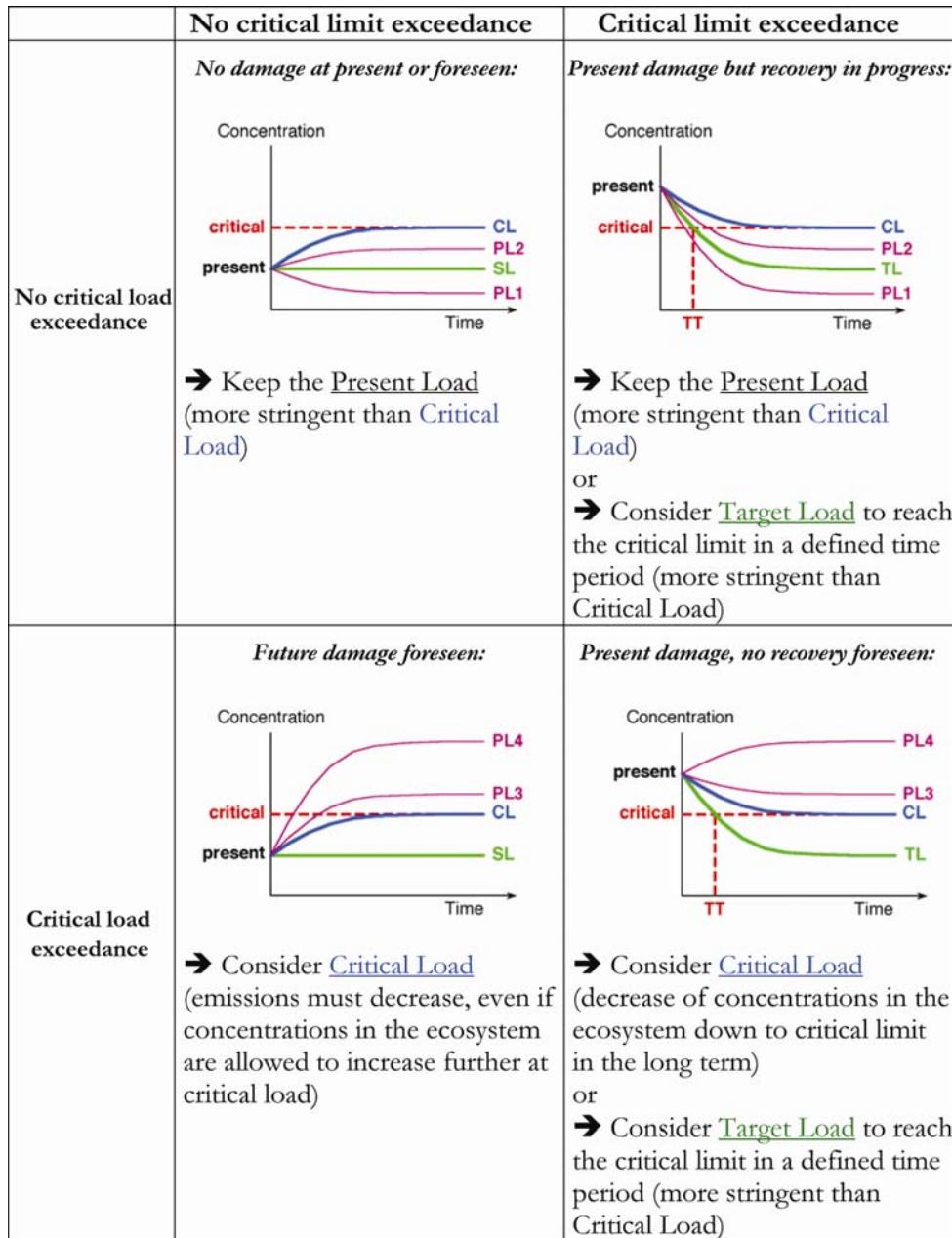
1 The effects of Pb have primarily been studied in relation to point source pollution rather
2 than area-wide atmospheric deposition. Thus, the effects of atmospheric Pb on aquatic
3 ecological condition remain to be defined. There is a paucity of data in the general literature that
4 explores Pb effects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

7 8 **7.6.3 Application of Critical Loads to Terrestrial and Aquatic Ecosystems**

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

26 27 *Calculation of Critical Loads*

28 This section summarizes various methods used to calculate critical loads (De Vries et al.,
29 2001, 2002, 2004; Groenenberg et al., 2002), with an emphasis on the most recent material.



CL - Critical load; PL - present load (2 cases); SL - Stand-still load; TL - Target load; TT - Target time

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).

1 *Critical Limits*

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

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

20

21 *Models*

22 Critical loads for heavy metals are typically calculated using a steady state model that
23 ignores internal metal cycling and keeps the calculations as simple as possible (De Vries et al.,
24 2004). The critical load is equal to the atmospheric input flux, which equals the sum of the
25 output fluxes from the system minus the other input fluxes (e.g., weathering) when the
26 concentration of Pb is at the critical limit. The input flux of heavy metals via weathering is
27 sometimes neglected, because quantitative estimates are highly uncertain, and weathering is
28 generally thought to be a relatively minor process (see Section 8.3.4.2).

29

1 **Critical Loads in Terrestrial Ecosystems**

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

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

15
16 **Critical Loads in Aquatic Ecosystems**

17 Doyle et al. (2003) modeled critical loads in surface water bodies assuming complete
18 mixing with dilution water entering from the terrestrial catchment area. Loss of metal was also
19 assumed to occur through downstream flushing and burial in sediment. Transfer of metal to
20 sediment was modeled as a first-order process dependant on the dissolved concentration and pH.
21 The inputs to the model included the following: water body area, terrestrial catchment area,
22 water body depth, sediment accumulation rate, thickness of biologically active sediment, net
23 precipitation, and water pH. The first-order rate constant for transfer to sediment was correlated
24 with pH. The model reached steady state within a few years. Transfer of Pb from the terrestrial
25 catchment to the water body was neglected, because the time to steady state could be on the
26 order of 10,000 years if the model included this source of Pb. However, the authors cited a
27 separate calculation that indicated that neglect of transfer of Pb from the catchment may lead to a
28 5-fold underestimation of Pb concentrations in the surface water. These results indicate that Pb
29 run-off from soil is more important than direct atmospheric deposition to the surface water
30 bodies considered in this study. Due to the long times required to achieve steady state, the
31 critical load methodology may not be appropriate for Pb in aquatic systems.

1 **Limitations and Uncertainties**

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

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

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

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

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

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

31

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