CHAPTER 2. HEALTH EFFECTS

2.1 INTRODUCTION

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

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

To help public health professionals and others identify potential health effects in persons with elevated PbB, the information in this section is organized by health effect.

As discussed in Appendix B, a literature search was conducted to identify relevant studies examining health effect endpoints. Figure 2-1 provides an overview of the database of epidemiology studies included in this chapter of the profile.

Since development of the 2007 Toxicological Profile on Lead (ATSDR 2007), results of numerous epidemiological studies have prompted growing attention to the adverse health effects of Pb exposures that result in blood Pb concentrations (PbB) of <10 µg/dL (EPA 2014c). Awareness of the potential adverse consequences of such exposures has led to changes in U.S. public health policy, with a focus on eliminating lead poisoning as a public health problem (CDC 2012d; EPA 2016b). In 2012, CDC accepted their Advisory Committee on Childhood Lead Poisoning Prevention (ACCLPP) recommendation to establish a PbB reference value for Pb, replacing the 10 µg/dL level of concern. The reference value is based on the 97.5th percentile of the PbB distribution among children 1–5 years of age in the United States, using data generated by NHANES (CDC 2012d). At that time, the PbB reference was approximately 5 µg/dL (NHANES 2007–2010) (CDC 2018a). ACCLPP recommended that the reference value be updated every 4 years using the two most recent NHANES cycles and would be used in recommendations for follow-up evaluations and identification of high-risk childhood populations (CDC 2012d). It is likely that PbB values among children will continue to decline; therefore, the primary focus of this toxicological profile is on health effects associated with low Pb exposure (i.e., those observed at PbB ≤5 µg/dL). Detailed information on effects at PbB ≤10 µg/dL is also presented to examine potential

exposure-response relationships. Information on health effects observed at higher PbB levels (>10 µg/dL) is also included to provide a comprehensive overview of the adverse effects of Pb.

Literature Search Strategy. The literature on health effects of Pb in humans is enormous, with countless epidemiological studies in workers and the general population, including children. Due to the extent of the Pb database in humans, it is impossible to cite all, or even most, of the studies on health effects of Pb; thus, this profile does not attempt to provide a comprehensive review of all literature; instead, the profile summarizes the major lines of epidemiological evidence regarding health effects in humans. Although the literature database on adverse effects of Pb in laboratory animals is also extensive, given the large number of studies available in humans, animal studies are not included in this toxicological profile. For a recent review of studies in animal models, the reader should consult the EPA's Integrated Science Assessment for Lead (EPA 2014c).

The following were used as primary sources to identify literature on health effects of Pb:

- The previous Toxicological Profile for Lead (ATSDR 2007) was used to identify literature published through 2007.
- The EPA (2014c) Integrated Science Assessment for Lead was used to identify literature published from 2006 to 2013.
- Literature searches were conducted from 2013 to 2019 to identify studies published after EPA (2014c).

In addition, recent reviews by NTP (2012) and NAS (2013) were consulted. As anticipated, the literature search revealed an extensive epidemiological database of literature published since 2013. To narrow the evaluation to those studies of greatest utility identifying health effects of low exposures to Pb, a series of inclusion criteria were defined; only studies meeting the criteria were considered for inclusion in the toxicological profile. These criteria are described further in Appendix B. Data from selected studies were tabulated and discussed in subsequent sections of this chapter.

Duration of Exposure. Typically, toxicological profiles organize the discussion of health effects according to exposure duration categories. However, this is not a particularly informative approach to the discussion of Pb epidemiology. The epidemiologic study of Pb toxicity in human populations has relied on internal dose metrics (e.g., PbB, bone Pb) for evaluating associations between health outcomes. These metrics are considered to represent relatively recent exposure history, in the case of PbB, and longer-term

cumulative exposure, in the case of CBLI or bone Pb. However, neither metric offers a confident estimate of exposure duration or of changes in Pb exposure over time (including peak exposure periods that may have occurred in the past), and, in general, the complete exposure history is not known. Health outcomes associated with acute exposures is available from clinical case studies of Pb poisoning (see Section 2.2). However, even in these cases, the exposure duration that proceeded the identification of the case is rarely known with certainty.

Routes of Exposure. For the general population, exposure to Pb occurs primarily via the oral route, with some contribution from the inhalation route, whereas inhalation exposures can be more important in occupational settings, depending on particle size. In addition, occupational exposure to organic Pb compounds may involve dermal absorption as a significant exposure route. This profile does not attempt to separate health effects by route of exposure. As noted previously, epidemiology studies have relied on internal dose metrics (e.g., PbB, bone Pb), which reflect Pb body burden (to varying degrees), irrespective of the route of exposure. The primary systemic toxic effects of Pb are the same regardless of the route of entry into the body,

Exposure Metric. To quantify exposure in humans, data are expressed in terms of absorbed Pb, and not in terms of external exposure levels (e.g., concentration in water) or dose (e.g., mg/kg/day). The most common metric of absorbed dose for Pb is the concentration of lead in blood (PbB), although other measures of exposure (e.g., concentration of Pb in bone, hair, teeth, or urine) are used; however, measurements of Pb in urine, teeth, and hair are not as reliable as measurements in blood or bone. PbB mainly reflects exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of Pb in bone (see Section 3.1). Pb in bone is considered a biomarker of cumulative or long-term exposure because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Most of the body burden of Pb (the total amount of Pb in the body) is distributed to the bone, with approximately 94 and 76% of the body burden found in bone in adults and children, respectively. The remainder is distributed to blood and soft tissues. However, the concentration of Pb in blood can vary considerably with age and physiology/lifestage (e.g., pregnancy, lactation, menopause). For this reason, measurement of Pb in bone has seen wider application in epidemiological studies of adults in which measures of cumulative lifetime exposures are of interest. However, bone Pb measurements require specialized radiologic equipment (e.g., K-shell x-ray fluorescence; XRF) and, as a result, are used less commonly than PbB in human epidemiology. Since most of the epidemiology has relied on PbB as the dose metric, this profile has focused on describing dose-response relationships based on PbB to facilitate comparisons across studies and endpoints. This

approach also aligns with public health practices, which rely on PbB for evaluating elevated exposures to Pb (CDC 2012d; EPA 2016b). However, it is recognized that some health outcomes may be correlated with cumulative exposure, in which case, bone Pb may be a better dose metric than PbB. For these outcomes, short-term variation in PbB may contribute to exposure classification error (i.e., the same PbB could be observed in individuals who have different bone Pb). The exposure history of the subjects may also be an important factor in determining associations observed between outcomes and blood or bone Pb. Some studies of historically exposed occupational populations (e.g., former workers) have found stronger associations between bone Pb and health outcomes than with PbB, while some studies of concurrently exposed populations have found stronger associations with PbB (Shih et al. 2007).

Confounding Factors and Effect Modifiers. Bias can occur in epidemiological studies when the background risk of the outcome being measured is not the same in the exposed and reference groups. Confounders are variables that affect the measured outcome and are also associated with the Pb exposure metric (e.g., PbB, bone Pb). For example, Pb body burden increases with age; therefore, age can be a confounding factor if it is also a risk factor for the outcome (e.g., renal or cardiovascular disease). Not adjusting for confounders may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on whether it is a negative or positive confounding variable. Effect modifiers are variables that affect the measured outcome independently of the Pb exposure metric. For example, renal disease from any cause can affect blood pressure and, thereby, could interact with Pb to change blood pressure. Effect modifiers can also be confounders, if they are associated with the Pb exposure metric (e.g., socio-economic status [SES] and cognitive development). Recall bias may also contribute to uncertainties and should be considered as a confounding factor. For example, interviews of parents are a standard method for estimating potential co-variables that might affect child development in prospective studies, as there are no alternatives for studies in children. Thus, inaccurate recall may potentially influence study outcomes. Failure to account for important effect modifiers can result in underestimation or overestimation of the apparent strength of the association, depending on the direction of the effect of the modifying variable. Confounding factors and effect modifiers are discussed in greater detail in sections that describe specific categories of health effects. Epidemiological studies provide information about the strengths of statistical associations between exposure metrics (e.g., blood Pb) and health outcomes. However, statistical associations do not necessarily reflect causal associations. Evidence for causal associations can include demonstration of exposure-response relationships, occurrence of the outcome or its precursors in controlled studies conducted in experimental models (*in vivo* and *in vitro*), and consistency of observed statistical associations with known modes of action of Pb.

Overview of Health Effects of Pb. The health effects of Pb are diverse, and exposure to Pb is associated with toxicity to every organ system. This is not surprising because the mechanisms of action associated with Pb-induced toxicity, including perturbations of ion homeostasis and transport, protein binding, oxidative stress, and inflammation, are common to all cell types. In addition, Pb is widely distributed throughout the body, and has been measured in all tissues evaluated (see Section 3.1.2). For all organ systems, toxicity has been observed at PbB $\leq$10 μg/dL. Neurological effects of Pb are of greatest concern because effects are observed in infants and children; furthermore, these effects may result in life-long decrements in neurological function. Children are also more vulnerable because of behaviors that increase ingestion of Pb surface dusts (e.g., hand-to-mouth activity) and because gastrointestinal absorption of ingested Pb is higher in children compared to adults, possibly due to a combination of physiological differences and differences in diet and nutrition. The weight-of-evidence for all adverse health effects is strongly supported by studies in animal models and *in vitro* systems; see EPA (2014c) for a review of this literature.

Effects observed in association with PbB are briefly described below. Note that for some of the effects listed below, study results are not consistent, which limits interpretation of observations; this is reviewed in more detail in subsequent sections for each organ system in Chapter 2. The most extensive epidemiological databases examining Pb are for neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects.

- **Neurological Effects:**
  - **Children.** Decreased cognitive function; altered mood and behaviors that may contribute to learning deficits, altered neuromotor and neurosensory function, peripheral neuropathy, and encephalopathy.
  - **Adults.** Decreased cognitive function including attention, memory, and learning; altered neuromotor and neurosensory function; altered mood and behavior; and decreased peripheral nerve conduction velocity.

- **Renal Effects.** Decreased GFR, proteinuria, enzymuria, impaired tubular transport, and histopathological damage.

- **Cardiovascular Effects.** Increased systolic and diastolic blood pressure, increased risk of hypertension, atherosclerosis, altered cardiac conduction, increased risk of heart disease, and increased mortality due to cardiovascular disease.

- **Hematological Effects.** Inhibition of δ-ALAD leading to decreased blood hemoglobin and anemia, decreased activity of other erythrocyte enzymes, and altered plasma erythropoietin (EPO) levels.

- **Immunological Effects.** Perturbation of humoral and cell-mediated immune systems, decreased resistance to disease, sensitization, autoimmunity, and inflammation.

- **Reproductive Effects:**
  - **Males.** Effects on sperm, alterations in semen quality, decreased fertility, histopathological damage to the testes, and possible altered serum concentrations of reproductive hormones.
  - **Females.** Possible alterations in serum concentrations of reproductive hormones, decreased fertility, spontaneous abortion, preterm birth, and earlier age at the onset of menopause.

- **Developmental Effects.** Decreased birth weight and size, decreased anthropometric measures in children, and delayed onset of puberty in males and females.

Other health outcomes associated with PbB include the following:

- **Respiratory Effects.** Decreased lung function, increased bronchial hyperreactivity, increased risk of asthma, and obstructive lung disease.

- **Hepatic Effects.** Possible increases in plasma liver enzymes and cholesterol, enlarged liver, and increased thickness of gall bladder wall.

- **Endocrine Effects.** Possible alterations in serum of thyroid hormones, altered cortisol responses, alteration in serum growth factors, and decreased serum vitamin D levels.

- **Gastrointestinal Effects.** Abdominal pain/colic, nausea, vomiting, and diarrhea and/or constipation.

- **Musculoskeletal Effects.** Bone loss, osteoporosis, dental caries, tooth loss, and periodontitis.

- **Ocular Effects.** Possible macular degeneration and cataracts.

- **Cancer.** Increased risk of cancer, including all cancers, cancer of the respiratory tract, intestinal tract, and larynx, and glioma.

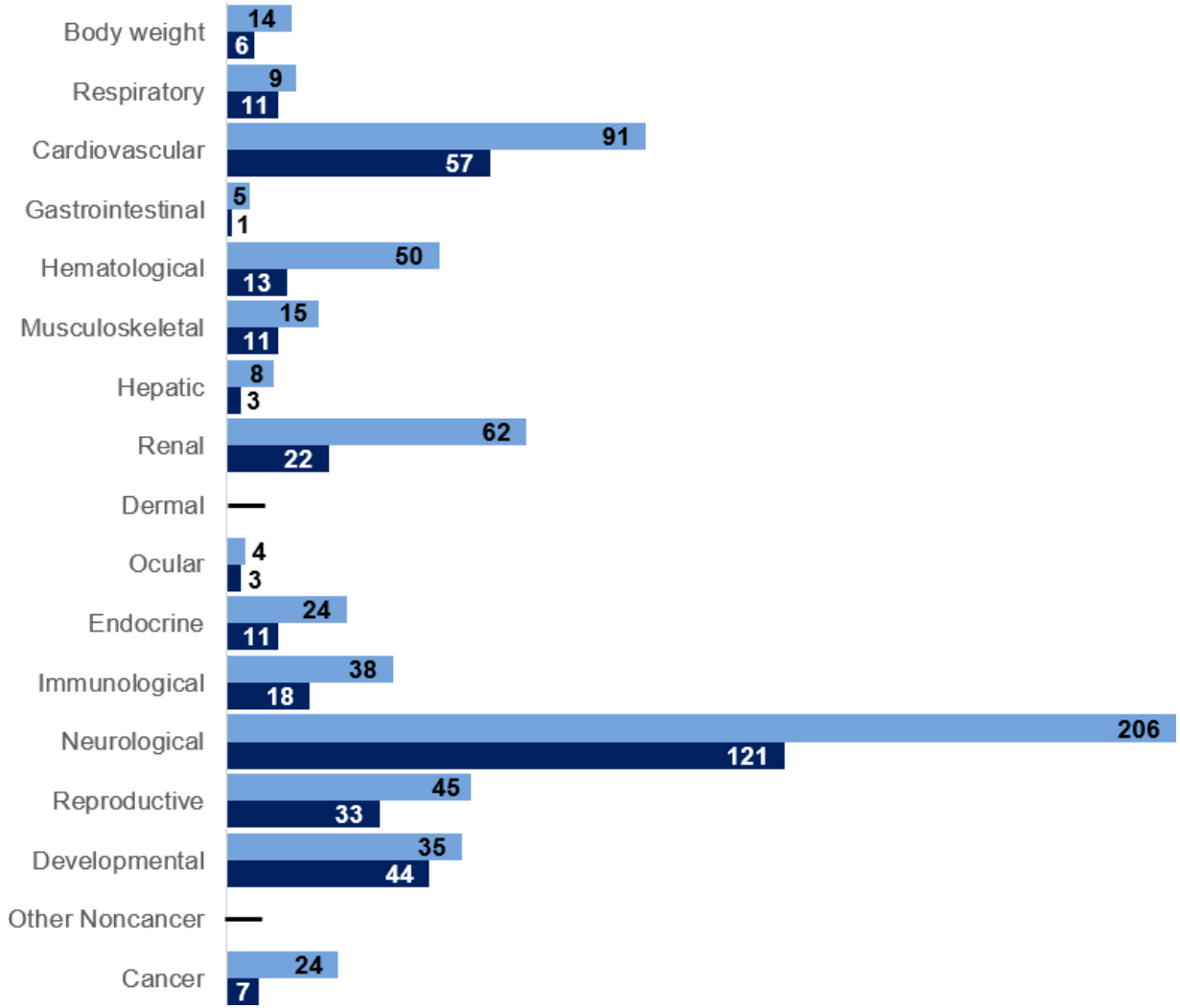
Many specific health effect endpoints have been evaluated in numerous studies. To provide the reader with a weight-of-evidence for these endpoints, the profile indicates if results are consistent and corroborated in numerous studies or if results are inconsistent (or mixed).

Figure 2-1 shows the numbers of epidemiological studies included in this chapter of the toxicological profile, based on health outcome studied. The number of studies evaluating effects at PbB ≤10 µg/dL also is indicated. The PbB ≤10 µg/dL was selected to evaluate effects at the lowest PbB (e.g., ≤5 µg/dL) and to evaluate potential exposure-response relationships for PbB ≤10 µg/dL. As noted above, due to the enormous number of epidemiological studies published, the profile does not attempt to provide a comprehensive review of all literature. Therefore, this figure should not be interpreted as depicting all epidemiological studies that have been published on Pb toxicity.

Figure 2-1. Overview of the Number of Studies Examining Associations Between PbB and Health Effects[a]

Most studies examined the potential cardiovascular, renal, and neurological effects of lead

A subset of studies evaluating health effects for **PbB ≤10 µg/dL** compared to **all PbB studies** (counts represent studies examining endpoint)



[a]Includes studies discussed in Chapter 2. A total of 694 epidemiological studies (including those finding no effect) have examined toxicity; some studies examined multiple endpoints.

2.2 ACUTE LEAD TOXICITY

Overview. No controlled studies in humans have evaluated the acute toxicity of Pb (acute Pb poisoning). Available information is anecdotal, obtained from numerous case reports. Thus, data are not sufficient to establish a dose-response relationship for acute toxicity relative to PbB. Acute Pb toxicity is characterized by symptoms of abdominal pain/colic, vomiting, constipation, peripheral neuropathy, and cerebral edema and encephalopathy, which can lead to seizures, coma, and death. Children are more susceptible than adults to acute Pb poisoning. Additional information on toxicity of ingested Pb debris (e.g., Pb shot) is provided in Appendix C.

Rather than reviewing numerous case reports, the information presented below was taken from the following reviews: Beers et al. (1999); Chisolm (1977); Klaassen (2001); Landrigan (1995); NAS (1972); Needleman (2004); and Skerfving and Bergdahl (2015). Citations are only specifically noted below if quantitative information is discussed.

Confounding Factors, Effect Modifiers, and Uncertainties. There are several uncertainties from case reports on acute toxicity of Pb. Therefore, it is difficult to establish dose-response relationships for acute toxicity relative to PbB. Uncertainties include:

- Baseline PbB data are rarely available.
- There is a lack of quantitative data on the dose of Pb ingested.
- No information on the fractional absorption of ingested Pb.
- Time from ingestion of Pb to development of symptoms of acute Pb toxicity is often unknown.
- Time from ingestion of Pb to first clinical evaluation and PbB assessment is often unknown.
- Gastrointestinal symptoms and general malaise are typically the first symptoms of acute Pb toxicity to appear; these general symptoms are often attributed to other causes, leading to an initial misdiagnosis or delay in diagnosis.
- Data to develop PbB time-concentration curves are incomplete.
- Numerous factors may contribute to individual susceptibility to acute Pb exposure, including age, intercurrent illness, underlying developmental issues, dietary and nutritional status, concurrent medication use, and exposure to other chemicals.

Clinical Presentation of Acute Pb Toxicity. The onset of acute toxicity is rapid, usually occurring within 1–5 days of exposure. The main organ systems involved are the gastrointestinal, hematological, and

neurological systems. Signs and symptoms increase in severity with increasing PbB, ranging from mild to severe. Gastrointestinal effects include abdominal colic/pain, nausea, vomiting, diarrhea, and constipation. Massive loss of gastrointestinal fluids can lead to dehydration. Hematological effects include decreased hemoglobin synthesis, anemia, and acute hemolytic crisis characterized by anemia and hemoglobinuria. Numerous neurological symptoms are associated with acute Pb toxicity, including headache, hyperirritability, decreased activity, paresthesia, muscle pain and weakness, ataxic gait, decreased consciousness, cerebral edema leading to seizures and coma, encephalopathy, and death. Other reported symptoms include astringency of the mouth, metallic taste in the mouth, and thirst.

Susceptibility of Children. Children are more susceptible than adults to Pb poisoning because the fractional absorption of ingested Pb is higher than in adults and the developing central nervous system is more vulnerable to toxicity compared to a fully developed nervous system (Needleman 2004). In addition to being more sensitive than adults, acute toxicity in children may have long-lasting effects. For example, children who recover from acute encephalopathy can have long-term decreases in cognitive abilities, attention deficits, and impaired behavior. Children are also susceptible due to increased exposure.

Dose-Response Relationship for Acute Toxicity Relative to PbB. As noted above, data from case reports are not sufficient to establish a dose-response relationship for acute toxicity relative to PbB. Some general observations can be made from available reports; however, dose-response relationships are highly uncertain and may not apply to individuals acutely exposed to Pb. At PbB <30 µg/dL, signs and symptoms of acute toxicity typically are not observed. This should not be interpreted to mean that no Pb-induced adverse effects (e.g., decreased hemoglobin synthesis) occur at PbB <30 µg/dL, but that symptoms causing individuals to seek medical intervention (e.g., abdominal colic and vomiting) typically are not observed at PbB <30 µg/dL. As PbBs increase to >30 µg/dL, signs and symptoms of gastrointestinal and neurological toxicity are observed, with severity increasing with PbB. Pb-induced encephalopathy has been reported at PbB <100 µg/dL, but is more commonly associated with PbB >100 µg/dL (NAS 1972). In a review of 96 cases of death due to acute Pb poisoning in children, death occurred at PbB >100 µg/dL (NAS 1972).

2.3 DEATH

Overview. Numerous epidemiological studies have investigated associations between Pb exposure and death. Studies include exposure of workers and general populations, and report a wide range of PbB levels. In the general population, studies have shown significant associations between PbB and mortality

due to disease of blood and blood-forming organs. In occupationally exposed individuals, mortality due to infection, endocrine diseases, and digestive diseases were associated with PbB in male workers, but not female workers, while mortality due to respiratory disease was associated with PbB in a cohort of male workers. In addition, studies of the general population and Pb occupations show an association between PbB and cumulative "all-cause" mortality (including cancer). However, results are inconsistent and interpretation may be limited due to confounding factors. Studies assessing associations between PbB and mortality due to cardiovascular diseases and cancer are discussed in Sections 2.5 and 2.19, respectively, and are not reviewed here.

The following causes of death have been associated with PbB:

- ≤10 µg/dL:
  - Increased risk of death from all causes (including cancer and cardiovascular disease); evaluated in a few studies with generally consistent results.
- >10 µg/dL:
  - Increased risk of death from all causes (including cancer and cardiovascular disease); evaluated in several studies with positive associations in some studies.
  - Increased risk of death from chronic or unspecified nephritis or non-malignant kidney disease; evaluated in several studies with positive associations in some studies.
  - Increase risk of death from infection; demonstrated in one study.
  - Increased risk of death from endocrine disease; demonstrated in one study.
  - Increased risk of death from digestive disease; evaluated in several studies with positive associations in some studies.
  - Increased risk of death from diseases of the blood and blood forming organs; demonstrated in one study.
  - Increased risk of death from respiratory diseases (emphysema, pneumonia, and other respiratory diseases); evaluated in several studies with positive associations in some studies.

Confounding Factors and Effect Modifiers. Numerous factors can influence results of epidemiological studies evaluating associations between Pb exposure and mortality, including age, sex, BMI, ethnicity, poverty level, education, alcohol consumption, smoking status, hypertension, diabetes, family history of diseases, activity level, total cholesterol, postmenopausal status, nutritional status, and co-exposure with other metals (i.e., arsenic or cadmium). Failure to account for these factors may attenuate or strengthen

the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Measures of Exposure. Studies examining the association between Pb exposure and mortality evaluate exposure by measurement of PbB.

Characterization of Effects. Numerous epidemiological studies have assessed associations between PbB and mortality. Studies of general populations and workers are briefly summarized in Table 2-1. In the general population, at PbB ≤10 µg/dL, a positive dose-response relationship was suggested for all-cause mortality and mortality due to coronary heart disease (Khalil 2009, 2010; Menke et al. 2006; Schober et al. 2006), although Weisskopf et al. (2009) did not show an increased risk for all-cause mortality. At >10 µg/dL, results of occupational exposure and general population studies are mixed and do not establish a pattern of effects or exposure-response relationships. In the general population, findings of the Lustberg and Silbergeld (2002) study suggested dose-response for PbB and all-cause mortality. In Pb workers, a dose-effect relationship was observed for all-cause mortality and mortality due to endocrine disease, infection, and digestive disease (Chowdhury et al. 2014; Kim et al. 2015), although Malcolm and Barnett (1982) did not observe a dose-effect relationship between Pb and all-cause mortality in Pb battery workers.

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
PbB ≤10 µg/dL			
Cheung et al. 2013 Cross-sectional study; n=3,482 (NHANES III)	Mean: 4.44	All-cause mortality[c]	**OR: 1.045 (1.013 1.079)***
Khalil 2010; Khalil et al. 2009 Prospective cohort study; n=533 women (age 65–87 years)	Quintiles • Q1: <4 • Q2: 4 • Q3: 5 • Q4: 6–7 • Q5: >7	All-cause mortality[c]	HR Q1 (reference) HR Q2: 0.80 (0.45,1.42) HR Q3: 0.70 (0.39, 1.24) HR Q4: 0.60 (0.34, 1.06) HR Q5: 1.20 (0.69, 2.09) p-trend=0.905 **Spline for 5th knot: p=0.009*** Wald test: p=0.0843
Khalil et al. 2009 Prospective cohort study; n=533 women (age 65–87 years)	Mean: 5.3 <8 (n=453) ≥8 (n=79)	All-cause mortality[c]	**Adjusted HR ≥8 µg/dL: 1.59 (1.02, 2.49); p=0.041***
		All-cause mortality excluding deaths due to cancer and cardiovascular disease	Adjusted HR ≥8 µg/dL: 1.22 (0.48, 3.10); p=0.673
Menke et al. 2006 Longitudinal study; n=13,946 (NHANES 1988–1994; mean age 44.4 years)	Mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.63	All-cause mortality[c]	Adjusted HR T1 (reference) T2: 0.91 (0.72, 1.15) **T3: 1.25 (1.04, 1.51)*** **p-trend=0.002***
Neuberger et al. 2009 Retrospective cohort study; mortality data from Oklahoma State Department of Health; 1999–2001	5.8	Tuberculosis	SMR: 0.0 (0.0, 10.80)
		Bronchitis, emphysema, asthma	SMR: 1.10 (0.863, 13.84)
		Kidney disease	SMR: 0.984 (0.573, 1.576)
Schober et al. 2006 Longitudinal study; n=9,757 (NHANES III; age ≥40 years)	Tertiles • T1: <5; mean 2.6 • T2: 5–9; mean 6.3 • T3: >10, mean 11.8	All-cause mortality[c]	**RR T2: 1.24 (1.05, 1.48)*** **RR T3: 1.59 (1.28, 1.98)*;** **p-trend<0.001**

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Weisskopf et al. 2009 Longitudinal study; n=868 men (Normative Aging Study; age 21–80 years)	Mean (SD): 5.6 (3.4) Tertiles: • T1: <4 • T2: 4–6 • T3: >6	All-cause mortality[c]	Adjusted HR • T1: 1 (reference) • T2: 0.99 (0.71, 1.37) • T3: 1.01 (0.71, 1.44) • p-trend=0.92
PbB >10 µg/dL			
Barry and Steenland 2019 Retrospective study; n=58,368 male workers (10-year follow-up of Chowdhury et al. 2014)	Q1: 0–<5 Q2: 5–<25 Q3: 25–<40 Q4: ≥40 T1: 0–<25 T2: 25–<40 T3: ≥40	All-cause mortality[c]	**HR Q4: 1.38 (1.24, 1.53)***
		Chronic obstructive pulmonary disease	HR Q4: 1.46 (0.94, 2.28)
		Chronic renal disease	HR T3: 1.81 (0.91, 3.57)
		Cerebrovascular disease (stroke)	SMR Q4: 0.73 (0.58, 0.91)
		Ischemic heart disease	SMR Q4: 0.70 (0.63, 0.77)
Chowdhury et al. 2014 Survey study; n=58,368 male workers (mean age 38.9 years)	Quartiles • Q1: 0–<5 • Q2: 5–<25 • Q3: 25–<40 • Q4: ≥40	All-cause mortality[c]	**SMR Q4: 0.80 (0.75, 0.84)*** SMR overall: 0.69 (0.66, 0.71)
		Chronic obstructive pulmonary disease	SMR Q4: 0.86 (0.64, 1.12) SMR overall: 0.65 (0.54, 0.78)
		Chronic renal disease	SMR Q4: 1.01 (0.58, 1.64) SMR overall: 0.65 (0.44, 0.93)
Cooper 1988; Cooper et al. 1985 Cohort study; n=4,519 battery workers; 2,300 smelters	Mean • Battery (n=1326): 62.7 • Smelters (n=537): 79.7	Nonmalignant respiratory disease	Battery PMR: 0.90 (0.74, 1.10) Smelter PMR: 0.76 (0.53, 1.11)
		Cirrhosis of the liver	Battery PMR:1.29 (0.96, 1.73) Smelter PMR: 0.63 (0.35, 1.15)
		Chronic or unspecified nephritis	**Battery PMR: 2.06 (1.26, 3.18)*; p<0.01** Smelter PMR: 1.86 (0.80, 3.66)
		Chronic nephritis	Battery PMR: 1.48 (0.88, 2.49) Smelter PMR: 1.20 (0.50, 2.86)

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Kim et al. 2015 Cross-sectional study; n=81,067 inorganic Pb workers (54,788 males; 26,279 females; age 20–≤50 years)	Mean • Males: 8.8 • Females 5.8 Tertiles: • T1: <10 • T2: 10–20 • T3: >20	All-cause mortality[c]	**Males: RR T3: 1.36 (1.03, 1.79)*; p<0.05** Females: RR T3: 1.30 (0.41, 4.16)
		Non-malignant death	Males: RR T3: 0.95 (0.56, 1.51) Females RR T3: 0.99 (0.13, 7.19)
		Infection	**Males: RR T2: 3.73 (1.06, 13.06)*; p<0.05** Females: not reported
		Endocrine disease	**Males: RR T3: 4.25 (0.90, 20.04)*; p<0.1** Females: not reported
		Respiratory disease	Males: RR T2: 1.46 (0.28, 7.49) Females: RR T2: 3.49 (0.31, 39.05)
		Digestive disease	**Males: RR T3: 3.23 (1.33, 7.86)*; p<0.05** Females: RR T2: 3.66 (0.33, 40.70)
Lundstrom et al. 1997 Retrospective cohort study; n=3,979 workers	Mean: • In 1950: 62.2 • In 1987: 33.2	All-cause mortality[c]	Total cohort SMR: 0.9 (0.8, 1.0)
		Respiratory disease	Total cohort SMR: 0.4 (0.2, 0.8)
		Digestive organs	Total cohort SMR: 0.6 (0.3, 1.1)
Lustberg and Silbergeld 2002 Longitudinal study; n=4,292; age 30–74 years (NHANES II)	Tertiles: • T1 (n=818): <10 • T2 (n=2,735): 10–19 • T3 (n=637): 20–29	All-cause mortality[c]	RR T2: 1.17 (0.90, 1.52) **RR T3: 1.46 (1.14, 1.86)***
Malcolm and Barnett 1982 Retrospective cohort study; n=754 Pb battery workers	Group1 (non-occupational exposed): not reported Group 2: (light occupational Pb exposure): mean 57 Group 3: (high occupational Pb exposure): not reported	All-cause mortality[c]	Group 3 SMR: 1.07; p=0.134

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
McDonald and Potter 1996 Prospective cohort study; n=454 pediatric patients diagnosed with Pb poisoning, Massachusetts, 1923–1966, followed through 1991; age of diagnosis <1–9 years	Mean 113	Diseases of the blood and blood forming organs	**SMR: 9.68 (1.95, 28.28)***
		Nervous-system and sense-organ diseases	SMR: 2.86 (0.57, 8.35)
		Respiratory diseases	SMR: 1.95 (0.78, 4.02)
		Pneumonia	SMR: 2.10 (0.68, 4.90)
		Digestive system diseases	SMR: 1.37 (0.44, 3.21)
		Genitourinary system diseases	SMR: 1.69 (0.02, 9.43)
		Chronic nephritis	SMR: 5.00 (0.06, 27.82)
		All-cause mortality[c]	**SMR: 1.74 (1.40, 2.15)***
McElvenny et al. 2015 Cohort study; n=9,122 workers; mean age 29.2 years	Mean: 44.3 Range: 2.3–321.5	All-cause mortality[c]	**Males: SMR 1.10 (1.06, 1.14)*** Females: SMR 1.00 (0.91, 1.09) **Total SMR: 1.09 (1.05, 1.12)***
		Respiratory system diseases	**Males: SMR: 1.17 (1.06,1.30)*** Females: SMR: 1.24 (0.98, 1.57) **Total SMR: 1.18 (1.08, 1.30)***
		Digestive system diseases	**Males: SMR: 1.22 (1.03, 1.45)*** Females: SMR: 0.84 (0.52, 1.35) Total SMR: 1.16 (0.99, 1.36)
		Genitourinary diseases	Males: SMR: 1.02 (0.72,1.44) Females: SMR: 0.67 (0.28, 1.60) Total SMR: 0.95 (0.69, 1.31)
		Non-malignant kidney disease	Males: SMR: 1.30 (0.76, 2.24) Total SMR: 1.29 (0.79. 2.11

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Selevan et al. 1985 Retrospective cohort study; n=1,987 male workers	Mean: 56.3	All tuberculosis	SMR: 1.39 (0.69, 2.49)
		Diseases of the central nervous system	SMR: 0.84 (0.61, 1.12)
		Diseases of the respiratory system	SMR: 1.25 (0.92, 1.66)
		Other respiratory diseases	**SMR: 1.87 (1.28, 2.64)***
		Diseases of the digestive system	SMR: 0.51 (0.26, 0.89)
		Diseases of the genitourinary system	SMR: 0.93 (0.42, 1.77)
		Chronic and unspecified nephritis and other renal sclerosis	SMR: 1.92 (0.88, 3.64)
		All other	SMR: 0.88 (0.67, 1.14)
Steenland et al. 1992 Cohort study (same cohort as Selevan et al. 1985); n=1,990 male smelter workers	Mean: 56.3	All-cause mortality[c]	**SMR: 1.07 (1.00, 1.14)***
		Non-malignant respiratory disease	**SMR: 1.44 (1.16, 1.77)***
		Emphysema	**SMR: 2.20 (1.45, 3.20)***
		Pneumonia and other respiratory disease	**SMR: 1.88 (1.34, 2.56)***
		Acute kidney disease	SMR: 0.91 (0.02, 5.07)
		Chronic kidney disease	SMR: 1.26 (0.54, 2.49)
Steenland et al. 2017 Cohort study; n=88,187 Pb workers (United States n=58,313, United Kingdom n=9,122, Finland n=20,752)	Median: 26 Tertiles: • T1: 20–<30 • T2: 30–<409 • T3: >40	All-cause mortality[c]	**HR T1: 1.15 (1.10, 1.21)***
		Stroke	**HR T1: 1.24 (1.03, 1.50)***
		Ischemic heart disease	**HR T1: 1.14 (1.04, 1.26)***
		Chronic obstructive pulmonary disease	**HR T1: 1.43 (1.10, 1.86)***
		Chronic kidney disease	HR T3: 1.54 (0.77, 3.08)

Table 2-1. Summary of Epidemiological Studies Evaluating Death[a]

Reference and study population	PbB (µg/dL)	Mortality outcome	Effects[b]
Wong and Harris et al. 2000 Cohort study; n=4,519 battery workers; 2,300 smelters (same cohort as Cooper et al. 1985)	Mean: • All workers: 64.0 • Battery workers: 62.7 • Smelters: 79.7	All-cause mortality[c]	**SMR: 1.045 (1.012, 1.08)*; p<0.01**

[a]Studies assessing death due to cardiovascular disease and cancer are discussed in Sections 2.5 and 2.19, respectively.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[c]Includes cancer and/or cardiovascular deaths.

CI = confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PbB = blood lead concentration; PMR = proportionate mortality ratio; RR = rate ratio or relative risk; SD = standard deviation; SMR = standard mortality ratio

2.4 BODY WEIGHT

Overview. Compared to other health effect endpoints, there is little information on Pb exposure and body weight measures. However, a few epidemiological studies have evaluated effects of Pb exposure on body weight in children, adolescents, and adults. The studies reviewed below focused on effects at PbB ≤10 µg/dL. Inverse associations have been observed between PbB and BMI, and decreased risks of being overweight or obese have been reported. However, some studies did not observe associations and one study reported a positive association between PbB and the risk of obesity in women.

Note that studies evaluating the effects of exposure to Pb on birth weight are reviewed in Section 2.18 (Developmental).

The following effects on body weight have been associated with PbB ≤10 µg/dL:

- Decreased BMI and risk of being overweight or obese in children and adolescents; observed in a few studies.
- Decreased BMI and risk of being overweight or obese in adults; not corroborated.
- Increased risk of obesity in women; not corroborated.

Measures of Exposure. Most studies evaluating effects of chronic Pb exposure on body weight evaluate exposure by measurement of PbB. A few other studies examining associations between Pb exposure and body weight used Pb concentration in urine, bone, and/or dentin as biomarkers of exposure; however, these studies did not report PbB (Kim et al. 1995; Liu et al. 2019a; Padilla et al. 2010; Shao et al. 2017).

Confounding Factors and Effect Modifiers. Numerous factors contribute to body weight (or BMI), including age, sex, race, nutrition, diet, daily activity level, intercurrent illness, genetic pre-disposition for body type, income level, education, and alcohol and tobacco use. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Effects at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating effects of PbB ≤10 µg/dL on body weight are briefly summarized in Table 2-2 and an overview of results is provided in Table 2-3; study details are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 1. Studies have been conducted in children and adolescents (Burns et al. 2017; Cassidy-Bushrow et al. 2016; Hauser et al. 2008; Scinicariello et al. 2013) and adults (Scinicariello et al. 2013; Wang et al. 2015). The largest study evaluating associations between PbB and body weight is a study of children, adolescents, and adults participating in NHANES, 1999–2006; this study included adjustments for numerous confounding factors (see the *Supporting Document for Epidemiological Studies for Lead*, Table 1) (Scinicariello et al. 2013). In children and adolescents (n=10,693), results show an inverse association between PbB and BMI-Z score and risk of being overweight or obese. In a smaller study in children (n=131), inverse associations were observed between PbB and BMI and BMI-Z score (Cassidy-Bushrow et al. 2016). Other studies in small populations of boys showed no associations between weight, BMI and/or BMI-Z score (Burns et al. 2017; Hauser et al. 2008). Results of studies in adults are mixed. The largest study in adults (n=15,899) shows inverse associations between PbB and BMI and risk of being overweight and obese, with a negative trend (p-trend: ≤0.01) over quartiles (Scinicariello et al. 2013). No association was observed between PbB and BMI in a small study on women (n=107) (Ronco et al. 2010) or a larger study in men (n=2235) (Wang et al. 2015). In contrast, the risk of being obese was increased in a large population (n=3323) of women (Wang et al. 2015). Thus, except for the Wang et al. (2015) study, available studies show either no association or an inverse association between PbB ≤10 µg/dL and body weight and/or BMI.

Mechanisms of Action. The mechanisms involved in the development of Pb-induced changes in body weight have not been established. However, alterations of the hypothalamic-pituitary-adrenal axis, stress-induced elevations in glucocorticoid levels, oxidative stress, and altered lipid metabolism have been proposed (reviewed by Scinicariello et al. 2013; Shao et al. 2017; Wang et al. 2015).

Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Burns et al. 2017 Prospective cohort of 481 Russian boys enrolled at age 8–9 years and followed until age 18 years	Median 3.0	HT-Z score	**Adjusted β (95% CI), HT-Z score per unit lnPbB: -0.26 (-0.40, -0.13); p<0.001***
		BMI-Z score	Adjusted β (95% CI), BMI-Z score per unit lnPbB: -0.14 (-0.31, 0.04); p=0.12
Cassidy-Bushrow et al. 2016 Birth cohort of 131 children, 2–3 years of age	Mean (SD): 2.45 (2.53)	BMI	**Adjusted RR (95% CI) for BMI ≥85th percentile 0.57 (0.33, 0.98); p=0.041***
		BMI-Z score	**Adjusted β (95% CI) for BMI Z-score: -0.35 (-0.60, -0.10); p=0.012***
Hauser et al. 2008 Cross-sectional study of 489 boys, 8–9 years of age	Mean: 3	Weight	Adjusted β (95% CI), per unit log-PbB: -0.761 (-1.54, 0.02); p=0.067
		BMI	Adjusted β (95% CI), per unit log-PbB: -0.107 (-0.44, 0.23); p=0.53
Ronco 2010 Cross-sectional study of 107 women of childbearing age (median age: 27 years) from Chile; data collection period not reported	Median • All: 1.0 • Low weight: 1.7 • Normal weight: 2.3 • Overweight: 1.0	BMI	No differences in PbB were observed between BMI categories

Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Scinicariello et al. 2013 Cross-sectional study of children and adolescents (n=10,693; age 3–19 years) adults (n=15,899, age ≥20 years) using NHANES data (1999–2006)	Gmean (SE) • Children/adolescents: 1.12 (0.02) • Adults: 1.59 (0.02) • Quartiles (all): o Q1: ≤0.70 o Q2: 0.71–1.09 o Q3: 1.10–1.60 o Q4: ≥1.61	BMI-Z score (children and adolescents)	**Adjusted β (SE) (BMI Z-score per PbB quartile):** • **Q3: −0.15 (0.06); p=0.01*** • **Q4: -0.33 (0.07); p ≤ 0.01*** • **p-trend: ≤0.01***
		Overweight (children and adolescents)	**Adjusted OR for Q4: 0.67 (0.52, 0.88)***
		Obesity (children and adolescents)	**Adjusted OR** • **Q3: 0.70 (0.54, 0.90)*** • **Q4: 0.42 (0.30, 0.59)***
		BMI (adults)	**Adjusted β (SE) (BMI per quartile):** • **Q2: −0.90 (0.20); p ≤ 0.01*** • **Q3: −1.41 (0.22); p ≤0.01*** • **Q4: −2.58 (0.25); p ≤0.01*** • **p-trend: ≤0.01***
		Overweight (adults)	**Adjusted OR for Q4: 0.79 (0.65–0.95)***
		Obesity (adults)	**Adjusted OR** • **Q2: 0.76 (0.66–0.87)*** • **Q3: 0.66 (0.56–0.77)*** • **Q4: 0.42 (0.35–0.50)***

Table 2-2. Summary of Epidemiological Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Wang et al. 2015 Cross-sectional study of 5,558 adults (men: 2,235, ages 39–65 years; women: 3,323, ages 40–65 years) from 16 locations in China	**PbB:** Men • Median: 4.40 • Quartiles: o Q1: ≤29.00 o Q2: 29.01–44.00 o Q3: 44.01–62.16 o Q4: ≥62.17 Women: • Median: 3.78 • Quartiles: o Q1: ≤25.13 o Q2: 25.14–37.79 o Q3: 37.80–54.35 o Q4: ≥54.36	BMI	β (SE) per PbB quartile • Men o Q4: 0.01 (0.20) o p-trend: 0.82 • **Women** o **Q4: 0.59 (0.17); p<0.05*** o **p-trend: <0.001***
		Overweight	Adjusted OR • Men o Q4: 0.95 (0.72,1.26) o p-trend: 0.74 • Women o Q4: 1.16 (0.92, 1.46) o p-trend: 0.07
		Obesity	Adjusted OR • Men o Q4: 0.88 (0.48, 1.61) o p-trend: 0.99 • **Women** o **Q4: 1.86 (1.16, 2.98)*** o **p-trend: <0.01***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 1 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

BMI = body mass index; BMI-Z = BMI z-scores; CI = confidence interval; Gmean = geometric mean; HT-Z = height z-scores; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; RR = risk ratio; SD = standard deviation; SE = standard error

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Table 2-3. Effects on Body Weight Associated with Mean Blood Lead Concentrations (PbBs) ≤10 µg[a]

Mean PbB (µg/dL)	Population (n)[b]	Weight	BMI	BMI-Z score	Overweight	Obese	Reference
3.0	C (481 boys)	–	–	0	–	–	Burns et al. 2017
2.45	C (131)	–	↓	↓	–	–	Cassidy-Bushrow et al. 2016
3	C (489 boys)	0	0	–	–	–	Hauser et al. 2008
1.0	A (107 women)	–	0	–	–	–	Ronco et al. 2010
1.12	C, Ad (10,693)[c]	–	–	↓	↓	↓	Scinicariello et al. 2013
1.59	A (15,899)[c]	–	↓	–	↓	↓	Scinicariello et al. 2013
4.40	A (2,235, men)	–	0	–	0	0	Wang et al. 2015
3.78	A (3,323, women)	–	0	–	0	↑	Wang et al. 2015

[a]↑ = increased; ↓ = decreased; 0 = no change; – = not assessed.
[b]Unless otherwise specified, study was conducted in males and females.
[c]Participants from the National Health and Nutrition Examination Survey 1999–2006.

A = adults; Ad = adolescents; BMI = body mass index; BMI-Z = BMI z-scores; C = children

2.5 RESPIRATORY

Overview. Few epidemiological studies have evaluated respiratory effects associated with exposure to Pb; those that are available include cross-sectional studies in adults and prospective and cross-sectional studies in children. Associations have been observed between PbB and decreased lung function, increased bronchial hyperreactivity, increased number and severity of symptoms of respiratory disease, and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease). Although most studies found associations between respiratory effects and PbB, other studies did not observe associations.

The following respiratory effects have been associated with PbB:

- ≤10 µg/dL:
  - Decreased lung function; corroborated in a few studies, including studies in children.
  - Increased bronchial hyperreactivity.
  - Increased risk of asthma and obstructive lung disease; evaluated in a few studies with mixed results.

- >10 µg/dL:
  - Decreased lung function.
  - Symptoms of respiratory disease (e.g., shortness of breath).
  - Increased risk/prevalence of asthma; evaluated in a few studies with mixed results.

Measures of Exposure. Studies evaluating the association between respiratory effects and Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. The etiology for most respiratory diseases is multifactorial; therefore, several factors may contribute to clinical findings. Factors that may contribute to the development of respiratory diseases include poor housing conditions, exposure to allergens (e.g., pet dander, seasonal allergies), exposure to tobacco smoke and other respiratory irritants, and asthma compounded by obesity (Ali and Ulirk 2013). In addition, Aligne et al. (2000) reported that children living in urban settings have an increased risk of asthma. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. General trends for studies showing a relationship between PbB and respiratory effects are shown in Table 2-4. Compared to other toxicological endpoints (e.g., neurological or cardiovascular effects), few studies have evaluated adverse respiratory effects associated with PbB. Data are from cross-sectional studies in adults (Bagci et al. 2004; Bener et al. 2001; Chung et al. 2015; Min et al. 2008a; Pugh Smith and Nriagu 2011; Rokadia and Agarwal 2013), and prospective (Joseph et al. 2005; Rabinowitz et al. 1990) and cross-sectional (Wells et al. 2014) studies in children. Over a range of PbBs that includes PbB ≤10 µg/dL and PbB >50 µg/dL, studies provide evidence for effects in Pb workers compared to controls or associations between PbB and decreased pulmonary function tests indicative of obstructive pulmonary disease (forced expiratory volume in 1 second [FEV_1], FEV_1/forced vital capacity [FVC] ratio, forced expiratory flow at 25–75% of FVC [$FEF_{25–75}$]), increased bronchial hyperreactivity (indicative of asthma), symptoms of respiratory disease (cough, shortness of breath), and increased risk of respiratory diseases (e.g., asthma and obstructive lung disease). With the exception of a prospective study in children, which showed no increased risk of asthma at umbilical cord PbB ≥10 µg/dL compared to <10 µg/dL (Rabinowitz et al. 1990), studies showed positive associations between PbB and respiratory effects.

Table 2-4. Overview of Respiratory Effects in Adults and Children Chronically Exposed to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Decreased lung function	Chung et al. 2015; Leem et al. 2015; Little et al. 2017; Zeng et al. 2017
	Increased bronchial responsiveness	Min et al. 2008a
	Lung disease (asthma and obstructive lung disease)	Joseph et al. 2005; Rokadia and Agarwal 2013; Wang et al. 2017a; Wells et al. 2014; Zeng et al. 2016
>10–30	Lung disease (asthma)	Pugh Smith and Nriagu 2011
>30–50	Decreased lung function	Bagci et al. 2004
>50	Symptoms of lung disease (phlegm)	Bener et al. 2001
	Lung disease (asthma)	Bener et al. 2001

Effect at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating respiratory effects of PbB ≤10 µg/dL are summarized in Table 2-5, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 2. Studies show associations between PbB ≤10 µg/dL and decreased lung function, increased bronchial hyperreactivity, and increased risk of asthma; findings are consistent with obstructive lung disease. In a cross-sectional study in adults from China with mean PbB of 2.50 µg/dL, an inverse association was observed for the FEV_1/FVC ratio in a population; results are consistent with obstructive airway disease (Chung et al. 2015). In a large pooled cross-sectional study, Korean adults showed a decrease in the FEV_1/FVC ratio in the highest exposure quartile (Leem et al. 2015). A small study in children with a mean PbBs of 5.53 µg/dL show inverse associations between PbB and pulmonary functions tests, including FEV_1 and FVC (Little et al. 2017). Increased bronchial reactivity in response to methacholine challenge, consistent with a diagnosis of asthma, was observed in adults with mean PbB of 2.96 µg/dL (Min et al. 2008a). In addition, risk of obstructive lung disease was observed in a large NHANES population of adults with a mean PbB of 1.73 µg/dL (Rokadia and Agarwal 2013). Studies in children examining associations between PbB and risk of asthma do not provide consistent results. A large prospective study showed an increased risk of asthma in black children with PbB <5 and ≥5 µg/dL compared to white children with PbB <5 µg/dL; however, no increased risk was observed for white children with PbB ≥5 µg/dL compared to white children with PbB <5 µg/dL (Joseph et al. 2005). The underlying causes for the racial disparity of results have not been established. However, the study authors noted the following as possible contributors: socio-economic factors; racial differences in IgE; differences in housing conditions and indoor Pb sources (e.g., Pb paint); and genetic variability in susceptibility to Pb toxicity (e.g., vitamin D receptor gene). In cross-sectional studies, asthma risk was

Table 2-5. Summary of Epidemiological Studies Evaluating Respiratory Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Decreased lung function			
Chung et al. 2015 Cross-sectional study; n=870 adults	Mean: 2.50 Tertiles: • T1: <2.03 • T2: 2.03–2.81 • T3: >2.81	FVC%	Correlation coefficient: 0.070
		FEV_1%	Correlation coefficient: 0.00
		FEV_1/FVC ratio	**Correlation coefficient: -0.115; p<0.01***
			OR T3: 0.006 (0, 0.286)*
			p-trend: 0.03*
Leem et al. 2015 Pooled cross-sectional study; n=5,972 adults	Mean: • Men: 2.92 • Women: 2.33 Quartiles (men and women) • Q1: ≤1.85 (reference) • Q2: 1.86–2.43 • Q3: 2.44–3.16 • Q4: ≥3.17	FEV_1/FVC ratio	**Difference (SE) between reference and Q4: -0.6 (0.3); p=0,025***
Little et al. 2017 Cross-sectional study; n=184 boys and 189 girls (age ≥10–≤15.9 years)	Mean: • Boys: 5.27 • Girls: 3.82	FVC	Boys, β (SE), per log10 increase in PbB: -5.11 (4.47); p=0.25
			Girls, β (SE), per log10 increase in PbB: -12.90 (5.25); p=0.02*
Zeng et al. 2017 Cross-sectional study; n=200 children (ages 5–7 years)	**PbB:** Median • Control: 3.57 • Exposed: 5.53	FEV_1	Regression coefficient for exposed: -0.02 (-0.100, 0.043)
		FVC	Regression coefficient for exposed: FVC: -0.015 (-0.093, 0.063)
Increased bronchial responsiveness			
Min et al. 2008a Cross-sectional study; n=523 adults	Mean (SD): 2.96 (1.59)	BR	**A 1 µg/dL increase in PbB was associated with a higher BR; β (SE): 0.018 (0.007)***

Table 2-5. Summary of Epidemiological Studies Evaluating Respiratory Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Asthma			
Joseph et al. 2005 Prospective study; n=4,634 children (ages 3 months to 3 years)	Mean • White: 3.2 • Black: 5.5	Asthma	All compared to PbB <5 µg/dL in white children
			HR white (PbB ≥5): 2.3 (0.8, 6.7); p=0.12
			HR black (PbB <5): 1.8 (1.3, 2.4); p<0.01*
			HR black (PbB ≥5): 1.5 (1.2, 1.8); p<0.01*
			HR black (PbB ≥10): 3.0 (1.2, 7.1); p=0.01*
Rokadia and Agarwal 2013[c] Pooled cross-sectional study; n=9,575 adults (8,411 without OLD; 1,164 with OLD)	Mean • Non-OLD: 1.18 • OLD: 1.73	OLD	**OR for all OLD: 1.94 (1.10, 3.42)***
			OR for mild OLD: 1.21 (0.55, 2.65)
			OR for moderate-severe OLD: 3.49 (1.70, 7.15)*
Wang et al. 2017a Cross-sectional study; n=930 children (mean age: 5.74 years)	Gmean (GSD) • All: 1.86 (1.21) • Boys: 1.89 (1.22) • Girls: 1.83 (1.20)	Asthma	**OR (all participants), <5 versus ≥5 µg/dL: 5.50 (1.69, 17.94); p=0.005***
			OR (boys), <5 versus ≥5 µg/dL: 6.40 (1.49, 27.42); p=0.012*
			OR (girls), <5 versus ≥5 µg/dL: 4.73 (0.44, 50.60); p=0.199
Wells et al. 2014[c] Cross-sectional study; NHANES 2005–2006; n=1,430 children (ages 4–12 years)	Gmean: 1.07	Asthma	OR for asthma with atopy: 0.97 (0.61, 1.55)
			OR for asthma with no atopy: 1.07 (0.86, 1.33)

Table 2-5. Summary of Epidemiological Studies Evaluating Respiratory Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Zeng et al. 2016 Cross-sectional study; n=470 children (ages 3–8 years)	Median • Haojiang area: 4.75 • Guiyu area: 6.24	Asthma	**OR for asthma at PbB ≥5 µg/dL: 9.50 (1.16, 77.49); p<0.01***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 2 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[c]Study population was from NHANES.

BR = bronchial responsiveness; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second (L/s); FEV_1% = percent of predicted FEV_1; FVC = forced vital capacity (L); FVC% = percent of predicted FVC; Gmean = geometric mean; GSD = geometric standard deviation; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; OLD = obstructive lung disease; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error

increased in Taiwanese children, with elevated risks in the total population and for boys, but not for girls (Wang et al. 2017a) and in Chinese children with PbB ≥5 µg/dL (Zeng et al. 2016). In contrast, a large cross-sectional study of children participating in NHANES did not observe an association between PbB (mean 1.07 µg/dL) and asthma, with or without atopy (Wells et al. 2014).

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of toxicity to the respiratory system. EPA (2014c) specifically noted that oxidative stress through reactive oxygen species (ROS), resulting in tissue damage and inflammation and immune effects, is a plausible mechanism for the underlying cause of respiratory damage. Increased ROS, along with depletion of antioxidants, results in inflammation and production and release of metabolites and cytokines. Immune-mediated inflammation is observed with asthma and bronchial hyperreactivity.

2.6 CARDIOVASCULAR

Overview. A large number of epidemiological studies showing adverse effects on the cardiovascular system associated with Pb exposure have been published. Most studies evaluated effects in adults, although a few studies in children have been conducted. The effect of Pb exposure on blood pressure is the most studied cardiovascular outcome, with results providing consistent evidence of positive associations between Pb exposure and blood pressure. Other cardiovascular endpoints (atherosclerosis, cardiac conduction, cardiovascular disease, and mortality due to cardiovascular disease) also show positive and inverse associations with PbB, although the majority of studies had positive associations. In some cases, although no associations between PbB and cardiovascular outcomes were observed, associations were observed for bone Pb, a biomarker of cumulative Pb exposure that, among individuals with high historical Pb exposures, typically remains elevated for many years after the PbB declines to ≤10 µg/dL; these cases are noted in the discussions below.

The following cardiovascular effects have been associated with PbB:

- ≤10 µg/dL:
  - Greater systolic and diastolic blood pressure:
    - In adults; corroborated in multiple studies.
    - In children; evaluated in a few studies.
    - During pregnancy; evaluated in a few studies.

  - Greater risk of hypertension:
    - In adults, including during pregnancy; evaluated in numerous studies.
  - Greater risk of atherosclerosis; evaluated in a few studies.
  - Altered cardiac conduction; evaluated in a few studies.
  - Greater risk of mortality due to cardiovascular diseases; evaluated in a few studies with mixed results.
- >10 µg/dL:
  - Increased systolic and diastolic blood pressure:
    - In adults; corroborated in multiple studies and meta-analyses.
    - In children; evaluated in a few studies.
  - Increased risk of hypertension; corroborated in multiple studies.
  - Atherosclerosis; evaluated in a few studies.
  - Increased risk or prevalence of heart disease; evaluated in a few studies.
  - Increased mortality due to cardiovascular diseases; corroborated in multiple studies.

Measures of Exposure. PbB and bone Pb concentrations have been used as biomarkers to evaluate cardiovascular effects of Pb exposure. However, PbB may not provide the ideal biomarker for long-term exposure to target tissues that contribute a hypertensive effect of Pb. Because the development of cardiovascular effects has a long latency period, associations between PbB and cardiovascular disease at concurrent PbB ≤10 µg/dL may be related to higher past Pb exposures. Bone Pb, a metric of cumulative or long-term exposure to Pb, appears to be a better predictor of Pb-induced elevations in blood pressure and alterations in cardiac conduction than PbB.

Confounding Factors and Effect Modifiers. Numerous factors affect blood pressure, including age, body mass, race, smoking, alcohol consumption, ongoing or family history of cardiovascular/renal disease, LDL cholesterol levels, and various dietary factors (e.g., dietary calcium). In addition, renal disease, as well as Pb-induced renal damage, can lead to cardiovascular effects, including increased blood pressure (EPA 2014c; NTP 2012); thus, interpretation of studies examining cardiovascular outcomes is complicated by the link between cardiovascular and renal function. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome (e.g., Møller and Kristensen 1992). For example, adjusting for alcohol consumption will decrease the apparent association between PbB and blood pressure, if alcohol consumption contributes to Pb intake and, thereby, PbB (Bost et al. 1999; Hense et al. 1993; Hertz-Picciotto and Croft 1993; Wolf et al. 1995). Varying approaches and breadth of

inclusion of these may account for the disparity of results that have been reported. Measurement error may also be an important factor. Blood pressure estimates based on multiple measurements or, preferably, 24-hour ambulatory measurements, are more reproducible than single measurements (Staessen et al. 2000). Ambulatory measurements also can decrease bias in estimates related to increases in blood pressure that can accompany clinic visits (Yang et al. 2018).

Characterization of Effects. General trends between studies showing a relationship between PbB and cardiovascular effects are shown in Table 2-6. Over the PbB range of ≤10–>50 µg/dL, results of epidemiological studies provide evidence for increased blood pressure and hypertension, atherosclerosis (increased intimal medial thickening and peripheral artery disease), heart disease (myocardial infarction, ischemic heart disease, left ventricular hypertrophy, cardiac arrhythmias, and angina), and increased risk of mortality due to cardiovascular diseases. The effect of Pb exposure on blood pressure is the most studied cardiovascular outcome. A review by Navas-Acien et al. (2007) concluded that available literature provides evidence that "is sufficient to infer a causal relationship of Pb exposure and hypertension" and evidence that "is suggestive but not sufficient to infer a causal relationship of Pb exposure with clinical cardiovascular outcomes" (cardiovascular, coronary heart disease, and stroke mortality; and peripheral arterial disease). Well-controlled studies in laboratory animals provide additional support regarding effects of Pb on blood pressure; see EPA (2014c) for additional information.

Table 2-6. Overview of Cardiovascular Effects in Adults and Children Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased blood pressure and hypertension	Almeida Lopes et al. 2017; Al-Saleh et al. 2005; Barry et al. 2019; Bost et al. 1999; Bushnik et al. 2014; Cheng et al. 2001; Chu et al. 1999; Den Hond et al. 2002; Disha et al. 2019; Elmarsafawy et al. 2006; Faramawi et al. 2015; Gambelunghe et al. 2016; Gerr et al. 2002; Glenn et al. 2003; Gump et al. 2005, 2011; Hense et al. 1993; Hu et al. 1996a; Korrick et al. 1999; Lee et al. 2016a, 2016b; Martin et al. 2006; Muntner et al. 2005; Nash et al. 2003; Obeng-Gyasi and Obeng-Gyasi 2018; Park et al. 2009b; Perlstein et al. 2007; Proctor et al. 1996; Rothenberg et al. 2002; Schwartz 1995; Scinicariello et al. 2010, 2011; Vupputuri et al. 2003; Wells et al. 2011; Yang et al. 2017, 2018; Yazbeck et al. 2009; Zhang et al. 2011; Zota et al. 2013

Table 2-6. Overview of Cardiovascular Effects in Adults and Children Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
	Atherosclerosis[a]	Ari et al. 2011; Muntner et al. 2005; Navas-Acien et al. 2004;
	Heart disease[b] and cardiac function	Chen et al. 2017; Cheng et al. 1998; Eum et al. 2011; Jain et al. 2007; Jing et al. 2019; Park et al. 2009a
	Mortality due to cardiovascular disease	Aoki et al. 2016; Khalil et al. 2009; Lanphear et al. 2018; Menke et al. 2006; Schober et al. 2006; Weisskopf et al. 2009
>10–30	Increased blood pressure and hypertension	Coate and Fowles 1989; Factor-Litvak et al. 1999; Grandjean et al. 1989; Han et al. 2018; Harlan et al. 1985; Møller and Kristensen 1992; Pirkle et al. 1985; Rabinowitz et al. 1987
	Atherosclerosis[a]	Pocock et al. 1988; Poreba et al. 2011, 2012
	Heart disease[b] and cardiac function	Karakulak et al. 2019; Poreba et al. 2013
	Mortality due to cardiovascular disease	Barry and Steenland 2019; Lustberg and Silbergeld 2002; Min et al. 2017; Schober et al. 2006; Steenland et al. 2017
>30–50	Increased blood pressure and hypertension	Aiba et al. 1999; Al-Saleh et al. 2005; Factor-Litvak et al. 1996, 1999; Ghiasvand et al. 2013; Glenn et al. 2006; Rapisarda et al. 2016; Weaver et al. 2008; Weiss et al. 1986, 1988
	Atherosclerosis[a]	Karakulak et al. 2017
	Heart disease[b]	Bockelmann et al. 2002; Jain et al. 2007; Kieltucki et al. 2017
	Mortality due to cardiovascular disease	Barry and Steenland 2019; Gerhardsson et al. 1995a; Steenland et al. 2017
>50	Increased blood pressure and hypertension	Kirby and Gyntelberg 1985; Were et al. 2014
	Atherosclerosis[a]	Kirby and Gyntelberg 1985
	Mortality due to cardiovascular disease	Cooper 1988; Cooper et al. 1985; Fanning 1988; Gerhardsson et al. 1995a; McDonald and Potter 1996

[a]Atherosclerosis includes increased intimal medial thickening and peripheral artery disease.
[b]Heart disease includes myocardial infarction, ischemic heart disease, left ventricular hypertrophy, cardiac arrhythmias, and angina.

Numerous studies provide a weight of evidence for associations between PbB and increased blood pressure over a wide PbB range in adults (Table 2-6). Results of meta-analyses estimate small but consistent increases in blood pressure per doubling of PbB. The largest meta-analysis of 31 studies published between 1980 and 2001 included a total of 58,518 subjects (Nawrot et al. 2002); blood pressure

data from studies included in the analysis are shown in Table 2-7 and Figures 2-2 and 2-3. Nawrot et al. (2002), in an update of an earlier meta-analysis by Staessen et al. (1994), estimated the increase in systolic pressure per doubling of PbB to be 1 mmHg (95% CI 0.5, 1.4) and the increase in diastolic pressure to be 0.6 mmHg (95% CI 0.4, 0.8). The range of mean (or median) PbBs for studies included in the analysis was 2.28–63.82 µg/dL. Although a PbB mean was not estimated for the entire study population, only nine studies had a mean PbB <10 µg/dL; therefore, it is likely that the overall PbB mean for the entire study population was >10 µg/dL. Similar outcomes were observed in two other meta-analyses (Schwartz 1995; Staessen et al. 1994). A meta-analysis reported by Staessen et al. (1994) included 23 studies (published between 1984 and 1993; 33,141 subjects) and found a 1 mmHg (95% CI 0.4, 1.6) increase in systolic blood pressure and 0.6 mmHg (95% CI 0.2, 1.0) increase in diastolic pressure per doubling of PbB. Schwartz (1995) conducted a meta-analysis that encompassed a similar time frame (15 studies published between 1985 and 1993) and found a 1.25 mmHg (95% CI 0.87, 1.63) increase in systolic blood pressure per doubling of PbB (diastolic not reported). The latter analysis included only those studies that reported a standard error (SE) on effect measurement (e.g., increase in blood pressure per doubling of PbB). Of the 15 studies included in the Schwartz (1995) analysis, 8 were also included in the Staessen et al. (1994) analysis. The estimated increase in blood pressure per doubling of PbB in these meta-analyses is small; however, on a population basis, the consequences of increased blood pressure includes increased risks of serious and potentially fatal effects, including atherosclerosis, stroke, and myocardial infarction. Increased blood pressure during pregnancy has been associated with PbB and bone Pb (Rothenberg et al. 2002; Wells et al. 2011; Yazbeck et al. 2009); these studies are discussed in more detail below (*Effect at Blood Pb Levels ≤10 µg/dL*).

Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number[a]	Population[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
1[h]	Pocock et al. 1984[i,j]; Shaper et al. 1981	7,379	GP	100	Y	49 (40–59)	145	82	15.13 (2.07–66.3)[a,e]
2	Kromhout 1988[i,j]; Kromhout et al. 1985[i]	152	GP	100	Y	67 (57–76)	154	92	18.23 (10.77–27.97)[a,c]
3	Moreau et al. 1982[j], 1988; Orssaud et al. 1985[i,j]	431	WC	100	Y	41 (24–55)	131	75	18.23 (8.91–49.94)[a,e]
4	Weiss et al. 1986[i], 1988[i]	89	WC	100	Y	47 (30–64)	122	83	24.45 (18.65–29.01)[m,x]

Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number[a]	Population[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
5	de Kort and Zwennis 1988[i,j]; de Kort et al. 1987[i]	105	BC	100	N	40 (25–80)	136	83	29.22 (4.35–83.29)[a,e]
6	Lockett and Arbuckle 1987[i]	116	BC	100	Y	32 (?–?)	119	80	37.5 (14.92–95.52)[a,e]
7	Parkinson et al. 1987[i]	428	BC	100	Y	36 (18–60)	127	80	27.97 (6.01–49.52)[a,c]
8	Rabinowitz et al. 1987[i]	3,851	GP	0	Y	28 (18–38)	121	76	7.04 (3.73–10.15)[a,c]
9	Elwood et al. 1988a[i,j], 1988b[k]	1,136	GP	100	Y	56 (49–65)	146	87	12.64 (6.01–26.11)[g,c]
10	Elwood et al. 1988a, 1988b[i,j,l]	1,721	GP	50	Y	41 (18–64)	127	78	10.15 (4.56–23.21)[g,c]
11	Gartside et al. 1988[i]; Harlan 1988; Harlan et al. 1985; Pirkle et al. 1985; Ravnskov 1992[m]	6,289	GP	53	Y	30 (10–74)	127	80	13.47 (2.07–95.93)[g,e]
12	Neri et al. 1988[i,j,n]	288	BC	100	?	? (?–?)	?	?	45.17 (6.01–65.06)[a,e]
13	Neri et al. 1988[i,o]	2,193	GP	?	Y	45 (25–65)	?	?	23.41 (0–47.03)[m,e]
14	Grandjean et al. 1989, 1991[i,p]	1,050	GP	48	Y	40 (40–40)	?	?	11.6 (3.94–60.09)[a,e]
15	Reimer and Tittelbach 1989[i]	58	BC	100	?	32 (?–?)	134	81	39.99 (12.85–70.24)[a,c]
16	Apostoli et al. 1990[i]	525	GP	48	Y	45 (21–60)	132	84	13.05 (2.07–28.18)[a,e]
17	Morris et al. 1990[i,j]	251	GP	58	Y	? (23–79)	?	?	7.46 (4.97–38.95)[a,e]
18	Sharp et al. 1988[i,j], 1989[i], 1990[i]	249	WC	100	N	43 (31–65)	128	83	6.63 (2.07–14.92)[p,e]
19	Staessen et al. 1984[i,q]	531	WC	75	Y	48 (37–58)	126	78	11.4 (4.14–35.22)[g,e]
20	Møller and Kristensen 1992[i,j,r]	439	GP	100	Y	40 (40–40)	?	?	13.68 (4.97–60.09)[a,e]
21	Hense et al. 1993[i,j]	3,364	GP	51	Y	48 (28–67)	129	80	7.87 (1.24–37.09)[a,e]
22	Maheswaran et al. 1993[i]	809	BC	100	Y	43 (20–65)	129	84	31.7 (0–98.01)[a,e]
23	Menditto et al. 1994	1,319	GP	100	Y	63 (55–75)	140	84	11.19 (6.22–24.66)

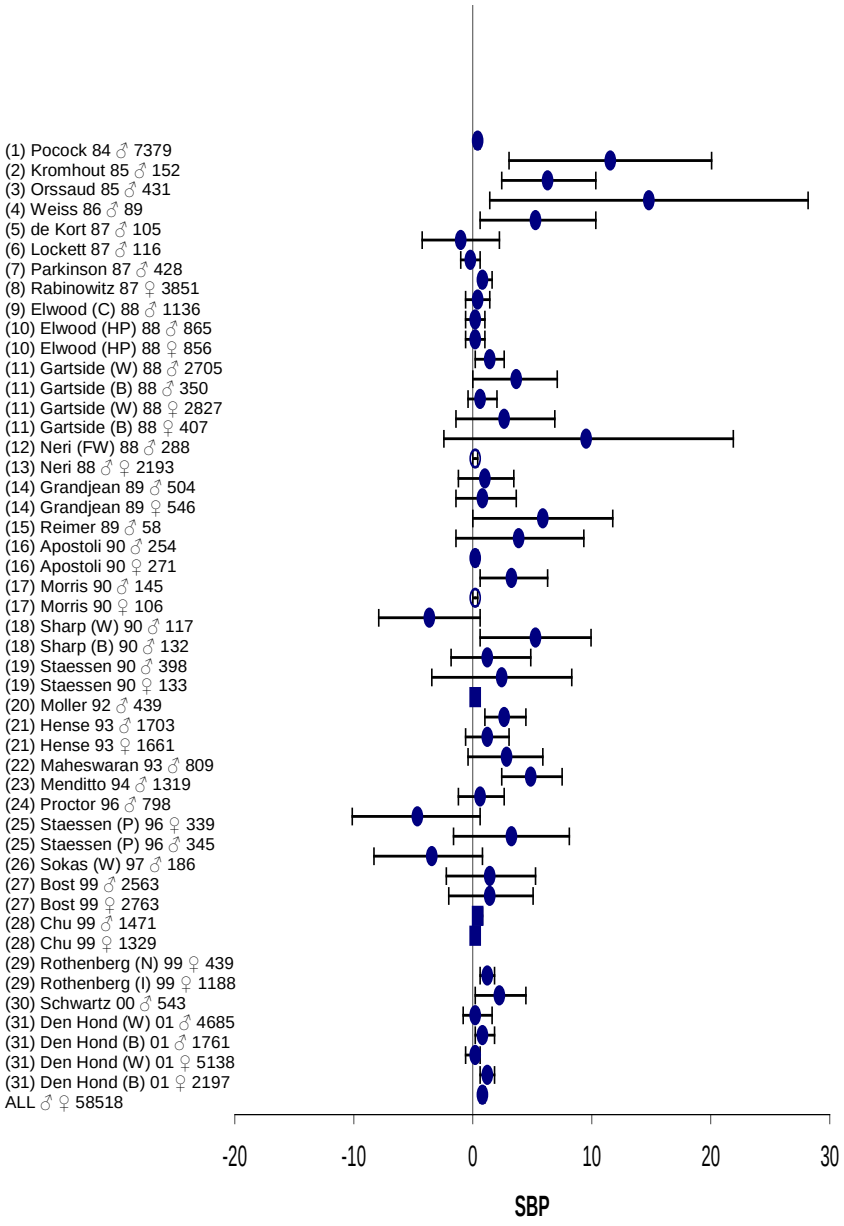
Table 2-7. Characteristics of the Study Population in Meta-Analyses of Effects of Lead (Pb) on Blood Pressure

	Reference	Number[a]	Population[b]	Men (%)[c]	HT[d]	Age (years)[e]	SBP[f]	DBP[f]	Lead (µg/dL)[g]
24	Hu et al. 1996a; Proctor et al. 1996[s]	798	GP	100	Y	66 (43–93)	134	80	5.59 (0.41–35.02)[p,e]
25	Staessen et al. 1996a[i], 1996b[i,t]	728	GP	49.3	Y	46 (20–82)	130	77	9.12 (1.66–72.52)[g,e]
26	Sokas et al. 1997[u]	186	BC	99	Y	43 (18–79)	130	85	7.46 (2.07–30.04)[p,e]
27	Bost et al. 1999	5,326	GP	48	Y	48 (16–?)	135	75	63.82 (?–?)[g]
28	Chu et al. 1999	2,800	GP	53	Y	44 (15–85)	123	78	6.42 (0.41–69)[a,e]
29	Rothenberg et al. 1999a, 1999b	1,627	GP	0	Y	27 (?–?)	110	59	2.28 (?–?)[g]
30	Schwartz et al. 2000c	543	BC	100	Y	58 (41–73)	128	77	4.56 (1.04–20.1)[a,e]
31	Den Hond et al. 2001[v]	13,781	GP	53.2	Y	48 (20–90)	125	73	3.11 (0.62–55.94)[g,e]

[a]Number of persons in whom relevant data were available.
[b]Study population: BC = blue collar workers; GP = sample from general population; WC = white collar employees.
[c]Men: Percentage of men.
[d]HT: Indicates whether the sample included (Y = yes) or did not include (N = no) hypertensive patients.
[e]Age: Mean age or midpoint of age span (range or approximate range given between parentheses).
[f]SBP, DBP: Mean systolic and diastolic blood pressures.
[g]Lead: Measure of central tendency: A = arithmetic mean; G = geometric mean; M = midpoint of range; P = P_{50} (median). The spread of blood lead is given between parentheses: c = P_5–P_{05} interval; P_{10}–P_{90} interval, or interval equal to 4 times the standard deviation; e = extremes; x = approximate limits of distribution.
[h]Number refers to reference in Figures 2-2 and 2-3.
[i]Included in the Staessen et al. (1994) meta-analysis.
[j]Included in the Schwartz (1995) meta-analysis.
[k]Caerphilly Study.
[l]Welsh Heart Program.
[m]NHANES (National Health and Nutrition Examination Survey).
[n]Foundry workers.
[o]Canadian Health Survey.
[p]Glostrup Population Study, cross-sectional analysis (1976).
[q]London Civil Servants.
[r]Glostrup Population Study, longitudinal analysis (1976–1987).
[s]Normative Aging Study.
[t]PheeCad (Public Health and Environmental Exposure to Cadmium) Study.
[u]Because of missing information, only the effect in whites is included.
[v]NHANES III.

Source: Nawrot et al. 2002

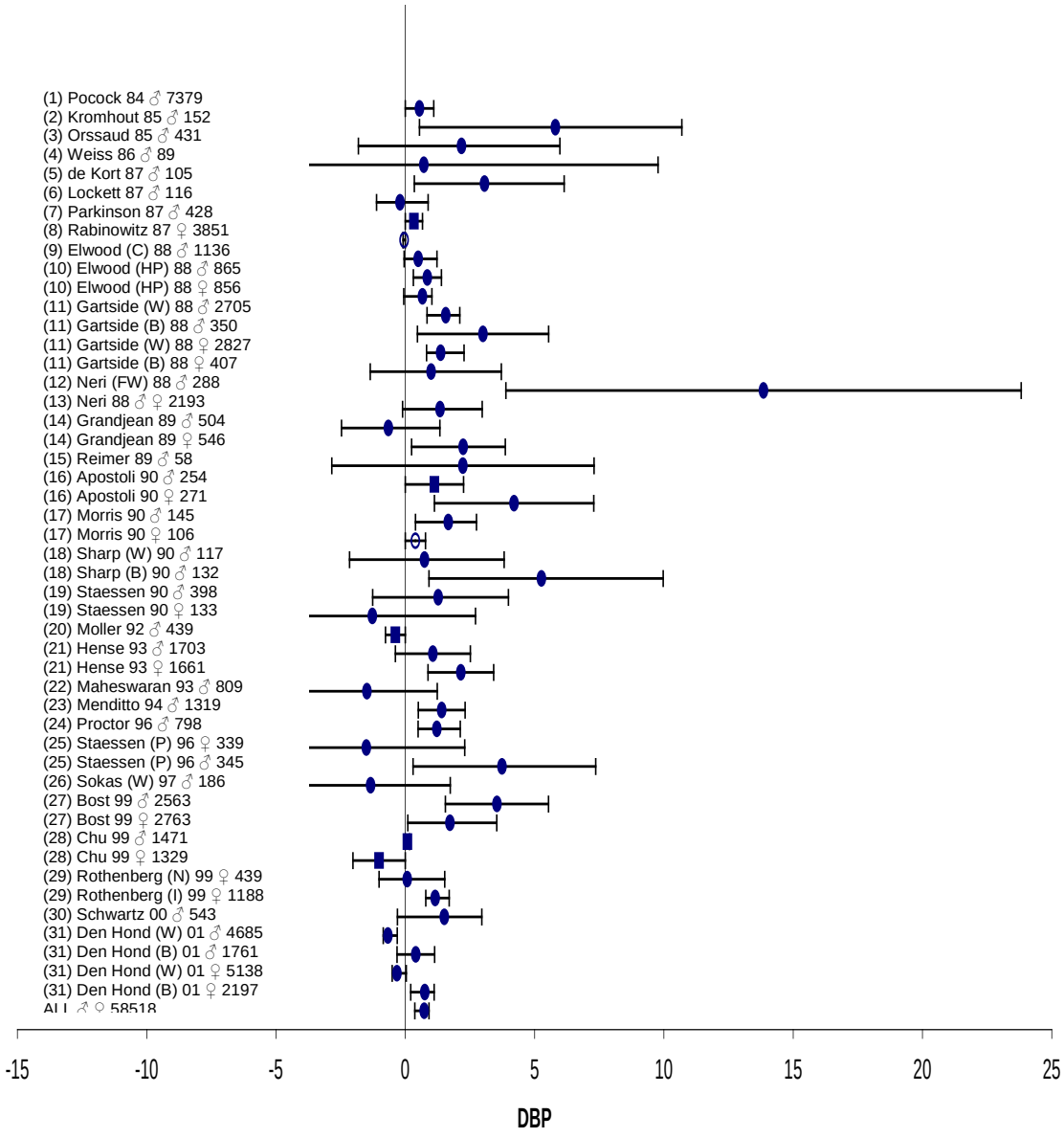
Figure 2-2. Change in the Systolic Pressure Associated with a Doubling of the Blood Lead Concentration (PbB)*



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 2-7 for more details on study groups.

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

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



*Data were digitized from Nawrot et al. 2002. Circles represent means (mmHg) of individual groups; squares represent combined groups; and open circles represent nonsignificant associations (plotted as zero). Bars represent 95% confidence limits. See Table 2-7 for more details on study groups.

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

Within individual studies, dose-effect relationships are evident at PbB ≤10 µg/dL. A positive dose-effect was observed for PbB and diastolic blood pressure (Zota et al. 2013). An observed positive dose-effect was observed for tibia Pb concentration and hypertension (Hu et al. 1996a). No dose-effect was observed for PbB and pulse pressure (PP), although a positive dose-effect was observed for tibia Pb and PP (Perlstein et al. 2007). In a cross-sectional study of women, diastolic hypertension was observed to have a positive dose-effect when pre- and postmenopausal women were analyzed together and when postmenopausal women were analyzed alone. In contrast, a dose-effect relationship was not observed for PbB and hypertension in a cross-sectional study of men and women (Muntner et al. 2005). A positive dose-effect relationship was observed for PbB and peripheral artery disease (PAD) (Muntner et al. 2005). In men, tibia blood levels had a positive dose-effect relationship with QT interval, but a negative dose-effect relationship with atrioventricular conduction defect (Eum et al. 2011). Studies have also found positive dose-effect relationships between mortality due to cardiovascular disease, myocardial infarction, and stroke and PbB (Menke et al. 2006; Schober et al. 2006).

Several studies have evaluated associations between PbB and cardiovascular function in children (Ahn et al. 2018; Factor-Litvak et al. 1999, 1996; Gump et al. 2005, 2011; Kapuku et al. 2006; Khalil et al. 2009, 2010; Lustberg and Silbergeld 2002; Menke et al. 2006; Schober et al. 2006; Zhang et al. 2011). Results show alterations in cardiovascular function, including increases in blood pressure and altered cardiovascular function under stress (decreased stroke volume and cardiac output) over a PbB range from <10 to approximately 40 µg/dL.

Effect at Blood Pb Levels ≤10 µg/dL. Studies investigating relationships between PbB ≤10 µg/dL and cardiovascular effects have evaluated effects on blood pressure (including hypertension), atherosclerosis, heart disease (alterations in cardiac conduction and ischemic heart disease), and death due to cardiovascular disease.

Increased blood pressure and hypertension. Numerous studies of large populations show associations between PbB ≤10 µg/dL and increased systolic and/or diastolic blood pressure and increased risk of hypertension and prehypertension (see Table 2-8). The lowest mean PbB associated with increased systolic and diastolic is 1.33 µg/dL (Obeng-Gyasi and Obeng-Gyasi 2018). A few studies did not show associations between PbB and blood pressure parameters; however, positive associations between bone Pb concentrations and blood pressure at concomitant PbB ≤10 µg/dL were observed (Barry et al. 2019; Gerr et al. 2002; Hu et al. 1996a; Korrick et al. 1999; Zhang et al. 2011). Studies are briefly summarized

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Women and men combined (not stratified by sex)[c]			
Almeida Lopes et al. 2017 Population-based study; n=948 adults (≥40 years of age)	Gmean: 1.97 Quartiles: • Q1: ≤1.32 • Q2: 1.32–1.93 • Q3: 1.93–2.76 • Q4: >2.76	SBP	**Change in SBP, Q4: -0.00 (-0.00, -0.00); p-trend: 0.002***
		DBP	**Change in DBP, Q4: 0.06 (0.04, 0.09); p-trend: <0.001***
		Hypertension	**OR, Q4: 2.54 (1.17, 5.53)***
Faramawi et al. 2015[d] Cross-sectional study; n=13,757	Mean: 3.44	SBP	**β (SE), mmHg for change in blood pressure SD per µg/dL: 0.07 (0.02); p<0.01***
		DBP	β (SE), for change in blood pressure SD per µg/dL: 0.04 (0.03); p=0.08
Gambelunghe et al. 2016 Cross-section study; n=4,452 adults	Mean: 2.8 Quartiles: • Q1: 0.15–1.9 • Q2: 1.9–2.5 • Q3: 2.5–3.3 • Q4: 3.3–25.8	SBP	**Regression coefficient, β, Q4 versus Q1–Q3 (mmHg): 1.7; p=0.01***
		DBP	**Regression coefficient, β, Q4 versus Q1–Q3 (mmHg): 1.3; p<0.001***
		Hypertension	**OR, Q4 versus Q1–Q3: 1.3 (1.1–1.5); p=0.004***
Lee et al. 2016b Cross-sectional study; n=8,493 adults	Study population mean not reported Quartiles: • Q1: 0.206–1.539 • Q2: 1.540–2.056 • Q3: 2.057–2.716 • Q4: 2.717–24.532	Prehypertension	**OR, versus Q1:** • **Q2: 1.24 (1.04, 1.48)*** • **Q3: 1.27 (1.06, 1.52)*** • **Q4: 1.30 (1.07, 1.60)*** • **p-trend: 0.0152***
Martin et al. 2006 Cross-sectional study; n=964 (ages 50–70 years)	Mean: 3.5	SBP	**β, mmHg per 1 µg/dL: 0.99 (0.47,1.51); p<0.01***
		DBP	**β, mmHg per 1 µg/dL: 0.51 (0.24, 0.79); p<0.01***

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Zota et al. 2013[d] Cross-sectional study; n=8,194 (ages 40–65 years)	Mean: 1.69 Quintiles: • Q1: ≤1.05 • Q2: 1.06–1.44 • Q3: 1.45–1.90 • Q4: 1.91–2.69 • Q5: >2.70	Elevated SBP (≥140 mmHg)	OR (Q5): 1.23 (0.92, 1.65); p-trend: 0.06
		Elevated DBP (≥90 mmHg)	**OR (Q3): 1.56 (1.11, 2.19)* OR (Q4): 1.80 (1.24, 2.60)* OR (Q5): 1.77 (1.25, 2.50)* p-trend 0.0002**
Obeng-Gyasi and Obeng-Gyasi 2018 Cross-sectional study; n=22,747 adults	Mean: 1.33	SBP	**β, increase in blood pressure (mmHg) per unit increased in ln PbB: 0.238 (0.122, 0.355); p=0.0001***
		DBP	**β, increase in blood pressure (mmHg) per unit increased in ln PbB: 0.132 (0.049, 0.215); p=0.002***
Women and men (stratified by sex)[c]			
Bost et al. 1999 Cross-sectional study; n=2,563 males and 2,763 females	Mean • M: 3.7 • F: 2.6	SBP	M: no association with PbB (regression coefficient not reported)
			F: no association with PbB (regression coefficient not reported)
		DBP	**M: β, per doubling of PbB: 0.78 (0.01, 1.55)***
			F: regression coefficients not reported
Bushnik et al. 2014 Population-based survey; n=2,214 males and 2,336 females	Mean • All: 1.64 • Non-hypertensive: 1.59 • Hypertensive: 1.74	SBP	All β, mmHg per 1 µg/dL: 1.85 (-0.20, 3.90); p=0.075
			M β, mmHg per 1 µg/dL: 2.17 (-0.08, 4.42); p=0.058
			F β, mmHg per 1 µg/dL: 0.76 (-2.72, 4.24); p=0.656
		DBP	**All β, mmHg per 1 µg/dL: 1.91 (0.75, 3.08); p=0.002***
			M β, mmHg per 1 µg/dL: 2.36 (0.94, 3.79); p=0.002*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
			F β, mmHg per 1 µg/dL: 1.43 (-0.51, 3.38); p=0.142
		Hypertension	**All β, mmHg per 1 µg/dL: -3.87 (-7.46, -0.29); p=0.035***
			M β, mmHg per 1 µg/dL: -6.37 (-15.02, 2.29); p=0.142
			F β, mmHg per 1 µg/dL: -4.18 (-8.78, 0.42); p=0.073
Chu et al. 1999 Population-based survey study; n=1,471 males and 1,329 females	Mean • M: 7.3 • F: 5.7	SBP	**M β (SE), mmHg per 1 log_{10} µg/dL: 0.185 (0.076); p=0.015***
			F β (SE), mmHg per 1 log_{10} µg/dL: -0.057 (0.109); p=0.603
		DBP	M β (SE), mmHg per 1 log_{10} µg/dL: 0.075 (0.053); p=0.159
			F β (SE), mmHg per 1 log_{10} µg/dL: -0.083 (0.072); p=0.250
Hense et al. 1993 Population-based survey study; n=1,703 males and 1,661 females	Mean • M: 8.3 • F: 6.0	SBP	**M β, mmHg per 1 µg/dL: 0.29 (0.08, 0.49)***
			F β, mmHg per 1 µg/dL: 0.17 (-0.14, 0.48)
		DBP	M β, mmHg per 1 µg/dL: 0.08 (-0.06, 0.23)
			F β, mmHg per 1 µg/dL: 0.29 (0.09, 0.49)*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Lee et al. 2016a Cross-sectional study; n=5,920 men and 6,059 women	Gmean (95% CI) • Men: 2.396 • Women: 1.919 Tertiles: • Men o T1: <2.096 o T2: 2.096–2.886 o T3: >2.886 • Women o T1: <1.516 o T2: 1.516–2.147 o T3: >2.14	SBP	M difference, T3 versus T1: 0.25 (-0.90, 1.41)
			F difference, T3 versus T1: 1.48 (0.29, 2.67)
		DBP	M difference, T3 versus T1 : 0.73 (-0.12, 1.60)
			F difference, T3 versus T1: 1.059 (0.308, 1.811)
		Hypertension	M OR, T3: 0.88 (0.72, 1.07)
			F OR, T3: 1.26 (0.999, 1.58)
		Prehypertension	M OR, T3: 0.95 (0.79, 1.16)
			F OR, T3: 1.22 (1.01, 1.48)*
Men only[c]			
An et al. 2017 Cross-sectional study; n=310 male smelters (21–61 years of age)	Gmean: 5.839	SBP	β, per doubling of PbB: -0.636 (-2.661, 1.389); p=0.537
		DBP	β, per doubling of PbB: -1.182 (-2.763, 0.399); p=0.142
Barry et al. 2019 Cross-sectional study; n=211 male Pb workers	Median (range): 2.5 (0–34.0) • Quartiles o Q1: <1.6 o Q2: 1.6–2.5 o Q3: 2.6–4.2 o Q4: ≥4.3 Bone Pb (tibia) median, µg/g (range): 13.8 (0–127.3) • Bone Pb quartiles: o Q1: <9.6 o Q2: 9.6–13.7 o Q3: 13.8–19.5 o Q4: ≥19.6	SBP	Regression coefficient (SE) for PbB Q4: 7.33 (4.40); p=0.10 PbB continuous: 0.19 (0.30) 0.52 Bone Pb Q4: 5.32 (5.26); p=0.31 **Bone Pb continuous: 0.36 (0.15); p=0.02***

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Cheng et al. 2001[e] Longitudinal study; n=833 men Analysis for hypertension limited to 474 participants who had no history of definite hypertension; analysis for SBP limited to 519 participants who were free from definite hypertension at baseline	PbB mean (all): 6.09 Tibia Pb (µg/g) • Borderline: 23.46 • Definite: 22.69 Patella Pb (µg/g) • Borderline: 33.73 • Definite: 32.72	Hypertension (borderline and definite)	RR, per 1 SD increase in PbB: 1.00 (0.76, 1.33)
			RR, per 1 SD increase in tibia Pb: 1.22 (0.95, 1.57)
			RR, per 1 SD increased in patella Pb: 1.29 (1.04, 1.61); p<0.05*
		SBP	RR, per 1 SD increase in PbB: -0.13 (-1.35, 1.09)
			RR, per 1 SD increase in tibia Pb: 1.37 (0.02, 2.73); p<0.05*
			RR, per 1 SD increased in patella Pb: 0.57 (-0.71, 1.84)
Elmarsafawy et al. 2006[e] Cross-sectional study; n=471	Mean • Low Ca^{2+} intake: 6.6 • High Ca^{2+} intake: 6.6	Hypertension	**Low Ca^{2+}: OR: 1.07 (1.00, 1.15)***
			High Ca^{2+}: OR: 1.03 (0.97, 1.11)
Glenn et al. 2003 Occupational longitudinal study; n=496	Mean: 4.6	SBP	**β (SE; 95% CI), per 1 SD increased in PbB: 0.64 (0.25; 0.14, 1.14)***
		DBP	β (SE; 95% CI); per 1 SD increased in PbB: 0.09 (0.17; -0.24, 0.43)
Hu et al. 1996a[e] Case-control study of men (n=146) with hypertension and controls (n=444)	Mean • Cases: 6.9 • Controls: 6.1	Hypertension	**Risk of hypertension based on tibia Pb: logistic β (SE): 0.19 (0.0078); p=0.01*** PbB was not associated with hypertension
			OR for 1 µg/g change in tibia Pb: 1.019 (1.004, 1.035)*
			OR for quintile range (8–37 µg/g): 1.5 (1.1, 1.8)*
Perlstein et al. 2007[e] Cross-sectional study; n=593	Mean: 6.12	PP	PbB: no trend over quintiles (p=0.82)
			Bone Pb: p-trend=0.02*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Proctor et al. 1996[e] Cross-sectional study; ≤74 years (n=681); >74 years (n=117)	Mean: • All: 6.5 • ≤74 years: 6.5 • >74 years: 6.3	SBP	All β, mmHg per 1 ln µg/dL PbB: 0.85 (-1.1, 2.7); p>0.05
			≤74 β, mmHg per 1 ln µg/dL PbB: 1.2 (-0.86, 3.2); p>0.05
		DBP	**All β, mmHg per 1 ln µg/dL PbB: 1.2 (0.11, 2.2); p≤0.05***
			≤74 β, mmHg per 1 ln µg/dL PbB: 1.6 (0.42, 2.7); p≤0.01*
Yang et al. 2018 Cross-sectional study; n=236 Pb workers	Gmean (IQR): 4.50 (2.60–9.15)	SBP	Regression (β) coefficients, expressed as change pressure (mmHg) per 2-fold increase in PbB: • Office blood pressure: 0.79 (-0.17, 1.76) p=0.11 24-hour ambulatory pressure: 0.29 (-0.82, 1.41) p=0.60
		DBP	Regression (β) coefficients, expressed as change pressure (mmHg) per 2-fold increase in PbB: • **Office: 0.87 (0.03, 1.72) p=0.043*** • 24-hour ambulatory: -0.25 (-0.97, 0.48) p=0.50
		Hypertension	OR: • Office: 0.89 (0.62–1.28); p=0.052 • 24-hour ambulatory: 1.21 (0.94–1.57); p=0.14
Women only[c]			
Al-Saleh et al. 2005 Case-control study of women with hypertension (n=100) and control subjects (n=85)	Mean • Hypertension: 4.75 • Controls: 4.56	Hypertension	OR for PbB ≥3.85 compared to PbB <3.85: 5.27 (0.93, 29.86); p=0.06

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Korrick et al. 1999 Case-control study of women with hypertension (n=89) and control subjects (n=195)	Mean (all): 3	Hypertension	PbB: no increased risk (ORs not reported)
			Patella Pb OR per 1 µg/g increase in PbB: 1.03 (1.00, 1.05); p=0.02*
Nash et al. 2003 Cross-sectional study; n=2,165 all; 1,084 premenopausal, and 663 postmenopausal	Mean (all): 2.9 Quartiles; mean (range) • Q1: 1.0 (0.5–1.6) • Q2: 2.1 (1.7–2.5) • Q3: 3.2 (2.6–3.9) • Q4: 6.4 (4.0–31.1)	SBP	**All β (SE), mmHg per 1 ln µg/dL PbB: 0.32 (0.16); p=0.03***
			Premenopausal β (SE), mmHg per 1 ln µg/dL PbB: 0.14 (0.26); p=0.59
			Postmenopausal β (SE), mmHg per 1 ln µg/dL PbB: 0.42 (0.21); p=0.29
		DBP	**All β (SE): 0.25 (0.09), mmHg per 1 ln µg/dL PbB; p=0.009***
			Premenopausal β (SE), mmHg per 1 ln µg/dL PbB: 0.38 (0.25); p=0.12
			Postmenopausal β (SE) mmHg per 1 ln µg/dL PbB: 0.14 (0.13); p=0.04*
		Hypertension	**Percent of total population with hypertension: p-trend<0.001*** (Q1: 19.4; Q2: 20.6; Q3: 25.5 Q4: 28.3)
Women and men stratified by race[c]			
Den Hond et al. 2002[d] Cross-sectional study n=4,685 MW; 5,138 FW; 1,761 MB; and 2,197 FB	Mean • MW: 3.6 • FW: 2.1 • MB: 4.2 • FB: 2.3	SBP	MW β, per doubling of PbB: 0.3 (-0.2, 0.7); p=0.29
			FW β, per doubling of PbB: 0.1 (-0.4, 0.5); p=0.80
			MB β, per doubling of PbB: 0.9 (0.04,1.8); p=0.04*
			FB β, per doubling of PbB: 1.2 (0.4,2.0); p=0.004*
		DBP	**MW β, per doubling of PbB: -0.6 (-0.9, -0.3); p=0.0003***

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
			FW β, per doubling of PbB: -0.2 (-0.5, 0.1); p=0.13
			MB β, per doubling of PbB: 0.3 (-0.3, 1.0); p=0.28
			FB β, per doubling of PbB: 0.5 (0.01, 1.1); p=0.047*
Muntner et al. 2005[d] Cross-sectional study; n=9,961 (men and women), stratified by race (W, B, MA)	Mean: 1.64 Quartiles: • Q1: <1.06 • Q2: 1.06–1.63 • Q3: 1.63–2.47 • Q4: ≥2.47	Hypertension	W (Q4) OR: 1.10 (0.87, 1.41); p-trend=0.61
			B (Q4) OR: 1.44 (0.89, 2.32); p-trend=0.06
			MA (Q4) OR: 1.54 (0.99, 2.39); p-trend=0.04*
Park et al. 2009b[d] Cross-sectional study; n=12,500 all, 2,130 MW (<50 years old); 2,152 MW (≥50 years old); 1,048 MB (<50 years old); 540 MB (≥50 years old); 2,429 FW (<50 years old); 2,180 FW (≥50 years old); 1,409 FB (<50 years old); and 612 FB (≥50 years old)	Mean • MW (<50 years old) 4.02 • MW (≥50 years old) 4.92 • MB (<50 years old) 4.55 • MB (≥50 years old) 7.57 • FW (<50 years old) 2.09 • FW (≥50 years old) 3.53 • FB (<50 years old) 2.52 • FB (≥50 years old) 4.49	Hypertension	MW OR: 1.06 (0.92, 1.22)
			FW OR: 1.16 (1.04, 1.29)*
			MB OR: 1.17 (0.98, 1.38)
			FB OR: 1.19 (1.04, 1.38)*
			M (<50 years old) OR: 0.98 (0.80, 1.22)
			M (>50 years old) OR: 1.20 (1.02, 1.41)*
			F (<50 years old) OR: 1.23 (1.04, 1.46)*
			F (>50 years old) OR: 1.09 (0.94, 1.26)
Scinicariello et al. 2010[d] Cross-sectional study; n=6,016 (stratified by race)	Mean • W 2.87 • B 3.59 • MA 3.33	SBP	**W β (SE), mmHg per ln µg/dL PbB: 1.05 (0.37); p=0.01***
			B β (SE), mmHg per ln µg/dL PbB: 2.55 (0.49); p=0.001*
			MA β (SE), mmHg per ln µg/dL PbB: 0.84 (0.46); p=0.08
		DBP	W β (SE), mmHg per ln µg/dL PbB: -0.14 (0.49); p=0.77

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
			B β (SE), mmHg per ln µg/dL PbB: 1.99 (0.44); p=0.0002*
			MA β (SE), mmHg per ln µg/dL PbB: 0.74 (0.74); p=0.06
Scinicariello et al. 2011[d] Cross-sectional study; n=16,222 all; 4,538 MW; 4,319 FW; 1,767 MB; 1,854 FB; 1,925 MMA; and 1,819 FMA	Mean • All 1.41 • MW 2.20 • FW 1.55 • MB 2.44 • FB 1.81 • MMA 2.47 • FMA 1.56	SBP	**All β (SE), per ln µg/dL PbB: 1.07 (0.35); p<0.05***
			MW β (SE), per ln µg/dL PbB: 0.87 (0.53); p>0.05
			FW β (SE), per ln µg/dL PbB: 0.89 (0.55); p>0.05
			MB β (SE), per ln µg/dL PbB: 2.30 (0.71); p<0.05*
			FB β (SE), per ln µg/dL PbB: 2.40 (1.14); p<0.05*
			MMA β (SE), per ln µg/dL PbB: 0.10 (0.70); p>0.05
			FMA β (SE), per ln µg/dL PbB: -0.03 (0.64); p>0.05
		DBP	**All β (SE): 0.71 (0.27): p<0.05***
			MW β (SE): 0.90 (0.45): p<0.05*
			FW β (SE): 0.95 (0.38): p<0.05*
			MB β (SE): 2.75 (0.82); p<0.05*
			FB β (SE), per ln µg/dL PbB: 0.30 (0.81); p>0.05
			MMA β (SE), per ln µg/dL PbB: -1.34 (0.66); p<0.05*
			FMA β (SE), per ln µg/dL PbB: -0.74 (0.44); p>0.05

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Vupputuri et al. 2003[d] Cross-sectional study; n=14,952 total; n=5,360 MW; 5,188 FW; 2,104 MB; and 2,300 FB	Mean • MW 4.4 • FW 3.0 • MB 5.4 • FB 3.4	SBP	MW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.29 (-0.24, 0.83)
			FW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.34 (-0.49, 1.17)
			MB β, per 1 SD (3.3 µg/dL) increase of PbB: 0.82 (0.19, 1.44); p<0.05*
			FB β, per 1 SD (3.3 µg/dL) increase of PbB: 1.55 (0.47, 2.64); p<0.01*
		DBP	MW β, per 1 SD (3.3 µg/dL) increase of PbB: 0.01 (-0.38, 0.40); p≥0.05
			FW β, per 1 SD (3.3 µg/dL) increase of PbB: -0.04 (-0.56, 0.47) p≥0.05
			MB β, per 1 SD (3.3 µg/dL) increase of PbB: 0.64 (0.08, 1.20); p<0.05*
			FB β, per 1 SD (3.3 µg/dL) increase of PbB: 1.07 (0.37, 1.77); p<0.01*
		Hypertension	MW OR: 1.04 (0.93, 1.16); p=0.47
			FW OR: 1.32 (1.14, 1.52) p<0.001*
			MB OR: 1.08 (0.99, 1.19); p=0.08
			FB OR: 1.39 (1.21, 1.61); p<0.001*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Children and young adults[c]			
Ahn et al. 2018 Cross-sectional study; n=1,776 adolescents (ages 10–18 years)	Mean (95% CI): 1.192 (1.165, 1.219) Quartiles • Males o Q1: <1.07 o Q2: 1.07–1.341 o Q3: 1.342–1.655 o Q4: >1.655 • Females o Q1: <0.839 o Q2: 0.839–1.076 o Q3: 1.077–1.371 o Q4: >1.371	DBP	Mean difference with doubling of PbB, continuous variable: -0.680 (-1.581, 0.221)
		SBP	Mean difference with doubling of PbB, continuous variable: -0.099 (-1.098, 0.898)
		Prehypertension	OR, continuous variable: 0.906 (0.629, 1.305)
Gerr et al. 2002 Cross-sectional study; n=508 young adults (ages 19–29 years)	PbB mean associated with the following bone Pb concentrations: • <1 µg/g: 1.91 (1.58) • 1–5 µg/g: 2.31 (2.06) • 6–10 µg/g: 2.43 (2.36) • >10 µg/g: 3.15 (2.28)	SBP	**Increase (mmHg) associated with bone Pb >10 µg/g (SE): 4.26 (1.48); p=0.004***
		DBP	**Increase (mmHg) associated with bone Pb >10 µg/g (SE): 2.80 (1.25); p=0.03***
Gump et al. 2005 Prospective study; n=122 children assessed at 9 years of age	Cord PbB mean: 2.97	SBP	**β (SE), mmHg log µg/dL: 12.16 (4.96); p=0.016***
		DBP	β (SE), mmHg per log µg/dL: 8.45 (4.54); p=0.066
Gump et al. 2011 Cross-sectional study; n=140 children (ages 9–11 years)	Mean: 1.01 Quartiles: • Q1: 0.14–0.68 • Q2: 0.69–0.93 • Q3: 0.94–1.20 • Q4: 1.21–3.76	SBP	Under acute stress, p-trend over quartiles: 0.31
		DBP	Under acute stress, p-trend over quartiles: 0.29
		TPR	**Under acute stress, p-trend over quartiles: 0.03***

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Zhang et al. 2011 Prospective longitudinal study; n=457 mother-child pairs; children evaluated at ages 7–15 years	• Mean umbilical cord: 5.51 • Mean child concurrent: 2.96 • Median maternal postnatal tibia Pb (µg/g): 9.3	SBP	Maternal tibia Pb, boys, β, mmHg increased per maternal tibia Pb (13 µg/g): -0.34 (-1.98, 1.30)
			Maternal tibia Pb, girls, β mmHg increased per maternal tibia Pb (13 µg/g): 2.11 (0.69, 3.52); p=0.025*
		DBP	Maternal tibia Pb, boys, β, mmHg increased per maternal tibia Pb (13 µg/g): -0.83 (-2.05, 0.38)
			Maternal tibia Pb, girls, β, mmHg increased per maternal tibia Pb (13 µg/g): 1.60 (0.28, 2.91); p=0.007*
Blood pressure during pregnancy[c]			
Disha et al. 2019 Cross-sectional study; n=44 healthy pregnant women; n=23 pre-eclamptic women	**PbB:** Mean • Control: 2.38 • Pre-eclampsia: 3.42	SBP	**Pearson correlation (mmHg): 0.71; p<0.0001***
		DBP	**Pearson correlation (mmHg): 0.57; p=0.004***
Rothenberg et al. 2002 Longitudinal study; n=667 pregnant women	Mean: 1.9 Bone (calcaneus) Pb (µg/g) mean:10.7	SBP	Ln-PbB, β: -0.04 (-1.26, 1.18)
			Bone Pb, β: 0.70 (0.04, 1.36)*
		DBP	Ln-PbB, β: 0.20 (-0.78, 1.18)
			Bone Pb, β: 0.54 (0.01, 1.08)*
Wells et al. 2011 Cross-sectional study; n=285 pregnant women during labor	Umbilical cord PbB • mean: 0.66 • Quartiles: o Q1: <0.46 o Q2: 0.47–0.65 o Q3: 0.66–0.95 o Q4: 0.96–6.47	SBP	**Q4 versus Q1 increase in SBP in mmHg at admission: 6.87 (1.51, 12.21); p<0.05***
			Q4 versus Q4 maximum increase in SBP in mmHg: 7.72 (1.83, 13.60); p<0.05*
		DBP	**Q4 versus Q1 increase in DBP in mmHg at admission: 4.40 (0.21, 8.59); p<0.05***
			Q4 versus Q4 maximum increase in DBP in mmHg: Q4: 8.33 (1.14, 15.53); p<0.05*

Table 2-8. Summary of Epidemiological Studies Evaluating Effects on Blood Pressure at Mean Blood Lead Concentration (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[a,b]
Yazbeck et al. 2009 Cross-sectional study; n=971 pregnant women	Mean • Participants with PIH: 2.2 • Participants without PIH: 1.9	PIH	**OR for PIH for an increase of 1 log_{10} µg/dL in PbB; 3.29 (1.11, 9.74); p=0.03***

[a]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[b]If bone Pb is noted under results, study did not show associations between PbB and blood pressure parameters; however, results showed associations between bone Pb concentrations and increased blood pressure at concomitant PbB ≤10 µg/dL.
[c]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[d]Study population was from NHANES.
[e]Study population was from the Normative Aging Study.

B = black; CI = confidence interval; CL = confidence limit; DBP = diastolic blood pressure; F = female(s); Gmean = geometric mean; M = male(s); MA = Mexican American; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PIH = pregnancy-induced hypertension; PP = pulse pressure; RR = rate ratio; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; TPR = total peripheral resistance; W = white

in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3.

The magnitude of effect on blood pressure observed in individual large-scale, cross-sectional studies is consistent with results of meta-analyses (see discussion above on *Characterization of Effects*). For example, Martin et al. (2006) reported that systolic and diastolic blood pressure increased by 0.99 (95% CI 0.47, 1.51; $p<0.01$) mmHg and 0.51 (95% CI 0.24, 0.79; $p<0.01$) mmHg, respectively, per 1 µg/dL increase in PbB.

Several studies have examined the relationship between PbB and blood pressure with study populations stratified according to gender, race, and/or age. For example, within study populations, positive associations were observed between PbB and systolic and diastolic blood pressure in men but not in women (Bushnik et al. 2014; Chu et al. 1999; Hense et al. 1993). A cross-sectional study reported an increased risk of prehypertension (defined as a diastolic blood pressure of at least 80 mmHg but below 90 mmHg or a systolic blood pressure of at least 120 mmHg but below 140 mmHg) in women but not in men, although PbB was lower ($p<0.05$) in women (1.9 µg/dL) than men (2.4 µg/dL) (Lee et al. 2016a). However, other studies did not find differences between men and women (Bost et al. 1999; Scinicariello et al. 2011). Stratification by sex and age indicates additional differences between men and women. For example, Park et al. (2009b) reported a greater risk of hypertension in men >50 years of age (odds ratio [OR] 1.20; 95% CI 1.02, 1.41), but not in men <50 years of age (OR 0.98; 95% CI 0.80, 1.22), whereas in women, the opposite effect of age was observed, with a greater risk of hypertension in women <50 years of age (OR 1.23; 95% CI 1.04, 1.46) but not >50 years of age (OR 1.09; 95% CI 0.94, 1.26). Studies that stratify populations by race have found race differences in effect sizes on blood pressure. Large-scale cross-sectional studies based on data from NHANES have found larger effect sizes in non-Hispanic blacks and Mexican-Americans than in whites (Den Hond et al. 2002; Muntner et al. 2005; Scinicariello et al. 2011; Vupputuri et al. 2003). Cross-sectional studies based on data from NHANES have consistently shown elevations of systolic blood pressure in association with increasing PbB among black males and females, with less consistency in findings for other demographic groups or for diastolic blood pressure (Den Hond et al. 2002; Nash et al. 2003; Scinicariello et al. 2010, 2011; Vupputuri et al. 2003). Scinicariello et al. (2011) estimated increases in systolic blood pressure ranging from 1.07 to 2.4 per 1 ln increase in PbB (equivalent to approximately 0.7–1.66 per doubling of PbB). The largest effects sizes were observed in black males (2.3; SE 0.71 per ln PbB) and black females (2.4; SE 1.14). Den Hond et al. (2002) estimated the effect size for systolic blood pressure in black males and females to be 0.9 mmHg (95% CI 0.04, 1.8) and 1.2 mmHg (95% CI 0.4, 2.0) per doubling of PbB, respectively. Vupputuri et al.

(2003) estimated the effect size for systolic blood pressure in black males and females to be 0.82 mmHg (95% CI 0.19, 1.44) and 1.55 mmHg (95% CI 0.47, 2.64) per 1 standard deviation (SD) increase (3.3 µg/dL) of PbB, respectively. As discussed above (see *Confounding Factors and Effect Modifiers*), numerous co-variables and confounders affect studies of associations between PbB and blood pressure, complicating comparisons between studies.

Few studies have evaluated effects of chronic Pb exposure in children or young adults on blood pressure parameters at PbB at ≤10 µg/dL (Ahn et al. 2018; Gerr et al. 2002; Gump et al. 2005, 2011; Zhang et al. 2011). Studies are briefly summarized in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3. Population sizes in these studies are small (n=122–1,776) compared to studies in adults. Positive associations were observed between concurrent PbB and increased systolic and diastolic blood pressure in young adults (Gerr et al. 2002). Two prospective studies suggest that prenatal exposure to Pb is associated with increased blood pressure in childhood (Gump et al. 2005; Zhang et al. 2011). Umbilical cord PbB was positively associated with increased systolic, but not diastolic, blood pressure in children (Gump et al. 2005). Maternal postnatal bone Pb concentration was associated with increased systolic and diastolic blood pressure in girls, but not boys; however, no association was observed between umbilical cord PbB or patella Pb concentration and increased blood pressure (Zhang et al. 2011). No association between PbB and diastolic or systolic blood pressure or risk of prehypertension in a larger population of adolescents (n=1,776) with a mean PbB of 1.19 µg/dL (Ahn et al. 2018).

Effects of Pb on blood pressure and hypertension at PbB at ≤10 µg/dL have also been evaluated during pregnancy (Disha et al. 2019; Rothenberg et al. 2002; Wells et al. 2011; Yazbeck et al. 2009). Studies are briefly summarized in Table 2-8, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3. Increases in systolic and diastolic blood pressure during pregnancy and labor were associated with PbB ≤10 µg/dL umbilical cord PbB, or bone Pb concentrations with concomitant PbB ≤10 µg/dL (Rothenberg et al. 2002; Wells et al. 2011; Yazbeck et al. 2009). Pregnancy-induced hypertension has been positively associated with PbB ≤10 µg/dL (Yazbeck et al. 2009). A small cross-sectional study reported a positive association between PbB and increased systolic and diastolic blood pressure in women with pre-eclampsia (Disha et al. 2019).

Atherosclerosis. Few studies have evaluated associations between PbB ≤10 µg/dL and atherosclerosis (Ari et al. 2011; Muntner et al. 2005; Navas-Acien et al. 2004). Studies are briefly summarized in Table 2-9, with additional details provided in the *Supporting Document for Epidemiological Studies for*

Lead, Table 3. Ari et al. (2011) reported a positive correlation between PbB and intimal medial thickening of the greater carotid artery in non-diabetic hemodialysis patients at a concurrent PbB of 0.41 µg/dL. Peripheral artery disease was positively associated with PbB levels ≥2.47 µg/dL, with a positive trend across quartiles, in a study of a large NHANES 1999–2002 (age 18 years or older) population (Muntner et al. 2005), whereas analyses restricted to adult (≥40 years old) participants of NHANES 1999–2000 reported a positive trend for the risk of peripheral artery disease, although ORs for PbB quartiles (highest PbB quartile >2.90 µg/dL) were not associated with peripheral artery disease (Navas-Acien et al. 2004).

Cardiac function and heart disease. Several studies have investigated cardiac function and heart disease, including a series of studies conducted in men from the Normative Aging Study in the greater Boston, Massachusetts area that evaluated associations between PbB ≤10 µg/dL and alterations in cardiac conduction and ischemic heart disease (Cheng et al. 1998; Eum et al. 2011; Jain et al. 2007; Park et al. 2009a). Studies are briefly summarized in Table 2-10, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 2. Studies on the Normative Aging Study population show positive associations between bone Pb concentrations (at concomitant PbB ≤10 µg/dL) and changes to electrocardiograms (prolonged QT and QRS intervals) and atrioventricular conduction defect; however, no associations were observed between PbB and conduction abnormalities (Cheng et al. 1998; Eum et al. 2011; Park et al. 2009a). For ischemic heart disease, increased risks were associated with PbB and with tibia and patella Pb concentrations (Jain et al. 2007). A 1 SD increase in PbB was associated with a 1.27-fold increase in risk for ischemic heart disease (Jain et al. 2007). In addition to the evaluations of the Normative Aging Study population, a large cross-sectional study of 2,163 men and 3,185 women found an increased risk of cardiovascular disease (including coronary artery disease, myocardial infarction, and stroke) for women in the two highest exposure PbB quartiles (Q3: 3.77–5.460 µg/dL; Q4: ≥5.461 µg/dL), although risk was not increased for men in any PbB quartile (Q4: ≥6.25 µg/dL) (Chen et al. 2017). Other studies have evaluated left ventricular function and structure, heart rate variability, and QRS-T wave angle (Jing et al. 2019l Yang et al. 2017; Yu et al. 2019a). A small (n=179) prospective study in adults with a mean PbB of 4.18 µg/dL showed an inverse association between PbB and left ventricular systolic function, but not left ventricular diastolic function or left ventricular structure (Yang et al. 2017). Results of a small (n=328) cross-sectional study in newly hired male Pb workers did not observe an association between PbB (mean 4.54 µg/dL) and heart rate variability (Yu et al. 2019a). A large (n=7,179) study of NHANES III participants showed that PbB was associated

Table 2-9. Summary of Epidemiological Studies Evaluating Atherosclerosis at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Ari et al. 2011 Clinical study; n=50 adult male and female hemodialysis patients and 48 age- and sex-matched controls	Mean • Hemodialysis patients: 0.41 • Controls: 0.10	Greater carotid artery intima-media thickness	**β (SE), mm per µg/dL PbB: 0.101 (0.040); p=0.013***
Muntner et al. 2005[c] Cross-sectional study; n=9,961participants	Mean: 1.64 Quartiles: • Q1: <1.06 • Q2: 1.06–1.63 • Q3: 1.63–2.47 • Q4: ≥2.47	PAD	**OR for prevalence in Q4: 1.92 (1.02–3.61)*** **p-trend (across quartiles): <0.001***
Navas-Acien et al. 2004[c] Cross-sectional study; n=2,125 participants	Mean: 2.07 Quartiles: • Q1: <1.45 • Q2: 1.45–2.07 • Q3: 2.07–2.90 • Q4: >2.90	PAD	OR for prevalence in Q4: 2.88 (0.87, 9.47) **p-trend (across quartiles) for risk: 0.02***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs
[c]Study population was from NHANES.

CI = confidence interval; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PAD = peripheral artery disease; pb = lead; SE = standard error

Table 2-10. Summary of Epidemiological Studies Evaluating Heart Disease at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Chen et al. 2017 Cross-sectional study; n=5,348 adults (men: 2,163; women: 3,185) aged ≥18 years	Quartiles: • Men o Q1: ≤2.900 o Q2: 2.901–4.400 o Q3: 4.401–6.248 o Q4: ≥6.249 • Women o Q1: ≤2.50 o Q2: 2.501–3.770 o Q3:3.771–5.460 o Q4: ≥5.461	Cardiovascular disease	ORs: Men, Q4: 1.01 (0.58, 1.78); p-trend: 0.59 **Women, Q3: 1.65 (1.03, 2.66)*** **Women, Q4, 1.93 (1.22, 3.04); p-trend: <0.01***
Cheng et al. 1998[d] Longitudinal study; n=775 men (n=277 for men <65 years of age)	PbB mean: 5.8 Bone Pb, µg/g, mean (SD) • Tibia: 22.2 (13.4) • Patella: 30.8 (19.2)	QT interval	β, msec per 10-fold increase in PbB: -0.65 (-10.40, 9.10); p=0.90
			β, msec per 10-fold increase in tibia Pb: 5.03 (0.83, 9.22); p=0.02*
			β, msec per 10-fold increase in patella Pb: 3.00 (0.16, 5.84); p=0.04*
		QRS interval	β, msec per 1 unit increase in PbB: -3.49 (-10.72, 3.75); p=0.35
			β, msec per 1-fold increase in tibia Pb: 4.83 (1.83, 7.83); p<0.01*
			β, msec per 1-fold increase in patella Pb: 2.23 (0.10, 4.36); p=0.04*
		IVCD	**OR for a 10-fold increase in tibia Pb: 2.23 (1.28, 3.90); p<0.01***

Table 2-10. Summary of Epidemiological Studies Evaluating Heart Disease at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Eum et al. 2011[d] Prospective longitudinal study; n=600 men	PbB baseline mean: 5.8 PbB Tertiles: • T1: <4 • T2: 4–6 • T3: >6 Tibia Pb (µg/g) baseline mean: 21.6 Tertiles: • T1: <16 • T2: 16–23 • T3: >23	QT interval	PbB OR for T3: 1.31 (0.69, 2.48); p-trend: 0.41
			Tibia OR for T3: 2.53 (1.22, 5.25)*; p-trend: 0.003*
		Atrioventricular conduction defect	PbB OR for T3: 0.52 (0.19, 1.45); p-trend: 0.16
			Tibia OR for T3: 0.23 (0.06, 0.87); p-trend: 0.03
Jain et al. 2007[d] Longitudinal prospective study; n=837 men	PbB baseline mean • Non-cases 6.2 • Cases 7.0 Patella Pb (µg/g) baseline mean • Non-cases 30.6 • Cases 36.8	Ischemic heart disease	**PbB β per 1 SD increase in PbB: 1.27 (1.01, 1.59)***
			PbB HR per 1 log increased in PbB: 1.45 (1.01, 2.06); p=0.05*
			Patella Pb HR per 1 log increased in bone Pb: 2.64 (1.09, 6.37); p=0.05*
Park et al. 2009a[d] Longitudinal prospective study; n=613 men	• PbB median (IQR): 5 (4–7) • Patella Pb (µg/dL), median (IQR): 26 (18–37) • Tibia Pb (µg/dL), median (IQR): 19 (14–27)	QT interval	PbB β for msec increase per IQR: 1.3 (-0.76, 3.36)
			Patella β for msec increase per IQR: 2.64 (0.13, 5.15)*
			Tibia β for msec increase per IQR: 2.85 (0.29, 5.40)*
Yang et al. 2017 Prospective study; n=179 adults (50.3% women); follow-up period 11.9 years	PbB baseline Gmean: 4.19	Left ventricular systolic function	β, per doubling of PbB for ejection fraction (%): 0.150 (-1.019, 1.320); p=0.800
			β, per doubling of PbB for global longitudinal strain (%): -0.392 (-0.753, -0.030); p=0.034*
			β, per doubling of PbB for regional longitudinal strain (%): -0.618 (-1.167, -0.068); p=0.028*

Table 2-10. Summary of Epidemiological Studies Evaluating Heart Disease at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
			β, per doubling of PbB for regional longitudinal strain rate (per second): -0.056 (-0.097, -0.015); p=0.008*
			β, per doubling of PbB for regional radial strain (%): -1.825 (-3.740, 0.090); p=0.062
			β, per doubling of PbB for regional radial strain rate (per second): -0.113 (-0.226, -0.0002); p=0.050*
		Left ventricular structure	β, per doubling of PbB for left ventricular mass (g/m^2): -1.399 (-4.504, 1.707); p=0.375
			β, per doubling of PbB for end-diastolic diameter (cm): -0.064 (-0.134, 0.006); p=0.072
			β, per doubling of PbB for relative wall thickness: 0.0065 (-0.0031, 0.0162); p=0.185
Yu et al. 2019a Cross-sectional study; n=328 newly hired male Pb workers	Mean: 4.54	Heart rate variability	Regression (β) coefficients (95% CI) per 10-fold increase in PbB: • Supine position: 3.0 (-20.4, 33.0); p=0.82 • Standing position: -6.0 (-26.2, 19.7); p=0.61 • Orthostatic change: -8.8 (-31.8, 17.5); p=0.47

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[c]If bone Pb is noted under results, study did not show associations between PbB and blood pressure parameters; however, results showed associations between bone Pb concentrations and increased blood pressure at concomitant PbB ≤10 µg/dL.
[d]Study population was from the Normative Aging Study.

CI = confidence interval; Gmean = geometric mean; HR = hazard ratio; IQR = intraquartile range; IVCD = intraventricular conduction defect; OR = odds ratio; Pb = lead; SD = standard deviation

with an abnormal QRS-T wave angle in men (mean PbB: 4.10 µg/dL), but not in women (mean PbB: 2.93 µg/dL) (Jing et al. 2019).

Mortality due to cardiovascular disease. Mortality due to cardiovascular disease at PbB ≤10 µg/dL has been examined in large prospective and longitudinal studies, which provide mixed results. Studies are briefly summarized in Table 2-11, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 3. Three of these were conducted in large studies of men and women participating in NHANES (Aoki et al. 2016; Lanphear et al. 2018; Menke et al. 2006; Schober et al. 2006). Aoki et al. (2016), Lanphear et al. (2018), and Menke et al. (2006) observed positive associations of mortality due to cardiovascular disease, including ischemic heart disease, myocardial infarction, and stroke and at PbB ≤10 µg/dL, including positive trends for mortality with increasing PbB.

In contrast, Schober et al. (2006) did not find increased cardiovascular mortality risk at PbB <10 µg/dL, although risk was increased at PbB ≥10 µg/dL and a positive trend for mortality was observed with increasing PbB. For PbB, no increased risk or positive trend for morality due to cardiovascular was observed in men from the Normative Aging Study (Weisskopf et al. 2009). In women, the risk of mortality due to coronary heart disease was increased at PbB ≥8 µg/dL compared to PbB <8 µg/dL (Khalil et al. 2009).

Associations Between Bone Pb and Cardiovascular Effects. Several studies have evaluated associations between bone Pb concentration and blood pressure and cardiac outcomes. Results provide evidence that long-term exposure to Pb produces adverse effects on the cardiovascular system.

Increased blood pressure and hypertension. Numerous studies show associations between bone Pb concentration and increased blood pressure and increased risk of hypertension (see Table 2-12). The most studied population is older men participating in the Normative Aging Study. Results consistently show positive associations between tibia Pb and systolic blood pressure (Cheng et al. 2001), pulse pressure (Jhun et al. 2015; Perlstein et al. 2007; Zhang et al. 2010), and risk of hypertension (Cheng et al. 2001; Elmarsafawy et al. 2006; Hu et al. 1996a; Peters et al. 2007). The association between bone Pb and elevated pulse pressure suggests that Pb may alter cardiovascular function through loss of arterial elasticity (Jhun et al. 2015; Perlstein et al. 2007; Zhang et al. 2010). Associations between patella Pb and blood pressure outcomes have been somewhat less consistent, with some studies showing positive associations (Hu et al. 1997; Jhun et al. 2015; Perlstein et al. 2007; Peters et al. 2007; Zhang et al. 2010) and other studies showing no associations (Cheng et al. 2001; Elmarsafawy et al. 2006). Other study

Table 2-11. Summary of Epidemiological Studies Evaluating Mortality due to Cardiovascular Disease at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Aoki et al. 2016[c] Prospective study; n=18,602	Mean: 1.73	Mortality due to cardiovascular disease	**RR, per 10-fold increase in PbB: 1.44 (1.05, 1.98)***
Khalil et al. 2009 Prospective study; n=533 women	Mean: 5.3	Mortality due to coronary heart disease	**PbB ≥8.0 compared to women with PbB <8.0. HR: 3.08 (1.23, 7.70); p=0.016***
Menke et al. 2006[c] Longitudinal study; n=13,946	Baseline mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.63	Mortality due to cardiovascular disease	**HR for T3 versus T1: 1.55 (1.08, 2.24)*; p-trend: 0.003***
		Mortality due to myocardial infarction	**HR for T3 versus T1: 1.89 (1.04, 3.43)*; p-trend: 0.007***
		Mortality due to stroke	**HR for T3 versus T1: 2.51 (1.20, 5.26)*; p-trend: 0.017***
			RR for T3 versus T1: 1.55 (1.16, 2.07)*; p-trend: <0.01*
Lanphear et al. 2018[c] Longitudinal study; n=14,289	Mean: 2.71	Mortality due to cardiovascular disease	**HR for PbB increase from 1.0 to 6.7 µg/dL: 1.70 (1.30, 2.22)***
		Mortality due to ischemic heart disease	**HR for PbB increase from 1.0 to 6.7 µg/dL: 2.08 (1.52, 2.85)***
Weisskopf et al. 2009[d] Longitudinal study; n=868 men	Mean: 5.6 Tertiles • T1: <4 • T2: 4–6 • T3: >6	Mortality due to cardiovascular disease	HR for T3 versus T1: 1.10 (0.67, 1.80); p-trend: 0.72

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 3 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[c]Study population was from NHANES.
[d]Study population was from the Normative Aging Study.

CI = confidence interval; HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; Pb = lead; RR = risk ratio

populations examined include adults (Martin et al. 2006), young adults (Gerr et al. 2002), current and former Pb workers (Glenn et al. 2003; Lee et al. 2001), women (Korrick et al. 1999), pregnant women (Rothenberg et al. 2002), and mother-child pairs (Zhang et al. 2011). Although study results are not consistent, positive associations between bone Pb and blood pressure and risk of hypertension have been reported. Navas-Acien et al. (2008) conducted a meta-analysis of 10 studies (see Table 2-12 for studies included in the analysis) to evaluate associations between tibia and patella Pb and blood pressure outcomes. Positive associations were observed between tibia Pb and systolic blood pressure and hypertension risk, but no associations were observed between tibia Pb and diastolic blood pressure or between patella Pb and systolic blood pressure, diastolic blood pressure, or hypertension risk.

Table 2-12. Associations Between Bone Pb and Blood Pressure Outcomes

		Blood pressure outcome			
Reference	Population	Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Cheng et al. 2001[a]	833 men[b]	↑ T 0 P	–	–	↑ T 0 P
Elmarsafawy et al. 2006	471 men[b]	–	–	–	↑ T (at low dietary calcium) 0 P (at high dietary calcium)
Gerr et al. 2002[a]	508 young adults[c]	↑ T	↑ T	–	–
Glenn et al. 2003[a]	496 male Pb workers[d]	↑ T ↑ P	0 T 0 P	–	–
Glenn et al. 2006[a]	575 adult Pb workers[e]	↓ T	0 T	–	–
Hu et al. 1996a[a]	590	–	–	–	↑ T ↑ P
Jhun et al. 2015	727 men[b]	–	–	↑ T ↑ P	–
Korrick et al. 1999[a]	689 women (214 cases; 475 controls)[f]	–	–	–	0 T ↑ P
Lee et al. 2001[a]	924 adult Pb workers (789 cases; 135 controls[e]	↑ T	0 T	–	↑ T
Martin et al. 2006[a]	964 adults	0 T	0 T	–	↑ T
Perlstein et al. 2007	593 men[b]	–	–	↑ T ↑ P	–

Table 2-12. Associations Between Bone Pb and Blood Pressure Outcomes

		Blood pressure outcome			
Reference	Population	Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Peters et al. 2007	512 men[b]	–	–	–	↑ T (with high stress) ↑ P (with high stress)
Rothenberg et al. 2002[a]	1,006 pregnant women	–	–	–	↑ C (3rd trimester) 0 T (3rd trimester)
Schwartz et al. 2000c[a]	543 male Pb workers[d]	0 T	0 T	–	0 T
Weaver et al. 2008	652 Pb workers[e]	0 P	0 P	–	0 P
Zhang et al. 2010	612 men[b]	–	–	↑ T ↑ P	–
Zhang et al. 2011	457 mother-child pairs[g]	↑ T (girls) 0 T (boys)	↑ T (girls) 0 T (boys)	–	–

[a]Included in the Navas-Acien et al. (2008) meta-analysis.
[b]Participants in the Normative Aging Study.
[c]19–29 years of age.
[d]Current and former Pb workers in the United States.
[e]Current and former Pb workers in South Korea.
[f]Nurses Health Study.
[g]Based on maternal bone Pb measurement.

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; C = calcaneus bone; P = patella; Pb = lead; T = tibia

Cardiac function. Several studies evaluating associations between bone Pb and cardiac function, disease, and mortality were conducted in participants of the Normative Aging Study (see Table 2-13). For tibia Pb, positive associations have been observed for QT and QRS intervals (Cheng et al. 1998; Eum et al. 2011; Park et al. 2009a), atrioventricular and intraventricular block (Cheng et al. 1998), and ischemic heart disease (Jain et al. 2007). For patella Pb, positive associations were observed for QT and QRS intervals (Cheng et al. 1998; Park et al. 2009a). Both tibia Pb and patella Pb were positively associated with ischemic heart disease (Jain et al. 2007), and patella and tibia Pb were associated with an increased risk of coronary heart disease (Ding et al. 2016, 2019). However, no association was observed between tibia or patella Pb and all cardiovascular mortality or mortality due to ischemic heart disease (Weisskopf et al. 2009).

Table 2-13. Associations Between Bone Pb and Cardiac Function, Disease, and Mortality

		Outcome		
Reference	Population	Function	Disease	Mortality
Cheng et al. 1998	775 men[a]	↑ T (QT and QRS intervals; AV block; IV block) ↑ P (QT and QRS intervals) 0 P (AV block; IV block)	–	–
Ding et al. 2016	589 men[a]	–	↑ P (CHD)	–
Ding et al. 2019	594 men[a]	–	↑ T (CHD) ↑ P (CHD)	–
Eum et al. 2011	600 men[a]	↑ T (QT and QRS intervals) 0 P (QT and QRS intervals)	–	–
Jain et al. 2007	837 men[a]	–	↑ T (IHD) ↑ P (IHD)	–
Park et al. 2006	413 men[a]	0 T (HRV with MetS) 0 T (HRV without MetS) ↑ P (HRV with MetS) 0 P (HRV without MetS)	–	–
Park et al. 2009a	613 men[a]	↑ T (QT interval) ↑ P (QT interval)	–	–
Weisskopf et al. 2009	868 men[a]	–	–	0 T (all cardiovascular or IHD deaths) 0 P (all cardiovascular or IHD deaths)

[a]Participants in the Normative Aging Study.

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; AV = atrioventricular; CHD = coronary heart disease; HRV = heart rate variability; IHD = ischemic heart disease (defined as myocardial infarction or angina pectoris); IV = intraventricular; MetS = metabolic syndrome (three or more of the following: obesity, diabetes, hypertension, and dyslipidemia); P = patella; Pb = lead; T = tibia

Mechanisms of Action. Several studies and recent reviews include discussions of mechanisms that may be involved in Pb-induced effects on cardiovascular function (Faramawai et al. 2015; Ghiasvand et al. 2013; Mitra et al. 2017; Nawrot et al. 2002; Shiue et al. 2014; Weisskopf et al. 2009; Xu et al. 2015; Zota et al. 2013). Control of cardiovascular function is multi-factorial; therefore, numerous mechanisms are likely involved in Pb-induced cardiovascular effects. Specific mechanisms for cardiovascular effects include: impairment of renal function; effects on vascular smooth muscle, including constrictive effects and disruption of NO-induced vasodilatory actions; increase of sympathetic nervous system activity;

altered chemoreceptor activity; and altered regulation of the renin-angiotensin-aldosterone axis and the renal kallikrein system. In addition, general mechanisms of toxicity of Pb, including oxidative stress, inflammation, and altered transport of ions across cellular membranes, also are likely to be involved (see Section 2.21).

2.7 GASTROINTESTINAL

Overview. Few epidemiological studies have evaluated gastrointestinal effects associated with chronic exposure to Pb. Almost all available studies were conducted in small numbers of workers with PbB >10 µg/dL, although one study included a group of workers with PbB ≤10 µg/dL. Study results consistently show gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea, and/or constipation) associated with PbB ranging from 8.04 µg/dL to approximately 100 µg/dL. As reviewed in Section 2.2 (Acute Lead Toxicity), acute exposure to Pb is associated with gastrointestinal symptoms and intestinal paralysis.

The following gastrointestinal effects have been associated with PbB:

- ≤10 µg/dL:
  - Gastrointestinal symptoms (abdominal colic/discomfort).
- >10 µg/dL:
  - Gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea and/or constipation); corroborated in a few studies.

Measures of Exposure. Studies examining the association between gastrointestinal effects of Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Most epidemiological studies on gastrointestinal effects of Pb are survey or cross-sectional studies of small populations of workers. In general, studies did not consider factors, such as age, diet, nutritional factors, alcohol use, and potential exposure to other occupational chemicals or limitations such as study design (cross-sectional and survey). Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. In contrast to the large number of epidemiological studies evaluating effects of Pb on other organ systems (e.g., neurological and cardiovascular outcomes), few epidemiological studies have investigated the gastrointestinal effects of chronic exposure to Pb (see Table 2-14). With the exception of a survey study conducted in 497 workers (Rosenman et al. 2003), studies were conducted in small worker populations (n=69–155). Increased gastrointestinal symptoms (abdominal colic/pain, nausea, vomiting, diarrhea, and/or constipation) were observed in all studies. The lowest PbB associated with increased gastrointestinal symptoms showed an increased percentage of workers reporting abdominal colic and discomfort at a mean PbB of 8.04 µg/dL, compared to controls (PbB 5.76 µg/dL) (Kuruvilla et al. 2006). For example, 18.9% of painters reported abdominal colic compared to 0 in the control group.

Effect at Blood Pb Levels ≤10 µg/dL. See discussion above on Kuruvilla et al. (2006).

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of gastrointestinal toxicity. EPA (2014c) specifically noted that oxidative stress through ROS could result in gastrointestinal toxicity; as a result, damage to the intestinal mucosa epithelium is possible.

2.8 HEMATOLOGICAL

Overview. Pb-induced toxicity to the hematological system has long been established. Pb inhibits heme synthesis, leading to the development of microcytic, hypochromic anemia. Numerous epidemiological studies have evaluated hematological effects associated with exposure to Pb in adults and children. Most studies were cross-sectional in design and evaluated effects on heme synthesis and subsequent changes in erythrocyte hemoglobin parameters and anemia. Studies in adults (general populations and workers) and children consistently show inhibition of heme synthesis enzymes, particularly δ-ALAD, and subsequent decreases in blood hemoglobin, red blood cell parameters (e.g., mean cell hemoglobin, mean cell volume), and development of anemia. Other hematological effects observed in epidemiological studies include alterations in erythrocyte function (decreased activities of pyrimidine 5'-nucleotidase and membrane Ca^{2+}/Mg^{2+}ATPase), changes in serum EPO concentration, and decreased platelet count.

Table 2-14. Summary of Studies Evaluating Gastrointestinal Symptoms Associated with Chronic Exposure to Lead (Pb)

Reference and study population	PbB (µg/dL)	Outcomes evaluated[a]	Effects[b]
Awad el Karin et al. 1986 Cross-sectional study; n=92 exposed; 40 controls	Range of means (by job category): 48.1–80.7 Controls mean: 21.2	Abdominal colic	• Exposed (% reporting symptom) 41.3; **exposed versus control p=0.01*** • Control (% reporting symptom): 7.5
		Constipation	• Exposed (% reporting symptom) 41.4; **exposed versus control p=0.01*** • Control (% reporting symptom): 10.0
Baker et al. 1979 Survey study; n=160 Pb workers	Range of means (by job category): 41.8–87.2	Gastrointestinal symptoms	• **Mean PbB at which symptoms are present: 101.24 µg/dL (p<0.01)*** • PbB, symptom absent: 65.98 µg/dL
		Abdominal pain	• **PbB, symptoms present: 100.77 µg/dL (p<0.01)*** • PbB, symptom absent: 68.25 µg/dL
Kuruvilla et al. 2006 Cross-sectional study; n=155; exposed workers: n=105 (52 battery workers; 53 painters); controls: n=50	Mean • Battery workers:42.40 • Painters: 8.04 • Controls: 5.76	Abdominal colic	• **Battery workers (% reporting symptom): 17.3; p<0.01*** • **Painters (% reporting symptom):18.9; p<0.01*** • Controls (% reporting symptom): 0
		Abdominal discomfort	• **Battery workers (% reporting symptom): 19.2; p<0.01*** • **Painters (% reporting symptom): 26.4; p<0.001*** • Controls (% reporting symptom): 2
		Vomiting	• Battery workers (% reporting symptom): 1.9 • Painters (% reporting symptom): 1.9 • Controls (% reporting symptom): 0
		Constipation	• Battery workers (% reporting symptom): 0 • Painters (% reporting symptom): 1.9 • Controls (% reporting symptom): 2

Table 2-14. Summary of Studies Evaluating Gastrointestinal Symptoms Associated with Chronic Exposure to Lead (Pb)

Reference and study population	PbB (µg/dL)	Outcomes evaluated[a]	Effects[b]
Matte et al. 1989 Survey study; n=69 (46 manufacturing and 23 battery repair workers)	• Mean: not reported • Workers stratified by PbB <60 and ≥60	Nausea	• PbB <60 (% reporting symptom): 7 • PbB ≥60 (% reporting symptom): 14 • PR (95% CI): 2.0 (0.5, 7.9)
		Abdominal pain	• PbB <60 (% reporting symptom): 12 • PbB ≥60 (% reporting symptom): 18 • PR (95% CI): 1.5 (0.5, 4.6)
Rosenman et al. 2003 Survey study; n=497 workers	• Range 10–70 • Stratification by PbB: o 10–24 (n=139) o 25–29 (n=98) o 30–39 (n=171) o 40–49 (n=58) o 50–59 (n=22) o ≥60 (n=9)	Abdominal pain	AdjOR (95% CI) for PbB: • 10–24: 1 (reference) • 25–29: 0.62 (0.28, 1,37) • 30–39: 0.98 (0.53, 1.82) • **40–49: 2.15 (1.03, 4.49)*** • 50–59: 1.54 (0.52, 5.23) • ≥60: NR

[a]Gastrointestinal symptoms include abdominal colic, nausea, vomiting, diarrhea, and/or constipation.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

AdjOR = adjusted odds ratio (adjusted by age, ethnicity group, company screening, and smoking status); CI = confidence interval; NR = not reported; PbB = blood lead concentration; PR: prevalence ratio

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The following hematological effects have been associated with PbB:

- ≤10 μg/dL:
  - Inhibition of δ-ALAD; demonstrated in a few studies.
  - Decreased blood hemoglobin; evaluated in several studies with mixed results.
  - Decreased platelet count.
  - Decreased plasma EPO in adult males.
- >10 μg/dL:
  - Dose-dependent decreased heme synthesis due to inhibition of δ-ALAD and other heme metabolism enzymes; demonstrated in numerous studies.
  - Anemia and decreased blood hemoglobin; demonstrated in numerous studies.
  - Decreased activity of other erythrocyte enzymes (pyrimidine 5'-nucleotidase or red blood cell membrane Ca^{2+}/Mg^{2+}ATPase); demonstrated in a few studies.
  - Altered plasma EPO concentration:
    - Decreased in adult males; evaluated in a few studies with mixed results.
    - Decreased in pregnant females; demonstrated in one study, but findings not corroborated.
    - Mixed results (both increases and decreases observed) in children; evaluated in a few studies.

Measures of Exposure. Studies evaluating the association between hematological effects and Pb exposure most commonly evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. In general, available epidemiological studies on hematological effects do not control for factors, including concomitant exposure to other chemicals, that may affect the hematological system. In addition, dietary insufficiency of iron is the primary cause of microcytic, hypochromic anemia; however, few studies evaluated this as an effect modifier. Age and renal function are also confounding factors, as impairment of renal function can affect renal EPO synthesis and PbB. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. General trends for studies showing a relationship between PbB and hematological effects are shown in Table 2-15. Most epidemiological studies of hematological effects have examined effects on heme metabolism and its consequences, with fewer studies examining other

hematological endpoints (altered serum levels of EPO, altered erythrocyte function, and decreased platelet count). As noted above, Pb-induced toxicity to the hematological system, specifically inhibition of heme synthesis enzymes and resulting anemia and decreased erythrocyte hemoglobin, have long been established. Numerous epidemiological studies in adults and children provide consistent evidence that δ-ALAD activity is inversely correlated with PbB over a PbB range of <10–>50 µg/dL (see Table 2-15) with δ-ALAD inhibition and subsequent effects of inhibition showing concentration-dependence for PbB (Murata et al. 2009; Schwartz et al. 1990). A few studies have reported other hematological effects, including decreased platelet count in Pb workers at PbB of 5.4 µg/dL (Conterato et al. 2013) and >41 µg/dL (Barman et al. 2014). Inhibition of non-heme metabolism enzymes in erythrocytes was also associated with PbB. In Pb workers, membrane Ca^{2+}/Mg^{2+}ATPase was inhibited at a PbB range of approximately 29–42 µg/dL (Abam et al. 2008), and pyrimidine 5'-nucleotidase was inhibited at a PbB of >50 µg/dL (Buc and Kaplan 1978). Pyrimidine 5'-nucleotidase also was inhibited in children (aged 1–5 years) with a PbB range of 30–72 µg/dL (Angle et al. 1982).

Table 2-15. Overview of Hematological Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Altered heme synthesis[a]	Ahamed et al. 2006; Ergurhan-Ilhan et al. 2008; Wang et al. 2010
	Anemia and/or decreased measures of RBC hemoglobin[b]	Ahamed et al. 2006; Conterato et al. 2013; Olivero-Verbel et al. 2007; Queirolo et al. 2010; Riddell et al. 2007; Ukaejiofo et al. 2009
	Increased hemoglobin	Chen et al. 2019
	Decreased platelet count	Conterato et al. 2013
	Decreased EPO	Sakata et al. 2007
>10–30	Altered heme synthesis[a]	Ahamed et al. 2005, 2006; Counter et al. 2008, 2009; Grandjean and Lintrup 1978; La-Llave-Leon et al. 2017; Lauwerys et al. 1978; Mohammad et al. 2008; Murata et al. 2009; Piomelli et al. 1982 Rabinowitz et al. 1985; Roels et al. 1975, 1976; Roels and Lauwerys 1987; Schumacher et al. 1997; Stuik 1974
	Anemia and/or decreased measures of RBC hemoglobin[b]	Adebonojo 1974; Ahamed et al. 2007; Karita et al. 2005; Li et al. 2018; Schwartz et al. 1990; Shah et al. 2010
	Altered RBC function[c]	Abam et al. 2008; Huel et al. 2008
	Decreased platelet count	Barman et al. 2014
	Decreased EPO	Graziano et al. 1991, Liebelt et al. 1999

Table 2-15. Overview of Hematological Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
	Increased EPO	Factor-Litvak et al. 1999;
>30–50	Altered heme synthesis[a]	Ademuyiwa et al. 2005; Alessio et al. 1976; Conterato et al. 2013; Fukumoto et al. 1983; Griffin et al. 1975; Murata et al. 2009; Roels et al. 1976; Secchi et al. 1974; Solliway et al. 1996
	Anemia and/or decreased measures of RBC hemoglobin[b]	Chwalba et al. 2018; Conterato et al. 2013; Dobrakowski et al. 2016; Schwartz et al. 1990; Solliway et al. 1996
	Altered RBC function	Abam et al. 2008; Angle et al. 1982; Buc and Kaplan 1978
	Increased reticulocytes	Kalahasthi and Barman 2016
	Decreased EPO	Romeo et al. 1996
	Increased EPO	Factor-Litvak et al. 1998; Graziano et al. 2004;
>50	Altered heme synthesis[a]	Cools et al. 1976; Gurer-Orhan et al. 2004; Jin et al. 2006; Meredith et al. 1978; Murata et al. 2009; Pagliuca et al. 1990; Schwartz et al. 1990
	Anemia and/or decreased measures of RBC hemoglobin[b]	Baker et al. 1979; Lilis et al. 1978; Malekirad et al. 2013; Grandjean1979; Patil et al. 2006; Roels et al. 1979
	Decreased EPO	Romeo et al. 1996
	Altered RBC function[c]	Buc and Kaplan 1978

[a]Inhibition of heme synthesis measured by decreased δ-ALAD activity, elevated RBC levels or urinary levels of heme precursors (e.g., protoporphyrin, erythrocyte protoporphyrin, free erythrocyte protoporphyrin), and/or increased RBC zinc protoporphyrin/heme ratio.
[b]Decreased blood hemoglobin, hematocrit, erythrocyte count, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and/or mean cell volume.
[c]Altered erythrocyte function includes inhibition of pyrimidine 5'-nucleotidase or decreased RBC membrane Ca^{2+}/Mg^{2+}ATPase.

ALAD = aminolevulinic acid dehydratase; EPO = serum erythropoietin; RBC = red blood cell

Several studies have evaluated the relationship between PbB and serum EPO levels in adults (Graziano et al. 1991; Osterode et al. 1999; Romeo 1996; Sakata et al. 2007) and children (Factor-Litvak 1998, 1999; Graziano et al. 2004; Liebelt et al. 1999). Erythropoietin is a glycoprotein hormone produced in renal proximal tubules that regulates steady-state and accelerated erythrocyte production. As a compensatory response to conditions producing low blood oxygen (e.g., anemia), proximal tubular cells release EPO, resulting in stimulated erythrocyte production. However, if renal function is compromised due to disease or toxicity (e.g., Pb-induced renal damage), the compensatory increases in serum EPO may be diminished or absent. Results of three cross-sectional studies in adult male workers are inconsistent, showing

decreased serum EPO levels at PbB 6.4–65.1 µg/dL (Romeo et al. 1996; Sakata et al. 2007), but no effect on EPO at a PbB of 45.5 µg/dL (Osterode et al. 1999). Study populations in these cross-sectional studies were small (n for exposed groups=10–27). In a subgroup of 48 pregnant women (selected from a larger cohort of 1,502 pregnant women), serum EPO was decreased; the range of PbB means based on hemoglobin stratifications was 23.1–36.2 µg/dL (Graziano et al. 1991). Studies in children have yielded mixed results on associations between PbB and serum EPO. Results of a series of prospective studies of children (n=280) in former Yugoslavia indicate that serum EPO levels in Pb-exposed children exhibit age-dependence (Factor-Litvak et al. 1998, 1999; Graziano et al. 2004). Serum EPO was increased in children 4.5 (mean PbB: 39.3 µg/dL) and 6.5 years of age (mean PbB: 36.2 µg/dL), but not in children 9.5 (mean PbB: 28.1 µg/dL) or 12 years of age (mean PbB: 30.6 µg/dL) (Factor-Litvak et al. 1998, 1999; Graziano et al. 2004). The study authors suggested that the capacity for compensatory increases in EPO in response to Pb-induced anemia declines over time, possibly due to Pb-induced damage to the renal proximal tubule. In contrast to increases in EPO levels observed in the Yugoslavian cohort, Liebelt et al. (1999) showed decreased EPO levels in a group of children ages 1–6 years (n=95) who had a mean PbB of 18 µg/dL.

Effect at Blood Pb Levels ≤10 µg/dL. Epidemiological studies evaluating hematological effects of PbB ≤10 µg/dL are summarized in Table 2-16, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 4. Studies were conducted in small populations (n for exposed groups=25–391), except for two larger (n=855–2,861) cross-sectional studies in children (Liu et al. 2015a; Riddell et al. 2007). In general, studies show inverse associations between PbB ≤10 µg/dL and δ-ALAD activity and blood hemoglobin in adults and children, although results are mixed. Negative correlations between PbB and δ-ALAD activity (measured by plasma δ-ALAD activity or zinc protoporphyrin:heme ratio) have been observed in children (Wang et al. 2010), adolescent males (Ahamed et al. 2006), and adults (Wang et al. 2010) at mean PbB of 5.95–9.96 µg/dL; however, no effect on δ-ALAD activity was observed in children with a mean PbB of 7.11 µg/dL (Ahamed et al. 2005). Differences in δ-ALAD activity were observed for male automotive repair workers (mean PbB: 7.9 µg/dL) and male controls (mean PbB: 2.6 µg/dL). Additionally, two studies in adults showed that blood hemoglobin concentration was lower in Pb workers (mean PbB: 5.4–7.0 µg/dL) compared to controls (mean PbB: 1.5–3.0 µg/dL) (Conterato et al. 2013; Ukaejiofo et al. 2009). In contrast, blood hemoglobin and erythrocyte count were increased in adults living near an electronic waste site (median PbB 8.7 µg/dL), compared to controls (median PbB 8.7 µg/dL) (Chen et al. 2019). In children with mean

Table 2-16. Summary of Epidemiological Studies Evaluating Hematological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Heme metabolism			
Ahamed et al. 2005 Cross-sectional study; n=62 children (ages 4–12 years)	Mean (SD) • Group 1: 3.93 (0.61) • Group 2: 7.11 (1.25)	δ-ALAD activity	No difference between groups: • Group 1: 4.82 (1.25) • Group 2: 4.56 (1.20)
Ahamed et al. 2006 Cross-sectional study; n=39 adolescent males (ages 15–18 years)	Mean (SD): 9.96 (3.63) Range: 4.62–18.64	δ-ALAD activity	**A negative correlation between PbB and blood δ-ALAD activity: r= -0.592; p<0.001***
Ergurhan-Ilhan et al. 2008 Cross-sectional study; n=25 male automotive repair workers (mean age 16.8 years): 24 male controls (mean age 16.3 years)	Mean (SD) • Controls: 2.6 (2.0) • Workers: 7.9 (5.2)	ALAD index	• Controls: 0.40 (0.34) • **Workers: 0.73 (0.47); p=0.048***
		ZPP:heme ratio	• Controls: 26.4 (7) • **Workers: 37.2 (15.9); p=0.045***
Wang et al. 2010 Cross-sectional study; n=307 children (ages 4–13 years) and 391 adults (ages 16–77 years) from China	Median • Children: 6.83 • Adults: 5.95	δ-ALAD activity	Pearson correlation coefficients: • **Children: -0.256; p<0.05*** • **Adults: -0.213; p<0.05***
		ZPP	Pearson correlation coefficients: • **Children: 0.135; p<0.05*** • **Adults: 0.083; p<0.05***
Blood hemoglobin/erythrocyte count			
Chen et al. 2019 Cross-sectional study; n=158 exposed adults living near an electronic waste area (mean age: 44 years); n=109 controls (mean age: 47 years)	Median (P_{25}, P_{75}) • Control: 5.1 (3.9, 8.4) • Exposed: 8.7 (6.2, 12.2)	Hb	Median (P_{25}, P_{75}), g/dL • Control: 123.0 (107.0, 143.0) • **Exposed: 137.0 (119.5, 150.0), p=0.001***
		Erythrocyte count	RBC count ($x10^3$), median (P_{25}, P_{75}): • Control: 4.2 (3.5, 4.6) • **Exposed: 4.5 (4.1, 4.8), p=0.001***

Table 2-16. Summary of Epidemiological Studies Evaluating Hematological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Conterato et al. 2013 Cross-sectional study; n=50 painters; 36 controls	Mean (SE) • Control: 1.5 (0.1) • Painters: 5.4 (0.4)	Hb	Mean (SE), µg/dL • Control: 15.4 (0.2) • **Painters: 15.0 (0.1); p<0.05***
Liu et al. 2015a Cross-sectional study; n=855 children (age range: 3–7 years)	PbB quartiles: • Q1: 2.20–5.16 • Q2: 5.16–7.33 • Q3: 7.33–10.62 • Q4: 10.62–37.78 Erythrocyte Pb quartiles: • Q1: 5.98–13.52 • Q2: 13.52–19.35 • Q3: 19.35–28.42 • Q4: 28.42–101.01	Hb	Change in Hb compared to Q1: • PbB Q3: 1.45 (-0.28, 3.18) • Erythrocyte Pb o **Q3: -3.01 (-4.71,1.31); p<0.05*[,c]** o **Q4: -3.97 (-5.68, -2.27); p<0.05***
Olivero-Verbel et al. 2007 Cross-sectional study, n=189 children (age range 5–9 years)	Mean (SE): 5.49 (0.23)	Hb	Spearman correlation coefficient: 0.069; p=0.348
Queirolo et al. 2010 Cross-sectional study; n=222 children (age: 5–45 months)	Mean (SD): 9.0 (6.0)	Hb	**Blood Hb <10.5 g/L was a predictor of PbB; β (95% CI): 2.40 (0.77, 4.03); p<0.01***
Riddell et al. 2007 Cross-sectional study; n=2,861 children (age 6 months–5 years)	Mean: 6.9	Hb	**A 1 g/dL increase in Hb was associated with a 3% decrease in PbB (p=0.043)***
Ukaejiofo et al. 2009 Cross-sectional study; n=81 Pb workers; 30 controls	Mean (SD) • Controls: 3.00 (0.19) • Workers: 7.00 (0.07)	Hb	Mean (SE), g/dL • Controls: 12.96 (0.089) • **Workers: 12.05 (1.62); p<0.001***

Table 2-16. Summary of Epidemiological Studies Evaluating Hematological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Zentner et al. 2006 Cross-sectional study; n=55 newborns	Umbilical mean (SD): 3.9 (3.6)	Hb	Pearson correlation coefficient: -0.04; p=0.721
Other hematological effects			
Conterato et al. 2013 Cross-sectional study; n=50 painters; 36 controls	Mean (SE) • Control: 1.5 (0.1) • Painters: 5.4 (0.4)	Platelet count	Mean (SE), % • Control: 244.3 (8.3) • **Painters: 203.7 (6.5); p<0.05***
Sakata et al. 2007 Cross-sectional studies: n=27 exposed workers; 9 controls	Mean (SD); range • Controls: 2.4 (1.1) • Workers: 6.4 (2.2)	EPO	Mean (SD), mU/mL: • Controls:18.8 (4.6) • **Workers: 12.7 (3.5); p<0.01***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 4 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.
[c]The discrepancy between the 95% confidence limits and the p-value appears to be caused by an error in the reporting of the upper confidence limit (i.e., -1.31, rather than 1.31).

ALAD index = log(active δ-ALAD/non-activated δ-ALAD); δ-ALAD = δ-aminolevulinic acid dehydratase; CI = confidence interval; EPO = serum erythropoietin; Hb = hemoglobin; Pb = lead; SD = standard deviation; SE = standard error; ZPP = zinc-protoporphyrin

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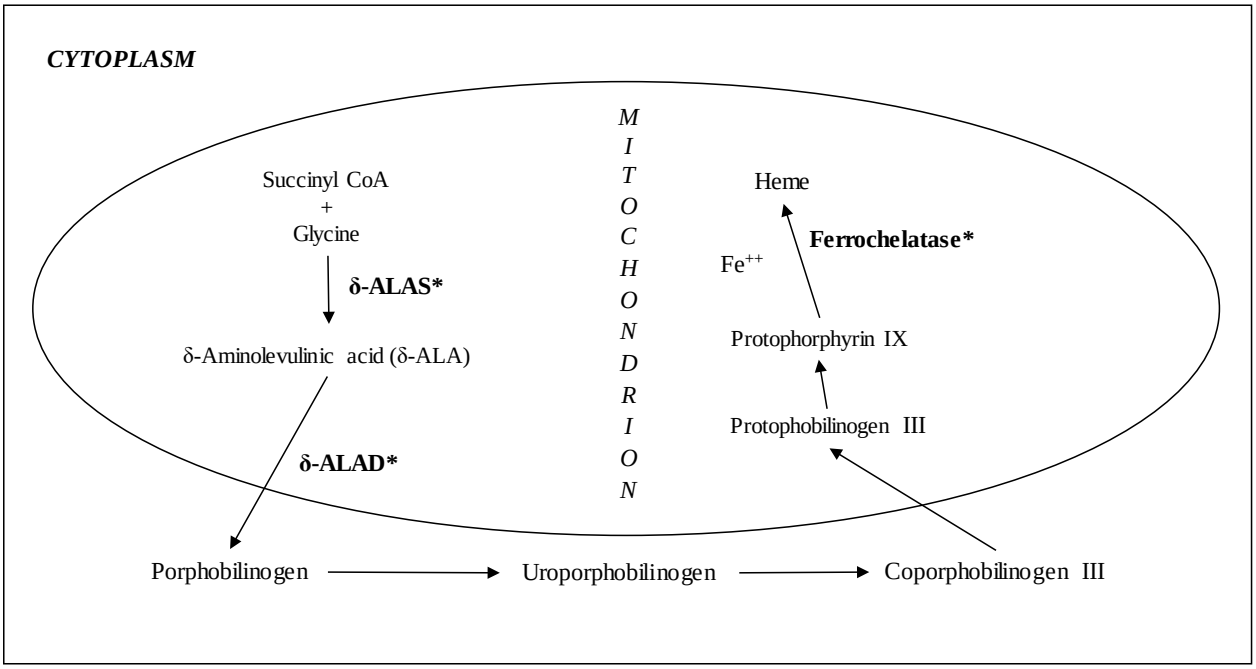
PbB of 6.9–9.0 µg/dL, there was an inverse association between blood hemoglobin concentrations and PbB (Queirolo et al. 2010; Riddell et al. 2007) and erythrocyte Pb concentration (Liu et al. 2015a). At lower PbB in newborns (PbB 3.9 µg/dL) and children (PbB 5.5 µg/dL), no correlation was found; however, these study populations were small (n=50–189) (Olivero-Verbel et al. 2007; Zentner et al. 2006). Thus, data are not adequate to establish an exposure-response relationship for decreased hemoglobin at PbB ≤10 µg/dL. Studies in small groups of workers (n=27–50) showed lower platelet count (PbB 5.4 µg/dL) and serum EPO concentrations (PbB 6.4 µg/dL) compared to controls (Conterato et al. 2013; Sakata et al. 2007). Although these findings have not been evaluated in other studies with PbB ≤10 µg/dL, similar effects have been observed at PbB >10 µg/dL.

Mechanisms of Action. Pb inhibits heme synthesis by inhibiting δ-ALAD and ferrochelatase (see Figure 2-4). As a consequence, the activity of the rate-limiting enzyme of the pathway, δ-aminolevulinic synthetase (δ-ALAS), which is feedback inhibited by heme, is subsequently increased. The end results of these changes in enzyme activities are increased urinary porphyrins, coproporphyrin, and δ-amino-levulinic acid (δ-ALA), increased blood and plasma δ-ALA, increased erythrocyte protoporphyrin (EP), and decreased hemoglobin. The impairment of heme synthesis by Pb may have a far-ranging impact not limited to the hematopoietic system. EPA (1986) provided an overview of the known and potential consequences of the reduction of heme synthesis as shown in Figure 2-5. Solid arrows indicate well-documented effects, whereas dashed arrows indicate effects considered to be plausible further consequences of the impairment of heme synthesis.

In addition to decreased hemoglobin synthesis, general mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of adverse effects to the hematological system. EPA (2014c) specifically noted effects of oxidative stress (altered antioxidant enzymes, decreased cellular glutathione, and lipid peroxidation) as an important mechanism for hematological effects. As reviewed in Section 3.2.3 (Toxicokinetics, Distribution), 99% of Pb in blood is distributed to erythrocytes, providing a toxicokinetic mechanism for hematological effects (Bergdahl et al. 1997a, 1998, 1999; Hernandez-Avila et al. 1998; Manton et al. 2001; Schutz et al. 1996; Smith et al. 2002).

Figure 2-4. Pb Interactions in the Heme Synthesis Pathway

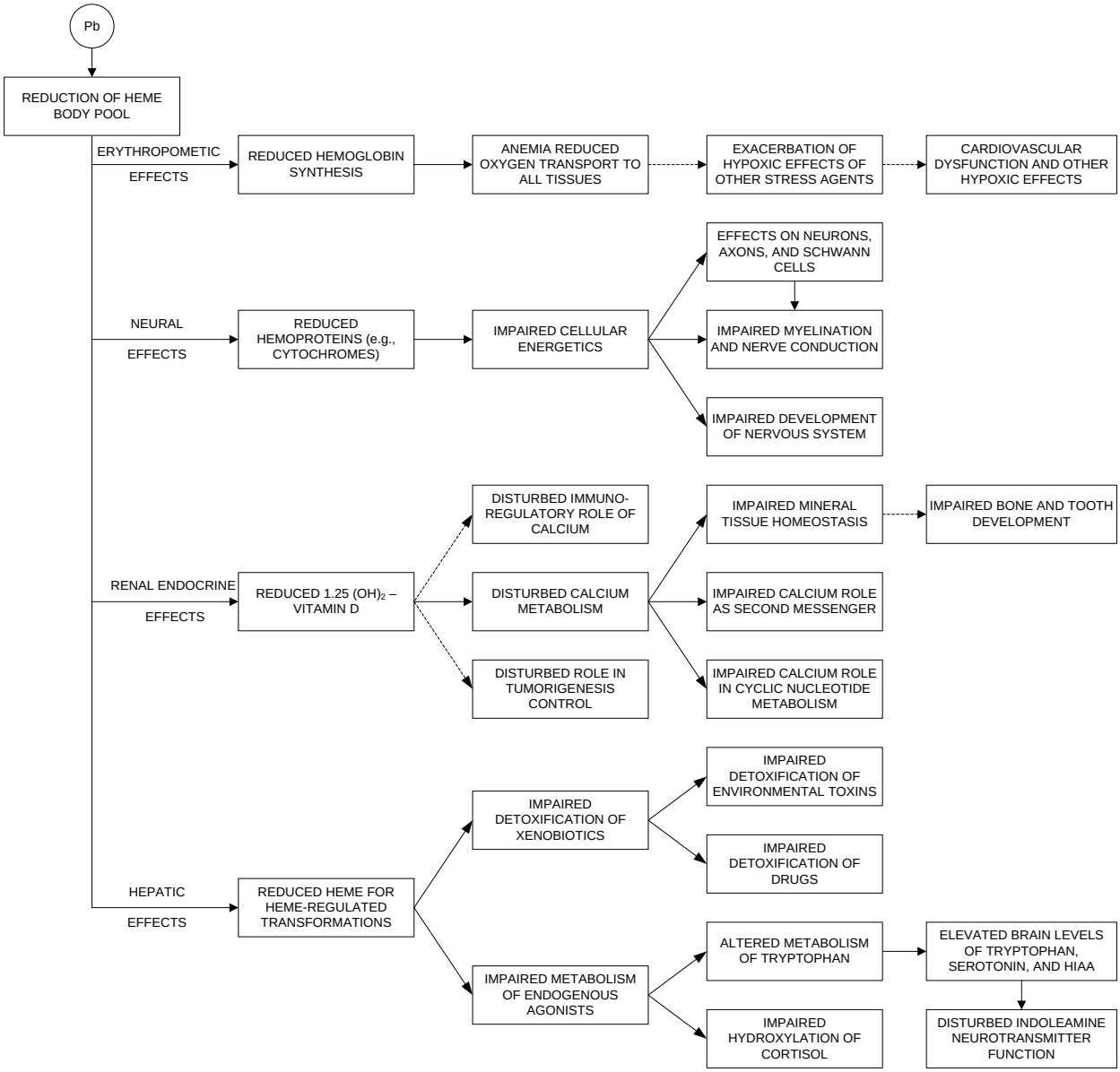


Abbreviations as noted in Ahamed and Siddiqui (2007): δ-ALAS = delta-aminolevulinic acid synthetase; δ-ALAD = delta-aminolevulinic dehydratase; CoA = coenzyme A

*Activity of enzymes inhibited by lead.

Source: Reprinted from Ahamed and Siddiqui (2007) with permission from Elsevier.

Figure 2-5. Multiorgan Impact of Reduction of Heme Body Pool by Lead



Source: EPA 1986a

2.9 MUSCULOSKELETAL

Overview. Few epidemiological studies have evaluated musculoskeletal effects associated with Pb exposure; thus, limited data are available to fully describe the exposure-response relationship or evaluate the weight-of-evidence for certain effects. Studies provide evidence of bone loss, increased markers of bone metabolism/turnover, and adverse periodontal and dental effects (periodontal bone loss, tooth loss, periodontal disease, dental caries). However, within dose ranges (≤10, 10–30, 30–50, and >50 µg/dL),

few studies examined the same endpoints. Available studies include a prospective study in women and cross-sectional studies in adults and children, with some studies in large populations.

The following musculoskeletal effects have been associated with PbB:

- ≤10 µg/dL:
  - Bone loss or markers of increased bone or joint tissue metabolism.
  - Periodontal bone loss.
  - Tooth loss.
  - Dental caries.
  - Periodontitis.
- >10 µg/dL:
  - Muscle soreness/weakness.
  - Osteoporosis/decreased bone mineral density (BMD) in adults.
  - Increased BMD in children.
  - Periodontal disease.
  - Dental caries.

Measures of Exposure. Most studies examining the association between musculoskeletal effects and Pb exposure have evaluated exposure by measurement of PbB, although some studies also evaluated exposure by bone Pb concentration.

Confounding Factors and Effect Modifiers. A complicating factor in the interpretation of studies examining associations between PbB and bone loss or measures of bone metabolism is that increased bone metabolism (bone turnover or loss) can result in higher PbB due to Pb released from bone into the blood (reverse causality). This contributes to confounding from other factors that are associated with bone loss, including nutrition, age, pregnancy and menopause, and activity. Results of studies examining Pb-induced periodontal or dental effects need to account for dental hygiene, diet/nutrition, and previous dental interventions. For example, interpretation of results on associations between dental caries and PbB would be uncertain if daily fluoride intake or prophylactic dental treatments (e.g., fluoride treatments or coating of molars during childhood) were not considered as confounding factors. Studies that rely on *in vivo* estimates of bone Pb (e.g., XRF) as the exposure metric for changes in BMD should also consider the potential for changes in BMD affecting the measurement of the concentration of Pb in bone mineral (Hu et al. 2007).

Characterization of Effects. Studies evaluating musculoskeletal effects associated with PbB provide evidence of bone loss, altered bone or joint tissue metabolism, and adverse periodontal and dental effects (periodontal bone loss, tooth loss, periodontal disease, dental caries). Due to the small number of studies, it is difficult to establish exposure-response relationships; in addition, within specific dose-ranges (≤10, 10–30, 30–50, and >50 µg/dL), few studies examined the same endpoints. Effects associated with chronic Pb exposure are shown in Table 2-17. In adults, decreased BMD has been observed over a PbB range of ≤10–>50 µg/dL (Campbell and Auinger 2007; Dongre et al. 2013; Khalil et al. 2008; Lee and Park 2018), although BMD was not decreased in women at PbB ≤10 µg/dL (Pollack et al. 2013). BMD was increased in a single study in children with a mean PbB of 23.6 µg/dL (Campbell et al. 2004). The study authors suggested that the effect may represent accelerated bone maturation due to Pb-induced inhibition of parathyroid hormone-related peptide and transforming growth factor β-1. The study authors also noted that the accelerated bone maturation may be a predisposing factor for osteoporosis later in life. Sun et al. (2008a, 2008b) showed that PbB was associated with increased prevalence of osteoporosis (mean PbB men: 20.22 µg/dL; women 15.50 µg/dL). Periodontal disease (including periodontitis), periodontal bone loss, tooth loss, and dental caries have been reported over a PbB range of ≤10–30 µg/dL (Arora et al. 2009; Campbell et al. 2000a; Dye et al. 2002; Gemmel et al. 2002; Kim and Lee 2013; Kim et al. 2017a; Moss et al. 1999; Youravong and Teanpaisan 2015). Most studies examining periodontal and dental effects of Pb are conducted in populations with PbB ≤10 µg/dL. Muscle soreness and weakness has also been reported, although at higher PbB (40–49 µg/dL) (Rosenman et al. 2003).

Table 2-17. Overview of Musculoskeletal Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Bone loss/increased bone metabolism	Khalil et al. 2008; Lee and Park 2018; Machida et al. 2009; Nelson et al. 2009
	Tooth loss	Arora et al. 2009
	Periodontal bone loss	Dye et al. 2002
	Periodontitis	Kim and Lee 2013
	Dental caries	Gemmel et al. 2002; Kim et al. 2017a; Moss et al. 1999

Table 2-17. Overview of Musculoskeletal Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>10–30	Osteoporosis	Sun et al. 2008a, 2008b
	Decreased bone mineral density (adults)	Campbell and Auinger 2007
	Increased bone mineral density (children)	Campbell et al. 2004
	Periodontal disease	Youravong and Teanpaisan 2015
	Dental caries	Campbell et al. 2000a
>30–50	Muscle soreness/weakness	Rosenman et al. 2003
	Decreased bone mineral density	Campbell and Auinger 2007
>50	Decreased bone mineral density	Dongre et al. 2013

Effects at Blood Pb Levels ≤10 µg/dL. Epidemiological studies of musculoskeletal effects associated with PbB ≤10 µg/dL have examined effects on bone and periodontal and dental health; studies are briefly summarized in Table 2-18, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 5. A prospective study in women reported an increased rate of bone loss at PbB ranges of 4–7 and 8–21 µg/dL and an increased risk of non-spine fractures at a PbB range of 8–21 µg/dL (Khalil et al. 2008). In cross-sectional studies, markers of bone metabolism were positively associated with PbB in women at mean PbBs of <2 and 2.9 µg/dL, although no relationship was observed for these markers and PbB in men (mean PbB: 1.2 µg/dL) (Machida et al. 2009; Nelson et al. 2011). In non-occupationally exposed men and women (n=443), PbB (mean 4.44 µg/dL) was negatively associated with BMD (Lee and Park 2018). However, no associations between PbB and BMD have been observed in cross-sectional studies in women at slightly lower PbB median PbB (1.8–2.2 µg/dL) (Machida et al. 2009; Pollack et al. 2013). Studies examining periodontal and dental effects include large (n=2,805–10,033) cross-sectional studies in adults and children (Dye et al. 2002; Kim and Lee 2013; Kim et al. 2017a; Moss et al. 1999). Positive associations have been observed between PbB and presence of dental furcations in male and female adults (mean PbB: 1.9–3.3 µg/dL) (Dye et al. 2002), periodontitis in adult males (PbB mean 3.1 µg/dL), but not females (mean PbB: 2.2) (Kim and Lee 2013), and dental

Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Bone metabolism			
Khalil et al. 2008 Prospective cohort study; n=533 women (age range: 65–87 years).	**PbB:** Mean (SD): 5.3 (2.3) Tertiles: • T1 (n=122): ≤3 (reference) • T2 (n=332): 4–7 • T3 (n=79): 8–21	Bone loss	Percentage rate of calcaneus bone loss • **T1: -1.01 (-1.27, -0.74)*** • **T2: -1.41 (-1.57, -1.24)*** • **T3: -1.49 (-1.86, -1.10)*; p=trend: 0.03**
		Non-spine fractures	**HR T3: 2.50 (1.25, 5.03)*; p-trend: 0.016**
Lee and Park 2018 Cross-sectional study; n=443 adults (age range: 39–69 years)	**PbB:** Gmean: 4.44	BMD	**Regression coefficient, β (SE), for BMD: -1.27 (0.48); p<0.01***
Machida et al. 2009 Cross-sectional study; n=1,225 female Japanese farmers (age range: 35–75 years)	**PbB:** Median • Premenopausal (n=261): 1.6 • Perimenopausal (n=319): 2.0 • Younger postmenopausal (n=397): 1.8 • Older postmenopausal (n=248): 1.7	BALP	Spearman's correlation coefficients • **All women: 0.143; p=0.000*** • **Perimenopausal women: 0.234; p=0.000***
		OC	Spearman's correlation coefficients • **All women: 0.191; p=0.000*** • **Perimenopausal women: 0.391; p=0.000***
		NTx	Spearman's correlation coefficients • **All women: 0.181; p=0.000*** • **Perimenopausal women: 0.261; p=0.000***
		BMD	Spearman's correlation coefficients • All women: -0.016; p=0.570 • Perimenopausal women: -0.101; p=0.071

Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Nelson et al. 2011 Cross-sectional study; n=329 males (mean age: 65 years) and n=342 females (mean age: 62 years)	Median (range) • Males: 2.2 (0.5–25.1) • Females: 1.9 (0.5–25.4)	uNTX-I	β, change in biomarker per 5 µg/dL increase in ln-PbB • Males: 1.06 (0.95, 1.18) • **Females: 1.45 (1.21, 1.74)***
		uCTX-II	β, change in biomarker per 5 µg/dL increase in ln-PbB • Males: 1.07 (0.97, 1.18) • **Females: 1.28 (1.04, 1.58)***
		C2C (65 years)	β, change in biomarker per 5 µg/dL increase in ln-PbB • Males: 1.00 (0.94, 1.04) • Females: 1.00 (0.92, 1.08)
		CPII	β, change in biomarker per 5 µg/dL increase in ln-PbB • Males: 0.99 (0.93, 1.05) • Females: 1.09 (0.97, 1.22)
		HA	β, change in biomarker per 5 µg/dL increase in ln-PbB • Males: 1.01 (0.88, 1.05) • Females: 0.96 (0.71, 1.29)
		COMP	β, change in biomarker per 5 µg/dL increase in ln-PbB • **Males: 1.08 (1.00, 1.18)*** • Females: 0.96 (0.87, 1.06)
Pollack et al. 2013 Cross-sectional study; n=249 premenopausal women (ages 18–44 years)	Mean (SD): 1.03 (0.64)	BMD	β per log-unit increase in PbB: 0.004 (-0.029, 0.020)

Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Periodontal and dental effects			
Arora et al. 2009 Cross-sectional study; n=333 men (age range: 50–94 years)	PbB Tertiles • T1: ≤4.0 (reference) • T2: 4.2–6.4 • T3: 7.0–35.0 Bone Pb (µg/g) Tertiles for tibia • T1: ≤15.0 (reference) • T2: 16.0–23.0 • T3: 24.0–96.0 Tertiles for patella • T1: ≤22.0 (reference) • T2: 23.0–36.0 • T3: 37.0–126.0	Tooth loss	OR PbB (compared to T1) • T3: 0.88 (0.52, 1.50); p-trend=0.57 OR Tibia Pb (compared to T1) • **T2: 1.81 (1.02, 3.18)*** • **T3: 3.03 (1.60, 5.76)*; p-trend=0.001*** OR Patella Pb (compared to T1) • **T3: 2.41 (1.30, 4.49)*; p-trend 0.005***
Dye et al. 2002 Cross-sectional study in 10,033 participants in NHANES III (ages 20–69 years)	Mean (SE) • Males: 3.3 (0.12) • Females: 1.9 (0.05)	Presence of dental furcations	**β (SE), for presence of dental furcations (combined men and women): 0.13 (0.05); p=0.005***

Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Gemmel et al. 2002 Cross-sectional study in 498 children (age range: 6–10 years) from rural (n=239) and urban (n=259) settings.	Mean (SD) • Rural: 1.7 (1.0) • Urban: 2.9 (2.0)	Dental caries	Regression coefficient (SE): • Rural: -0.15 (0.09); p=0.09 • **Urban: -0.22 (0.08); p=0.005***
Kim and Lee 2013 Cross-sectional study; n=3,966 adults (≥20 years of age)	**PbB:** Mean (SE): • Men o no periodontitis: 2.625 (0.028) o periodontitis: 3.118 (0.057); p<0.001 • Women, o no periodontitis: 1.906 (0.025) o periodontitis: 2.222 (0.052); p<0.001	Periodontitis	OR (95% CI), per doubling of PbB: • **Men: 1.699 (1.154, 2.503)*** • Women: 1.242 (0.833, 1.850)
Kim et al. 2017a Cross-sectional study; n=2,805 school-aged children (age range: ≤9–≥12 years)	**PbB:** Gmean: 1.53 Range: 0.11–4.89	Dental caries	PR for combined teeth with caries and filled teeth • **Deciduous teeth: 1.14 (1.02, 1.27)*** • Permanent teeth: 0.83 (0.69, 0.99)

Table 2-18. Summary of Epidemiological Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b,c]
Moss et al. 1999 Cross-sectional study; n=24,901 participants (2–5 years old: n=3,547; 6–11 years old: n=2,894; ≥12 years: n=18,460) in NHANES III	Mean (SE): • Age 2–5 years: 2.9 (0.12) • Age 6–11 years: 2.1 (0.08) • Age 12–17 years: 2.5 (0.06)	Dental caries in children (ages 5–17 years)	**OR per 5 µg/dL increased in PbB: 1.8 (1.3, 2.5)***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 5 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[c]If bone Pb is noted under results, study did not show associations between PbB and musculoskeletal effects; however, results showed associations between bone Pb concentrations and musculoskeletal effects at concomitant PbB ≤10 µg/dL.

BALP = bone-specific alkaline phosphatase (marker of bone metabolism); BMD = bone mineral density; C2C = serum cleavage neoepitope of type II collagen (marker of joint tissue metabolism); CI = confidence interval; COMP = serum cartilage oligomeric matrix protein (marker of joint tissue metabolism); CPII = serum type II procollagen synthesis C-propeptide (marker of joint tissue metabolism); Gmean = geometric mean; HA = serum hyaluronic acid (marker of joint tissue metabolism); HR = hazard ratio; NHANES = National Health and Nutrition Examination Survey; NTx = N-telopeptide cross-linked collagen type I (marker of bone metabolism); OC = osteocalcin (marker of bone metabolism); OR = odds ratio; Pb = lead; PR = prevalence ratio; SD = standard deviation; SE = standard error; uCTX-II = C-telopeptide urine fragments of type II collagen (marker of joint tissue metabolism); uNTX-I = urine cross-linked N telopeptide of type I collagen (marker of joint tissue metabolism)

caries in children ages 6–17 years (PbB 2.1–2.4 µg/dL) (Moss et al. 1999). Kim et al. (2017a) reported that the prevalence of dental caries and filled teeth in children was increased for deciduous teeth, but not for permanent teeth; the mean PbB was 1.53 µg/dL, with all PbB <5 µg/dL. One study in adult males showed an association between bone Pb and tooth loss, but not PbB and tooth loss (Arora et al. 2009).

Mechanisms of Action. In bone and teeth, Pb substitutes for calcium (see Section 3.1.2, Toxicokinetics, Distribution). As reviewed by EPA (2014c) and Mitra et al. (2017), several mechanisms may be involved in the development of bone and periodontal/dental effects. Possible mechanisms include the following:

- Alterations in plasma growth hormones and calcitropic hormones (e.g., 1,25-[OH]2D3) leading to altered bone cell differentiation and function.
- Suppression in bone cell proliferation due to altered growth factors and hormones, including growth hormone, epidermal growth factor, transforming growth factor-beta 1 (TGF-β), and parathyroid hormone-related protein.
- Alterations in vitamin D-stimulated production of osteocalcin production, with inhibition of secreted bone-related proteins (e.g., osteonectin and collagen).
- Increased chondrogenesis through alterations of multiple signaling pathways, including TGF-β, bone morphogenic protein, activator protein-1, and nuclear factor kappa B.
- Inhibition of the posteruptive enamel proteinases.
- Decreased microhardness of tooth surface enamel.

2.10 HEPATIC

Overview. Few epidemiological studies have evaluated hepatic effects associated with exposure to Pb, with most available studies comparing hepatic effects in small numbers of workers with PbB >10 µg/dL to controls with PbB lower than workers. Results of studies evaluating effects of Pb on liver function tests are inconsistent and do not demonstrate exposure-response relationships. Liver enlargement and increased gall bladder wall thickness was observed in workers with mean PbB of ≥28.66 µg/dL. Observed effects are consistent with oxidative stress. Histopathological effects of the liver associated with Pb have not been established.

The following hepatic effects have been associated with PbB >10 µg/dL:

- Greater plasma liver enzymes; evaluated in a few studies with mixed results.

- Greater total cholesterol.
- Enlarged liver and increased thickness of gall bladder wall.

Measures of Exposure. Studies examining the association between hepatic effects Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Most epidemiological studies on hepatic effects of Pb were of small populations of workers using cross-sectional designs. In general, studies did not consider factors, such as age, diet, concurrent diseases, and potential exposure to other workplace chemicals that could affect hepatic function in association with, or independent of, Pb exposure. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. In contrast to the large number of epidemiological studies evaluating effects of Pb on other organ systems (e.g., neurological and cardiovascular outcomes), few studies have investigated the hepatic effects of Pb. Brief study descriptions are provided in Table 2-19. Available studies were conducted in small populations (n=23–100) of workers with mean PbB of 5.4–77.5 µg/dL. The most serious effects reported for Pb-induced hepatic damage are liver enlargement and greater gall bladder wall thickness observed in workers with low PbB (28.66 µg/dL) and high PbB (40.58 µg/dL), respectively, compared to the control group (PbB 8.34 µg/dL) (Kasperczyk et al. 2013). However, these findings have not been corroborated in other studies. The study authors stated that no signs consistent with liver necrosis were observed. A cross-sectional study of a Chinese population evaluated the association between PbB and non-alcoholic fatty liver disease in China (Zhai et al. 2017). In women, a positive association between PbB and non-alcoholic fatty liver disease was observed in the two highest PbB quartiles (4.50–6.59 and >6.59 µg/dL; upper range not reported); no association was observed for men in the highest PbB quartile (>7.29 µg/dL; upper range not reported).

Most studies evaluated hepatic toxicity by liver function tests measuring plasma levels of liver enzymes. As shown in Table 2-20, results on effects of Pb on liver function tests are inconsistent and do not demonstrate exposure-response relationships. For example, Patil et al. (2007) reported greater alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in spray painters with a mean PbB of 22.32 µg/dL, but no change in ALT or AST in battery workers or silver jewelry workers with higher mean PbB (53.64 and 48.56 µg/dL, respectively), compared to controls (mean PbB: 12.52 µg/dL). Similarly, AST was elevated in painters with a mean PbB of 5.4 µg/dL, but no change in AST was

Table 2-19. Summary of Epidemiological Studies Evaluating Hepatic Effects Associated with Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Outcomes evaluated	Effects[b,c]
Al-Neamy et al. 2001 Cross-sectional study; n=100 workers; 100 controls	Mean (SD) • Workers: 77.5 (42.8) • Controls: 19.8 (12.3)	LFTs	• Greater: LDH, AP • No difference: ALT, AST, GGT, bilirubin, albumin
Can et al. 2008 Cross-sectional study; n=22 battery workers; 38 muffler repair workers; 24 controls	Mean (SD) • Battery workers: 36.83 (8.13) • Muffler workers: 26.99 (9.42) • Controls: 14.81 (3.01)	LFTs	Battery workers: • Greater LDH, AP, TC Muffler workers: • Greater" LDH, AP
Chen et al. 2019 Cross-sectional study; n=158 exposed adults living near an electronic waste area; 109 controls	Median (P_{25}, P_{75}) • Control: 5.1 (3.9, 8.4) • Exposed: 8.7 (6.2–12.2)	LFTs	• Greater: GGT • No difference: AST, ALT, LDH
Conterato et al. 2013 Cross-sectional study; n=50 painters; 23 battery workers; and 36 controls	Mean (SE) • Painters: 5.4 (0.4) • Battery workers 49.8 (4.0) • Controls: 1.5 (0.1)	LFTs	Painters: • Greater: AST • No difference: GGT Battery workers: • No difference: AST, GGT
Hsiao et al. 2001 Longitudinal study (baseline 1989; follow-up 1999); n=30 battery workers	Baseline: 60 Follow-up: 30	LFTs	No correlation of PbB to ALT

Table 2-19. Summary of Epidemiological Studies Evaluating Hepatic Effects Associated with Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Outcomes evaluated	Effects[b,c]
Kasperczyk et al. 2013 Cross-sectional study; n (from Pb-Zn processing facility): 57 low Pb exposure; 88 high Pb exposure; and 36 controls	Mean (SD); range • Low Pb: 28.66 (6.60); 20–35 • High Pb: 40.58 (6.74); 35–60 • Control: 8.34 (2.91)	Liver size	• Low PbB: Greater • High BPb: Greater
		Gall bladder wall thickness	• Low PbB: Greater • High PbB: Greater
		LFTs	• Low PbB: o No difference: ALT, AST, LDH, GGT, bilirubin
			• High PbB: o No difference: ALT, LDH, AST, bilirubin o Greater AST, GGT
Khan et al. 2008 Cross-sectional study; n=87 workers; 61 controls	Median (range) • Workers: 29.1 (9.0–61.1) • Controls: 8.3 (1.0–21.7)	LFTs	• Greater ALT, GGT, albumin • No change: AP, bilirubin
Kristal-Boneh et al. 1999 Cross-sectional study; n=56 exposed; 87 controls	Mean (SD) • Workers: 42.3 (14.9) • Controls: 2.7 (3.6)	Cholesterol and lipoproteins	• Greater: TC, HDL • No change: LDL, TG, HDL:TC ratio
Patil et al. 2007 Cross-sectional study; n=30 battery workers; 30 silver jewelry workers; 30 spray painters[a]; 35 controls	Mean (SD) • Battery workers: 53.63 (16.98) • Silver jewelry workers: 48.56 (7.39) • Spray painters: 22.32 (8.87) • Controls: 12.52 (4.08)	LFTs	Battery workers: • Greater percentage change: albumin, bilirubin • No change: ALT, AST Silver jewelry workers: • Lesser percentage change: albumin compared to controls • No change: ALT, AST, bilirubin compared to controls Spray painters: • Greater percentage change: ALT, AST • Decreased percentage change: albumin • No change: bilirubin

Table 2-19. Summary of Epidemiological Studies Evaluating Hepatic Effects Associated with Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Outcomes evaluated	Effects[b,c]
Zhai et al. 2017 Cross-sectional study; n=214 men and 610 women with non-alcoholic fatty liver disease	Quartiles (Q) Men: • Q1: ≤3.60 • Q2: 3.61–5.29 • Q3: 5.30–7.28 • Q4: ≥7.29 Women: • Q1: ≤2.97 • Q2: 2.98–4.49 • Q3: 4.50–6.59 • Q4: ≥6.60	Non-alcoholic fatty liver disease	• Men[d]: no association were observed for any PbB quartile • Women[d]: positive association between PbB at the two highest quartiles; OR (95% CI) o **Q3: 1.495 (1.024, 2.181)*** o **Q4: 1.613 (1.082, 2.405)*** o p for trend: 0.019

[a]Reporting inconsistencies regarding number of spray painters evaluated; reported as 30 and 35.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[c]Unless otherwise specified, comparisons are to control groups.
[d]Comparison to lowest PbB quartile.

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; CI = confidence interval; GGT = gamma-glutamyl transpeptidase; HDL = high-density lipoprotein; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; LFT = liver function test (plasma activity of hepatic enzymes); Pb = lead; Q = quartiles; SD = standard deviation; SE = standard error; TC = total cholesterol; TG = triglycerides; Zn = zinc

Table 2-20. Effects on Liver Function Tests Associated with Chronic Exposure to Lead (Pb)[a]

Mean PbB (µg/dL)	Population (n)[b]	ALT	AST	GGT	LDH	AP	Reference
5.4	P (50)	–	↑	0	–	–	Conterato et al. 2013
8.7	G (158)	0	0	↑	0	↑	Chen et al. 2019
22.32	P (35)[c]	↑	↑	–	–	–	Patil et al. 2007
26.99	Pb-A (38)	0	0	0	↑	↑	Can et al. 2008
28.66	Pb-Zn (57)	0	0	0	0	0	Kasperczyk et al. 2013
29.1	Pb (87)	↑	–	↑	–	0	Khan et al. 2008
30	B (30)	0	–	–	–	–	Hsiao et al. 2001
36.83	B (22)	0	0	0	↑	0	Can et al. 2008
40.58	Pb-Zn (88)	0	↑	↑	0	↑	Kasperczyk et al. 2013
48.56	J (30)	0	0	–	–	–	Patil et al. 2007
9.8	B (23)	0	0	0	–	–	Conterato et al. 2013
53.63	B (30)	0	0	–	–	–	Patil et al. 2007
77.5	Pb (100)	0	0	0	↑	↑	Al-Neamy et al. 2001

[a]Reporting inconsistencies regarding number of spray painters evaluated; reported as 30 and 35.

↑ = increased; 0 = no change; – = not assessed; ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; B = battery workers; G = general population; GGT = gamma-glutamyl transpeptidase; J = silver jewelry workers; LDH = lactate dehydrogenase; MDA: malondialdehyde; P = painters; Pb = Pb-exposed industrial workers; Pb-A = Pb-exposed auto workers; Pb-Zn = Pb-zinc processers

observed in battery workers with a mean PbB of 49.8 µg/dL, compared to controls with a mean PBB of 1.5 µg/dL (Conterato et al. 2013). Effects in painters with lower PbB compared to other workers with higher PbB may be due to co-exposure to other occupational chemicals. In a cross-sectional study of residents living close to an electronic waste site in China, PbB (median PbB: 8.7 µg/dL) was associated with an increase in gamma-glutamyl transpeptidase (GGT) compared to controls (median PbB: 5.1 µg/dL), although no effects were observed for ALT or AST (Chen et al. 2019). In addition to liver enzymes, total serum cholesterol and high-density lipoprotein (HDL)-cholesterol were greater in workers with a mean PbB of 26.99–42.3 µg/dL, compared to controls with a mean PbB 2.7–14.81 µg/dL (Can et al. 2008; Kristal-Boneh et al. 1999).

Effect at Blood Pb Levels ≤10 µg/dL. See discussion above on Conterato et al. (2013), Chen et al. (2019), and Zhai et al. (2017).

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of hepatic toxicity. EPA (2014c) specifically noted that oxidative stress

through ROS can result in damaged function and histopathological damage to the liver, including peroxidation of lipid membranes.

2.11 RENAL

Overview. Numerous epidemiologic studies in adults show that exposure to Pb can cause altered kidney function and contribute to the development of chronic kidney disease (CKD). A few studies in children also show decreases in renal function. Pb-induced nephrotoxicity is characterized by proximal tubular nephropathy, glomerular sclerosis, and interstitial fibrosis (Diamond 2005; Goyer 1989; Loghman-Adham 1997). Functional deficits in humans that have been associated with excessive Pb exposure include enzymuria, low- and high-molecular weight proteinuria, impaired transport of organic anions and glucose, and depressed GFR. A few studies have revealed histopathological features of renal injury in humans, including intranuclear inclusion bodies and cellular necrosis in the proximal tubule and interstitial fibrosis (Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979). Studies show consistent evidence of renal damage and reduced renal function associated over a wide range of PbB (≤10–>50 µg/dL), with the overall dose-effect pattern suggesting an increasing severity of nephrotoxicity associated with increasing PbB.

The following renal effects have been associated with PbB:

- ≤10 µg/dL:
  - Decreased GFR; corroborated in numerous studies.
  - Proteinuria; demonstrated in a few studies.
  - Chronic kidney disease (CKD); demonstrated in two studies.
- >10 µg/dL:
  - Decreased GFR; corroborated in numerous studies.
  - Enzymuria; corroborated in numerous studies.
  - Proteinuria; corroborated in numerous studies.
  - Impaired tubular transport; demonstrated in a few studies.
  - Histopathological damage; demonstrated in a few studies.

Measures of Effect. Endpoints demonstrating renal damage include various measures of glomerular and tubular dysfunction. Effects on GFR typically are assessed from measurements of creatinine clearance, serum creatinine concentration, or blood urea nitrogen (BUN). Increased excretion of albumin

(albuminuria) is an indication of damage to the glomerular endothelium or basement membrane, resulting in increased filtration of albumin, or impaired function of the proximal tubule, resulting in decreased reabsorption of filtered albumin. Increased excretion of low molecular weight serum proteins (e.g., 2μG or retinol-binding protein) are an indication of impaired reabsorption of protein in the proximal tubule. Increased excretion of enzymes associated with the renal tubule (renal tubular enzymuria) is an indication of injury to renal tubular cells resulting in release of membrane or intracellular enzymes into the tubular fluid. Pb-induced renal tubular enzymuria is most commonly evaluated from measurements of urinary N-acetyl-D-glucosaminidase (NAG). Increased excretion of NAG has been found in Pb-exposed workers in the absence of increased excretion of other proximal tubule enzymes (e.g., alanine aminopeptidase, alkaline phosphatase, glutamyltransferase) (Pergande et al. 1994). Indices of impaired transport include altered clearance or transport maxima for organic anions (e.g., p-aminohippurate, urate) or glucose (Biagini et al. 1977; Hong et al. 1980; Wedeen et al. 1975). Proximal tubular injury can also be confirmed through histopathological examination of renal tissue, although few studies provide this information (Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979).

Measures of Exposure. Most studies evaluating renal damage use PbB as the biomarker for exposure, although more recent epidemiological studies have explored associations between toxicity and bone Pb concentrations. These studies provide a basis for establishing PbB, and, in some cases, bone Pb concentration ranges associated with specific nephrotoxicity outcomes.

Confounding Factors and Effect Modifiers. Inconsistencies in the reported outcomes for renal effects across studies may derive from several causes, including failure to account for confounding factors and effect modifiers. Various factors can affect kidney function, including age, underlying diseases (e.g., hypertension), and concomitant exposure to other nephrotoxicants (e.g., cadmium). Results of epidemiological studies of general populations have shown an effect of age on the relationship between GFR (assessed from creatinine clearance of serum creatinine concentration or cystatin C) and PbB (Kim et al. 1996a; Muntner et al. 2003; Payton et al. 1994; Staessen et al. 1990, 1992). Pb-induced decrements in renal function can lead to higher Pb body burden due to decreased excretion of Pb (i.e., reverse causality) (Bellinger 2011; Diamond et al. 2019; Evans and Elinder 2011; Marsden 2003). Thus, reverse causality potentially confounds interpretation of the dose-response relationship between PbB and decreased renal function. Pb exposure has also been associated with increases in GFR (Hsiao et al. 2001; Roels et al. 1994). This may represent a benign outcome or a potentially adverse hyperfiltration, which may contribute to subsequent adverse renal effects. Hypertension can be both a confounder in studies of associations between Pb exposure and creatinine clearance (Perneger et al. 1993) and a covariable with Pb

exposure (Harlan et al. 1985; Muntner et al. 2003; Payton et al. 1994; Pirkle et al. 1985; Pocock et al. 1984, 1988; Tsaih et al. 2004; Weiss et al. 1986). Renal damage can cause increased blood pressure, which in turn can result in further damage to the kidneys. In addition, varying uncertainty also exists across studies in exposure history of subjects and in the biomarkers assessed.

Characterization of Effects. A large number of studies showing decrements in renal function associated with Pb exposure in humans have been published (Table 2-21). Most of these studies are of adults whose exposures were of occupational origin; however, a few environmental, mixed, and/or unknown exposures are represented, and a few studies of children are also included. Although these studies demonstrate adverse renal effects across the PbB range, some studies did not find associations (Buchet et al. 1980; de Kort et al. 1987; Fadrowski et al. 2010; Gennart et al. 1992; Huang et al. 2002; Karimooy et al. 2010; Mujaj et al. 2019; Omae et al. 1990). However, collectively, the body of evidence demonstrates that long-term exposure to Pb is nephrotoxic. General trends regarding the relationship between PbB and qualitative aspects of the kidney response are shown in Table 2-21. Decreased GFR and proteinuria have been observed in association with PbB ≤10 µg/dL; the significance of these studies is discussed in greater detail below. Enzymuria and proteinuria have been observed in association with PbB >10–≤50 µg/dL. Functional deficits, including enzymuria, proteinuria, impaired transport, and depressed GFR have been observed at PbB >50 µg/dL. Histopathological findings, including tubular atrophy, focal sclerosis of glomeruli, and periglomerular and interstitial fibrosis have also been observed at PbB >50 µg/dL. The overall dose-effect pattern suggests an increasing severity of nephrotoxicity associated with increasing PbB, with effects on glomerular filtration evident at PbBs <10 µg/dL, enzymuria and proteinuria becoming evident >10 µg/dL, and severe deficits in function and pathological changes occurring in association with PbBs >50 µg/dL.

Table 2-21. Overview of Renal Effect Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased GFR	de Burbure et al. 2006
	Decreased GFR	Åkesson et al. 2005; Fadrowski et al. 2010; Harari et al. 2018; Lin et al. 2001; Khan et al. 2010a; Kim et al. 1996a; Lin et al. 2003; Lin et al. 2006a, 2006b; Muntner et al. 2003; Navas-Acien et al. 2009; Payton et al. 1994; Pollack et al. 2015; Spector et al. 2011; Staessen et al. 1992, 2001; Yu et al. 2004

Table 2-21. Overview of Renal Effect Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
	Proteinuria chronic kidney disease	Navas-Acien et al. 2009; Harari et al. 2018; Pollack et al. 2015
>10–≤30	Decreased GFR	Kim et al. 1996a; Staessen et al. 1990
	Enzymuria	Bernard et al. 1995; Chia et al. 1994; Sonmez et al. 2002; Sun et al. 2008b
	Proteinuria	Bernard et al. 1995; Chia et al. 1995a, 1995b
>30–≤50	Increased GFR	Hsiao et al. 2001; Roels et al. 1994
	Decreased GFR	Orisakwe et al. 2007; Weaver et al. 2003a, 2003b, 2005a; Wedeen et al. 1975
	Enzymuria	Cardenas et al. 1993; Cardozo dos Santos et al. 1994; Fels et al. 1994; Garcon et al. 2007; Gerhardsson et al. 1992; Kim et al. 1996a; Kumar and Krishnaswamy 1995; Lin and Tai-yi 2007; Mortada et al. 2001; Pergande et al. 1994; Roels et al. 1994; Verberk et al. 1996; Verschoor et al. 1987; Weaver et al. 2003a, 2003b, 2005a
	Proteinuria	Factor-Litvak et al. 1999; Fels et al. 1998; Garcon et al. 2007; Gerhardsson et al. 1992; Kumar and Krishnaswamy 1995; Mortada et al. 2001; Pergande et al. 1994; Verschoor et al. 1987
	Impaired tubular transport	Pinto de Almeida et al. 1987
>50	Decreased GFR	Baker et al. 1979; Biagini et al. 1977; Cramer et al. 1974; Ehrlich et al. 1998; Hong et al. 1980; Lilis et al. 1968, 1980; Onuegbu et al. 2011; Wedeen et al. 1975, 1979
	Enzymuria	Cabral et al. 2012; Gao et al. 2010; Garcon et al. 2007
	Proteinuria	Cabral et al. 2012; Gao et al. 2010; Garcon et al. 2007
	Impaired tubular transport	Biagini et al. 1977; Ehrlich et al. 1998; Hong et al. 1980; Wedeen et al. 1975
	Histopathological changes	Biagini et al. 1977; Cramer et al. 1974; Wedeen et al. 1975, 1979

GFR = glomerular filtration rate

Effects at Blood Pb Levels ≤10 µg/dL. Studies of renal function in populations with PbB ≤10 µg/dL provide evidence for effects of Pb on GFR in children and adults. Results are summarized in Table 2-22, with study details provided in the *Supporting Document for Epidemiological Studies for Lead,* Table 6. Most studies found that increasing PbB was associated with decreased GFR; however, one study found evidence for increasing GFR in children (de Burbure et al. 2006).

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Åkesson et al. 2005 Cross-sectional study; n=820 adult women	Median: 2.2	CCr	**Linear regression β coefficient (mL/minute per µg/dL): -0.018 (95% CI -0.03, -0.006)***
		GFR	**Linear regression β coefficient (mL/minute per µg/dL): -0.02 (95% CI -0.03, -0.009)***
		UPHC	Linear regression β coefficient (µg/L per µg/dL): reported as NS
		UNAG	Linear regression β coefficient (U/g creatinine per µg/dL): reported as NS
Barry et al. 2019 Cross-sectional study; n=211 adult men	Median: 2.5	GFR	Linear regression coefficient (SE) for: PbB Q4: -2.71 (4.16); p=0.52 PbB continuous: -0.13 (0.28); p=0.65 Bone Pb Q4: -5.66 (4.86); p=0.25 Bone Pb Continuous: -0.15 (0.11); p=0.18
de Burbure et al. 2006 Cross-sectional study; n>800 children (ages 8.5–12.3 years)	Mean range (three locations) Control: 2.81–3.81 Exposure: 3.64–6.51	SCr	**Decreased 7% (p<0.01) in Q4 (PbB >5.59 µg/dL), compared to Q1 (PbB <2.85 µg/dL)***
		Sβ2M	**Decreased 9% (p<0.01) in Q4 (PbB >5.86 µg/dL), compared to Q1 (PbB <3.10 µg/dL)***
Fadrowski et al. 2010 Cross-sectional study; n=769 adolescents (ages 12–20 years)	Median: 1.5 Quartiles: • Q1: <1.0 • Q2: 1.0–1.5 • Q3: 1.6–2.9 • Q4: >2.9	GFR	• **Change in GFR (mL/minute/1.73 m^2) Q4 compared to Q1: -6.6 (-12.6, -0.7)*** • **p-Trend across Q1–Q4=0.009*** • **Mean difference in GFR associated with a 2-fold increase in blood lead level: -2.9 (-5.0, -0.7)***

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Harari et al. 2018 Prospective cohort study; n=2,567 adults; with a 16-year follow-up period	Median at baseline (range): 2.5 (0.15–25.8) Quartiles (range): • Q1: 1.5 (0.15–1.85) • Q2: 2.2 (1.85–2.47) • Q3: 2.9 (2.47–3.30) • Q4: 4.6 (3.30–25.8)	GFR	At follow-up, GFR for Q1 decreased from 89 to 62 mL/minute from baseline **Additional decreases in GFR, mL/minute/ 1.73 m^2, per quartile:** • **Q3: -2.6 (-4.0, -1.2); p<0.001*** • **Q4: -2.3 (-3.8, -0.85); p=0.002*** • **p-trend: <0.001***
		CKD	**HR for Q4 compared to combined Q1–Q3: 1.49 (1.07–2.08); p=0.02***
Kim et al. 1996a Retrospective cohort study; n=459 men	Mean: 9.9	SCr	• **Regression coefficient (SE) for all participants (µmol/L per µg/dL): 0.033 (0.012); p=0.005*** • **Regression coefficient (SE) for PbB ≤10 (µmol/L per µg/dL): 0.060 (0.019); p=0.002***
Khan et al. 2010 Cross sectional study children (ages 1–6 years) of Pb workers (n=123) and controls (n=123)	Median • Control: 6.7 • Exposed: 8.10	SCr	• **Serum creatinine (µmol/L): control: 52; exposed: 56; p≤0.01*** • **Spearman's correlation coefficient: r=0.13; p≤0.05***
Lin et al. 2001 Prospective, longitudinal study; n=110 patients with chronic renal insufficiency	Low PbB mean: 3.9 High PbB mean: 6.6	CCr	• **18 Months CCr (mL/second) mean±SD: low Pb: 0.72±0.25; high Pb: 0.59±0.22 µg/dL (p=0.007)*** • **21 Months CCr (mL/second) mean±SD: low Pb: 0.70±0.24; High Pb: 0.57±0.22 µg/dL (p=0.006)*** • **24 Months CCr (mL/second) mean±SD: low Pb: 0.70±0.24; High Pb: 0.55±0.22 µg/dL (p=0.001)***

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Lin et al. 2003 Prospective, longitudinal study; n=202 patients with chronic renal insufficiency	Baseline: 5.3 After 24-month observation, prior to chelation[e] • Placebo: 5.9 • Chelation: 6.1	GFR	• **GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo 25.5±12.3; chelation 34.4±14.7 (p=0.01)*** • **Change in GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo -6.0±5.8; chelation 2.1±5.7 (p>0.001)***
Lin et al. 2006a Prospective, longitudinal study; n=124 patients with chronic renal insufficiency	After 24-month observation, prior to chelation[e] • Placebo: 3.0 • Chelation: 2.6	GFR	• **GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo 38.0±8.9; chelation 47.9±17.0 (p=0.0493)*** • **Change in GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo -4.6±4.3; chelation 6.6±10.7 (p>0.0005)***
		UP (24-hour)	• Urine protein (g) following chelation: placebo 1.11±1.63; chelation: 0.92±1.16 (p=0.6236)
Lin et al. 2006b Prospective, longitudinal study; n=238 patients with type II diabetes and progressive diabetic neuropathy	End of 12-month observation, prior to chelation[e] • Placebo: 5.9 • Chelation: 7.5	GFR	• **GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo 13.1±4.5; chelation 18.0±7.3 (p=0.0352)*** • **Decrements in GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo 13.2±7.6; chelation 4.4±6.8 (p>0.0045)***
Lin-Tan et al. 2007 Placebo-controlled clinical study; n=116 non-diabetic patients with chronic kidney disease	Mean after 51-month chelation • Placebo: 6.0 • Chelation: 3.5	GFR	• **GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo 23.7±10.8; Chelation 35.4±17.0 (p<0.0001)*** • **Change in GFR (mL/minute/1.73 m^2) following treatment (mean±SD): placebo -12.7±8.4; chelation -1.8±8.8 (p>0.0001)***
		UP (24-hour)	UP (mean±SD): placebo 0.96±1.04; chelation: 0.81±0.86 (p=0.3369)

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Mujaj et al. 2019 Cross-sectional study; n=447 newly hired male workers	Mean: 4.34	GFR	β, per doubling of PbB: -0.281 (-3.07, 2.50); p=0.84
		ACR	β, per doubling of PbB: -0.071 (-0.14, 0.59); p=0.06
Muntner et al. 2003 Cross-sectional study; n=4,813 hypertensive; n=10,398 normotensive adults[g]	Normotensive Mean: 3.30±0.10 Quartiles • Q1 (reference): 0.7–1.6 • Q2: 1.7–2.8 • Q3: 2.9–4.6 • Q4: 4.7–52.9 Hypertensive Mean: 4.21±0.14 Quartiles: • Q1 (reference): 0.7–2.4 • Q2: 2.5–3.8 • Q3: 3.9–5.9 • Q4: 6.0–56.0	GFR	Estimated GFR, mL/minute (mean±SD) • Normotensive: 115±0.7 • **Hypertensive: 95±0.7 (p<0.001)***
		SCr	OR for elevated SCr in hypertensive patients: **Q2: 1.47 (1.03, 2.10)*** **Q3: 1.80 (1.34, 2.42)*** **Q4: 2.41 (1.46, 3.97)*** **p-trend: <0.001***
		CKD	OR for elevated CKD in hypertensive patients: Q2: 1.44 (1.00, 2.09) **Q3: 1.85 (1.32, 2.59)*** **Q4: 2.60 (1.52, 4.45)*** **p-trend: <0.001***
Navas-Acien et al. 2009[f] Cross-sectional study; n=14,778 adults	Mean: 1.58 Quartiles: • Q1 (reference): ≤1.1 • Q2: >1.1–1.6 • Q3: >1.6–2.4 • Q4: >2.4	GFR	ORs for reduced GFR • Q2: 1.10 (0.80, 1.51) • Q3: 1.36 (0.99, 1.85) • **Q4: 1.56 (1.17, 2.08)*** • **p-trend: <0.001***
		Albuminuria	ORs for albuminuria • Q2: 0.83 (0.66, 1.04) • Q3: 0.92 (0.76, 1.12) • Q4: 1.19 (0.96, 1.47) • **p-trend: <0.001***

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Payton et al. 1994 Cross-sectional study; n=744 men	Mean: 8.1	CCr	**Regression coefficient, β (SE), mL/minute per µg/dL: -0.0403 (0.0198); p=0.0426***
Pollack et al. 2015 Prospective cohort study; n=257 premenopausal women	Median: 0.88 Tertiles: • T1 (reference): <0.72 • T2: 0.72–1.10 • T3: >1.10	GFR	• **Regression β coefficient (% change per twofold increase in PbB): -3.73 (-6.55, -0.83)*** • **Regression β coefficient (% change per 2-fold increase in PbB) by tertile:** o **T2: -8.28 (-14.07, -2.5); p<0.05*** o **T3: -6.79 (-13.10, -0.49); p<0.05***
		SCr	Regression β coefficient (% change per 2-fold increase in PbB): 3.47 (0.86, 6.16)
		BUN	Regression β coefficient (% change per 2-fold increase in PbB): -0.13 (-4.97, 4.96)
		Blood albumin	Regression β coefficient (% change per 2-fold increase in PbB): -0.38 (-1.28, 0.52)
		Blood glucose	Regression β coefficient (% change per 2-fold increase in PbB): 0.93 (-0.28, 2.15)
		Blood protein	Regression β coefficient (% change per 2-fold increase in PbB): -0.76 (-1.61, 0.09)

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Spector et al. 2011[f] Cross-sectional study; n=3,941 adults	Mean (all): 1.7 Mean (≥60 years) Tertiles (all): • T1 (reference): ≤1.3 • T2: >1.3–2.2 • T3: >2.2	GFR	• **All participants: change in GFR (mL/minute/1.73 m^2) per 2-fold increase in PbB: -1.9 (-3.2, -0.7)*** • **All participants: OR for reduced GFR by tertiles** o T2: -1.6 (-4.2, 1.0) o **T3: -3.3 (-5.3, -1.4)*** o **p-trend: 0.001*** • **Participants ≥60 years: change in GFR (mL/minute/1.73 m^2) per 2-fold increase in PbB: -4.5 (-5.6, -3.3)**
Staessen et al. 1992 Cross-sectional study; n=1,981 adults (965 men; 1,016 women)	Mean men: 11.4 Mean women: 7.5	CCr	**Partial regression coefficient (SE) for CCr (mL/minute per log µg Pb/L):** • **Men: -13.1 (4.0); p≤0.001*** • **Women: -30.1 (3.4); p≤0.001***
Staessen et al. 2001 Cross-sectional study; n=200 17-year-old adolescent girls	Mean control: 1.4 Mean exposed area 1: 1.8 Mean exposed area 2: 2.7	Serum cystatin C	**Change in per 2-fold increase in PbB: +3.6% (1.5, 5.7)***
		Urine β_2-microblobulin	**Change per 2-fold increase in PbB: +16.0% (2.7, 31)***
Tsaih et al. 2004 Prospective study; n=448 (66–72 years of age); n=26 participants with diabetes, and n=115 participants with hypertension	Mean at baseline: 6.5 Mean at follow-up: 4.5	SCr	Baseline regression β coefficients (mg/dL per ln µg/dL): • All participants: 0.009 (SE 0.006) • **Participants with diabetes: 0.076 (SE 0.023); p<0.05*** • Participants with hypertension: 0.008 (0.010); Follow-up (4–8 years) regression β coefficients (mg/dL per ln µg/dL): • Participants with diabetes: 0.223 (SE 0.183); **Participants with hypertension: 0.352 (0.097); p<0.05***

Table 2-22. Summary of Epidemiological Studies Evaluating Renal Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated[c]	Result[d]
Yu et al. 2004 Prospective longitudinal study; n=121 patients with chronic renal insufficiency; progression of renal insufficiency was evaluated for 48 months	Mean: 4.2	GFR	**Change in GFR (mL/minute/1.73 m^2 per 1 µg/dL): -4.0 (p=0.0148)***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 6 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]A variety of methods are used to estimate GFR (Chao et al. 2015). Each has limitations for application to both clinical evaluations and epidemiology. The preferred method is to measure the clearance of substance from plasma that is known to be eliminated solely by glomerular filtration and is not reabsorbed in the renal tubule. Typically, in the clinical setting, this is accomplished with intravenous administration of GFR markers, such as ^{125}I-iothalmate, for the radiocontrast agent (e.g., iohexol). These procedures are feasible in the clinical setting, but not in epidemiology studies in which invasive procedures and administration of such agents is not practical or possible. Clearance of endogenous creatinine is an alternative that has had wide use in epidemiology. However, it requires concurrent measurements of serum creatinine and the rate of urinary excretion of creatinine, which can be accurately determined only with a carefully timed urine sample that can represent the amount of glomerular filtrate formed over a given time interval. Achieving accurately timed urine samples requires a rigidly implemented and supervised collection protocol, which is not always feasible, particularly in large-scale epidemiology studies. Alternatives to clearance methods are measurement of endogenous metabolites in plasma whose clearance approximates GFR. Typically, this is achieved with endogenous creatinine or cystatin C. The serum concentration of these two metabolites strongly correlates with GFR; however, the relationship between concentration and GFR is also affected by other variables, including age, sex, race, and creatinine muscle mass. Several approaches have been developed to improve estimates of GFR from serum creatinine that attempt to account for these co-variables. These methods rely on multiple variable regression models that relate GFR to serum creatinine and other significant determinants of GFR (Cockcroft and Gault 1976; Levey et al. 1999, 2009). An evaluation of two of the more commonly used methods for estimating GFR from serum creatinine, the CKD-EPI and MDRD equations, found that both achieved a median difference between calculated and measured GFR (from clearance measurements) that range from 2 to 6 mL/minute per 1.73 m^2 (Levey et al. 2009). The interquartile range in the difference was approximately 18 mL/minute per 1.73 m^2 in a validation dataset consisting of data for 3,986 study subjects. This suggests that approximately 25% of the GFR estimates from these methods are expected to be in error of the true GFR by >18 mL/minute (or approximately 15% of the GFR in a healthy adult, 120 mL/minute).
[d]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[e]Blood lead estimated by EDTA mobilization.
[f]Population from NHANES.

ACR = albumin-to-creatinine ratio; BUN = blood urea nitrogen; CCr = creatinine clearance; CI = confidence interval; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; EDTA = ethylenediaminetetraacetic acid; GFR = glomerular filtration rate; HR = hazard ratio; MDRD = Modification of Diet in Renal Disease; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; Sβ2M = serum β_2-microglobulin; SCr = serum creatinine concentration; SD = standard deviation; SE = standard error; UNAG = urine *N*-acetyl-β-D-glucosaminidase; UP = urine protein; UPHC = urine human complex-forming protein (α1-microglobulin)

A few studies have examined associations between low PbB and GFR in children and adolescents (de Burbure et al. 2006; Fadrowski et al. 2010; Khan et al. 2010a; Staessen et al. 2001). de Burbure et al. (2006) examined serum creatinine in a cross-sectional study of approximately 800 children (age range 8.5–12.3 years) who resided near nonferrous smelters. Serum creatinine and cystatin C decreased (indicating an increase in GFR) by approximately 7% in the upper quartile PbB group (mean 7.8 µg/dL) compared to the lowest quartile (<2.84 µg/dL). Fadrowski et al. (2010) examined adolescents (12–20 years, n=769). GFR (estimated from serum cystatin C) decreased with increasing PbB. In the upper quartile PbB group (>2.9 µg/dL), the decrease was 6.6 mL/minute/1.73 m^2, which represented approximately a 6% decrease in GFR. In a smaller study of younger children of Pb-exposed workers (ages 1–6 years; n=123; PbB: 8.1 µg/dL), serum creatinine was higher compared to controls (ages 1–6 years; n=123; PbB: 6.7 µg/dL) (Khan et al. 2010), indicating decreased GFR. Several factors may have contributed to the different outcomes in these studies (decrease or increase in GFR), including a different age range of the study groups, different approaches to adjusting outcome metrics for confounders, and different exposures (e.g., co-exposure to Pb, cadmium, and mercury in the de Burbure et al. 2006 study).

A smaller study of adolescents (17 years of age, n=200) also found evidence for higher serum cystatin C (indicating lower GFR) in a group with a mean PbB of 2.7 µg/dL compared to a group with a mean PbB of 1.4 µg/dL (Staessen et al. 2001).

A larger number of studies have been conducted in adult populations (Table 2-22). These include several prospective studies (Harari et al. 2018; Lin et al. 2001, 2003, 2006a, 2006b; Lin-Tan et al. 2007; Pollack et al. 2015; Tsaih et al. 2004; Yu et al. 2004). Most of these studies have examined changes in GFR in patients who had ongoing renal disease and depressed GFR (Lin et al. 2001, 2003, 2006a, 2006b; Lin-Tan et al. 2007; Yu et al. 2004). In adult participants with a median baseline PbB of 2.5 µg/dL, GFR decreased from 89 to 62 mL/minute after 16 years; GFR further decreased with increasing PbB (Harari et al. 2018). In addition, the risk of CKD was increased in participants with a median PbB of 4.6 µg/dL compared to participants with a PbB range of 0.15–3.30 µg/dL. In adult patients who had indications of renal insufficiency (e.g., serum creatinine concentration >1.5 mg/dL), GFR increased following repeated chelation therapy with calcium disodium ethylenediaminetetraacetic acid (EDTA) (Lin et al. 2003, 2006b). Yu et al. (2004) estimated the decline in GFR in patients with renal insufficiency to be approximately 4 mL/minute/1.73 m^2 per 1 µg/dL increase in PbB. A prospective study of premenopausal women estimated the decline in GFR to be approximately 3.73% per doubling of PbB (Pollack et al. 2015). The median PbB in the cohort was 0.88 µg/dL. A prospective study of older males found an association between increased serum creatinine (indicative in decreasing GFR) and PbB in subjects

diagnosed with hypertension or diabetes. Mean PbBs were 6.5 µg/dL at baseline and 4.5 µg/dL at follow-up (Tsaih et al. 2004).

Several large cross-sectional studies have examined associations between PbB and GFR in adults (Table 2-22). Three large studies relied on data collected in the NHANES (Munter et al. 2003; Navas-Acien et al. 2009; Spector et al. 2011). The Munter et al. (2003) study, which included 4,813 hypertensive subjects and 10,938 normotensive subjects, found an association between increasing PbB and decreasing GFR in the hypertensive group. Navas-Acien et al. (2009) included 14,788 adult subjects and reported decreased GFR (<60 mL/minute/1.73 m^2) among participants in the highest PbB quartile (mean >2.4 µg/dL). Spector et al. (2011) included 3,941 adults. In the age group ≥60 years, the estimate for the decline in GFR was 4.5 mL/minute/1.73 m^2 per doubling of PbB. The mean PbB in this group was 2.2 µg/dL. Several smaller cross-sectional studies have also found associations between increasing PbB and decreasing GFR in adult populations in which mean or median PbBs were <10 µg/dL (Åkesson et al. 2005; Payton et al. 1994; Staessen et al. 1992). Collectively, these studies indicate that Pb exposure is associated with decreasing GFR, and effects on GFR are evident in populations with PbB <10 µg/dL. People with on-going renal disease or hypertension may be more vulnerable to the effects of Pb. Estimates of the decline in GFR associated with increasing PbB vary across studies, with some studies indicating declines of 3–6 mL/minute/1.73 m^2 at PbB <10 µg/dL (Pollack et al. 2015; Spector et al. 2011; Yu et al. 2004). However, as noted above, the estimates may be inflated by reverse causality for associations between decreasing GFR and increasing Pb body burden.

Associations Between Bone Pb and Renal Effects. Studies evaluating associations between bone Pb and renal function are summarized in Table 2-23. Weaver et al. (2003a, 2005a, 2005b, 2006, 2009) conducted a series of studies evaluating associations between bone Pb and metrics of renal GFR (e.g., serum creatinine concentration, creatinine clearance calculated from serum creatinine concentration, BUN) and renal tubular injury (urinary NAG) in current and former Pb workers in South Korea. These studies provide evidence that tibia Pb is positively associated with serum creatinine concentration in older workers (Weaver et al. 2003a, 2005a, 2005b) and in male, but not female, workers (Weaver et al. 2009); and negatively associated with tibia Pb and creatinine clearance in male workers (Weaver et al. 2009) and in workers with vitamin D receptor (VDR) genotypes BB and Bb (Weaver et al. 2006). Tibia Pb was also positively associated with urinary NAG in older workers (Weaver et al. 2005a). Studies of participants of the longitudinal Normative Aging Study have found positive associations between tibia Pb and serum creatinine concentration in participants with diabetes (Tsaih et al. 2004) and with ALAD genotypes 1-2 and 2-2 (Wu et al. 2003a). One cross-sectional study did not find an association between tibia Pb and

estimated GFR (Barry et al. 2019). A small case-control study did not find an association between tibia Pb and end-stage renal disease. Taken together, the results suggest that long-term exposure to Pb is associated with diminished renal function.

Table 2-23. Associations Between Bone Pb and Renal Function

		Effect						
Reference	Population	GFR	SCr	CCr	NAG	RBP	BUN	ESRD
Barry et al. 2019	211 adult men	0 (T)	–	–	–	–	–	–
Muntner et al. 2007	55 adult ESRD patients; 53 controls	–	–	–	–	–	–	0 T
Tsaih et al. 2004	448 men[a]	–	0 T ↑ T (diabetics) 0 P 0 P (diabetics)	–	–	–	–	–
Weaver et al. 2003a	803 adult Pb workers; 135 controls[b]	–	0 T (all workers) ↑ T (>46 years[c])	0 T[c]	0 T[c]	0 T[c]	0 T[c]	–
Weaver et al. 2005a	803 adult Pb workers[b]	–	↑ T (>46 years[c])	–	↑ T (>46 years)[c]	–	–	–
Weaver et al. 2005b	795 adult Pb workers[b]	–	↑ T (>40.6 years)	–	–	–	–	–
Weaver et al. 2006	647 adult Pb workers[b]	–	0 T (VDR[d]) 0 T (VDR[e]) 0 P (VDR[d]) 0 P (VDR[e])	0 T (VDR[d]) ↓ T (VDR[e]) 0 P (VDR[d]) 0 P (VDR[e])	–	–	–	–
Weaver et al. 2009	398 adult male and 139 female Pb workers[b]	–	↑ T (M) 0 T (F)	↓ T (M) 0 T (F)	–	–	0 T (M) ↑ T (F)	–

Table 2-23. Associations Between Bone Pb and Renal Function

		Effect						
Reference	Population	GFR	SCr	CCr	NAG	RBP	BUN	ESRD
Wu et al. 2003a	709 men[a]	–	↑ T (ALAD[f]) 0 P	0 T ↓ P	–	–	–	–

[a]Participants in the Normative Aging Study.
[b]Current and former Pb workers in South Korea.
[c]Data were analyzed for all study participants and by age tertiles (Tertile 1: ≤36 years old; Tertile 2: 36.1–46 years old; Tertile 3: >46 years old). Any association observed in a specific age tertile are noted. If no association was observed for all participants and for all age tertiles, this is noted with a single entry of 0.
[d]Vitamin D receptor genotype bb.
[e]Vitamin D receptor genotypes BB and Bb.
[f]Interaction between ALAD genotype (ALAD 1-2/2-2 versus ALAD 1-1).

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; ALAD = aminolevulinic acid dehydratase; BUN = blood urea nitrogen; CCr = creatinine clearance; ESRD = end-stage renal disease; F = female; M = male; NAG = N-acetyl-D-glucosaminidase; P = patella; Pb = lead; RBP = retinol binding protein; SCr = serum creatinine concentration; T = tibia; VDR = vitamin D receptor

Mechanisms of Action. Several mechanisms have been established or proposed as mechanisms for kidney damage associated with exposure to Pb, including general mechanisms of Pb-induced toxicity (reviewed in Section 2.21). Mechanisms of renal damage associated with Pb exposure were recently reviewed in detail by EPA (2014c), including oxidative stress, inflammation, apoptosis of glomerular and tubular cells, alterations in renal gangliosides (plasma membrane lipids that play a role in the control of GFR), changes in renal vascular tone, and alterations in the renin-angiotensin-aldosterone system. As discussed in Pb Section 3.1.2 (Toxicokinetics, Distribution), Pb is distributed to the kidney, providing a toxicokinetic mechanism for direct effects to the kidney.

2.12 DERMAL

No epidemiological studies evaluating adverse dermal effects of chronic exposure to Pb were identified.

2.13 OCULAR

Few epidemiological studies have evaluated non-neurological ocular effects of Pb exposure, with studies examining associations with macular degeneration (Erie et al. 2009; Park et al. 2015) and cataract development (Schaumberg et al. 2004). In a cross-sectional study of 3,865 participants with a mean PbB of 2.69 µg/dL participating in the Korea National Health and Nutrition Examination study (2008–2011),

the risks of age-related early (adjusted OR 1.12; 95% CI 1.02, 1.23; p=0.009) and late (adjusted OR 1.25; 95% CI 1.05, 1.50; p=0.015) macular degeneration were increased (Park et al. 2015). A cross-sectional study of human donor eyes with (n=25) and without (n=36) age-related macular degeneration found no association between Pb concentration in the retinal pigment epithelium-choroid complex and subjects with age-related macular degeneration and normal subjects (Erie et al. 2009). A prospective study of 642 men participating in the Normative Aging Study found no association between PbB (range: 1.0–35.0 µg/dL) and risk of cataracts, although the risk of cataracts was increased in association with tibia Pb levels (Schaumberg et al. 2004). A prospective cohort study of 634 male participants of the Normative Aging Study found an association between patellar bone Pb concentration and incidence of primary open-angle glaucoma, with an HR of 5.06 (95% CI 1.61, 15.88; p=0:005) (Wang et al. 2018).

2.14 ENDOCRINE

Effects of chronic exposure to Pb on reproductive hormones are reviewed in Section 2.17 (Reproductive).

Overview. Effects on endocrine systems have been evaluated in several epidemiological studies in adults (general populations and workers), adolescents, and children. Investigations have focused on effects on thyroid function, cortisol levels, vitamin D levels, serum levels of other growth factors, and diabetes. Associations between PbB and thyroid function, assessed by measurement of serum thyroid hormone levels, is the most investigated endocrine outcome, although results do not demonstrate a consistent pattern of effect or dose-response relationships. Other endocrine endpoints have been evaluated in only a few studies.

The following endocrine effects have been associated with PbB:

- ≤10 µg/dL:
  - Altered serum levels of thyroid hormones (thyroxine [T4], triiodothyronine [T3], thyroid-stimulating hormone [TSH]); evaluated in multiple studies. Few effects were observed and results do not demonstrate consistent patterns of effects or exposure-response relationships.
  - Altered salivary cortisol awakening response in pregnant women.
  - Increased stress-induced salivary cortisol response in children.
  - Decreased serum levels of insulin-like growth factor-1 (IGF-1) in children.

- >10 µg/dL:
  - Altered serum levels of thyroid hormones (T4, T3, TSH); evaluated in a few studies; results do not demonstrate consistent patterns of effects or exposure-response relationships.
  - Increased thyroid peroxidase antibodies.
  - Decreased serum levels of vitamin D; evaluated in a few studies in children with consistent results.

Measures of Exposure. Studies evaluating the association between endocrine effects and Pb exposure evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Results of epidemiological studies on endocrine effects have not been consistent. In general, statistical analyses were not rigorous and potential confounding factors and effect modifiers were not fully considered. Exposure to other metals and other chemical with endocrine effects is an important confounding factor to consider when interpreting study results. Although a few studies were of large populations (e.g., NHANES participants); most studies examined relatively small populations and used cross-sectional designs.

Characterization of Effects. General trends for studies showing a relationship between PbB and endocrine effects are shown in Table 2-24. Several studies have evaluated associations between PbB and effects on serum levels of thyroid hormones (T4, T3, and TSH) at mean PbB ranging from <1 to 71 µg/dL; an overview of study results is presented in Table 2-25. Based on evaluation of thyroid hormones, it is unclear if PbB is associated with altered thyroid function. At PbB ≤10 µg/dL, results of epidemiological studies, including cross-sectional studies of large NHANES populations, show associations between PbB and some alterations in serum levels of thyroid hormones; however, results do not demonstrate apparent patterns or exposure response relationships (see discussion below on *Effect at Blood Pb Levels ≤10 µg/dL*). Increased thyroid peroxidase (TPO) antibodies were observed at PbB ≤10 µg/dL, although TSH was not increased. Epidemiological studies at PbB >10 µg/dL, conducted in smaller populations (n=25–309), show more effects on thyroid hormones than observed at PbB ≤10 µg/dL. However, similar to studies at lower PbB, results are inconsistent. Kahn et al. (2014) found decreased T4 ($p<0.0001$) and increased TPO antibodies ($p=0.0002$) during the second trimester of pregnancy in women (n=144) with mean PbB 20.00 µg/dL compared to women (n=147) with PbB of 5.57 µg/dL; no increase in TSH was observed. The adjusted OR (95% CI) for testing positive for TPO antibodies was 2.41 (1.563, 3.82). Results indicate that autoimmunity is a potential mechanism for altered thyroid function. This finding has not been corroborated in other studies.

Table 2-24. Overview of Endocrine Effects Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Altered levels of thyroid hormones[a], and increased TPO antibodies	Abdelouahab et al. 2008; Dundar et al. 2006; Luo and Hendryx 2014; Mendy et al. 2013; Nie et al. 2017; Yorita Christensen 2013
	Altered salivary cortisol levels	Braun et al. 2014; Gump et al. 2008
	Decreased serum IGF-1	Fleisch et al. 2013
>10–30	Altered levels of thyroid hormones[a] and increased TPO antibodies	Gustafson et al. 1989; Kahn et al. 2014; Lamb et al. 2008; Lopez et al. 2000
>30–50	Decreased serum vitamin D level	Luo and Hendryx 2014; Mahaffey et al. 1982; Rosen et al. 1980
>50	Altered levels of thyroid hormones[a]	Lopez et al. 2000; Pekcici et al. 2010; Robins et al. 1983; Singh et al. 2000; Tuppurainen et al. 1988
	Decreased serum vitamin D level	Rosen et al. 1980

[a]Thyroid hormones: T4, T3, and/or TSH.

IGF-1 = insulin-like growth factor-1; PbB = blood lead concentration; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone; TPO = thyroid peroxidase

Table 2-25. Effects on Thyroid Hormones Associated with Blood Lead Concentration (PbB)

Mean PbB (µg/dL)	Number of participants	T4		T3		TSH	Reference
		Total	Free	Total	Free		
PbB ≤10 µg/dL							
0.93	1,109 adolescents[a]	0	0	0	0	0	Chen et al. 2013
1.3	1,587 adults[a]	↓	0	0	0	0	Yorita Christensen 2013
1.52	4,652 adults[a]	↓	0	0	0	0	Mendy et al. 2013
1.74	87 women	0	–	0	–	↓	Abdelouahab et al. 2008
1.75	4,409 adults[a]	0	0	0	0	0	Chen et al. 2013
1.82	6,231 adults[a]	–	0	–	↑	0	Luo and Hendryx 2014
3.5	3,350 women	–	–	–	–	0	Nie et al. 2017
4.1	2,278 men	–	–	–	–	0	Nie et al. 2017
6.3[b]	24 infants[b]	–	0	–	–	0	Iijama et al. 2007
7.3	42 adolescents	–	↓	–	0	0	Dundar et al. 2006
PbB >10 µg/dL							
20.00	291 adults	–	↓	–	–	0	Kahn et al. 2014
20.56	309 pregnancy[c]	–	↓	–	–	–	Lamb et al. 2008
24.1	151 adults	0	0	–	–	0	Schumacher et al. 1998
25	68 children	0	0	–	–	–	Siegel et al. 1989

Table 2-25. Effects on Thyroid Hormones Associated with Blood Lead Concentration (PbB)

Mean PbB (µg/dL)	Number of participants	T4		T3		TSH	Reference
		Total	Free	Total	Free		
31	77 adults	–	0	–	0	0	Erfurth et al. 2001
<33.19[c]	6,231 adults[a]	0	–	–	↑	0	Luo and Hendryx 2014
39.5	25 adults	↑	–	–	–	↑	Gustafson et al. 1989
50.9	75 adults	↑	↓	0	–	0	Lopez et al. 2000
51.9	47 adults	↓	↓	–	–	0	Robins et al. 1983
51.9	58 adults	0	–	↓	–	↑	Singh et al. 2000
56.1	176 adults	↓	↓	0	–	0	Tuppurainen et al. 1988
71.1	65 adults	–	↑	–	↑	↑	Pekcici et al. 2010

[a]NHANES population.
[b]Umbilical cord PbB; assessments in infants.
[c]Mean not reported.

↑ = Increased; ↓ = decreased; 0 = no change; – = not assessed; NHANES = National Health and Nutrition Examination Survey; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid-stimulating hormone

Studies also have investigated alterations in serum levels of vitamin D at PbB >30 µg/dL (Mahaffey et al. 1982). In children and adolescents, serum levels of 1,25-dihydroxycholecalciferol were negatively associated with PbB over a range of 30–120 µg/dL (Mahaffey et al. 1982). Similar results were observed for vitamin D in children with PbB >50 µg/dL (Rosen et al. 1980). However, in children with PbB <10 µg/dL, no associations between PbB and vitamin D levels were observed (Kemp et al. 2007) (see discussion below on *Effect at Blood Pb Levels ≤10 µg/dL*). Studies investigating associations between PbB and other endocrine outcomes (salivary cortisol levels, serum levels of growth factors and diabetes) were conducted in populations with PbB ≤10 µg/dL (see discussion below on *Effect at Blood Pb Levels ≤10 µg/dL*).

Effect at Blood Pb Levels ≤10 µg/dL. Epidemiological studies of endocrine effects associated with PbB ≤10 µg/dL have examined thyroid function, as assessed by serum levels of thyroid hormones (Abdelouahab et al. 2008; Chen et al. 2013; Dundar et al. 2006; Iijama et al. 2007; Luo and Hendryx 2014; Mendy et al. 2013; Yorita Christensen 2013), cortisol levels and cortisol responses to stress (Braun et al. 2014; Gump et al. 2008), vitamin D levels (Kemp et al. 2007), IGF-1 levels (Fleisch et al. 2013), and diabetes (Moon 2013); study details are summarized in *Supporting Document for Epidemiological Studies for Lead,* Table 7. Studies examining thyroid function, including several large cross-sectional studies of NHANES populations (Chen et al. 2013; Mendy et al. 2013; Luo and Hendryx 2014; Yorita Christensen 2013), report inconsistent results; see Table 2-25. Results of NHANES studies at low PbB

(range of means: 0.93–1.82 µg/dL) are mixed, showing decreased total T4 and no change for free T4 (Mendy et al. 2013; Yorita Christensen 2013), and no change for total or free T4 (Chen et al. 2013; Luo and Hendryx 2014). The NHANES studies did not show associations between PbB and T3 or TSH levels, except for an increase in FT3 (Luo and Hendryx 2014). In smaller studies, decreased TSH and increased free T4 were observed at PbB of 3.10 and 7.3 µg/dL, respectively (Abdelouahab et al. 2008; Dundar et al. 2006). In a large, cross-sectional study, increased TPO antibodies were observed in women with PbBs >2.9 µg/dL, with a significant positive trend (p=0.008) for increased TSH; in men, there was no association (Nie et al. 2017). Thus, few effects on measures of thyroid function have been observed at PbB ≤10 µg/dL, and results do not demonstrate consistent patterns of effects or exposure-response relationships. Results of studies examining other endocrine effects associated with PbB have not been corroborated. Study findings include: associations between PbB and decreased cortisol awakening response during pregnancy at PbB ≥5.1 µg/dL (Braun et al. 2014); enhanced salivary cortisol response to cold stress in children at PbB 1.1–6.2 µg/dL (Gump et al. 2008); no association between PbB and basal cortisol levels or cortisol levels under stress (Ngueta et al. 2018); no association between PbB and serum vitamin D in children at PbB means 4.94–6.54 µg/dL (Kemp et al. 2007); decreased serum IGF-1 in children at PbB 5–9 µg/dL (Fleisch et al. 2013); and no association between PbB and diabetes in children at mean PbB 4.08 µg/dL (Moon 2013).

Mechanisms of Action. Adverse effects on the endocrine system (non-reproductive effects) associated with chronic Pb exposure have not been established; therefore, mechanisms of toxicity have not been identified. Thyroid function could be decreased through stimulation of autoimmunity to the thyroid gland, as shown by increased thyroid peroxidase antibodies (Kahn et al. 2014). In addition, general mechanisms of toxicity (reviewed in Section 2.21) of Pb would likely be involved in any endocrine toxicity.

2.15 IMMUNOLOGICAL

Overview. This section of the profile summarizes the immunological effects of Pb, exclusive of asthma, which is summarized in Section 2.5. Studies conducted in animal models have shown that Pb can perturb the humoral and cell-mediated immune systems, leading to decreased resistance to disease, sensitization, autoimmunity, and inflammation (EPA 2014c). These studies support epidemiological evidence of associations between Pb exposures (as indexed to PbB) and changes in biomarkers of humoral and cell-mediated immunity.

The following immunological effects have been associated with PbB:

- ≤10 µg/dL:
  - Increases in susceptibility to infections.
  - Sensitization to allergens.
  - Changes in indicators of humoral immunity (immunoglobulins, B-cells); demonstrated in several studies.
  - Changes in indicators of cell-mediated immunity (T-cells, eosinophils, neutrophils); demonstrated in several studies.
  - Changes in indicators of inflammatory response (circulating inflammation cytokines).
- >10 µg/dL:
  - Changes in indicators of humoral immunity (immunoglobulins, B-cells).
  - Changes in indicators of cell-mediated immunity (T-cells, natural killer [NK]-cells, neutrophils).
  - Changes in indicators of inflammatory response (inflammatory response of activated monocytes).
  - Decreases in circulating complement.

Measures of Exposure. Studies of associations between Pb exposure and immunological outcomes have relied on PbB as a biomarker of exposure. Most studies have been cross-sectional in design, which increases uncertainty in the interpretation of the results since the exposure history of the subjects is not necessarily indicated by the cross-sectional PbB measurement.

Confounding Factors and Effect Modifiers. The immune system is responsive to a multitude of environmental and physiological factors, which can be confounding factors or effect modifiers in studies of associations between Pb exposure and immunological outcomes. Factors that have been considered in some studies, but not consistently across studies, include age, sex, smoking, physical activity, allergen exposures, history of inflammatory disease, SES factors, recreational activities, and co-exposures to other chemicals. Immunological outcomes observed in epidemiological studies may also be secondary to other systemic effects of Pb (e.g., hematological, splenic gene expression) that affect the immune system.

Characterization of Effects. Table 2-26 lists epidemiological studies that have found associations between PbB and immunological outcomes, grouped by population PbB (typically mean or geometric

mean). Several studies have found alterations in immunological endpoints in association with PbB over the range <10–>50 µg/dL.

Table 2-26. Overview of Immunological Effects Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased susceptibility to infections	Krueger and Wade 2016; Park et al. 2019
	Sensitization to allergens	Jedrychowski et al. 2011; Pizent et al. 2008
	Changes in indicators of humoral immunity[a]	Hon et al. 2009, 2010; Karmaus et al. 2005; Min and Min 2015; Pizent et al. 2008; Sarasua et al. 2000; Wells et al. 2014; Xu et al. 2015
	Changes in indicators of cell-mediated immunity[b]	Boscolo et al. 2000; Conterato et al. 2013; Hsiao et al. 2011; Karmaus et al. 2005; Sarasua et al. 2000; Wells et al. 2014
	Changes in indicators of inflammatory response[c]	Kim et al. 2007, Sirivarasai et al. 2013; Songdej et al. 2010
>10–30	Changes in indicators of humoral immunity[a]	Heo et al. 2004, Lutz et al. 1999; Sun et al. 2003; Wang et al. 2017a
	Changes in indicators of cell-mediated immunity[b]	Alomran and Shleamoon 1988; Bergeret et al. 1990; Boscolo et al. 1999; Di Lorenzo et al. 2006; Fischbein et al. 1993; Kimber et al. 1986; Mishra et al. 2003; Queiroz et al. 1993, 1994; Sata et al. 1998; Valentino et al. 1991, 2007; Zhao et al. 2004
	Changes in indicators of inflammatory response[c]	Valentino et al. 2007
>30–50	Changes in indicators of humoral immunity[a]	Ewers et al. 1982; Heo et al. 2004; Pinkerton et al. 1998
	Changes in indicators of cell-mediated immunity[b]	Conterato et al. 2013; Fischbein et al. 1993; Garcia-Leston et al. 2012; Niu et al. 2015; Pinkerton et al. 1998
>50	Changes in indicators of humoral immunity[a]	Basaran and Undeger 2000
	Changes in indicators of cell-mediated immunity[b]	Basaran and Undeger 2000; Mishra et al. 2010; Undeger et al. 1996
	Decreases in circulating complement levels	Ewers et al. 1982; Undeger et al. 1996

[a]Immunoglobulins, B-cells.
[b]T-cells, natural killer (NK) cells, eosinophils, neutrophils and related receptors and cytokines.
[c]Circulating cytokines (e.g., C-reactive protein [CRP], interleukin-6 [IL-6], tumor necrosis factor-alpha [TNFα]).

Humoral immunity. Numerous epidemiological studies have examined associations between Pb exposure and circulating levels of immunoglobulins. These studies provide evidence that exposure to Pb is associated with increases in circulating IgE in children (Hon et al. 2009, 2010; Karmaus et al. 2005; Lutz

et al. 1999; Sun et al. 2003; Wang et al. 2017a) and in adults (Heo et al. 2004; Sarasua et al. 2000). IgE is an important mediator of hypersensitivity reactions and inflammation and Pb-induced perturbations in IgE may contribute to associations between Pb exposure and sensitization and inflammation. Although some studies have found changes in levels of other immunoglobins, the evidence for these effects is not as strong as for IgE (Alomran and Shleamoon 1988; Anetor and Adeniyi 1998; Ewers et al. 1982; Kimber et al. 1986; Pinkerton et al. 1998; Queiroz et al. 1994b; Ündeger et al. 1996). The association between circulating IgE levels and PbB appears to extend to PbB levels <10 µg/dL (Karmaus et al. 2005; Min and Min 2015; Pizent et al. 2008; Sarasua et al. 2000; Wells et al. 2014).

T-cells. T-cells are important mediators of immunity to self-cells (e.g., cancer cells and cells infected with virus) and for activation of B-cells and humoral immunity. Epidemiological studies provide evidence that exposure to Pb is associated with decreases in T-cell abundance in children (Karmaus et al. 2005; Lutz et al. 1999; Sarasua et al. 2000; Zhao et al. 2004) and increases in abundance in adults (Boscolo et al. 1999, 2000; Sarasua et al. 2000). Several studies in adults found no consistent effect on T-cell abundance (Fischbein et al. 1993; Mishra et al. 2010; Pinkerton et al. 1998; Ündeger et al. 1996; Yücesoy et al. 1997b). Most of the studies on T-cell abundance did not differentiate specific classes of T-cell population affected; however, evidence is stronger for effects on CD3+ cells (Karmaus et al. 2005; Lutz et al. 1999; Sarasua et al. 2000; Zhao et al. 2004), with some studies finding effects on abundances of CD4+ (T helper) or CD8+ (T cytotoxic) cells (Boscolo et al. 1999, 2000; Karmaus et al. 2005; Sarasua et al. 2000). The association between circulating T-cell abundance and PbB appears to extend to PbB levels ≤10 µg/dL (Boscolo et al. 2000; Karmaus et al. 2005; Sarasua et al. 2000).

Neutrophils. Neutrophils are phagocytic cells that function in the immune defense against bacterial infections. Epidemiological studies have found associations between Pb exposure and neutrophil function. The effects on cultured human PMNs in populations that had mean PbB >10 µg/dL includes suppression of chemotaxis, phagocytosis, respiratory oxidative burst, and antigen killing (Alomran and Shleamon 1988; Bergeret et al. 1990; Fischbein et al. 1993; Kimber et al. 1986; Queiroz et al. 1993, 1994; Valentino et al. 1991). In a worker population having mean PbB ≤10 µg/dL, increasing PbB was associated with decreases in circulating neutrophil abundance (Conterato et al. 2013), whereas in a worker population having mean PbB >10 µg/dL, PbB was associated with increases in neutrophil abundance (Di Lorenzo et al. 2006) and decreases in circulating complement levels (Ewers et al. 1982; Undeger et al. 1996).

NK cells. NK cells contribute to the immune defense (cytotoxicity) against tumor cells and viral infected cells. Although a few studies have found associations between PbB and NK cell abundance (Boscolo et al. 1999, 2000), most studies have found no associations (Fischbein et al. 1993; Garcia-Leston et al. 2011; Karmaus et al. 2005; Kimber et al. 1986; Mishra et al. 2003; Pinkerton et al. 1998; Sarasua et al. 2000; Undeger et al. 1996; Yucesoy et al. 1997) at population mean PbBs ≤10 or >10 μg/dL.

Lymphocyte activation. A few epidemiological studies have found associations between exposure to Pb and increased lymphocyte activation (HLA-DR expression) and proliferation in children (Lutz et al. 1999) and adults (Alomran and Shleamon 1988; Boscolo et al. 1999; Cohen et al. 1989; Fischbein et al. 1993; Kimber et al. 1986; Mishra et al. 2003). These studies found effects in populations that had PbB >10 μg/dL.

Sensitization. Epidemiological studies provided evidence for associations between exposure to Pb and sensitization. This evidence includes increased risk of atopy to airborne allergens in children (Jedrychowski et al. 2011) and adults (Pizent et al. 2008). Consistent with findings in animal studies which found that Pb exposure suppresses delayed type hypersensitivity (DTH), Hsiao et al. (2011) found that higher PbB was associated with decreases in circulating levels of IFN-γ γa T-helper cytokine known to be important in DTH). The above effects related to sensitization have been observed in populations that had mean PbB ≤10 μg/dL.

Inflammation. A few epidemiological studies have examined possible associations between Pb exposure and biomarkers of inflammation. Results for these studies suggest that Pb exposure can modify the control of inflammatory responses, including modifying macrophage NO release and ROS production in macrophages harvested from exposed children (Pineda-Zavaleta et al. 2004), and in adults, decreases in abundance of circulating monocytes (Conterato et al. 2013; Pinkerton et al. 1998), and lower circulating levels of HLA-DR+ (Fischbein et al. 1993) in adults. Three studies found evidence for effects indicative of enhancement or stimulation of inflammation in adults at mean PbB ≤10 μg/dL. Outcomes included increases in circulating tumor necrosis factor-alpha (TNFα) (Kim et al. 2007) and C-reactive protein (CRP) in men (Songdej et al. 2010; Sirivarasai et al. 2013).

Effect at Blood Pb Levels ≤10 μg/dL. Epidemiological studies that have evaluated immunological effects associated with PbB ≤10 μg/dL are summarized in Table 2-27, with additional details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 8. Outcomes that have been observed in populations with PbB ≤10 μg/dL include susceptibility to infections, sensitization in children and

adults, humoral and cell-mediated immunity in children and adults, and inflammation in children and adults.

Susceptibility to infections. A cross-sectional study of data from NHANES (1999–2012) found a trend for increasing OR for being seropositive for *H. pylori, T. gondii*, and *Hepatitis B* virus in a population that has a geometric mean PbB of 1.5 µg/dL (Krueger and Wade 2016).

Humoral immunity. Several studies have found associations between circulating IgE levels and PbB in populations with mean or geometric mean PbB levels ≤10 µg/dL (Karmaus et al. 2005; Min and Min 2015; Pizent et al. 2008; Sarasua et al. 2000; Wells et al. 2014). In general, these studies found increases in serum IgE levels in association with increasing PbB in children (Karmaus et al. 2005; Sarasua et al. 2000; Wang et al. 2017a; Wells et al. 2014) and adults (Min and Min 2015; Pizent et al. 2008). A cross-sectional study of children (3–7 years of age) found an association between increasing PbB and decreasing *Hepatitis B* virus antibody titers (Xu et al. 2015).

T-cells, neutrophils, and NK cells. Several studies have found associations between T-cell abundance and PbB in populations with mean or geometric mean PbB levels ≤10 µg/dL. In studies of children, T-cell abundances decreased (Karmaus et al. 2005), whereas in a study of adults, T-cell abundance increased (Boscolo et al. 2000). In a study of Pb workers, neutrophil abundance was lower in Pb workers compared to controls (Contertato et al. 2013). The worker populations included a group of painters in which the mean PbB was 5.4±0.4 (SE) µg/dL, compared to the control group (1.5±0.1, SE). A study of a population of atopic adult women with median PbB 6.6 µg/dL (25^{th}–75^{th} percentile range: 4.9–7.9), found an association between increasing PbB and increasing abundance of NK cells (CD4+CD45RO+; Boscolo et al. 2000).

Sensitization. Exposures to Pb that resulted in population geometric mean PbB ≤10 µg/dL was associated with increased risk of atopy to airborne allergens in children (Jedrychowski et al. 2011) and adults (Pizent et al. 2008). Higher PbB was associated with decreases in circulating levels of IFN-γ (a T-helper cytokine known to be important in DTH) in a population of children with a mean PbB of 8.8±0.45 (SD) µg/dL (Hsaio et al. 2011).

Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Sensitization			
Jedrychowski et al. 2011 Prospective study; n=224 children (at 5 years of age) of women recruited in the 2nd trimester of pregnancy	Gmean (95% CI:) Cord: 1.16 (1.12, 1.22) Maternal: 1.60 (1.52, 1.67)	Atopy	Adjusted RR: • **Cord PbB: 2.28 (1.12, 4.62)*** • Maternal PbB: 1.72 (0.98, 3.00)
Pizent et al. 2008 Cross-sectional study; n=216 adults (age range 19–67 years)	Gmean (95% CI:): • Male: 3.17 (0.99, 7.23) • Female: 2.16 (0.56, 7.35)	SPT	**Adjusted OR for positive SPT: 0.92 (0.86, 0.98)***
Humoral immunity			
Karmaus et al. 2005 Cross-sectional study; n=671 children (age 7–10 years)	Gmean (95% CI:): • Males: 2.78 (1.48, 4.82) • Females: 2.54 (1.10, 4.38)	IgE	**Mean serum IgE levels were higher (p≤0.05) in PbB strata >2.84 and >3.41 µg/dL***
		B-cells	**B-cell abundance was lower (p≤0.05) in PbB stratum 2.21–2.83 compared to <2.2 µg/dL***
Min and Min 2015 Cross-sectional study; n=4,287 adults (age ≥22 years)[c]	Gmean (95% CI:): • 1.46 (1.44, 1.50)	IgE	β for 1 $\log_{10}$ increase in IgE per 1 $\log_{10}$ increase in PbB: • **Q2 (1.1–1.69 µg/dL): 0.20 (0.05, 0.34)*** • **Q3 (1.7–2.6 µg/dL): 0.26 (0.10, 0.42)*** • **Q4 (2.61–26.4 µg/dL): 0.35 (0.20, 0.51)***
Pizent et al. 2008 Cross-sectional study; n=216 adults (age range 19–67 years)	Gmean (95% CI:): • Male: 3.17 (0.99, 7.23) • Female: 2.16 (0.56, 7.35)	IgE	**β log increase in IgE per log increase in PbB µg/L (SE), females not taking oral contraceptives or hormone replacement therapy: 0.600 (0.298); p=0.046***

Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Sarasua et al. 2000 Cross-sectional study; n=1,561 residents of communities with elevated levels of Cd or Pb in soil (age range 6 months–75 years) (1991)	Gmean (95% CI:) • Age 6–35 months: 7.0 (1.7, 16.1) • Age 36–71 months: 6.0 (1.6, 14.1) • Age 6–15 years: 4.0 (1.1, 9.2)	IgA	**β per 1 µg/dL PbB, age 6–35 months: 0.8, p<0.01***
		IgG	• **β per 1 µg/dL PbB, age 6–35 months: 0.8; p<0.01*** • **β per 1 µg/dL PbB, age 6–15 years: 7.5; p=0.02***
		IgM	**β per 1 µg/dL PbB, age 6–35 months: 1.0; p=0.03***
		B-cell count	**β per 1 µg/dL PbB, age 6–35 months: 16.9; p<0.01***
		B-cell%	**β per 1 µg/dL PbB, age 6–35 months: 0.19; p=0.02***
Wang et al. 2017a Cross-sectional study; n=930 children (mean age: 5.74 years; 469 boys and 461 girls)	**PbB** Gmean (GSD) • All: 1.86 (1.21) • Boys: 1.88 (1.22) • Girls: 1.83 (1.20)	IgE	• **All participants, β per ln-unit increase in PbB (2.72 µg/dL): 0.26 (0.009, 0.50); p=0.042*** • **Boys, β per ln-unit increase in PbB (2.72 µg/dL): 0.40 (0.03, 0.76); p=0.036*** • Girl, β per ln-unit increase in PbB (2.72 µg/dL): 0.02 (-0.35, 0.40); p=0.901
Wells et al. 2014 Cross-sectional study; n=1,788 children (age 2–12 years)[c]	Gmean (95% CI:) • 1.13 (1.04, 1.22)	IgE	**β per 1 µg/dL PbB for % increase per 1 µg/dL: 10.27 (3.52, 17.47)***
Xu et al. 2015 Cross-sectional study; n=590 children (age 3–7 years)	Gmean (SD of log PbB): • Male: 6.61 (0.19) • Female: 6.16 (0.18)	Hepatitis B virus	Antibody titers decreased with increasing PbB β signal to cut-off ratio per 1 µg/dL (SE) at two assessment dates: • **2011: -0.4467 (0.0225); p<0.001*** • **2012: 0.3661 (0.0193); p<0.001***

Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Cell-mediated immunity			
Boscolo et al. 2000 Cross-sectional study; n=30 atopic women (age range 19–49 years) and 30 non-atopic women	Median: • Atopic: 6.4 (4.9, 7.9) • Control: 5.5 (4.4, 6.7)	T-cell abundance	Positive correlation between PbB and T-cell abundances in non-atopic subjects (r for cell count): • **CD4+CD45RO-: 0.464; p<0.05*** • **CD3+ CD8+: 0.430; p<0.05*** • **CD3- HLA-DR+>: 0.435; p<0.05***
Conterato et al. 2013 Cross-section study of battery manufacture workers (n=59), and automobile painters (n=23); ages 15–61 years	Median: • Battery workers: 49.8 (4.0) • Painters: 5.4 (0.4) • Controls: 1.5 (0.1)	Neutrophil abundance	Mean (SE), $10^3/mm^3$: • **Battery workers: 2.87 (0.27); p<0.05*** • **Painters: 3.07 (0.13); p<0.05*** • Controls: 3.75 (2.49)
Hsiao et al. 2011 Cross-sectional study; n=214 children (primary school grades 5–6)	Mean (SD): • Allergic and residing near oil refinery: 8.80 (0.45) • Non-allergic and residing near oil refinery: 5.23 (0.36) • Other rural or urban groups, allergic or not: 3.16–3.83		Compared to all other groups, allergic group residing near the refinery had:
		IFN-γ	**>96% decrease in serum IFN-γ; p<0.05***
		IL-12	**>96% decrease; p<0.05***
		IL-4	**>500% increase; p<0.05***
		IL-25	**>500% increase; p<0.05***
Karmaus et al. 2005 Cross-sectional study; n=67 children (age 7–10 years)	Gmean (95% CI:): • Males: 2.78 (1.48, 4.82) • Females: 2.54 (1.10, 4.38)	T-cell and T_C	**Lower (p≤0.05) in PbB stratum 2.21–2.83 compared to <2.2 µg/dL***

Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Sarasua et al. 2000 Cross-sectional study; n=1,561; age range 6 months–75 years)	Gmean (95% CI:L): Age • 6–35 months: 7.0 (1.7, 16.1) • 36–71 months: 6.0 (1.6, 14.1) • Age 6–15 years: 4.0 (1.1, 9.2)	T-cell%	**β per 1 µg/dL PbB: -0.18; p=0.03***
		T-cell count	β per 1 µg/dL PbB: 7.2; p=0.59
		NK-cell%	β per 1 µg/dL PbB: 0.00; p=0.99
		NK-cell count	β per 1 µg/dL PbB: 1.3; p=0.60
Wells et al. 2014 Cross-sectional study; n=1,788 children (age 2–12 years)[c]	Gmean (95% CI:): 1.13 (1.04, 1.22)	Eosinophils %	**β for % increase per 1 µg/dL: 4.61 (2.44, 6.83)***
Inflammation			
Kim et al. 2007 Cross-sectional study; n=300 adults (mean age 24±2 years)	Mean (range): • Q1: 1.46 (0.337,1.885) • Q2: 2.22 (1.886, 2.511) • Q3: 2.77 (2.513, 3.103) • Q4: 3.93 (3.110, 10.470)		In males for PbB stratum >2.51 relative to lower PbB stratum. % per 1 µg/dL increase in PbB:
		TNFα	**23% (4, 55); p=0.015***
		WBC	**15% (0, 35); p=0.004***
		IL-6	26% (0, 55%); p=0.082
Sirivarasai et al. 2013 Cross-sectional study; n=924 male adults (mean age 43 years)	Mean: 5.45 Quartiles, mean (range): • Q1: 2.44 (1.23, 3.47) • Q2: 3.95 (3.48, 4.55) • Q3: 5.77 (4.56, 6.47) • Q4: 9.21 (6.48, 24.62)	CRP	CRP was higher in upper quartile PbB stratum compared to Q1 and Q2 (p<0.001). In Q4 stratum, adjusted OR was elevated for GSTM1 and GSTT1 null genotypes: • **-GSTM1-/- and GSTT1-/-: 1.98 (1.47, 2.55)*** • **-GSTM1-/-: 1.32 (1.03, 1.69)*** • **-GSTT1-/-: 1.65 (1.17, 2.35)***

Table 2-27. Summary of Epidemiological Studies Evaluating Immunological Effects at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population	PbB (µg/dL)	Outcome evaluated	Result[b]
Songdej et al. 2010 Cross-sectional study; n=9,145 adults (age >40 years)[c]	Gmean: 1.89		OR for <1.16 versus >3.09 µg/dL:
		CRP	• **Males: 2.85 (1.49, 5.45)*** • Females: 0.57 (0.43, 0.76)
		Fibrinogen	• Males: 1.15 (0.61, 2.16) • Females: 0.87 (0.57, 1.33)
		WBC	• Males: 1.55 (0.96, 2.49) • Females: 0.84 (0.62, 1.13)

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 8 for more detailed descriptions of studies.
[b]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[c]Study of NHANES participants.

Cd = cadmium; CI = confidence interval; CL = confidence limit; CRP = C-reactive protein; Gmean = geometric mean; GSTM1 = glutathione S-transferase Mu 1; GSTT1 = glutathione S-transferase theta 1; IFN-γ = interferon gamma; Ig = immunoglobulin antibody; IL = interleukin; NHANES = National Health and Nutrition Examination Survey; NK = natural killer; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error; SPT = skin prick test; TNFα = tumor necrosis factor-alpha; WBC = white blood cell

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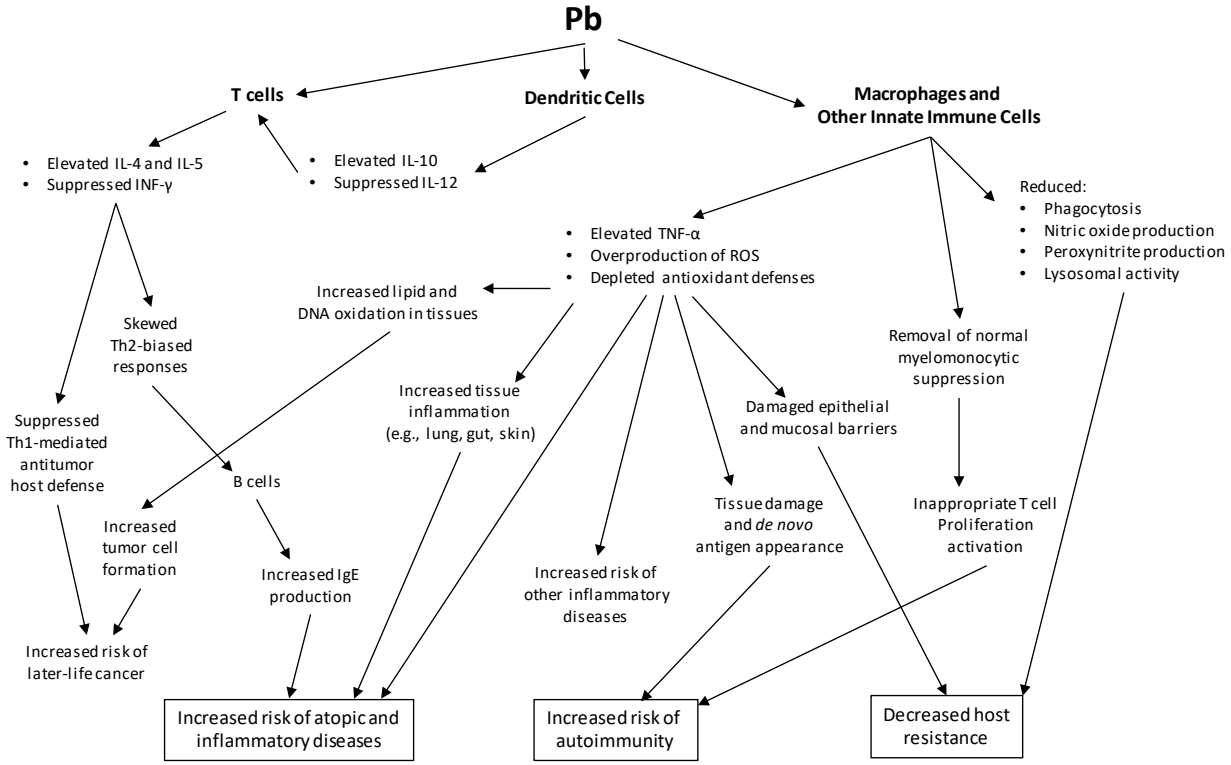
Inflammation. A few studies have found evidence for increases in circulating TNFα (Kim et al. 2007) and CRP (Songdej et al. 2010; Sirivarasai et al. 2013) in adults at mean PbB <10 µg/dL. These outcomes are indicative of enhancement or stimulation of inflammation.

Mechanisms of Action. Studies conducted in animal models and cell cultures have shown that Pb can disrupt the immune response through diverse mechanisms (EPA 2014c). Figure 2-6 shows the various potential pathways by which Pb may perturb the immune system and increase risk of atopy and inflammation, autoimmunity, and host resistance. In addition to its effects on T-cells, dendritic cells, and macrophages, Pb may also alter immune function at many other processes in the pathways shown in Figure 2-6.

Figure 2-6. Immunological Pathways by which Pb Exposure Potentially may Increase Risk of Immune-Related Diseases



Note: As shown in the figure, immunological pathways may increase risk of diseases such as cancer and inflammatory diseases in the cardiovascular, renal, and hepatic systems.

Source: EPA 2014c

2.16 NEUROLOGICAL

Overview. The literature on the neurobehavioral effects of Pb is extensive. With the improvement in analytical methods to detect Pb in the various biological media and in study designs, the concentrations of Pb, particularly in blood, associated with alterations in neurobehavioral outcomes continue to decrease, suggesting that there may be no threshold for the effects of Pb on intellectual function (CDC 2012d). Due to the enormous size of the database on neurobehavioral effects of Pb, this discussion has been limited to representative and/or major studies published on specific topics crucial to understanding dose-response relationships in the lower exposure ranges (e.g., PbB ≤10 µg/dL). For additional information, the reader is referred to a recent review of this topic (EPA 2014c).

Numerous epidemiological studies have evaluated effects of Pb on neurological function in children and adults. These studies show consistent evidence of associations between decrements in cognitive and neuromotor/neurosensory function with PbBs that range from ≤10 to >50 µg/dL. The PbB-effect relationship for cognitive effects in children extends well below 10 µg/dL, with no evidence for a threshold. In several PbB-effect models, the slope for decrements in cognitive function in children show greater increases at lower PbB ranges. These models predict that larger decrements in cognitive function would occur when PbB increases from 1 to 10 µg/dL, than when PbB increases to levels >10 µg/dL. All of the cognitive and neurobehavioral effects of Pb observed in children have also been observed in adults; however, it is not certain what life-stage exposures contribute most to outcomes in adults. A few studies that have followed children to early adulthood provide evidence of associations between childhood Pb exposure (e.g., PbB) and behavioral and neuroanatomical changes in adults, suggesting a possible role of exposures in childhood to adult outcomes. Other studies have found evidence of associations between cumulative Pb exposures (e.g., bone Pb) and neurological outcomes in adults.

The following neurobehavioral effects in children have been associated with PbB:

- ≤10 µg/dL:
  - Decreased cognitive function including full scale IQ (FSIQ).
  - Altered mood and behaviors that may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency.
  - Altered neuromotor and neurosensory function, including gross and fine motor skills, visual-motor integration, and hearing threshold.

- >10 µg/dL:
  - Decreased cognitive function including FSIQ.
  - Altered mood and behaviors, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency.
  - Altered neuromotor and neurosensory function, including gross and fine motor skills, visual-motor integration, hearing threshold, and visual evoked potentials.
  - Peripheral neuropathy.
  - Encephalopathy.

The following neurobehavioral effects in adults have been associated with increasing PbB:

- ≤10 µg/dL:
  - Decreased cognitive function including attention, memory, and learning.
  - Altered neuromotor and neurosensory function including decreased reaction time and walking speed, tremor, and increased risk of amyotrophic lateral sclerosis (ALS).
  - Altered mood and behavior including risk of various psychiatric symptoms including anxiety, depression, and schizophrenia.
- >10 µg/dL:
  - Reduced brain volume and altered brain neurochemistry.
  - Decreased cognitive function.
  - Altered neuromotor and neurosensory function.
  - Decreased peripheral nerve conduction velocity.

Measures of Exposure. Studies conducted in children have relied heavily on PbB as an exposure metric. Although bone or tooth Pb measurements may be informative, few studies have been conducted in children (Bellinger et al. 1994; Campbell et al. 2000b; Fergusson et al. 1993; Kim et al. 1995; Needleman et al. 1979, 1990, 1996, 2002; Wasserman et al. 2003). Maternal bone Pb has been used as an exposure metric for evaluating outcomes in children (Gomaa et al. 2002; Xu et al. 2015). Bone Pb has been used as metric of cumulative exposure in a growing number of epidemiological studies of adults (see Section 3.3.1, Biomarkers of Exposure). An association between a health outcome and bone Pb does not necessarily infer an association between the outcome and PbB (or *vice versa*) as indicated by studies in which associations are not consistent for the two metrics. These differences may reflect the relative importance of cumulative exposure on the given outcome, or differences in error associated with measurements of blood and bone Pb concentrations. A review by Shih et al. (2007) concluded that

negative associations between Pb and cognitive function are stronger for bone Pb (specifically tibia Pb) for environmental exposures and for PbB for occupational exposures.

Confounding Factors and Effect Modifiers. Various factors have the potential to contribute to bias in estimates of associations between PbB and neurobehavioral outcomes. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome. Neurological function can be influenced by numerous factors that may also correlate with Pb exposure in the population studied. A contributor to these correlations is the influence of SES-related factors on Pb exposure. Confounding factors that are typically evaluated in all high-quality studies include maternal education and IQ, SES, and HOME score (parental care). However, other factors have also been explored in some studies, including maternal substance abuse (including prenatal alcohol) and psychopathology, birth weight, exposure to tobacco smoke, nutritional status, and ALAD allele type. The relatively strong correlation between SES and PbB can result in overcontrol in studies of populations that have wide SES variability. Overcontrol will tend to attenuate the estimated association between PbB and the outcome (Bellinger 2004). However, SES may also modify the effect of Pb on neurological function (Bellinger et al. 1990; Ris et al. 2004; Tong et al. 2000). If this were to occur, then SES would also be an effect-modifier.

Characterization of Effects in Children. A large number of studies showing decrements in neurological function in children have been published (Table 2-28). Collectively, these studies support the concept that Pb affects cognitive function in children prenatally exposed to PbB ≤10 µg/dL, with numerous studies providing evidence for effects at PbB ≤5 µg/dL. Neurobehavioral functions that have been associated with PbB ≤10 µg/dL include decrements in cognitive function (learning and memory), altered behavior and mood (e.g., attention, hyperactivity, impulsivity, irritability, delinquency), and altered neuromotor and neurosensory function (visual-motor integration, dexterity, postural sway, changes in hearing and visual thresholds). These outcomes also have been observed in association with PbB >10 µg/dL. In children who have been followed to early adulthood, mean childhood PbBs of 13 µg/dL were associated with altered brain volume and neurochemistry (Brubaker et al. 2010; Cecil et al. 2008, 2011). PbBs >30 µg/dL are associated with a variety of decrements in cognitive function, behavior (e.g., depression, aggression), and nerve function (e.g., decrements in fine and gross motor skills, peripheral neuropathy). Encephalopathy has been observed in children who have experienced severe Pb poisoning typical of PbB >80 µg/dL (NAS 1972).

Table 2-28. Overview of Neurological Effects in Children Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Intellectual deficits[a]	Blackowicz et al. 2016; Baghurst et al. 1992; Bellinger and Needleman 2003; Bellinger et al. 1992; Boucher et al. 2014; Braun et al. 2012; Canfield et al. 2003; Chandramouli et al. 2009; Chiodo et al. 2004; Desrochers-Couture et al. 2018; Dietrich et al. 1986, 1987, 1989, 1991, 1992, 1993a; Emory et al. 2003; Evens et al. 2015; Geier et al. 2017; Gomaa et al. 2002; Hong et al. 2015; Hu et al. 2006; Jedrychowski et al. 2009; Jusko et al. 2008; Kordas et al. 2011; Krieg et al. 2010; Lanphear et al. 2000a, 2005, 2019; Lin et al. 2013; Liu et al. 2014b; Mazumdar et al. 2011; McLaine et al. 2013; Min et al. 2009; Miranda et al. 2009; Polanska et al. 2018; Rodrigues et al. 2016; Rooney et al. 2018; Ruebner et al. 2019; Schnaas et al. 2006; Shadbegian et al. 2019; Sobin et al. 2015; Tellez-Rojo et al. 2006; Vigeh et al. 2014; Wang et al. 2008; Wasserman et al. 1994, 1997, 2003; Zhang et al. 2013; Zhou et al. 2017
	Altered mood and behavior[b]	Arbuckle et al. 2016; Boucher et al. 2012; Braun et al. 2006, 2008; Choi et al. 2016; Dietrich et al. 2001; Froehlich et al. 2009; Fruh et al. 2019; Geier et al. 2018; He et al. 2019; Hong et al. 2015; Huang et al. 2016; Ji et al. 2018; Joo et al. 2017, 2018; Kim et al. 2013a, 2016; Liu et al. 2014a, 2015b; Park et al. 2016; Sioen et al. 2013; Stroustrup et al. 2016; Wang et al. 2008; Winter and Sampson 2017
	Altered neuromotor neurosensory function[c]	Chiodo et al. 2004; Dietrich et al. 1987, 1989, 1993b; Ethier et al. 2012; Fraser et al. 2006; Kim et al. 2013b; Liu et al. 2018b; Osman et al. 1999; Silver et al. 2016; Tellez-Rojo et al. 2006
	Altered brain anatomical development and activity	Cecil et al. 2008, 2011
>10–30	Intellectual deficits[a]	Baghurst et al. 1992; Bellinger et al. 1987, 1990, 1991; Chen et al. 2005, 2007; Dietrich et al. 1992, 1993a; Factor-Litvak et al. 1999; Hornung et al. 2009; Kordas et al. 2006; Magzamen et al. 2013, 2015; Marques et al. 2014; McMichael et al. 1988; Roy et al. 2011; Schnaas et al. 2000; Shen et al. 1998; Tong et al. 1996; Wasserman et al. 1994, 1997, 2000, 2003
	Altered mood and behavior[b]	Amato et al. 2013; Chen et al. 2007; Dietrich et al. 1993b, 2001; Lin et al. 2019; McFarlane et al. 2013; Neugebauer et al. 2015; Nkomo et al. 2017; Rothenberg et al. 1989; Roy et al. 2009; Wu et al. 2018
	Altered neuromotor neurosensory function[c]	Baghurst et al. 1995; Bhattacharya et al. 2006; Otto et al. 1985; Palaniappan et al. 2011; Parajuli et al. 2013, Ris et al. 2004; Robinson et al. 1985; Schwartz and Otto 1987, 1991

Table 2-28. Overview of Neurological Effects in Children Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
>30–50	Intellectual deficits[a]	do Nascimento et al. 2014; Royal et al. 2013
>50	Intellectual deficits[a]	Hou et al. 2013
	Altered mood and behavior[b]	Hou et al. 2013
	Altered neuromotor neurosensory function[c]	Hou et al. 2013;
	Peripheral neuropathy[d]	Erenberg et al. 1974; Landrigan et al. 1976; Schwartz et al. 1988; Seto and Freeman 1964
>80	Encephalopathy	NAS 1972

[a]Intellectual deficits include decreased IQ, cognitive function, verbal comprehension, language development, perceptual organization, processing speed, decreased math and reading aptitude, educational attainment, school performance, and memory.
[b]Altered mood and behavior includes hyperactivity, ADHD, decreased adaptive skills and emotional functioning, externalizing behaviors, internalizing behaviors, social problems, delinquent behavior, impulsive behavior, irritability, autistic behavior, altered sleep, and associations between child PbB and adult behavior (see McFarlane et al. (2013).
[c]Altered neuromotor neurosensory function includes decreased integrated motor activities, gross motor skills; fine motor speed and dexterity, and visual-motor integration.
[d]Peripheral neuropathy includes decreased motor and sensory nerve conduction velocity.

ADHD = attention-deficit/hyperactivity disorder; IQ = intelligence quotient; PbB = blood lead concentration

Characterization of Effects in Adults. A large number of studies showing decrements in neurological function in adults have been published (Table 2-29). These studies have found neurobehavioral effects in populations whose PbBs were ≤10 µg/dL. Neurobehavioral functions that have been associated with PbB ≤10 µg/dL include decreased cognitive function, altered behavior and mood, and altered neuromotor and neurosensory function. These outcomes also have been observed in association with PbB >10 µg/dL. PbBs in the range of 10–20 µg/dL, measured either during childhood or in adulthood, have been associated with decreased brain volume and changes in brain neurochemistry (Brubaker et al. 2010; Cecil et al. 2008; 2011; Hsieh et al. 2009). PbBs >30 µg/dL are associated with a variety of decrements in cognitive function, behavior and nerve function, including postural sway and stability; decreased walking speed; decreased visuospatial function and visual-motor performance; decrements in hearing; peripheral neuropathy; psychiatric symptoms (depression, panic disorders, anxiety, hostility, confusion, anger, and schizophrenia); and changes in regional brain volumes and neurochemistry.

Table 2-29. Overview of Neurological Effects in Adults Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Intellectual deficits[a]	Muldoon et al. 1996; Payton et al. 1998; Power et al. 2014; Seo et al. 2014; Shih et al. 2006; Weisskopf et al. 2007; Weuve et al. 2006; Wright et al. 2003b
	Altered mood and behavior[b]	Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010; Opler et al. 2004; Rajan et al. 2007, 2008; Rhodes et al. 2003
	Altered neuromotor neurosensory function[c]	Hwang et al. 2009; Ji et al. 2013; Krieg et al. 2005
	Neurological diseases (ALS)	Fang et al. 2010
>10–30	Intellectual deficits[a]	Mantere et al. 1982; Reuben et al. 2017
	Altered mood and behavior[b]	Beckley et al. 2018; Yoon and Ahn et al. 2016
	Altered neuromotor neurosensory function[c]	Chuang et al. 2007; Yokoyama et al. 1997
	Altered brain architecture and metabolism	Brubaker et al. 2010; Cecil et al. 2008, 2011; Hsieh et al. 2009
>30–50	Intellectual deficits[a]	Baker et al. 1983; Barth et al. 2002; Campara et al. 1984; Fazli et al. 2014; Goodman et al. 2002; Hogstedt et al. 1983; Meyer-Baron and Seeber 2000; Schwartz et al. 2005; Vlasak et al. 2019
	Altered mood and behavior[b]	Baker et al. 1983; Lucchini et al. 2000; Maizlish et al. 1995; Malekirad et al. 2013; Parkinson et al. 1986
	Altered neuromotor neurosensory function[c]	Baker et al. 1983; Barth et al. 2002; Chia et al. 1996; Choi et al. 2012; Ghiasvand et al. 2016; Haenninen et al. 1978; Iwata et al. 2005
	Altered nerve conduction	Araki et al. 1980, 1987, 2000; Chia et al. 1996; Hirata and Kosaka et al. 1993; Pasternak et al. 1989; Stollery et al. 1989, 1991

Table 2-29. Overview of Neurological Effects in Adults Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
>50	Intellectual deficits[a]	Arnvig et al. 1980; Campara et al. 1984; Fenga et al. 2016; Matte et al. 1989; Valciukas et al. 1978
	Altered mood and behavior[b]	Awad el Karim et al. 1986; Zimmerman-Tansella et al. 1983
	Altered neuromotor neurosensory function[c]	Hanninen et al. 1998
	Altered nerve conduction	Triebig et al. 1984
	Altered brain architecture	Jiang et al. 2008

[a]Intellectual deficits include decreased IQ, cognitive function, learning ability, verbal reasoning, logic, memory, and concentration.
[b]Altered mood and behavior include depression, panic disorders, anxiety, hostility, confusion, anger, and schizophrenia.
[c]Altered neuromotor neurosensory function includes postural sway; postural stability, decreased walking speed, decreased visuospatial function and visual-motor performance, hearing loss, and altered hearing threshold.

ALS = amyotrophic lateral sclerosis; PbB = blood lead concentration

Effects at Blood Pb Levels ≤10 µg/dL in Children. Numerous prospective and large cross-sectional studies provide a weight of evidence for decreased cognitive function, altered mood and behavior, and altered neuromotor and neurosensory function in children in association with exposures that result in PbB <10 µg/dL, with some studies showing effects at PbB ≤5 µg/dL. Study details are reviewed in the *Supporting Document for Epidemiological Studies for Lead*, Table 9. The cognitive outcome metric that has been most extensively studied and compared across studies is FSIQ. Tests of memory, learning, and executive function have also been used to assess cognitive function. Studies that attempt to identify associations between PbB and cognitive function must control for major factors known to influence or correlate with cognitive development and function, including SES, parental education and IQ, quality of caregiving, nutrition, and birth weight. Many of these same factors correlate with PbB and can confound associations between PbB and outcomes. Relationships between PbB and outcomes appear to be nonlinear. The Lanphear et al. (2005) pooled analysis and re-analyses (Crump et al. 2013; EPA 2014e) predict a nonlinear dose-response relationship for Pb in which the slope for the decrement in cognitive function in children increases with decreasing PbB. The biological significance of the observed supra-linear response has been the subject of several reviews and commentaries (Bowers and Beck 2006; Hornung and Lanphear 2014; Jusko et al. 2006). Decrements in cognitive function in children have been associated with increasing PbB measured at various life stages, including prenatal and various metrics of

child PbB including peak, concurrent, and cumulative. No specific life stage has been conclusively identified as the critical time period for exposure.

Cognitive function in infancy. Several prospective studies have evaluated cognitive function in infancy and early child cohorts having mean PbB <10 µg/dL (Table 2-30). In general, these studies provide evidence for decrements in cognitive function in association with increasing PbB. Several studies used the Mental Development Index (MDI) score from the Bayley Scales of Infant Development (BSID), allowing comparison of results across studies (Dietrich et al. 1986, 1987, 1989; Gomaa et al. 2002; Hu et al. 2006; Jedyrychowski et al. 2009; Liu et al. 2014b). Each study found decreases in MDI scores measured from 6 to 36 months in association with increasing prenatal (e.g., maternal) or neonatal PbB. Cohort mean PbB ranged from 1.2 to 7.1 µg/dL. In a cohort that had a mean PbB of 1.23 µg/dL (range 0.44–6.9 µg/dL), the change in MDI score measured at 24 months of age was -7.6 (95% confidence limit [CL] -14.7, -0.62) points per 1 $\log_{10}$ increase in cord PbB (Jedrychowski et al. 2009). The largest effect size was reported for a cohort that had a mean PbB of 8±3.8 (SD) µg/dL; the change in MDI score measured at age 6 months was -15±5.1 (SE, $p<0.03$) points per cord lnPbB (Dietrich et al. 1986). Studies that repeatedly measured MDI scores longitudinally within the same birth cohorts found that the associations observed at 6 months persisted to later ages (Dietrich et al. 1986, 1987, 1989, 1991; Jedyrychowski et al. 2009; Liu et al. 2014b). The association between Pb and declining cognitive behavior appears to be exacerbated by maternal prenatal psychosocial stress. A small prospective study conducted in Shanghai, China (139 mother-infant pairs) found larger effect sizes on language development in mothers who demonstrated higher prenatal stress (Zhou et al. 2017).

Cognitive function in early childhood - FSIQ. Prospective studies initiated at time of pregnancy or birth have consistently found decrements in child FSIQ in association with increasing cohort mean PbB <10 µg/dL measured at various stages of development (Table 2-30). Collectively, these studies provide evidence for effect sizes ranging from -1 to -6 FSIQ points in association with a 10-fold increase in PbB and larger effect sizes in cohorts or cohort strata having a lower mean PbB. These studies do not consistently point to a specific life stage as being more or less vulnerable, as negative associations with FSIQ have been observed with PbB measured during pregnancy, infancy, and childhood, and measured previous to or concurrently with the FSIQ evaluation. Results of an adult follow-up of a birth cohort suggest that FSIQ decrements observed in childhood may persist to adulthood (Mazumdar et al. 2011).

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Intellectual deficits			
Baghurst et al. 1992 Prospective cohort, n=494 children followed from birth to age 7 years	Quartile range: • Birth: 4.3, 15.0 • Mean 0–2 years: 11.6, 27.1 • Mean 0–3 years: 12.2, 28.2 • Mean 0–4 years: 12.2, 27.7 • Lifetime average (7 years):10.8, 24.8	FSIQ	β (SE) for PbB metrics per each ln PbB increase: • Prenatal: 0.6 (1.4), p=0.68 • **Mean 0–2 years: -4.6 (2.1), p=0.03*** • **Mean 0–3 years: -4.8 (2.3), p=0.04*** • **Mean 0–4 years: -4.6 (2.4), p=0.05*** • Lifetime average: -3.7 (2.5), p=0.14
Blackowicz et al. 2016 Retrospective study; n=12,319 third-grade Hispanic children	Mean (SD): • 4.16 (2.03)	ISAT	RR for failure on ISAT for 1 or 5 µg/dL increase in PbB: Reading ISAT: • **1 µg/dL increase: 1.07 (1.05, 1.10)*** • **5 µg/dL increase: 1.43 (1.25, 1.63)*** Math ISAT • **1 µg/dL increase: 1.09 (1.06, 1.12)*** • **5 µg/dL increase: 1.53 (1.32, 1.78)***
Bellinger et al. 1992; Bellinger and Needleman 2003 Prospective cohort, n=148 children followed from birth to age 10 years	Mean (SE): • 6 months: 6.7 (7.0) • 1 years: 7.7 (6.5) • 2 years: 6.5 (4.9)	FSIQ	β (SE) for PbB metrics per each 1 µg/dL increase in PbB: • Prenatal: -2.55 (2.56), p=0.57 • 6 months: -0.13 (0.15), p=0.39 • **2 years: -0.58 (0.21), p<0.007*** • **Peak <10 µg/dL: -1.56 (p=0.03)*** • Peak >10 µg/dL: -0.58 (p=NA)
Boucher et al. 2014 Prospective cohort, n=93 infants	Umbilical cord PbB: • Mean (SD): 4.8 (3.5) • Range: 0.5–17.8	FTII-fixed duration	**β 0.21 (0.07, 0.35); p≤0.01***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Braun et al. 2012 Prospective cohort, n=1,035 mother-infant pairs	Median (5th, 95th percentile) at age: • 1 years: 4.2 (1.3, 10.6) • 2 years: 4.6 (1.5, 13.4) • 3 years: 5.5 (2.3, 13.8) • 4 years: 5.9 (2.5, 12.8)	GCI	Coefficient for change in GCI (measured at year 4) per 10 µg/dL increase in PbB for PbB measured at each year: • PbB at 1 year: -2.5 (-5.6, 0.5) • **PbB at 2 years: -3.8 (-6.3, -1.4)*** • PbB at 3 years: -0.7 (-3.1, 1.6) • PbB at 4 years: -2.5 (-5.1, 0.1)
Canfield et al. 2003 Prospective cohort, n=172 children, followed from age 24–40 months to 5 years	Mean (SD): Lifetime average at age 5: 7.4 (4.3) Peak: 11.1 (7.1) Concurrent with FSIQ: 5.8 (4.1)	FSIQ	β per IQ for each 1 µg/dL increase in PbB at 5 years of age: Full cohort (n=172): • **Lifetime average: -0.57 (-0.93, -0.20); p=0.003*** • **Peak: -0.26 (-0.47, -0.05); p=0.02*** • **Concurrent: -0.61 (-0.99, -0.24); p <0.001*** Peak PbB <10 (n=101) • **Lifetime average: -1.52 (-2.94, -0.09); p=0.04*** • **Peak: -1.44 (-2.55, -0.33); p=0.01*** • **Concurrent: -1.79 (-3.00, -0.60); p=0.004***
Chandramouli et al. 2009 Prospective study; n=488 children followed from age 4–30 months (born 1992) to age 7–8 years	Mean (SD) at age 30 months: 4.22 (3.12)	Reading	• PbB 2–5 µg/dL OR: 0.88 (0.54, 1.43); p=0.608 • **PbB 5–10 µg/dL OR: 0.51 (0.32, 0.82); p=0.006***
		Writing	• PbB 2–5 µg/dL OR: 1.08 (0.69, 1.71); p=0.729 • **PbB 5–10 µg/dL OR:0.49 (0.31, 0.78); p=0.003***
		Standard assessment test scores	A 2-fold increase in PbB was associated with a 0.3-point (95% CI -0.5, -0.1) decrease in scores.

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Chiodo et al. 2004 Prospective study; n=237 children, age 7.5 years	Mean (SD, range): 5.4 (3.3, 1–25)	FSIQ	β (SE): • **<3 µg/dL: -0.10; p≤0.1*** • **<5 µg/dL: -0.12; p≤0.1*** • **<7.5 µg/dL: -0.14; p≤0.05*** • **<10 µg/dL: -0.18; p≤0.01*** • **Cohort: -0.20; p≤0.01***
Desrochers-Couture et al. 2018 Prospective study; n=609 mother-infant pairs with follow-up at age 3–4 years	Gmean (SD) • Cord: 0.76 (1.7) • Child: 0.70 (1.7)	FSIQ	Associations with PbB (β per 1 SD PbB: Cord PbB • **Male: -2.65 (-4.66, -0.48) p=0.04*** • Female: -0.18 (-1.63, 1.21) p=0.83 Child PbB • Male: -0.07 (-2.10, 2.17), p=0.96 • Female: 0.52 (-1.23, 2.40), p=0.63
Dietrich et al. 1986 Prospective study; n=280 mother-infant pairs	Prenatal (maternal): • Mean (SD): 8.0 (3.8) • Range: 1–27 Neonatal (age 10 days): • Mean (SD): 4.5 (2.9) • Range: 1–22	MDI	Associations with maternal PbB (n=245), β per lnPbB (SE): **-14.978 (6.114); p<0.02*** Associations with neonatal PbB (n=280), β per lnPbB (SE): **-15.110 (5.083); p<0.003*** In males: **F (1,122): 4.95; p=0.03***
Dietrich et al. 1987 Prospective study; n=185 mother-infant pairs	Mean (SD, range): • Prenatal (maternal): 8.3 (3.8, 1–27) • Neonatal (10 days): 4.9 (3.3, 1–24) • Neonatal (3 months): 6.3 (3.8, 1–22) • Neonatal (6 months): 8.1 (5.2, 1–36)	MDI	β per lnPbB (SE): • **3-month: -12.113 (4.727); p=0.01*** • **6-month: -2.117 (0.916); p=0.02***
		PDI	• **β (SE): -13.248 (4.250); p=0.002***
		Motor maturity	• **β (SE): -0.570 (0.260); p=0.03***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Dietrich et al. 1989 Prospective study; n=192 mother-infant pairs	Mean (SD, range): • Prenatal (maternal): 8.2 (3.6, 1–27) • Neonatal (10 days): 4.8 (3.1, 1–23) • Neonatal (3 months): 6.0 (3.5, 1–20) • Neonatal (6 months): 7.9 (4.8, 1–35) • Neonatal (9 months): 11.5 (6.9, 2–57) • Neonatal (12 months): 14.2 (7.3<4–47)	MDI	Structural Equation Model indicated associations (p≤0.05) between increasing prenatal PbB and 12-month MDI through decreasing birth weight. Standardized regression coefficients: • **Prenatal PbB → birth weight: -0.15, p≤0.05*** • **Birth weight → 12-month MDI: 0.18, p≤0.05***
Dietrich et al. 1991 Prospective study; n=258 4-year-old children	Mean (SD, range): (based on Dietrich et al. 1992) • Maternal (6–7 months): 8.2 (3.8, 1–27) • Neonatal (10 days): 4.8 (3.3, 1–26)	K-ABC scores	Coefficients per µg/dL neonatal PbB: • **Mental processing composite: -0.63; p<0.01*** • **Sequential processing: -0.68, p<0.01*** • **Simultaneous processing: -0.50; p<0.05*** • **Nonverbal: -0.63; p<0.01*** • **Achievement: -0.28; p<0.05***
Dietrich et al. 1992 Prospective study; n=259 5-year-old children	Mean (SD, range): • Maternal (6–7 months): 8.2 (3.8, 1–27) • Neonatal (10 days): 4.8 (3.3, 1–26) • Postnatal (5 years): 11.9 (6.4, 3–38)	FWS scores	Coefficients per µg/dL neonatal PbB: • **FWS(T): -0.26 p<0.1*** • **FWS(L): -0.20, p<0.01*** • **FWS(R) -0.13, p<0.1*** Coefficients per µg/dL concurrent PbB: • **FWS(T): -0.11 p<0.1*** • **FWS(L): -0.06, p<0.1*** • **FWS(R) -0.08, p<0.05***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Dietrich et al. 1993a Prospective study; n=253 6–7-year-old children	Mean (SD): • Maternal: 8.3 (3.7) • Birth: 5 (3.4) • 4–5 years: 11.8 (6.3)	FSIQ	Adjusted β (SE) in IQ per each 1 µg/dL: • Prenatal: 0.15 (0.21), • Lifetime average: -0.13 (0.11); • **Concurrent: -0.33 (0.14); p≤0.05***
Emory et al. 2003 Retrospective study; n=79 African-American mother-infant pairs	Mean (SD, 5th–95th percentile): • Maternal: 0.72 (0.86, 0.28–1.18)	FTII, Scaled Novelty Risk (risk of mental retardation later in life)	Score: PbB (SD): • Low risk: 0.65 µg/dL (0.80) • Medium risk: 0.89 µg/dL (0.88) • High risk: 1.01 µg/dL (0.126)
EPA 2014e (re-analysis of pooled cohort from Lanphear et al. 2005 with corrections to the database) Prospective; pooled-analysis; n=1,333 children (4.8–6 years of age) from seven prospective studies	Mean (95% CI): • Lifetime average: 12.4 (4.1, 34.8) • Peak: 18.0 (6.2, 47.0) • Concurrent with FSIQ: 9.7 (2.5, 33.2)	FSIQ	β in IQ for per each ln PbB (µg/dL) increase in PbB (95% CI): • **6–24 months: -2.21 (-3.38, -1304)*** • **Lifetime average: -3.14 (-4.39, -1.88)*** • **Peak: -2.86 (-4.10, -1.61)*** • **Concurrent: -2.65 (-3.69, -1.61)*** FSIQ change for concurrent PbB range: • **2.4–10 µg/dL: -3.8 points (-2.3, -5.3)*** • **10–20 µg/dL: -1.8 points (-1.1, -2.6)*** • **20–30 µg/dL: -1.1 (-0.7, -1.5)***
Evens et al. 2015 Population-based retrospective cohort study; n=47,168 children (third graders)	Mean (SD): 4.81 (2.22): Participants with PbB <10: 100%	ISAT reading scores	**Regression coefficient (SE): -0.60 (0.03); p<0.0001*** **Adjusted RR:** • **1 µg/dL: 1.06 (1.05, 1.07)*** • **5 µg/dL: 1.32 (1.26, 1.39)***
		Math	**Regression coefficient (SE): -0.50 (0.03); p<0.0001*** **Adjusted RR:** • **1 µg/dL: 1.06 (1.05, 1.07)*** • **5 µg/dL: 1.32 (1.26, 1.39)***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Geier et al. 2017 Cross-sectional study; n=1,411 children, age 6–15 years	Mean (SD): 1.32 (0.95) <P50: 0.2–1.007 P50–P75: 1.007–1.530 P75–P100: 1.530–13.50	Diagnosed with learning disability	**OR per µg/dL: 1.19 (1.00, 1.40) p=0.044*** OR for quartile relative to <50th percentile (<P50): • **P50–75: 1.46 (1.11, 1.92), p=0.0017*** • **P75–100: 1.95 (1.16, 3.29), p=0.0033***
Gomaa et al. 2002 Prospective study; n=197 children followed from birth to age 2 years	Umbilical cord mean (SD): 6.7 (3.4) Participants with PbB ≥10: 15.7%	MDI	**β (SE): -4.48 (2.04); p=0.03***
Hong et al. 2015 Cross-sectional study; n=1,001 children (ages 8–11 years)	Gmean (GSD): 1.80 (1.40) 5th–95th percentile range: 0.53–6.16	IQ	Regression coefficients per 10-fold increase in PbB: • **Verbal IQ: -2.64 (-4.98, -0.30); p=0.027*** • **Full-scale IQ: -7.23 (-13.39, -1.07); p=0.021***
Hu et al. 2006 Prospective study; n=146 mother-child pairs	Mean±SD (range): • Umbilical cord: 6.20±3.88 (0.9–20.0) • Child 12-month: 5.22±3.41 (0.9–20.4) • Child 24-month: 4.79±3.71 (0.8–36.8) • Maternal 1st trimester: 7.07±5.10 (1.49–43.6) • Maternal 2nd trimester: 6.08±3.15 (1.58–22.4) • Maternal 3rd trimester: 6.86±4.23 (1.53–33.1)	MDI	β per 1 SD change in ln PbB: • Umbilical cord: -0.35 (-4.72, 4.03); p=0.88 • Child 12-month: -2.38 (-6.24, 1.49); p=0.23 • Child 24-month: -1.00 (-3.93, 1.94); p=0.50 • **Maternal 1st trimester: -4.13 (-8.10, -0.17); p=0.04*** • Maternal 2nd trimester: -4.08 (-8.29, 0.12); p=0.06 • Maternal 3rd trimester: -2.42 (-6.38, 1.54); p=0.23

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Jedrychowski et al. 2009 Prospective study; n=444 children followed prenatally to age 3 years	Umbilical cord PbB • Gmean: 1.29 • Median: 1.23 • Range: 0.44–6.90	MDI	β per lg cord PbB±SE: • 12 months: -5.419±2.935 (-11.188, 0.3495); p=0.066 • **24 months: -7.653±3.577 (-14.684,-0.623); p=0.033*** • **36 months: -6.717±2.964 (-12.546, -0.889); p=0.024*** • **All participants with PbB <5 (combination of all testing times): -6.618±2.499 (-11.517, -1.719); p=0.008***
Jusko et al. 2008 Prospective study; n=174 children recruited at age 24–30 months and evaluated for FSIQ at 6 years	Lifetime average: • Mean (SD): 7.2 (4.1) • Range: 1.4–27.1 • Participants <10: 77%	FSIQ	• **Associations between increasing PbB and decreasing FSIQ measured at age 6 years (p=0.003)*** • **Comparison of children with PbB of 5–9.9 (high) to those with PbB <5 (low) showed a 4.9-point decrease in FSIQ score (low: 91.3; high 86.4; p=0.04)*** • Adjusted changes in IQ for each 1 µg/dL increase in peak lifetime PbB (p not reported): o 2.1–10 µg/dL: -1.2 o 10–20 µg/dL: -0.32 o 20–30 µg/dL: -0.15
Kim et al. 2013b Prospective birth cohort; n=884 mother infant pairs	Gmean (GSD): Early pregnancy: 1.4 (1.5) Late pregnancy: 1.3 (1.5)	MDI	**β per 1 µg/dL change in late pregnancy PbB: -1.94 (-3.60, -0.29); p=0.02***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Kordas et al. 2011 Prospective study; n=186 children followed prenatally (to age 4 years)	Mean (SD): • Umbilical cord: 6.6 (3.3) • 24 months: 8.1 (4.4) • 48 months: 8.1 (3.6)	MDI (24 months)	• **β (SE) Cord PbB: -0.7 (0.3); p<0.05*** • β (SE) Concurrent PbB: -0.1 (0.2)
		PDI (24 months)	• β (SE) Cord PbB: -0.4 (0.2) • β (SE) Concurrent PbB: -0.2 (0.2)
		GCI (48 months)	• β (SE) Cord PbB: -0.2 (0.3) • **β (SE) Concurrent PbB: -0.6 (0.2); p<0.05***
		Memory score	• β (SE) Cord PbB: 0.1 (0.1) • β (SE) Concurrent PbB: -0.3 (0.1)
Lanphear et al. 2000a Cross-sectional study; n=4,853 children (ages 6–16 years)	Gmean: 1.9 Participants with PbB • ≥5: 9.7% • ≥10: 2.1%	Arithmetic	Regression coefficients (SE): • PbB <2.5: -1.28 (0.98), p=0.20 • **PbB <5.0: -1.06 (0.48); p=0.03*** • **PbB <7.5: -1.06 (0.39); p=0.01*** • **PbB <10: -0.89 (0.32); p=0.008***
		Reading	Regression coefficients (SE): • PbB <2.5: -1.71 (0.93); p=0.07 • **PbB <5.0: -1.66 (0.36); p<0.001*** • **PbB <7.5: -1.53 (0.31); p<0.001*** • **PbB <10: -1.44 (0.30); p<0.001***
		Block design	Regression coefficients (SE): • PbB <2.5: -0.08 (0.22); p=0.72 • PbB <5.0: -0.05 (0.07); p-0.45 • **PbB <7.5: -0.11 (0.06); p=0.04*** • **PbB <10: -0.13 (0.06); p=0.03***
		Digit span	Regression coefficients (SE): • PbB <2.5: -0.25 (0.17); p=0.17 • PbB <5.0: -0.09 (0.07), p=0.20 • PbB <7.5: -0.09 (0.05); p=0.11 • **PbB <10: -0.08 (0.04); p=0.03***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Lanphear et al. 2005 (same cohorts used for Budtz-Jorgensen et al. 2013) Prospective; pooled-analysis; n=1,333 children (4.8–6 years of age) from seven prospective studies	Mean (96% CL): • Lifetime average: 12.4 (4.1, 34.8) • Peak: 18.0 (6.2, 47.0) • Concurrent with FSIQ: 9.7 (2.5, 33.2)	FSIQ	β in IQ for per each ln PbB (µg/dL) increase in PbB: • **6–24 months: -2.04 (-3.27, -0.81)*** • **Lifetime average: -3.04 (-4.33, -1.75)** • **Peak: -2.85 (-4.10, -1.60)*** • **Concurrent: -2.70 (-3.74, -1.66)*** FSIQ change for lifetime average PbB: • **2.4–10 µg/dL: -3.9 points (-2.4, -5.3)*** • **10–20 µg/dL: -1.9 points (-1.2, -2.6)*** • **20–30 µg/dL: -1.1 (-0.7, -1.5)***
Lanphear et al. 2019 (re-analysis of data reported in Lanphear et al. 2005; same cohorts used for Budtz-Jorgensen et al. 2013) Prospective; pooled-analysis; n=1,333 children (4.8–6 years of age) from seven prospective studies	Median (96% CL): • Lifetime average: 11.9 (3.6, 34.5) • Peak: 18.0 (6.2, 47.0) Concurrent with FSIQ: 9.7 (2.5, 33.2)	FSIQ	β in IQ for per each ln PbB (µg/dL) increase in PbB: • **6–24 months: -2.21 (-3.38, -1.04)*** • **Peak: -2.86 (-4.10, -1.61)*** • **Lifetime average: -3.25 (-4.51, -1.99)*** • **Concurrent: -2.65 (-3.69, -1.61)*** FSIQ change for concurrent PbB: • **2.4–10 µg/dL: -3.8 points (-2.3, -5.3)*** • **10–20 µg/dL: -1.8 points (-1.1, -2.6)*** • **20–30 µg/dL: -1.1 (-0.7, -1.5)***
Lin et al. 2013 Prospective (Taiwan Birth Panel Study; birth dates: April 2004–January 2005) of 230 mother-infant pairs from Taipei, Taiwan, followed until age 2 years	Umbilical cord • Mean (SD): 1.30 (0.75) • Range: 0.016–4.32	Cognitive score	Regression analysis comparing PbB ≥1.645 (75th percentile) and PbB <1.645. Adjusted β (SE): • **Total score: −4.23 (1.82); p<0.05*** • **Cognitive: −5.35 (2.19); p<0.05*** • Language: −2.53 (1.89); p≥0.05

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Liu et al. 2014b Prospective study; n=243 infants followed from birth to age 3 years	Umbilical cord (mean±SD): • Low PbB group: 1.35±0.26 • High PbB group: 5.63±0.32	MDI	Regression coefficients: • **6 months: -1.647 (-2.094, -1.200); p=0.016*** • **12 months: -1.458 (-1.832, -1.084); p=0.023*** • **24 months: -1.385 (-1.683, -1.087) p=0.033*** • **36 months: -1.291 (-1.550, -1.032); p=0.036*** Increasing PbB at ages 24 and 36 months was associated with decreasing MDI scores measured at 24 and 36 months, respectively; β: • **24 months: -1.403; p=0.026*** • **36 months: -1.298; p=0.036***
		PDI	**Regression coefficients at 36 months: -1.302 (-1.572, -1.031); p=0.041***
Mazumdar et al. 2011 A prospective of 43 adults followed from birth (1979–1981) to age 28–30 years	Mean (SD): • Cord: 6.5 (5.3) • 6 months: 8.0 (5.3) • 12 months: 10.0 (6.7) • Age 2 years: 7.7 (4.0) • Age 4 years: 6.7 (3.6) • Age 10 years: 3.0 (2.7)	FSIQ	Change in FSIQ per 1 µg/dL increase in PbB. β for average late childhood PbB (mean of 4- and 10-year PbB): • **Unadjusted: -1.89 (-3.30, -0.47), p<0.01*** • Adjusted for maternal IQ: -1.11 (-2.29, 0.06) • Other adjustments: 95% UCLs <0
McLaine et al. 2013 Population-based retrospective cohort study; n=3,406 children (kindergarteners)	Median: 4.2 Interquartile range: 2.6, 6.0	PALS-K scores	Mean differences (95% CI) in PALS-K scores (85% CL), compared to PbB <5: • PbB 5–9: -4.51 (-6.61, -2.85); p>0.182 • PbB ≥10: -10.13 (-13.30, -6.96); p>0.182 PR for falling below the PALS-K benchmark, compared to PbB <4: • **PbB 5–9: 1.21 (1.19, 1.23); p<0.001*** • **PbB ≥10: 1.56 (1.51, 1.60); p<0.001***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Min et al. 2009 Prospective study; n=267 children followed prenatally age 11 years	Mean (SD): • 4 years: 7.0 µg/dL (4.1)	FSIQ	Regression coefficient (SE): • **4 years: -0.50 (0.20), p<0.05*** • **9 years: -0.41 (0.19), p<0.05*** • **11 years: -0.54 (0.19); p<0.01***
Miranda et al. 2009 Population-based retrospective cohort study; n=57,678 4th grade children	Mean: 4.8 Median: 4 Range: 1–16	EOG scores	Multivariate regression coefficients for PbB (µg/dL) of: • **PbB 2: -0.30 (-0.58, -0.01); p<0.0001*** • **PbB 3: -0.46 (-0.73, -0.19); p<0.0001*** • **PbB 4: -0.52 (-0.79, -0.24); p<0.0001*** • **PbB 5: -0.80 (-1.08, -0.51); p<0.0001*** • **PbB 6: -0.99 (-1.29, -0.68); p<0.0001*** • **PbB 7: -1.07 (-1.40, -0.74); p<0.0001*** • **PbB 8: -1.35 (-1.73, -0.97); p<0.0001*** • **PbB 9: -1.20 (-1.64, -0.75); p<0.0001*** • **PbB ≥10: -1.75 (-2.09, -1.41); p<0.0001***
Polanska et al. 2018 Prospective study; n=538 mother-child pairs with follow-up of 303 children at age 2 years	Gmean (SD) (range) • 2nd trimester: 0.99 (0.15) (0.29, 2.63) • Cord: 0.96 (0.16) (0.24, 5.65)	BSID III	β score per µg/dL cord ln PbB: Cognitive score: • Females: 0.34 (-1.30, 1.98), p=0.68 • **Males: -2.07 (-4.07, -0.06), p=0.04*** Language score: • Females: -0.29 (-2.23, 1.65), p=0.77 • Males: -0.43 (-2.81, 1.95), p=0.72
Rodrigues et al. 2016 Prospective study; n=812 mother-child pairs with follow-up of 5251, children at age 2–3 years	Median (P24, P75, maximum) • Sirajdikhan: 7.6 (5.5, 10.4) • Pabna: <LOD (<LOD, 3.8, 13.8)	BSID III	β score per µg/L child PbB: Cognitive score: • **Sirajdikhan: -0.17 (0.09), p=0.05*** • Pabna: 0.02 (0.12), p=0.87

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Rooney et al. 2018 Longitudinal study; n=330 children with follow-up at age 12 and 17 years	Mean (SD) at age 8–12 years • Females: 4.42 (2.19) • Males: 5.26 (2.73)	Learning, memory, and executive function test	Genetic variants of N-methyl-D-aspartate receptors (NMDAR subunits GRIN2A and GRIN2B) were effect modifiers on associations between increasing PbB (at age 8–12 years) and decreasing performance on learning and memory and executive functions
Ruebner et al. 2019 Cross-sectional study; n=412 children (median age 15.4 years) from prospective study of CKD in children	Median (P24, P75): 1.2 (0.8, 1.8)	FSIQ, CPT	β score per µg/dL (95% CI): FSIQ: • **PbB: -2.1 (-3.9, -0.2), p=0.029*CPT variability score:** • **PbB: 1.8 (0.2, 3.5), p=0.033***
Schnaas et al. 2006 Prospective study; n=150 followed from birth to age 10 years	Maternal during full pregnancy • Gmean (range): 8.0 (1–33) Maternal PbB during pregnancy weeks 28–36 • Gmean (95% CI): 7.3 (1.5–17.4) Child 1–5 years • Gmean (range): 9.8 (2.8–36.4) Child 6–10 years • Gmean (range): 6.2 (2.2–18.6)	FSIQ	β assessed at age 6–10 years: • **Ln maternal PbB (28 weeks pregnancy): -4.00 (-6.37, -1.65); p=0.001*** • **Ln child PbB (6–10 years): -2.45 (-4.09, -0.81); p=0.003***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Shadbegian et al. 2019 Retrospective study; n=560,624 children with PbB measured at ages 0–5 years and cognitive assessments during school grades 3–8	Mean (SD) Whole cohort • <10 µg/dL: 3.66 (1.90) • ≤5 µg/dL: 2.89 (1.18) CEM stratum ≤5 µg/dL: 2.40 (1.24)	Standardized academic achievement tests	Percentile score change relative to ≤1 µg/dL CEM stratum (SE) for children who had geometric mean PbB >1 and ≤5 µg/dL: Math percentile for PbB strata: • 2 µg/dL: -0.38 (0.19), p>0.05 • **3 µg/dL: -0.56 (0.20), p<0.01*** • **4 µg/dL: -0.96 (0.23), p<0.001*** • 5 µg/dL: -0.51(0.30), p>0.05 Reading percentile for PbB strata: • **2 µg/dL: -0.55 (0.19), p<0.01*** • **3 µg/dL: -1.02 (0.20), p<0.001*** • **4 µg/dL: -1.31 (0.23), p<0.001*** • **5 µg/dL: -0.97 (0.30), p>0.001***
Sobin et al. 2015 Cross-sectional study; n=252 children (age 5.1–11.8 years)	Mean (SD): • Females: 2.7 (1.5) • Males: 2.4 (1.0) • 96% <5.0 µg/dL	Working memory	**β (SE): 0.11 (0.03), p<0.01***
Taylor et al. 2017 Prospective study; n=14,062 mother-infant pairs with follow-up of 404 children at age 4 years and n=2,217 children at age 8 years	Mean (SD): • Maternal (11 weeks): 3.67 (1.46) • Child (30 months): 4.22 (3.12)	FSIQ	β for score per µg/dL at age 8 years: Females: • **Verbal: 0.71 (0.11, 1.32), p=0.021*** • Performance: 0.57 (-0.11, 1.24), p=0.099 • Total: 0.73 (0.13, 1.33), p=0.017 Males: • Verbal: -0.15 (-0.90, 0.60), p=0.72 • Performance: -0.42 (-1.19, 0.35), p=0.29 • Total: -0.29 (-1.02, 0.44), p=0.44

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Tellez-Rojo et al. 2006 Prospective study; n=294 children followed from birth to age 2 years	Mean (SD): • Cord: 4.85 (3.0) • 12 months: 4.27 (2.14) • 24 months: 4.28 (2.25)	MDI	β per ln PbB 12 months: • <10 µg/dL: -0.15, p=0.57 • ≥10 µg/dL: -0.71, p=0.17 β per lnPbB 24 months: • **<10 µg/dL: -1.04, p<0.01*** • ≥10 µg/dL: 0.07, p=0.84
Vigeh et al. 2014 Prospective study; n=174 mother-child pairs, birth to 36 months	Mean±SD (range): • 1st trimester: 4.15±2.43 (1.6–20.5) • 2nd trimester: 3.44±1.28 (1.1–7.5) • 3rd trimester: 3.78±1.40 (1.5–8.0) • Umbilical cord: 2.86±1.09 (1.2–6.9).	ECDI score	**OR 1st trimester: 1.74 (1.18–2.57); p=0.005***
Wasserman et al. 1994, 1997, 2003 Prospective study; n=332 children age 4 years, 261 children age 7 years, 167 children age 10–12 years	Mean (SD): • Age 4 years: 9.6, Pristina 39.9, K. Mitrovica • Age 10–12 years: 6.1 (1.9), Pristina 30.9 (9.6), K. Mitrovica	FSIQ	β (SE) for each ln PbB increase: • **4 years: -9.43 (2.44); p=0.000*** • **Lifetime AUC 7 years: -8.59 (1.89); p<0.05*** • **Lifetime average 10–12 years: -5.31 (1.98); p<0.05***
Zhang et al. 2013 Population-based retrospective cohort study; n=8,831, 7,708, and 4,742 students in grades 3, 5, and 8, respectively	Mean (SD): 7.12 (7.26) Analysis: academic achievement	Math	• **OR 1–5 PbB (µg/dL): 1.42 (1.24, 1.63)*** • **OR 6–10 PbB (µg/dL): 2.00 (1.74, 2.30)*** • **OR >10 PbB (µg/dL): 2.40 (2.07, 2.77)***
		Science	• **OR 1–5 PbB (µg/dL): 1.33 (1.10, 1.62)*** • **OR 6–10 PbB (µg/dL): 2.22 (1.82, 2.72)*** • **OR >10 PbB (µg/dL): 2.26 (1.84, 2.78)***
		Reading	• **OR 1–5 PbB (µg/dL): 1.45 (1.27, 1.67)*** • **OR 6–10 PbB (µg/dL): 2.21 (1.92, 2.55)*** • **OR >10 PbB (µg/dL): 2.69 (2.31, 3.12)***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Zhou et al. 2017 Prospective study; n=139 mother-infant pairs followed from birth to 24–36 months	Gmean (95% CI) Mid-late pregnancy: 3.30 (3.05, 3.57)	Gesell Development Scale, prenatal stress Global Severity Index	β for development quotient per µg/dL: All children: • Adaptive behavior: 3.60 (-3.64, 10.83) • Language: -6.76 (-17.29, 3.77) • Social behavior: -6.45 (-15.55, 2.65) Children from mothers who exhibited high prenatal stress: • **Adaptive behavior: -17.93 (-35.83, -0.03)*** • **Language: -33.82 (-60.04, -7.59)*** • **Social behavior: -41.00 (-63.11 -18.89)***
Mood and behavior			
Arbuckle et al. 2016 Cross-sectional study; n=2,097 children aged 6–19 years	Gmean (95% CI) age 6–11 years: 0.91 (0.81, 0.99) age 12–19 years: 0.80 (0.74, 0.85)	ADD/ADHD	ORs for ln(PbB): • **ADD/ADHD: 2.39 (1.32, 4.32)*** • Emotional symptoms: 1.08 (0.68, 1.71) • **Hyperactivity/inattention: 2.33 (1.59, 3.43)*** • **Total difficulties: 2.16 (1.33, 3.51)***
Boucher et al. 2012 Prospective study; n=272 children (mean age 11.3 years)	Mean±SD (range): • Umbilical cord: 4.7±3.3 (0.8–20.9) • Current: 2.7±2.2 (0.4–12.8)	ADHD-inattentive type	Adjusted ORs: • T2 (n=94): 1.06 (0.42, 2.66) • T3 (n=91): 1.01 (0.38, 2.64)
		ADHD-hyperactive-impulsive type	• **T2(n=94): 4.01 (1.06, 15.23)*** • **T3(n=91): 5.52 (1.38, 22.12)***
		ODD and/or CD	• T2 (n=94): 1.90 (0.88, 4.11) • T3 (n=91): 1.53 (0.67, 3.49)
		Behavior problem scores	Umbilical cord PbB was not associated with associated with behavior problem scores (data not reported).

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Braun et al. 2006 Cross-sectional study; n=4,704 children (ages 4–15 years)	Quintiles: • Q1 (reference): ND–0.7 • Q2: 0.8–1.0 • Q3: 1.1–1.3 • Q4: 1.4–2.0 • Q5: ≥2.0	ADHD	Adjusted ORs: • Q2: 1.1 (0.4, 3.4); p=0.804 • Q3: 2.1 (0.7, 6.8); p=0.195 • Q4: 2.7 (0.9, 8.4);p=0.086 • **Q5: 4.1 (1.2, 14.0); p=0.026*** • **p-trend: 0.012***
Braun et al. 2008 Cross-sectional study; n=3,082 children (ages 8–15 years)	Quartiles: • Q1 (reference): 0.2–0.7 • Q2: 0.8–1.0 • Q3: 1.1–1.4 • Q4: >2.0	Conduct disorder	Adjusted ORs: • **Q2: 7.24 (1.06, 49.47)*** • **Q3: 12.37 (2.37, 64.56*)** • **Q4: 8.64 (1.87, 40.04)***
Choi et al. 2016 Longitudinal study; n=2,159 children (ages 7–9 years)	Gmean (GSD): • All participants >7 years: 1.62 (1.52) • Boys: 1.65 (1.75) • Girls: 1.47 (1.76); p<0.001, compared to boys	ADHD	• **RR for PbB ≥2.17 (compared to PbB <2.17): 1.552 (1.002, 2.403)***
Desrochers-Couture et al. 2019 Longitudinal study; n=212 Inuit children followed from birth and evaluated at mean age 11.4 and 18.5 years	Gmean (GSD) • Cord: 3.80 (1.84) • Child: 2.34 (1.86) • Adolescent: 1.63 (2.00)	ADHD	β per $\log_2$ µg/dL PbB: Child: • Externalizing: 0.61 (-0.63, 1.96) • Hyperactivity-impulsivity: 0.11 (-0.14, 0.37) • Oppositional defiant/conduct disorder: 0.02 (-0.20, 0.21) Adolescent: • **Externalizing interacting with child externalizing: 0.32 (0.08, 0.72)***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Dietrich et al. 2001 Prospective study; n=195 subjects (age 15–17 years)	Categories: Lowest: <10 Low: 10–15 Medium: 16–20 High: >20	SRDBS scores	β (SE): • **Prenatal PbB: 0.192 (0.076); p=0.002*** • **78-month PbB: 0.193 (0.061); p=0.002*** • **Average child PbB: 0.101 (0.047); p=0.036***
Froehlich et al. 2009 Cross-sectional study; n=2,588 children (ages 8–15 years)	Tertiles T1: 0.2–0.8 T2: 0.9–1.3 T3: >1.3	ADHD	Adjusted ORs: • T2: 1.7 (0.97, 2.9); p=0.06 • **T3: 2.3 (1.5, 3.8); p=0.001***
Fruh et al. 2019 Prospective study; n=1,006 mother-child pairs with follow-up at age 8 years; Massachusetts	**Erythrocyte Pb:** Median:1.1 25th–75th % range: 0.6	BRIEF and SDQ	β for change in score for an IQR increase in maternal 2nd trimester erythrocyte Pb: Parent-rated SDQ: • Total difficulties: 0.36 (-0.04, 0.77) • **Emotional problems: 0.18 (0.03, 0.33)*** Parent-rated BRIEF score: • Behavioral regulation index: 0.69 (-0.13, 1.51) • General executive composite: 0.73 (-0.06, 1.52) • **Plan organize: 0.85 (0.12, 1.59)***
Geier et al. 2018 Cross-sectional study; n=2,109 children, age 10–19 years	Mean (SD): 1.16 (1.27) Quartiles, range: • 0–50th: 0.2–0.88 • 50th–75th: 0.88–1.26 • 75th–100th: 1.26–34.8	ADD	OR for diagnosis of ADD: **Total sample (per µg/dL): 1.292 (1.025, 1.545) p=0.0301*** **Upper quartile PbB relative to 0–50th percentile as reference:** • **50–75th %: 1.28 (0.82, 2.00), p=0.2466*** • **75–100th %: 1.59 (1.05, 2.39), p=0.0130***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
He et al. 2019 Meta-analysis of seven studies of associations between PbB and risk of ADHD diagnosis	Range of study means: 0.73, 8.77	ADHD	Mean risk difference (95% CI): • **All studies (7): 0.59 (0.50, 0.68), p<0.0001*** • **PbB <3 µg/dL: 0.47 (0.39, 0.56), p<0.0001*** **Age 5–12 years compared to age >12 years: 1.35 (0.28, 2.41), p<0.0001***
Hong et al. 2015 A cross-sectional study; n=1,001 children (age 8–11 years)	Gmean (GSD): 1.80 (1.40) Range: 0.53–6.16	ADHD-hyperactive-impulsive type	**PbB (log-transformed) OR: 3.66 (1.18, 6.13); p=0.004***
		ADHD-inattentive type	• OR: 2.72 (-0.12, 5.56); p=0.060
		Total score	• **OR: 6.38 (1.36, 11.40); p=0.013***
Huang et al. 2016 Prospective study of mother-infant pairs with follow-up of 578 children at age 6–13 years	Mean (SD): 3.4 (3.1)	ADHD	β per 1 µg/dL: • **Hyperactivity: 1.2 (0.3, 2.0), p=0.01*** • **Restless-impulsive: 1.2 (0.3, 2.0), p=0.007*** • **Hyperactive-impulsive: 1.1 (0.2, 2.0), p=0.02***
Ji et al. 2018 Prospective study of mother-infant pairs recruited beginning 1998 with follow-up of 1,479 children at median age 9.6 years	Mean (SD): 2.2 (1.6) • All: 2.2 (1.6) • ADHD: 2.4 (1.9) • No neuro-developmental disorder: 2.1 (1.5)	ADHD	OR for ADHD diagnosis. Males and females: **OR per ln PbB (µg/dL): 1.25 (1.01, 1.56) p=0.045*** OR relative to <2 µg/dL reference: • 2–4 µg/dL: 1.08 (0.81, 1.44) p=0.622 • **5–10 µg/dL: 1.73 (1.09, 2.73) p=0.019*** OR relative to <5 µg/dL reference: • **5–10 µg/dL: 1.66 (1.08, 2.56) p=0.020*** Males: OR 5–10 µg/dL relative to <5 µg/dL reference: • **Males: 2.49 (1.46, 4.26) p=0.001*** • Females: 0.68 (0.27, 1.69) p=0.401

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
			Joint effects of sex and PbB: OR 5–10 µg/dL relative to <5 µg/dL reference: • **Males: 7.48 (4.29, 13.02) p <0.001*** • Females 0.69 (0.28, 1.71) p=0.426
Joo et al. 2017 Case-control study; n=214 child ADHD cases and 214 controls, age 6–10 years	Gmean (SD): Cases: 1.65 (1.45) Controls: 1.49 (1.48)		OR for ADHD diagnosis; OR per µg/dL: • All AHDH: 1.28 (0.89, 1.83) • **Inattention: 1.63 (1.03, 2.58), p<0.05*** • Hyperactivity/impulsivity: 1.04 (0.53, 2.07)
Joo et al. 2018 Prospective study; n=1,751 mother-infant pairs with follow-up of 575 children at age 5 years	Gmean (SD): Early pregnancy: 1.28 (1.48) Late pregnancy: 1.24 (1.57) Cord: 0.90 (1.57) 2 years: 1.55 (1.49) 3 years: 1.43 (1.44) 5 years: 1.29 (1.38	Behavioral problems (Child Behavior Checklist)	β for score per µg/dL: PbB at age 2 years: • **Females: 3.82 (1.25, 3.69)*** • Males: 0.22 (-1.87, 2.32) PbB at age 3 years: • Females: 2.43 (-1.00, 5.87) • Males: 0.48 (-2.17, 3.12) PbB at age 5 years: • **Females: 5.72 (0.44, 10.99)*** • Males: 1.37 (-2.06, 4.80)
Kim et al. 2016 Prospective study; n=2,473 children (age 7–8 years)	Mean (95% CI): • Ages 7–8 years: 1.64 (1.60, 1.68) • Ages 9–10 years: 1.58 (1.55, 1.61) • Ages 11–12 years: 1.58 (1.55, 1.61)	ASSQ	PbB (log transformed) β (SE): • **7–8 years: 0.151 (0.061, 0.242)*** • 9–10 years: -0.023 (-0.143, 0.097 • 11–12 years: 0.054 (-0.061, 0.170)
		SRS	• **PbB at 7–8 years: 2.489 (1.378, 3.600)*** • PbB at 9–10 years: 1.295 (-0.235, 2.825) • PbB at 11–12 years: β (SE): 0.724 (-0.727, 2.176)

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Liu et al. 2014a Prospective study; n=332 mother-infant pairs	Mean (SD): • Low PbB group o 1st trimester: 1.22 (0.28) o 2nd trimester: 1.01 (0.19) o 3rd trimester: 1.19 (0.23) o Delivery: 1.26 (0.25) • High PbB group o 1st trimester: 6.49 (0.62) o 2nd trimester: 5.63 (0.43) o 3rd trimester: 6.31 (0.51) o Delivery: 6.65 (0.55)	NBNA score	β: • **1st trimester: -4.86 (-8.831, -0.889); p=0.03*** • 2nd trimester: -3.98 (-8.180, 0.220); p=0.07* • 3rd trimester: -3.65 (-6.609, 1.309); p=0.21 • Delivery: -3.39 (-7.531, 0.751); p=0.11
Liu et al. 2015b Prospective study; n=665 children (ages 3–13 years)	Mean (SD): 6.26 (2.54)	Sleep onset delay	**β: 0.033 (0.009, 0.056); p=0.006***
Park et al. 2016 Case-control study of child (mean age 9 years) ADHD cases (n=114) and controls (n=114)	Gmean ± SD (range): Cases: 1.90±0.86 (0.37, 5.35) Controls 1.59±0.68 (0.18, 3.41) Q1: 0.18, 1.12 Q2: 1.13, 1.71 Q2: 1.72, 2.29 Q4: 2.30, 5.35	ADHD	OR for ADHD diagnosis: **All subjects: 1.60 (1.04, 2.25), p=0.03*** Relative to Q1: Q2: 1.26 (0.56, 2.84), p=0.39 Q3: 1.26 (0.55, 2.87), p=0.61 **Q4: 2.54 (1.09, 5.94), p=0.03***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Sioen et al. 2013 Prospective study; n=270 children, followed newborn to 8 years	Umbilical cord mean (25th–75th percentiles): 1.43 (0.73–2.53)	Hyperactivity	**OR: 2.940 (1.172, 7.380); p=0.022***
Stroustrup et al. 2016 Prospective study, n=948 mother-infant pairs with follow-up of 500 children at age 24 months	Median (IQR): 2nd trimester: 2.8 (2.7)	Temperament (TTS=easy, intermediate, or difficult); maternal postnatal depression (EPDS)	OR (95% CI) corresponding to a 1 unit change in ln(maternal PbB µg/dL) for TTS score, easy score as reference: • Intermediate: 0.88 (0.59, 1.3) • **Difficult: 1.52 (1.03, 2.26)*** Probability of demonstrating difficult TTS score was approximately doubled if EPDS score was high
Wang et al. 2008 Case-control study; n=630 children (ages 4–12 years)	Means (SE): • ADHD cases: 8.77 (3.89) • Controls: 5.76 (3.36) • Cases versus control: p<0.05 Tertiles: • T1 (reference): ≤5 • T2: 5–10 • T3: ≥10	ADHD	OR: • **T2: 4.92 (3.47, 6.98); p<0.01*** • **T3: 6.00 (4.11, 8.77); p<0.01***
Winter and Sampson 2017 Prospective study of birth cohort (n=1,255) with follow-up from birth to age 18 years (n=208)	Means (SD) at age <6 years: 6.14 (4.58)	Impulsivity, anxiety, or depression (Child Behavior Checklist)	β for score per µg/dL: • **Impulsivity: 0.08 (0.01, 0.16)*** • **Anxiety or depression: 0.11 (0.01, 0.21)***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Neuromotor neurosensory function			
Chiodo et al. 2004 Prospective study; n=237 children (age 7.5 years)	Mean (SD, range): 5.4 (3.3, 1–25)	Battery test performance	Tests with declines (β) at <3, <5, <7.5, or <10 µg/dL: • **Block design: <10, <5; p≤0.05*** • **Digit span backwards: <7.5; p≤0.05*** • **Beery visual-motor integration: <10, <5; p≤0.05*** • **MFF (number correct): <5; p≤0.05*** • **Attention-TRF: <3; p≤0.05*** • **Barkley-inattention: <5 <3; p≤0.05*** • **Withdrawn-TRF: <7.5, <3; p≤0.05*** • **Barkley off-task: <10, <5; p≤0.05*** • **Sternberg RT "Yes: <5, <3; p≤0.05*** • **Color naming: <5; p≤0.05*** • **CPT visual (number correct): none** • **Seashore rhythm: <3; p≤0.05*** • **Mental rotation RT "forward": <10, <7.5; p≤0.05***
Dietrich et al. 1987 Prospective study; n=185 mother-infant pairs	Mean (SD, range): • Prenatal (maternal): 8.3 (3.8, 1–27) • Neonatal (10 days): 4.9 (3.3, 1–24) • Neonatal (3 months): 6.3 (3.8, 1–22) • Neonatal (6 months): 8.1 (5.2, 1–36)	Motor maturity	Associations with 3-month ln PbB, β (SE): • **PDI: -13.248 (4.250); p=0.002*** • **Motor maturity: -0.570 (0.260); p=0.03*** Associations with 6-month ln PbB, β (SE): • **PDI: -2.117 (0.916); p=0.02*** • Motor maturity: -0.092 (0.056); p=0.11
		PDI	Associations with 3-month ln PbB, β (SE): • **PDI: -13.248 (4.250); p=0.002*** Associations with 6-month ln PbB, β (SE): • **PDI: -2.117 (0.916); p=0.02***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Dietrich et al. 1989 Prospective study; n=192 mother-infant pairs	Mean (SD, range): • Prenatal (maternal): 8.2 (3.6, 1–27) • Neonatal (10 days): 4.8 (3.1, 1–23) • Neonatal (3 months): 6.0 (3.5, 1–20) • Neonatal (6 months): 7.9 (4.8, 1–35) • Neonatal (9 months): 11.5 (6.9, 2–57) • Neonatal (12 months): 14.2 (7.3<4–47)	PDI	β (SE), 12 months: -14.09 (7.26); p=0.054 SEM indicated associations between increasing prenatal PbB and race and 12-month PDI. • **Prenatal PbB --> 12-month PDI: -0.47, p≤0.05*** • **Prenatal PbB x race --> birth weight: 0.97, p≤0.05*** • **Race --> 12-month MDI: -0.72, p≤0.05***
Dietrich et al. 1993b Prospective study; n=245 children (age 6 years)	Mean (SD): • Prenatal (maternal: 8.4 (3.8) • Neonatal: 4.8 (3.1) • Life average • 6 years: 10.1 (5.6) • Lifetime average quartile range: 7–22	Motor performance	Tests with (p≤0.05) declines (β) associated with neonatal (N), mean lifetime (L) or concurrent (C) PbB: • Bilateral coordination: N, M • Visual motor control: C • Upper limb speed and dexterity: C, M, N • Fine motor composite: C, M, N
Ethier et al. 2012 Prospective longitudinal, n=149 children (age 10–13 years)	Mean (SD, range): • Cord: 4.6 (3.1, 0.8–19.5) • 11 years: 2.6 (2.3, 0.4–12.8)	Delay of N150 latency of VEP	Association between increasing cord PbB and delay of N150 latency of VEP at multiple contracts. Mean latency (estimated from reported bar plot): • **≥4.15 µg/dL: ~160 ms, p<0.05*** • <4.15 µg/dL: ~153 ms (reference)
Fraser et al. 2006 Prospective study; n=101 children (age 5 years)	Mean (SD): Cord: 4.9 (3.7) Child: 5.3 (4.9)	Hand movements	**β -0.30, p≤0.01***
		Sway velocity	**β -0.28, p≤0.01***
		Transversal sway	**β 0.24, p≤0.05***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Kim et al. 2013b Prospective birth cohort, n=884 mother infant pairs	Gmean (GSD): Early pregnancy: 1.4 (1.5) Late pregnancy: 1.3 (1.5)	PDI	β per 1 µg/dL change in PbB: -1.69 (-3.65, -0.27); p=0.09
Liu et al. 2018b Cross-sectional study; n=234 children, age 3–7 years	Median (SE) e-waste location: 4.94 (0.20) reference location: 3.85 (1.81)	Hearing (pure tone conduction >25 dB)	OR for hearing loss per µg/dL (95% CI): • **Hearing loss 1.24 (1.029, 1.486) p<0.05*** • Low frequency loss: 1.02 (0.869, 1.190) • High frequency: 1.08 (0.839, 1.379)
Osman et al. 1999 Retrospective study; n=155 children (age 4–14 years)	Median (range): • 7.2 (1.9–28.1)	Hearing threshold	β per 1 change in PbB for right ear for full cohort: • **0.5 kHz: 0.054 (0.035, 0.074)*** • **1 kHz: 0.044 9 (0.026, 0.062)*** • **2 kHz: 0.048 (0.029, 0.066)*** • **4 kHz: 0.060 (0.039, 0.081)*** • **6 kHz: 0.068 (0.044, 0.092)*** • **8kHz: 0.072 (0.050, 0.094)*** β per 1 change in PbB for left ear: • **0.5 kHz: 0.051 (0.026, 0.075)*** • **1 kHz: 0.032 (0.014, 0.050)*** • **2 kHz: 0.036 (0.019, 0.053)*** • **4 kHz: 0.039 (0.020, 0.059)*** • **6 kHz: 0.004 (0.044, 0.049)*** • **8kHz: 0.047 (0.024, 0.080)*** **Association (p<0.05) between increasing PbB and increasing hearing threshold at all frequencies in PbB stratum <10 µg/dL (thresholds not reported)***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Polanska et al. 2018 Prospective study; n=539 mother-child pairs with follow-up of children at age 2 years; 280 blood samples and 303 cord blood samples were randomly chosen for analysis	Gmean (SD) (range) • 2nd trimester: 0.99 (0.15) (0.29, 2.63) • Cord: 0.96 (0.16) (0.24, 5.65)	BSID III	β score per µg/dL cord PbB: Motor score: • Females: 0.48 (-1.55, 2.52), p=0.64 • Males: -0.70 (-2.90, 1.51), p=0.53
Rodrigues et al. 2016 Prospective study with cross-sectional analysis of PbB and fine motor score; n=524 children, 20–30 months	Median (P25, P75, maximum) • Sirajdikhan: 7.6 (5.5, 10.4) • Pabna: <LOD (<LOD, 3.8, 13.8)	BSID III	β score (SE) per child lnPbB (µg/L): Fine motor score: • Sirajdikhan: 0.07 (0.11), p=0.50 • Pabna: -0.07 (0.11), p=0.50
Silver et al. 2016 Prospective study; infants assessed for hearing at 2 days and vision at 6 weeks; maternal blood Pb collected at mid pregnancy and late pregnancy and in cord blood	Exposure for infants with hearing data: Gmean (SD) Mid-pregnancy: 2.4 (2.5) Late-pregnancy: 2.7 (2.3) Cord: <LOQ Exposure for infants with vision data: Gmean (SD) Mid-pregnancy: 2.4 (2.6) (n=1,038); Late-pregnancy: 2.9 (2.2) (n=1,058); Cord: <LOQ (n=949)	Hearing at age 2 days (ABR); vision at age 6 weeks (GVA)	Percent change in score relative to <2 µg/dL (late-pregnancy) reference group **GVA score for PbB strata:** • **>3.8 µg/dL: -8.5 (-14.7, -2.4)*** • **2 - 3.8 µg/dL: -7.2 (-13.3, -1.1)*** **ABR C-P ratio for PbB strata:** • **>3.8 µg/dL: 4.6 (1.8, 7.4)*** • **2 - 3.8 µg/dL: 3.2 (0.0, 5.9)***

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Taylor et al. 2018 Prospective study; n=14,541 mother-infant pairs with follow-up of 1,558 children at age 7 years	Mean (SD) at gestation week 11 Mean (SD) 3.66 (1.55) Range: 0.20, 19.14	Motor skills (Movement Assessment Battery)	OR for scores per µg/dL prenatal PbB: • Heal to toe: 0.99 (0.74, 1.33), p=0.93 • Beanbag: 0.88 (0.58, 1.32), p=0.54 • Threading lace: 1.12 (0.83, 1.50), p=0.47 • Peg board (preferred hand): 1.19 (0.88, 1.60), p=0.26 • Peg board (non-preferred hand): 1.14 (0.85, 1.54), p=0.37
Tellez-Rojo et al. 2006 Prospective study; n=294 children (followed from birth to age 2 years)	Mean (SD): • Cord: 4.85 (3.0) • 12 months: 4.27 (2.14) • 24 months: 4.28 (2.25)	PDI	β per 1 ln change in PbB: 12 months: • <10 µg/dL: -0.01, p=0.98 • **≥10 µg/dL: -1.19, p=0.01*** 24 months: • **<10 µg/dL: -1.18, p<0.01*** • ≥10 µg/dL: 0.04, p=0.89
Zhou et al. 2017 Prospective study; n=139 mother-infant pairs followed from birth to 24–36 months	Gmean (95% CI) Mid-late pregnancy: 3.30 (3.05, 3.57)	Motor skills (Gesell Development Scale)	β (95% CI) for development quotient per µg/dL: All children: • Gross motor: 3.31 (-6.11, 12.73) • Fine motor: 0.49 (-11.27, 12.24)
Altered brain structure and chemistry			
Cecil et al. 2008 Prospective study; n=157 adults, age 19–24 years from a birth cohort born 1979–1984 from Cincinnati, Ohio	Mean (SD, range): • 6 month–6.5 years: 13.3 (5.9, 4.6–37.2)	Brain volume	Association (p≤0.001) between increasing childhood mean PbB and decreasing brain volume affecting 1.2% of the total gray matter. Effects were greater in males than females. Largest effects were in the anterior cingulate cortex.

Table 2-30. Summary of Epidemiological Studies Evaluating Neurological Effects in Children at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Cecil et al. 2011 Prospective study; n=159 adults, age 19–24 years from a birth cohort born 1979–1984 from Cincinnati, Ohio	Mean (SD, range): • 6 months–6.5 years: 13.3 (6.1, 4.7–37.2)	Brain metabolism	**Association (p<0.05) between increasing childhood mean PbB and decreasing regional levels of gray matter N-acetyl aspartate, glutamate-glutamine, creatine and phosphocreatine, and white matter cholines. Areas affected include the basal ganglia, cerebellum vermis, parietal white matter, and frontal white matter.***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 9 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

ABR = brainstem auditory response; ADD = attention deficit disorder; ADHD = attention-deficit/hyperactivity disorder; ASSQ = Autism Spectrum Screening Development Questionnaire; AUC = area under the curve; BRIEF = Behavior Rating Inventory of Executive Function; BSID = Bayley Scales of Infant Development CD = Conduct Disorder; CEM = Coarsened Exact Matching; CI = confidence interval; CKD = chronic kidney disease; CL = confidence limit; C-P = central-to-peripheral; CPT = Continuous Performance Test; ECDI = Early Child Development Inventory; EOG = End of Grade; EPDS = Edinburgh Postnatal Depression Scale; FSIQ = Full-Scale intelligence quotient; FTII = Fagan Test of Infant Intelligence; FWS = Filtered Word Subtest; GCI = General Cognitive Index; Gmean = geometric mean; GSD = geometric standard deviation; GVA = grating visual acuity; IQ = intelligence quotient; IQR = interquartile range; ISAT = Illinois Standard Achievement Test; K-ABC = Kaufman Assessment Battery for Children; LOD = limit of detection; LOQ = limit of quantitation; MDI = Mental Development Index; MFF = Matching Familiar Figures; MSEL = Mullen Scales of Early Learning; NA = not available; NBNA = Neonatal Behavioral Neurological Assessment; ND = not detected; ODD = Oppositional Defiant Disorder; OR = odds ratio; PALS-K = Phonological Awareness Literacy Screening-Kindergarten; Pb = lead; PDI = Psychomotor Development Index; PR = prevalence ratio; RR = relative risk; RT = reaction time; SD = standard deviation; SDQ = Strengths and Difficulties Questionnaire; SE = standard error; SRDBS = Self-Reported Delinquent Behavior Survey; SRS = Social Responsiveness Scale; TRF = Teacher Report Form from the Child Behavior Checklist; TTS = Toddler Temperament Scales; UCL = upper confidence limit; VEP = visual evoked potential

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FSIQ was assessed at age 28–30 years in 43 members of the Boston prospective study cohort (Bellinger et al. 1992). The change in FSIQ was -1.89 points (95% CI: -3.00, -047) per µg/dL increase in late child PbB (mean 6.7±3.6 at age 4 years, 3.0±2.7 at age 10 years). After adjustment for maternal IQ, the change in FSIQ was -1.11 (95% CI: -2.29, 0.06).

The largest study was a pooled analysis from seven individual prospective studies that evaluated FSIQ (Baghurst et al. 1992; Bellinger et al. 1992; Canfield et al. 2003; Dietrich et al. 1993a; Ernhart et al. 1989; Schnaas et al. 2000; Wasserman et al. 1997). The pooled cohort consisted for 1,333 children who were evaluated for FSIQ between ages 4.8 and 6 years (Lanphear et al. 2005, 2019). Co-variates considered in the analysis included study, maternal IQ, HOME score (Home Observation for Measurement of the Environment Inventory score), maternal education, marital status, birth weight, birth order, maternal age, race, and prenatal tobacco exposure. Of these, maternal IQ, HOME, and birth weight were included in the final models. When the full cohort was considered (PbB range 0.1–72 µg/dL), the adjusted change in FSIQ was loglinear, with greater changes in IQ per unit change in PbB at lower PbB levels. Several blood Pb metrics were explored in regression modeling, and slopes were significant for childhood, peak, lifetime average, or concurrent (with IQ testing) PbB. The model that used concurrent PbB had the highest r^2 (not reported). The covariate adjusted regression β for this model was -2.65 (95% CI: -3.69, -1.61) IQ points per 1 lnPbB. The unadjusted β was -4.84 (-5.98, -3.69). The concurrent PbB model predicts a decrease of 6.2 points in FSIQ when PbB increased from 1 to 10 µg/dL. In a PbB stratum maximum <7.5 µg/dL, the mean change in FSIQ was -2.53 (95% CI -4.48, -0.58) per 1 µg/dL change in PbB, and for a PbB stratum maximum ≥7.5 µg/dL, the mean change in FSIQ was -0.15 (95% CI -0.23, -0.07) per 1 µg/dL. Re-analyses of the pooled cohort reported in Lanphear et al. (2005) have been conducted (Crump et al. 2013; EPA 2014e). EPA (2014e) made several corrections to the dataset and obtained β coefficients that were similar to those reported in Lanphear et al. (2005). The results of the EPA (2014e) reanalysis are presented in Table 2-30.

The model that used early childhood PbB (6–24 months) had the highest r^2 (0.6433), although the r^2 was similar to concurrent PbB (0.6414). A benchmark dose (BMD) analysis of the pooled data from Lanphear et al. (2005) estimated BMDLs (95% lower one-sided confidence limit on BMD) ranging from 0.1 to 1 µg/dL for a 1% decrease in FSIQ for the best-fitting models (Budtz-Jorgensen et al. 2013). This BMD analysis provides supporting evidence that exposures to Pb may produce effects on cognitive function in populations whose PbBs are well below 5 µg/dL, and may extend to levels below 1 µg/dL.

In addition to the seven prospective studies included in the Lanphear et al. (2005, 2019) pooled analysis, more recent prospective studies have evaluated associations between PbB and FSIQ in children (Braun et al. 2012; Chiodo et al. 2004; Jusko et al. 2008; Kordas et al. 2011; Min et al. 2009; Schnaas et al. 2006; Taylor et al. 2017; Table 2-30). Each of these studies found significant associations between increasing PbB and decreasing FSIQ in study populations that had mean PbBs <10 µg/dL. The largest of these studies combined four Mexico City birth cohorts for a total of 1,035 mother-infant pairs (Braun et al. 2012). Cognitive function assessed at age 4 years (McCarthy General Cognitive Index [GCI]) decreased with increasing PbB measured at age 2 years. The adjusted effect of concurrent PbB was estimated as -3.8 (95% CI: -6.3, -1.4) points when PbB increased by 10 µg/dL. Similar to the findings of the Lanphear et al. (2005, 2019) study, covariate adjustment decreased the regression β by approximately 40% (from -6.4 to -3.8). The cohort mean PbB was 4.6 µg/dL (5^{th}–95^{th} percentile range 1.3–13.4). Studies of smaller cohorts from Mexico City found similar associations (Kordas et al. 2011; Schnaas et al. 2006). Schnaas et al. (2006) estimated the effect size to be a -4.0 (95% CI: -6.37, -1.65) point change in FSIQ measured at ages 6–10 years in association with a natural log increase in maternal PbB; the cohort geometric mean was 7.3 µg/dL (95% CI: 1.5, 17.4). Kordas et al. (2011) estimated the effect size to be -0.6 (SE 0.2) for a 1 µg/dL increase in concurrent PbB (mean 8.1 µg/dL ±4.4 SE). Prospective studies conducted in Cleveland, Ohio (Min et al. 2009) and Rochester, New York (Jusko et al. 2008) also found similar effect sizes for the associations between increasing PbB and decreasing IQ. In the Rochester study, the changes in FSIQ were larger at lower PbB, consistent with the outcomes of the Lanphear et al. (2005) study (Jusko et al. 2008). For the PbB range 2.1–10 µg/dL, the change in FSIQ measured at age 6 years was -1.2 per 1 µg/dL increase in PbB. This decreased to -0.32 and -0.15 for the ranges 10–20 and 20–30 µg/dL, respectively. In the Cleveland study, the change was -0.50±0.20 (SE) in FSIQ measured at age 4 years per 1 µg/dL increase in concurrent PbB (Min et al. 2009). A study conducted in Detroit, Michigan estimated the change in FSIQ to be -0.20 per 1 SD change in PbB (Chiodo et al. 2004). The decrement was significant ($p \leq 0.05$) in PbB strata <7.5 and <10 µg/dL. Not all prospective studies have found evidence for decreasing FSIQ in association with increased PbB. One of the largest birth cohorts that has been studied is the Avon Longitudinal Study of Parents and Children (ALSPC), conducted in the United Kingdom (Taylor et al. 2017). This study followed a cohort of approximately 14,000 births. In a follow-up of 2,127 children at age 8 years, increasing maternal PbB (mean 3^{rd} trimester PbB 3.67±1.46 SD) was associated with an increase in FSIQ in females and no change in FSIQ in males. The changes in FSIQ were 0.73 (95% CI: 0.13, 1.01) per 1 µg/dL increase in PbB in females and -0.29 (95% CI: -1.02, 0.44) in males. A prospective study of 609 mother-infant pairs, conducted in Canada, found that increasing cord PbB was associated with decreasing FSIQ when assessed in male children at age 3–4 years (Desrochers-Couture et al. 2018). The change in FSIQ in males was -2.61 points (95% CI: -4.66, -0.48) per 1 µg/dL

and the change in females was -0.18 (-1.63, 1.21). The geometric mean cord PbB was 3.80±1.86 (geometric standard deviation [GSD]).

Cross-sectional studies have also found associations between increasing PbB and FSIQ in children (Hong et al. 2015; Ruebner et al. 2019). A study conducted in South Korea evaluated PbB and FSIQ in 1,001 children 8–11 years of age (Hong et al. 2015). The estimated effect of PbB on FSIQ was -7.23 points (95% CI: -13.39, -1.07) per 10-fold increase in PbB. The 5th–95th percentile range for the cohort PbB was 0.53–6.16 µg/dL. A study of 412 children (median age 15 years) who were diagnosed with CKD found an association between increasing child PbB and decreasing FSIQ, after adjustment for CKD severity (Ruebner et al. 2019). The estimated effect of PbB on FSIQ was -2.1 (95% CI: -3.9, -0.2).

Cognitive function in early childhood–other than FSIQ. Several studies have examined outcomes other than IQ and have found associations between PbB and changes in cognitive function in children whose PbBs were <10 µg/dL (Table 2-30). These include prospective studies that used the same outcome metric, the BSID MDI, allowing comparison of outcomes across studies (Dietrich et al. 1986, 1987, 1989; Kim et al. 2013b; Polanska et al. 2018; Rodrigues et al. 2016; Tellez-Rojo et al. 2006). A prospective study of 884 children conducted in South Korea found inverse associations between PbB in late pregnancy (geometric mean 1.3±1.5, GSD) and MDI scores measured at age 6 months (Kim et al. 2103b). A prospective study of 294 children conducted in Mexico City found inverse associations between concurrent PbB (mean 4.27±2.14, SD) and MDI measured at 24 months in a PbB stratum <10 µg/dL (Tellez-Rojo et al. 2006). A prospective study conducted in Cincinnati, Ohio (approximately 190 infants) found declines in MDI scores at age 6 and 12 months in association with increasing maternal, neonatal, or infant PbB (Dietrich et al. 1986, 1987, 1989). A prospective study conducted in Poland (303 infants) found declines in MDI scores at age 2 years in males (but not females) in association with increasing cord PbB (range 0.24–5.65 µg/dL) (Polanska et al. 2018). A prospective study conducted in Bangladesh (324 infants) found declines in MDI scores at age 2–3 years in association with increasing child PbB (median 7.6 µg/dL, maximum 10.4 µg/dL) (Rodrigues et al. 2016).

Several large-scale retrospective studies linked academic performance for individual children with their corresponding blood Pb data recorded in state or local blood Pb registries (Blackowicz et al. 2016; Evens et al. 2015; Miranda et al. 2009; Shadbegian et al. 2019; Zhang et al. 2013; Table 2-30). Evens et al. (2015) linked individual 3rd grade Illinois Standard Achievement Test (ISAT) scores and PbB data (birth–72 months) for a population of 47,158 children in Chicago, Illinois. All children had PbB <10 µg/dL and the population mean was 4.8±2.2 µg/dL (SD). Increasing PbB was inversely associated with decreasing

covariate adjusted scores in math and reading. The adjusted relative risks (RRs) for failing scores was also significant for a 1 or 5 µg/dL increase in PbB. A follow-up to this study of the same data from Chicago that focused on Hispanic children who had PbB <10 µg/dL also found that increasing PbB was associated with decreasing scores in math and reading and significant RRs for failing scores (Blackowicz et al. 2016). Miranda et al. (2009) linked 4th grade reading End of Grade (EOG) scores and PbB data collected (birth–36 months) for a population of 57,678 children in North Carolina. The population mean PbB was 4.8 µg/dL (range 1–16 µg/dL); 94% of children had PbB <10 µg/dL. Increasing PbB was associated with decreasing covariate adjusted scores in all PbB strata, the lowest of which was 2 µg/dL. The effect size (change in score/µg/dL PbB) increased with increasing PbB. Another study conducted in North Carolina analyzed data on PbB and standardized achievement scores of children in grades 3–8 (Shadbegian et al. 2019). Increasing PbB was associated with decreasing score percentiles in math and reading among children who had PbBs within the range >1–≤5 µg/dL, relative to children who had PbBs <1 µg/dL. Zhang et al. (2013) linked Michigan Educational Assessment Program (MEAP) scores and PbB data (birth–72 months) of age for a population of approximately 21,000 children in Detroit, Michigan. Covariate adjusted ORs for failing scores in mathematics, science, and reading were significant for PbB strata 1–5, 6–10, and >10 µg/dL. A cross-sectional study of data from NHANES III examined associations between PbB and scores on tests of cognitive function (Wide Range Achievement Test-Revised [WRAT-R], Wechsler Intelligence Scales for Children-Revised [WISC-R]) in approximately 5,000 children 6–16 years of age (Lanphear et al. 2000a). Increasing PbB was significantly associated with decreasing scores in reading in blood strata <5.0, <7.5, and <10 µg/dL. McLaine et al. (2013) examined associations between PbB (9–72 months) and kindergarten readiness assessed from Phonological Awareness Literacy Screening-Kindergarten (PALS-K) scores in approximately 3,400 children in Providence, Rhode Island. The population median PbB was 4.2 µg/dL (interquartile range 2.9–6.0); 93% of children had PbB <10 µg/dL. Mean difference in covariate adjusted scores in blood strata 5–9 and ≥10 µg/dL compared to <4 µg/dL were in the inverse direction and adjusted prevalence ratios for test failure was significant in both strata. Genetic variants of N-methyl-D-aspartate receptors (NMDAR subunits GRIN2A and GRIN2B) were effect modifiers on associations between increasing PbB (at age 8–12 years) and decreasing performance tests of learning, memory, and executive function at age 17 years (Rooney et al. 2018).

Altered mood and behavior. Numerous studies have examined possible associations between neonatal and child PbB risk of behaviors that may contribute to learning deficits, including attention deficits, hyperactivity, autistic behaviors, conduct disorders, and delinquency (Table 2-30).

Several studies have examined attention-deficit/hyperactivity disorder (ADHD) as an outcome, allowing comparisons of outcomes across studies (Arbuckle et al. 2016; Boucher et al. 2012; Braun et al. 2006; Choi et al. 2016; Desrochers-Couture et al. 2019; Froehlich et al. 2009; Geier et al. 2018; He et al. 2019; Hong et al. 2015; Huang et al. 2016; Ji et al. 2018; Joo et al. 2017; Park et al. 2016; Wang et al. 2008). Collectively, the ADHD studies indicate that risk of childhood ADHD increases in association with increasing PbB within the range of PbB <10 µg/dL (Table 2-30). Several case-control studies have found associations between increasing PbB and increasing OR for ADHD diagnosis in children (Joo et al. 2017; Park et al. 2016; Wang et al. 2008). In the largest case-control study (630 cases), conducted in China, covariate-adjusted ORs for ADHD in children 4–14 years of age were 4.92 (95% CI 3.47, 6.98) for the PbB range 5–10 µg/dL and 6.00 (4.11, 8.77) for PbB ≥10 µg/dL compared to <5 µg/dL (Wang et al. 2008). Associations between increasing PbB and increasing OR for ADHD diagnosis in children have also been found in several prospective studies (Boucher et al. 2012; Huang et al. 2016; Ji et al. 2008). In the largest prospective study (1,479 children, median age 9.6 years), conducted in Boston, ORs were estimated relative to PbB <2 µg/dL (Ji et al. 2018). The OR for the PbB range of 2–4 µg/dL was 1.08 (95% CI 0.81, 1.44), and the OR for the PbB range of 5–10 µg/dL was 1.73 (95% CI 1.09, 2.73). The OR (5–10 µg/dL relative to <5 µg/dL) for male children (OR 2.49, 95% CI 1.46, 4.26) was larger than for female children (OR 0.68, 95% CI 0.27, 1.69). A prospective study of 272 children (mean age 11 years) conducted in Nunavik, Canada found elevated covariate adjusted ORs of 4.01 (95% CI 1.06, 15.23) for a PbB stratum 1.6–2.7 µg/dL and 5.52 (95% CI 1.38, 22.12) for the stratum 2.7–12.8 µg/dL (Boucher et al. 2012). A longitudinal study examined ADHD outcomes of 2,159 South Korean children (ages 7–9 years) who did not exhibit ADHD symptoms at recruitment (Choi et al. 2016). Two years following baseline assessment, the covariate adjusted relative risk of ADHD was estimated to be 1.552 (95% CI 1.002, 2.403) for children having PbB >2.17 µg/dL compared to ≤2.17 µg/dL. The geometric mean PbB for the cohort was 1.62 µg/dL ±1.52 (GSD). Several cross-sectional studies have also found associations between concurrent PbB and risk of ADHD (Braun et al. 2006; Froehlich et al. 2009; Hong et al. 2014). A study of data on approximately 4,700 children (age 4–15 years) reported in the 1999–2002 NHANES found elevated risk of ADHD in association with concurrent PbB >2 µg/dL and a significant trend in risk with increasing PbB (Braun et al. 2006). Froehlich et al. (2009) examined data for children 8–15 years of age from the 2001–2004 NHANES. Covariate adjusted ORs of ADHD were elevated for the PbB stratum >1.3 µg/dL (compared to ≥0.8 µg/dL). A cross-sectional study conducted in South Korea examined associations between PbB and ADHD rating scores of 1,001 children of age 8–11 years (Hong et al. 2015). One $\log_{10}$ increase of PbB was associated with increases in teacher-rated ADHD hyperactivity (OR 3.66; 95% CI 1.18, 6.13) and total ADHD score (OR 6.38; 95% CI 1.36, 11.40). The cohort geometric mean PbB was 1.8±1.4 µg/dL (SD).

Prospective studies have also provided evidence for associations between neonatal or early childhood PbB and other neurobehavioral outcomes, including neonatal behavior, emotional or temperament problems, anxiety or depression, sleep disorders, hyperactivity and impulsivity, autistic behavior, and delinquency (Dietrich et al. 2001; Fruh et al. 2019; Huang et al. 2016; Joo et al. 2018; Kim et al. 2016; Liu et al. 2014b, 2015b; Sioen et al. 2013; Stroustrup et al. 2016; Winter and Sampson 2017).

Altered neuromotor-neurosensory function. Numerous studies have examined possible associations between neonatal and child PbB and neuromotor or neurosensory function (Table 2-30). Several studies used the Psychomotor Development Index (PDI) score from the BSID, allowing comparison of results across studies (Dietrich et al. 1987, 1989; Kim et al. 2013b; Tellez-Rojo et al. 2006). Each study found inverse associations for PDI scores measured from 6 to 12 months in association with increasing prenatal (e.g., maternal) or neonatal PbB. Studies that repeatedly measured PDI scores longitudinally within the same birth cohorts found that associations observed at 6 months persisted to later ages (Dietrich et al. 1987, 1989, 1991; Tellez-Rojo et al. 2006). A prospective study conducted in China administered a neurobehavioral test battery to a birth cohort of 237 children at age 7 years (Chiodo at al. 2004). Significant declines in performance ($p \leq 0.05$) were observed in PbB strata that ranged from <3 µg/dL at the lowest to <10 µg/dL; most tests that showed significant declines at <10 µg/dL, also showed declines at <5 µg/dL ($p \leq 0.05$). A prospective study conducted in Nunavik, Canada evaluated fine motor control in a birth cohort at 5 years (Fraser et al. 2006). Significant changes in motor control assessed from sway and reaction times were associated with increasing concurrent PbB ($p \leq 0.01$). The cohort PbB mean was 5.3 µg/dL ±4.9 (SD). This birth cohort also exhibited changes in visual evoked potentials that were associated in increasing cord PbB (Ethier et al. 2012). The cohort cord PbB mean was 4.6±3.1 (SD). However, not all studies have found associations between PbB and neuromotor performance. A follow-up of a prospective birth cohort of approximately 14,500 pregnancies evaluated motor skills in 1,558 children at age 7 years (Taylor et al. 2018). Prenatal (gestation week 11) PbB was not associated with performance on a movement assessment battery (e.g., heel-to-toe, threading lace, peg board).

Several studies have examined associations between PbB and neurosensory function in infants or children (Ethier et al. 2012; Liu et al. 2018b; Silver et al. 2016). A prospective study conducted in Nunavik, Canada found changes in visual evoked potentials at age 5 years that were associated with increasing cord PbB (mean 4/6±3.1 µg/dL) (Ethier et al. 2012). A prospective study of 315 mother-infant pairs conducted in China found associations between increasing prenatal PbB and brainstem auditory response measured at age 2 days and grating visual activity measured at age 6 weeks (Silver et al. 2016). Geometric mean

late-pregnancy PbB was 2.7±2.3 (GSD) µg/dL. A cross-sectional study of 234 children (age 3–7 years), conducted in China, found that increasing PbB was associated with hearing loss (Liu et al. 2018b). The OR for hearing loss was 1.24 (95% CI 1.029, 1.486). The median PbB was 4.94±0.20 (SE) µg/dL.

Altered brain structure and neurochemistry. A follow-up to the Cincinnati prospective study (Dietrich et al. 1986) estimated whole brain volumes and imaged brain metabolites in 157–159 adults at age 19–24 years (Brubaker et al. 2010; Cecil et al. 2008, 2011; Table 2-30). Decreasing covariate adjusted brain volume was associated with increased childhood mean PbB (measured between ages 6 months and 6 years). Brain volume reductions that were associated with childhood PbB compromised approximately 1.2% of the total gray matter and were more severe in males compared to females. The largest effects were observed in the anterior cingulate cortex. This region of the brain is involved in controlling executive function, mood, and decision-making. Increasing childhood PbB was also associated with decreasing concentrations of various metabolites in the brain known to be important in the supporting metabolic structural integrity of neurons (e.g., lipid metabolism and myelin production). These included decreased N-acetyl aspartate (NAA) in the basal ganglia and cerebellar hemisphere, decreased glutamate-glutamine in the vermis and parietal white matter, decreased creatine and phosphocreatine in the basal ganglia, and decreased cholines in the cerebellum, parietal white matter, and frontal white matter. These changes in association with childhood PbB suggest that childhood Pb exposure may be indicators of longer-term changes in brain glutamate-associated lipid metabolism or neuronal architecture (Cecil et al. 2011).

Associations Between Bone Pb and Neurological Effects in Children. Few studies have been conducted to assess possible associations between bone Pb and neurological function in children (Table 2-31). Prospective studies of outcomes in children of mother-infant pairs have found associations between maternal or child bone Pb cognitive function (Campbell et al. 2000b; Gomaa et al. 2002; Needleman et al. 1996; Wasserman et al. 2003; Xu et al. 2015). Increasing bone Pb measured at age 24 months was associated with decrements in cognitive development (Gomaa et al. 2002) and behaviors indicative of attention deficit hyperactivity disorder assessed at age 7–15 years (Xu et al. 2015). Increasing child bone Pb measured later in childhood (ages 11–14 years) was associated with decrements in language processing (Campbell et al. 2000b); full scale, verbal, and performance IQ (Wasserman et al. 2003); and delinquent, aggressive, internalizing, externalizing behaviors (Needleman et al. 1996). A case-control study of adjudicated delinquency at age 12–18 years found associations between increasing bone Pb and delinquency (Needleman et al. 2002). A prospective study found associations between increasing bone Pb and difficult temperament at age 24 months (Stroustrup et al. 2016).

Table 2-31. Associations Between Bone Pb and Neurological Outcomes in Children

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Campbell et al. 2000b	156 males, age: 11–14 years	↑ T	–	–	Language processing
Gomaa et al. 2002	197 mother-infant pairs	↑ P[a] 0 T[a]	–	–	24-month MDI[b]
Needleman et al. 1996	301 males, age: 9–13 years	–	–	↑ T	Delinquent, aggressive, internalizing, externalizing behaviors
Needleman et al. 2002	194 male cases, 145 controls, age: 12–18 years	–	–	↑ T	Adjudicated delinquency
Stroustrup et al. 2016	948 mother-infant pairs, 760 children, age: 24 months	–	–	↑ T	Difficult temperament
Wasserman et al. 2003	167 children, age: 10–12 years	↑ T	–	–	IQ (full scale, verbal, performance)[c]
Xu et al. 2015	197 mother-infant pairs	–	–	↑ P[a]	Attenuation of effect of maternal self-esteem on ADHD assessed at age 7–15 years[d]

[a]Maternal bone lead measured within 1 month of birth.
[b]Bayley Scale.
[c]Wechsler Intelligence Scale for Children-III.
[d]Maternal self-esteem was evaluated with Coopersmith Self-Esteem Inventory. ADHD was evaluated with Conners' Parent Rating Scale-Revised and Behavior Rating Inventory of Executive Function.

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; ADHD = Attention deficit hyperactivity disorder; C = calcaneus bone; MDI = Mental Developmental Index; P = patella; Pb = lead; T = tibia; O = other

Effects at Blood Pb Levels ≤10 µg/dL in Adults. Numerous longitudinal and large cross-sectional studies in adults provide a weight of evidence for decreased cognitive function, altered mood and behavior, and altered neuromotor and neurosensory function in association with exposures that result in PbB <10 µg/dL,

with some studies showing effects in the 3–5 µg/dL range. Study details are reviewed in the *Supporting Document for Epidemiological Studies for Lead*, Table 10. Cognitive, neuromotor, and neurosensory outcomes have been evaluated with tests of memory, learning, executive function, reaction time, walking speed, and tremor. Pb exposure has been associated with risk of various psychiatric symptoms including anxiety, depression, and schizophrenia, and with risk of ALS. In some studies, associations were found between outcomes and PbB and/or bone Pb. Several studies have examined cohorts of people who had mean ages within the range 50–70 years. Studies of cognitive function in elderly populations must control for factors that contribute to age-related decrements in function, including confounding from the relationship between age and bone Pb, which increases with age. Longitudinal studies offer advantages over cross-sectional studies in that they can provide measurement changes in function of individual subjects with age.

Cognitive function. Numerous studies have examined possible associations between Pb exposure and cognitive function in adults (Table 2-32). Most of these studies have found associations between increasing Pb exposure, indicated by blood or bone Pb, and indications of decreased cognitive function (Muldoon et al. 1996; Payton et al. 1998; Power et al. 2014; Przybyla et al. 2017; Seegal et al. 2013; Seo et al. 2014; Shih et al. 2006; Weisskopf et al. 2007; Weuve et al. 2006, 2009; Wright et al. 2003b). However, not all studies have found associations (Kreig et al. 2005; Yu et al. 2019b). One of the largest cross-sectional studies analyzed data from NHANES III (1988–1994) found no associations between PbB and performance on neurobehavioral tests (Krieg et al. 2005). This study compared scores from several tests from the Neurobehavioral Evaluation System (NBES) and concurrent PbB in approximately 5,700 adults (age 20–50 years). Implemented tests measured processing speed, attention, learning, and memory (reaction time, symbol-digit substitution, serial digit learning). The geometric mean PbB was 2.51 µg/dL (range 0.7–42) and 96% of the cohort was <10 µg/dL. No significant associations (defined as $p \leq 0.05$) between PbB and cognitive outcomes were found. However, associations between PbB and cognitive performance may be stronger in elderly adults. An examination of a smaller cohort from the NHANES 1999–2000, restricted to ages ≥60 years (n=498), found an association between increasing PbB and decreasing scores on short-term memory (digit symbol test) (Przybyla et al. 2017). The geometric mean PbB in this study was 2.17 µg/dL. Several studies have examined smaller cohorts from longitudinal studies designed to evaluate health in aging populations. Studies of male cohorts from the Normative Aging Study have found significant ($p \leq 0.05$) associations between increasing blood and/or bone Pb and

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Cognitive abilities			
Krieg et al. 2005 Cross-sectional study; n=5,662 adults, age 20–59 years	Gmean (range): 2.51 (0.7, 41.8)	Simple visual reaction time	No associations between PbB and performance scores • Mean reaction time: p=0.24
		Symbol-digit substitution	• Mean total latency: p=0.27 • Number of errors: p=0.82
		Serial digit learning	• Trials to criterion: p=0.26 • Total score: p=0.24
Muldoon et al. 1996 Cross-sectional study; n=530 adult women, mean age 70 years	Mean (SD): • All: 4.8 (0.4) • Rural: 4.5 (0.4) • Urban: 5.4 (0.4) • Low: <4 • Medium: 4–7 • High: >7	Trailmaking B	• Urban o Medium PbB OR: 0.97 (0.40, 2.40) o High PbB OR: 0.79 (0.20, 3.04) • **Rural** o **Medium PbB OR: 2.05 (1.05, 4.02)*** o **High PbB OR: 2.60 (1.04, 6.49)***
		Digit symbol (correct)	• Urban o Medium PbB OR: 0.61 (0.25, 1.50) o High PbB OR: 0.64 (0.16, 2.47) • **Rural** o **Medium PbB OR: 2.03 (1.06, 3.88)*** o **High PbB OR: 3.73 (1.57, 8.84)***
		Incidental memory	• Urban o Medium PbB OR: 0.50 (0.22, 1.16) o High PbB OR:0.99 (0.28, 1.16) • Rural o Medium PbB: OR: 1.37 (0.77, 2.41) o High PbB: OR: 1.89 (0.83, 3.41)

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Payton et al. 1998 Longitudinal study; n=141 males, mean age 67 years	Mean (SD): • 5.5 (3.5) • Q1: 1.4 • Q2: 3.5 • Q3: 5.4 • Q4: 9.8	Pattern recognition	• **β: 0.074 (0.032), p=0.02***
		Vocabulary	• **β: -0.841 (0.20), p=0.0001***
		Word list memory	• **β: -0.182 (0.086), p=0.036***
		Boston naming test	• **β: -0.036 (0.016), p=0.028***
		Verbal fluency	• β: -0.230 (0.120), p=0.09
Power et al. 2014 Longitudinal study; n=584 adults females, mean age 61 years	Mean (SD): • 2.9 (1.9) Tibia Pb (µg/g): Mean (SD): • 10.5 (9.7) Patella Pb (µg/g) mean (SD): • 12.6 (11.7)	Overall cognition	β for 1-age year change in score per 1 SD PbB: -0.013 (-0.044, 0.017)
		Verbal memory	β for 1-age year change in score per 1 SD PbB: 0.006 (-0.037, 0.050)
Przybyla et al. 2017 Cross-sectional study; n=498 adults, age 60–84 years	Gmean (range): 2.17 (0.4, 16.4)	Digit symbol (correct)	β per lnPbB µg/dL: -0.10 (-0.20, -0.006), p=0.04
Seo et al. 2014 Cross-sectional study; n=31 retired female Pb workers, mean age 60.4 years, and 34 controls	Gmean (range): Exposed: 4.07 (0.88–13.5) Controls: 2.00 (1.24–6.47)	Verbal memory	Accuracy % (SD), exposed versus control: • 1-back test: 55.9 (19.8) versus 65.4 (19.4), p=0.056 • **2-back test: 61.4 (20.1) versus 77.2 (15.6), p=0.001***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Shih et al. 2006 Cross-sectional study; n=985 adults, mean age 59.4 years	Mean (SD): • 3.46 (2.23) Tibia Pb (µg/g) mean (SD): • 18.72 (11.24)	Language	• **B per 1 µg/g tibia Pb: -0.0083 (0.0023), p≤0.01***
		Processing speed	• **β per 1 µg/g tibia Pb: -0.0042 (0.0021), p<0.01***
		Eye-hand	• **β per 1 µg/g tibia Pb: -0.0079 (0.0020), p≤0.01***
		Executive function	• **β per 1 µg/g tibia Pb: -0.0075 (0.0019), p≤0.01***
		Verbal memory and learning	• **β per 1 µg/g tibia Pb: -0.0078 (0.0024), p≤0.01***
		Visual memory	• **β per 1 µg/g tibia Pb: -0.0067 (0.0023), p≤0.01***
		Visuoconstruction	• **β per 1 µg/g tibia Pb: -0.0122 (0.0027), p≤0.01***
Weisskopf et al. 2007 Longitudinal study cohort, n=1,089 males, mean age 68.7 years	Median (IQ range): • 5 (3–6) Tibia Pb (µg/g) median (IQ range): • 20 (13–28) Patella Pb (µg/g) median (IQ range): • 25 (17–37)	Vocabulary	**β per 3 µg/dL increase in PbB: -1.26 (-2.08, -0.44), p=0.003***
		Visuoconstruction (patella Pb)	**β per IQR: -0.067 (-0.11, -0.02), p=0.0041***
		Pattern comparison latency (tibia Pb)	**β: 0.079 (0.04, 0.12), p=0.0004***
Weuve et al. 2006 Longitudinal study cohort, n=915 males, mean age 68.7 years	Median (IQ range): • 5.2 (2.9) • 94% <10	Cognitive function	Change in MMSE score per IQR in PbB, 3 µg/dL: • **ALAD-2: IQR: -0.29 (-0.56, -0.02)*** • ALAD wildtype: IQR: -0.05 (-0.16, 0.06)
Weuve et al. 2009 Longitudinal study cohort, n=587 females, mean age 61 years	Mean (SD): • 2.9 (1.9) Tibia Pb (µg/g) median (SD): • 10.5 (9.7)	Cognitive function	Change in score per 1 SD in PbB or bone Pb: • PbB: -0.016 (-0.071, 0.039), p=0.57 • **Tibia: -0.051 (-0.099, -0.003), p=0.04*** • Patella Pb: -0.033 (-0.080, 0.014), p=0.17

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
	Patella Pb (µg/g) median (SD): • 12.6 (11.6)		
Wright et al. 2003b Longitudinal study cohort, n=736 males, mean age 68.2 years	Mean (SD): • All: 4.5 (2.5) • Q1: 2.5 • Q2: 4.0 • Q3: 5.9 • Q4: 8.9 Tibia Pb (µg/g) median (SD): • 22.4 (15.3) Patella Pb (µg/g) median (SD): • 29.5 (21.2)	MMSE score	Adjusted OR with 1 µg/dL increase in PbB or 1 µg/g increase in bone Pb: • **PbB: 1.21 (1.07, 1.36)*** • **Patella Pb: 1.02 (1.00, 1.03)*** • **Tibia Pb: 1.02 (1.00, 1.04)*** Effect of age increased with increasing PbB. β for age with increasing Pb for PbB quartile: • **Q1 -0.04 (-0.07, -0.02)*** • **Q2 -0.04 (-0.08, -0.01)*** • **Q3 -0.09 (-0.13, -0.06)*** • **Q4 -0.12 (-0.17, -0.02)***
Yu et al. 2019b Cross-sectional study; n=339 males, mean age 28.6 years	Gmean (IQR): 2.47 (2.00, 3.00)	Digit symbol (mean total latency)	β per $\log_{10}$ PbB: 5.4% (-0.4, 11.5), p=0.066
		Stroop reaction time incongruent trials	β per $\log_{10}$ PbB: 5.1% (-4.5, 15.6), p=0.30
		Stroop reaction time congruent trials	β per $\log_{10}$ PbB: -1.2% (-10.4, 9.0), p=0.81
		Stroop interference effect	β per $\log_{10}$ PbB: 23.0% (-15.4, 78.9), p=0.28

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Mood and behavior			
Bouchard et al. 2009 Cross-sectional study; n=1,987 adults (age 20–39 years)	Gmean±GSD (range): • 1.24 (1.96) • 99%≤10 • Q1: 0.6 • Q2: 0.9 • Q3: 1.2 • Q4: 1.3 • Q5: 3.0	Major depressive disorder	• **Adjusted ORs for PbB for Q5 relative to Q1: 2.32 (1.13, 4.75); p-trend=0.05*** • **Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 2.93 (1.24, 6.92); p-trend=0.03***
		Panic disorder	• **Adjusted ORs for PbB for Q5 relative to Q1: 4.94 (1.32, 18.48); p-trend=0.02*** • **Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 9.57 (1.28, 71.43); p-trend=0.01***
		Generalized anxiety disorder	• Adjusted ORs for PbB for Q5 relative to Q1**:** 1.53 (0.39, 5.96); p-trend=0.78 • Eliminating current smokers, adjusted ORs for PbB for Q5 relative to Q1: 1.59 (0.19, 13.31); p-trend=0.44
Buser and Scinicariello 2017 Cross-sectional study of 3,905 adults (age ≥20 years) from NHANES 2011–2012	Cohort stratified into PbB quartiles: • Q1: <0.7 • Q2: 0.70–1.06 • Q3: 1.07–1.67 • Q4: >1.67	Depression	Adjusted OR for depression symptoms in adult females (age 20–47 years) associated with increasing PbB: • **Q3: 1.86 (1.01, 3.41, p<0.05*** • **Q4: 2.97 (1.01, 8.74), p<0.05***
Fan et al. 2020 Cross-sectional study; n=994 adults, age >60 years	Mean (SD): 3.229 (2.357) • Q1: <2.027 • Q2: 2.027, 2.677 • Q3: 2.677, 3.058 Q4: ≥3.058	Depression symptoms (score on 30-point Geriatric Depression Scale ≥11)	OR for depression for PbB quartiles relative to Q1: • Q2: 1.28 (0.79, 2.08), p=0.315 • Q3: 1.36 (0.84, 2.22), p=0.216 • **Q4: 2.03 (1.23, 3.35), p=0.006*** • **p-trend=0.007***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Golub et al. 2010 Cross-sectional study; 4,195 adults (age ≥20 years) from NHANES 2005–2006	Cohort stratified into PbB quartiles: • Q1: ≤0.88 • Q2: 0.89–1.40 • Q3: 1.41–2.17 • Q4: 2.18–26.4		Adjusted OR for depression symptoms was elevated in PbB quartile 3 (95% CI): • **Q3: 1.25 (1.07, 1.47)***
Li et al. 2017a Cross-sectional study; n=1,931 pregnancies (age 13–42 years)	Gmean (range): 3.99 (0.80, 14.84)	Depression symptoms	β per log_{10} PbB: • Full cohort: 0.03 (-0.05, 0.10), p=0.466 • **PbB ≤2.57: 0.34 (0.12, 0.56), p=0.002*** • PbB >2.57: -0.09 (-0.19, 0.02), p=0.113
		Anxiety symptoms	β per log_{10} PbB: • Full cohort: 0.01 (-0.06, 0.08), p=0.770 • **PbB ≤2.57: 0.25 (0.04, 0.46), p=0.019*** • PbB >2.57: -0.08 (-0.18, 0.02), p=0.136
		Depression or anxiety symptoms (Global Severity Index)	β per log10 PbB: • Full cohort: 0.01 (-0.05, 0.07), p=0.815 • **PbB ≤2.57: 0.22 (0.05, 0.40), p=0.013*** • PbB >2.57: -0.07 (-0.16, 0.01), p=0.100
Opler et al. 2004 Case-control study; n=44 schizophrenia cases and 75 matched controls from birth cohorts	Cohort stratified into <15 or ≥15 µg/dL based on 2nd trimester ALA measurements	Schizophrenia	Adjusted OR for schizophrenia associated with high (≥15 µg/dL) prenatal PbB: 2.43 (0.99, 5.96), p=0.051
Opler et al. 2008 Case-control study; n=71 schizophrenia cases and 129 matched controls	Cohort stratified into <15 or ≥15 µg/dL based on 2nd trimester ALA measurements	Schizophrenia	**Adjusted OR for schizophrenia associated with high (≥15 µg/dL) prenatal PbB: 1.92 (1.05, 3.87), p=0.03***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Rajan et al. 2007 Longitudinal study cohort, n=1,075 males, mean age 67.1 years	Mean (SD): • All: 6.2 (4.1) Tibia Pb (µg/g) median (SD): • 22.1 (13.8) Patella Pb (µg/g) median (SD): • 31.4 (19.6)	Somatization, tibia Pb	**Adjusted OR for inter quartile increases in tibia Pb (14 µg/g) or patella Pb (20 µg/g): 1.21 (1.01, 1.46)***
		Global severity index, patella Pb	**OR: 1.23 (1.02, 1.47)***
Rhodes et al. 2003 Longitudinal study cohort, n=526 males, mean age 67.1 years	Mean (SD): • 6.3 (4.2) Tibia Pb (µg/g) median (SD): • 21.9 (13.5) Patella Pb (µg/g) median (SD): • 32.1 (19.8)	Phobic anxiety	**Adjusted OR for inter quintile increases in patella Pb (8.9 µg/dL: 1.91 (1.01, 3.61)***
		Combined symptoms	**Adjusted OR for inter quintile increases:** • **PbB OR: 2.91 (1.39, 6.09)*** • **Tibia Pb OR: 2.08 (1.06, 4.07)*** • **Patella Pb OR: 3.62 (1.62, 8.08)***
Scinicariello and Buser 2015 Cross-sectional study of 2,892 adults (age 20–39 years) from NHANES 2007–2010	**PbB:** Gmean (GSD) • 0.96 (0.02).	Depression	Adjusted OR for depression symptoms was not associated with increasing PbB (ORs were not reported).

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Neuromotor neurosensory function			
Casjens et al. 2018 Longitudinal study; n=1,188 males, age 55–86 years at follow-up	Median (% >9) • Baseline: 3.29 (2.27%) • 11-year follow-up: 2.59 (0.84%)	Olfaction (score on 12-point odor identification test ≤7)	Proportional OR for PbB stratum relative <5.0 µg/dL: Baseline: • 5–<9 µg/dL: 0.91 (0.65, 1.28) • ≥9 µg/dL: 1.96 (0.94, 4.11) Follow-up: • 5.0–<9.0 µg/dL: 1.04 (0.55, 1.94) • ≥9.0 µg/dL: 1.57 (0.47, 5.19)
		Dexterity (finger tapping errors)	OR (95% CI) for impaired performance <5.0 µg/dL: • 5.0 to <9.0 µg/dL: 0.87 (0.53, 1.44) • ≥9.0 µg/dL: 1.35 (0.49, 3.70) Follow-up: • **5.0–<9.0 µg/dL: 2.63 (1.26, 5.94)*** • ≥9.0 µg/dL: 0.80 (0.14, 4.59)
Hwang et al. 2009 Cross-sectional study; n=259 male steel workers, mean age 36.0 years	Mean (SD): 5.43 (3.46)	Hearing loss	Adjusted OR for hearing loss (>25 dB) at 3,000–8,000 Hz in PbB categories relative to ≤4 µg/dL: Loss at 3,000 Hz • 4–7 µg/dL: 0.75 (0.17, 3.29) • **≥7 µg/dL: 4.49 (1.28, 15.8); p<0.005*** Loss at 4,000 Hz: • **4–7 µg/dL: 3.54 (1.40, 8.97)* (p-value not reported)** • **≥7 µg/dL: 6.26 (2.35, 16.6); p<0.005*** Loss at 6,000 Hz: • 4–7 µg/dL: 2.11 (0.94, 4.47) • **≥7 µg/dL: 3.06 (1.27, 7.39); p<0.05***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Huh et al. 2018 Cross-sectional study; n=2,387 adults, age 19–85 years	Gmean (95% CI): 2.46 (2.41, 2.52)	Hearing loss (pure tone threshold >25 dB)	OR per doubling of PbB (95% CI): • Low frequency: 0.91 (0.52, 1.61) • Speech frequency: 1.21 (0.72, 2.04) • **High frequency: 1.88 (1.11, 3.17)***
Ji et al. 2013 Cross-sectional study; n=1,795 males and 1,798 females, age >50 years (median 61.2)	Mean (SD): • Females: 2.17 (0.06) • Males: 3.18 (0.12)	Walking speed	Mean change in walking speed (ft/sec) for PbB quintile relative to Q1 (≤1.2 µg/dL): • PbB 1.3–≤1.6. β: -0.024 (-0.112, 0.064), p=0.58 • PbB 1.7–≤2.1, β: -0.027 (-0.118, 0.063), p=0.54 • **PbB 2.2–≤2.9, β: -0.104 (-0.187, -0.021), p=0.02*** • **PbB 3.3–≤53.0, β: -0.114 (-0.191, -0.038), p=0.01*** • **p-trend=0.005***
Ji et al. 2015 Longitudinal study cohort, n=807 males, mean age 69 years	Mean (SD): 5.0 (2.7) • % <10: 96% Bone Pb, µg/g (SD) • Patella: 28.0 (18.4) Tibia: 21.2 (13.3)	Tremor	OR for tremor by PbB quintile: • Q5 (8–28), PbB: 0.84 (0.38, 1.86), p=0.72 • Q5 (40–165), patella Pb: 0.83 (0.31, 2.19), p=0.41 • Q5 (30–126): tibia Pb: 1.08 (0.46, 2.53), p=0.60

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Kang et al. 2018 Cross-sectional study; n=6,409 adults, age 20–87 years	Cohort stratified into PbB quartiles Females, weighted mean (SE) • Q1: 1.12 (0.01) • Q2: 1.61 (0.01) • Q3: 2.11 (0.01) • Q4: 3.03 (0.03) Males, weighted mean (SE) • Q1: 1.56 (0.01) • Q2: 2.22 (0.01) • Q3: 2.82 (0.01) • Q4: 4.22 (0.08)	Hearing loss (females)	• Q2: 0.947 (0.606 1.477) • Q3: 1.013 (0.698, 1.471) • **Q4: 1.502 (1.027, 2.196)***
		Hearing loss (males)	• **Q2: 1.368 (1.006, 1.859)*** • **Q3: 1.402 (1.005, 1.955)*** • **Q4: 1.629 (1.161, 2.287)***
Muldoon et al. 1996 Cross-sectional study; n=530 adult women, mean age 70 years	Mean (SD): • All: 4.8 (0.4) • Rural: 4.5 (0.4) • Urban: 5.4 (0.4) • Low: <4 • Medium: 4–7 • High: >7	Pegboard	OR for poor performance (low PbB reference) in the rural cohort: ANOVA, p=0.98 • Medium PbB OR: 1.37 (0.71, 2.65) • High PbB OR: 1.16 (0.45, 3.01)
		Upper extremity	ANOVA, p<0.01, in the rural cohort • Medium PbB: OR: 1.39 (0.73, 2.65) • **High PbB: OR: 2.43 (1.01, 5.83)***
		Lower extremity	ANOVA, p<0.01, in the rural cohort • Medium PbB OR: 1.29 (0.68, 2.47 • **High PbB OR: 2.84 (1.19, 6.74)***

Table 2-32. Summary of Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Neurological disease			
Fang et al. 2010 Case-control study; n=184 male ALS cases and 194 matched controls, mean age 63 years	Mean (range): • Controls: 1.76 (0.32–6.90) • Cases: 2.41 (0.72–7.58)	ALS	**Adjusted OR for ALS for doubling of PbB:** • **All cases (n=184): 1.9 (1.3, 2.7)*** • **Excluding progressive muscular atrophy and primary lateral sclerosis (n=151): 1.8 (1.2, 2.5)***
Kamel et al. 2002 Case-control study; n=109 ALS cases and 256 matched controls, age 30–80 years	Mean (range): • Cases: 3 of 194 had PbB >10 • Controls: <10 µg/dL	ALS	• **Adjusted OR for ALS (for a 1-µg/dL increase in PbB: 1.9 (1.4, 2.6)*** • **Adjusted OR for ALS relative to <2 µg/dL:** o **3–4 µg/dL: 14.3 (3.0, 69.3)*** o **5–14 µg/dL: 24.5 (4.3, 139.3)***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 10 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

ALA = aminolevulinic acid; ALAD-2 = delta-aminolevulinic acid dehydratase allele; ALS = amyotrophic lateral sclerosis; ANOVA = analysis of variance; CI = confidence interval; CL = confidence limit; Gmean = geometric mean; GSD = geometric standard deviation; IQ = intelligence quotient; IQR = interquartile range; MMSE = Mini-Mental Status Examination; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error

decreasing scores on cognitive tests, including short-term memory, verbal memory, and visuoconstruction (Payton et al. 1998; Weisskopf et al. 2007; Weuve et al. 2006). Cohort sizes in these studies ranged from approximately 600 to 1,100 and the mean PbB ranged from 2.9±1.9 to 5.5±3.5 µg/dL. Weuve et al. (2006) found that decreases in cognitive performance were associated with PbB in a cohort of ALAD-2 carriers, but not in a cohort that carried the wildtype ALAD allele. Studies of female cohorts (approximately 600 subjects) from the longitudinal Nurses' Health Study have found mixed outcomes (Power et al. 2014; Weuve et al. 2009). Weuve et al. (2009) found significant association between increasing tibia Pb, but not PbB, and scores on a telephone survey of cognitive function (the Telephone Interview for Cognitive Status, TIC). The TIC has been used to assess memory and executive function and has been used to evaluate dementia. The effect size was -0.051 (95% CI -0.099, -0.003) points per 1 SD of tibia Pb. Power et al. (2014) used the same telephone survey instrument and found no associations between blood or bone Pb and cognitive function; the effect size for PbB was -0.013 (95% CI: -0.044, 0.017) and the cohort mean PbB was 2.9±1.9 (SD) µg/dL. A cross-sectional study of approximately 1,000 adults from the Boston Memory Study found inverse associations ($p \leq 0.05$) between performance on cognitive tests and increasing tibia Pb, but not for PbB (Shih et al. 2006). The cohort mean blood Pb was 3.46±2.2 (SD) µg/dL. Cognitive function evaluated included language, processing speed, executive function, verbal memory and learning, and visuoconstruction. The effect sizes were substantially attenuated by race/ethnicity and years of educational and were no longer significant ($p<0.05$) when adjusted for these covariates. A cross-sectional study of approximately 500 adult females from the Study of Osteoporotic Fractures found significant associations ($p \leq 0.05$) between performance on cognitive tests and increasing PbB (Muldoon et al. 1996). The odds of performing worse on visual attention and short-term memory tests were significantly decreased ($p \leq 0.05$) in a PbB stratum 4–7 and to >7 µg/dL compared to stratum <4 µg/dL. A cross-sectional study of 339 newly hired male Pb workers did not find significant associations between PbB ($p \geq 0.05$) and performance on tests that measured attention, memory, and processing speed (Stroop test, Symbol Digit Test) (Yu et al. 2019b). The geometric mean PbB was 2.47 µg/dL.

Altered mood and behavior. Several studies have examined associations between Pb exposure assessed from blood or bone Pb and symptoms of psychiatric disorders (Table 2-32). Several studies have analyzed cross-sectional data from NHANES to explore associations between depression symptoms and PbB (Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010; Scinicariello and Buser 2015). Three studies found associations between PbB and depression in adult populations that had geometric mean PbBs that were 2–3 µg/dL compared to populations that have PbBs <1 (Bouchard et al. 2009; Buser and Scinicariello 2017; Golub et al. 2010). Buser and Scinicariello (2017) found stronger

associations in adult women than in men. Cross-sectional studies in other populations have found significant associations between PbB and symptoms of depression or anxiety (Fan et al. 2020; Li et al. 2017a). The Fan et al. (2020) study was restricted to adults >60 years (n=994) and found that increasing PbB was associated with increasing scores on the Geriatric Depression Scale. The OR for categorization as depressed was 2.04 (95% CI: 1.23, 3.35) in the upper quartile PbB stratum (≥3.06 µg/dL). The Li et al. (2017a) study examined a cross-sectional cohort of 1,931 pregnancies (age range 13–42 years) for depression, anxiety, and psychological stress. Increasing PbB was associated with increasing scores on depression and anxiety assessments; however, the association was stronger in the PbB stratum ≤2.57 µg/dL compared to a higher stratum >2.57 µg/dL. Associations between psychiatric disorders and Pb exposure metrics have also been studied in longitudinal studies (Rajan et al. 2007; Rhodes et al. 2003). Two studies of cohorts from the Normative Aging Study found significant ORs for blood or bone Pb and various psychiatric symptoms in males (mean age 67±7, SD), including somatization, phobic anxiety, and composite indices of distress. Mean PbBs in these cohorts were 6±4 (SD) µg/dL. Associations between PbB and psychiatric disorders have also been found in case-control studies (Opler et al. 2004, 2008). The largest was a study of 71 schizophrenia cases and 129 matched controls (Opler et al. 2008). The adjusted OR for schizophrenia was 1.92 (95% CI 1.05, 3.87) for the PbB stratum ≥15 µg/dL compared to 15 µg/dL. Because individual PbB data were not available, subjects were categorized into the high (<15 µg/dL) or low (15 µg/dL) PbB categories based on measurements of serum ALA and a regression model relating PbB and ALA derived from a different population (Graziano et al. 1990). Although the accuracy of the method for assigning subjects from Graziano et al. (1990) into low or high categories was, on average, approximately 90%, uncertainty in the actual regression model is likely to have resulted in some misclassification of individuals.

Altered neuromotor neurosensory function. Several studies have examined associations between Pb exposure assessed from blood or bone Pb and performance on tests of neuromotor or neurosensory function (Table 2-32). The largest study analyzed data from NHANES III (1988–1994) and found no association (p=0.34) between concurrent PbB and simple visual reaction time in a cohort of 5,700 adults (age 20–50 years; Krieg et al. 2005). The geometric mean PbB was 2.51 µg/dL (range 0.7–42) and 96% of the cohort was <10 µg/dL. A more recent analysis of data from NHANES (1999–2002) examined walking speed in cohorts of approximately 1,800 males or females and found a significant association between increasing PbB and decreasing walking speed in females in a PbB stratum 2.2–≤2.9 µg/dL compared to 1.6 µg/dL; there was a significant trend with increasing PbB (Ji et al. 2013). This outcome is consistent with a smaller cross-sectional study of women (mean age 70±4 years) that found significant decreases in upper and lower extremity reaction times in association with increasing PbB (Muldoon et al.

1996). A longitudinal study of a cohort from the Normative Aging Study found no significant associations between bone or blood Pb and hand tremor in males (mean age 60±7 years; Ji et al. 2015). The mean PbB for the cohort was 5.0±2.7 (SD) µg/dL. A longitudinal study of males (n=1,188), age range 50–86 years, conducted in Germany, found associations between increasing PbB and decreasing performance scores on tests of dexterity (Casjens et al. 2018). The median PbBs were 3.29 µg/dL at the start of the study (2.27% >9 µg/dL) and 2.29 µg/dL (0.84% >9 µg/dL) at the 11-year follow-up. This study examined several metrics of dexterity (finger tapping and aiming, line tracing, steadiness). The association with Pb was strongest for the finger tapping test. The OR for impaired performance on the finger tapping test at the follow-up was 2.63 (95% CI: 1.26, 5.94) for the PbB stratum 5.0–<9 µg/dL and 0.80 (95% CI: 0.14, 4.59) for the PbB stratum >9 µg/dL.

Several studies have examined associations between PbB and sensory function in adults, including olfaction (Casjens et al. 2018) and hearing (Huh et al. 2018; Hwang et al. 2009; Kang et al. 2018). Two studies examined association between PbB and hearing using data from the Korean National Health and Nutrition Examination Study (KNHANES) (Huh et al. 2018; Kang et al. 2018). Both studies found associations between increasing PbB and high-frequency hearing loss. The larger of the two studies (n=6,409) estimated ORs for high-frequency hearing loss in females and males in the age range 19–85 years. The ORs were 1.629 (95% CI: 1.161, 2.287) in the highest male PbB quartile (mean PbB: 4.2 µg/dL±0.04 SE) and 1.502 (95% CI: 1.027, 2.196) in the highest female PbB quartile (mean PbB: 3.03 µg/dL ±0.03 SE). A smaller cross-sectional study of steel workers (n=259) also found associations been increasing PbB and hearing loss that extended from 3,000 to 8,000 Hz in the PbB stratum ≥7 µg/dL (Hwang et al. 2009). Performance on an odor identification test was not associated with PbB in a longitudinal study of males (n=1,188), age range 50–86 years (Casjens et al. 2018).

Neurological diseases. Possible associations between Pb exposure and risk of ALS have been examined in case-control studies (Fang et al. 2010; Kamel et al. 2002). A case-control study of 184 male ALS cases and 194 matched controls found a significant association between increasing PbB and ALS (Fang et al. 2010). The mean PbB for cases was 2.41 µg/dL (range 0.72–7.58 µg/dL). A case-control study of 109 ALS cases (43 females, 66 males) and 194 matched controls estimated the OR for ALS to be 1.9 (95% CI: 1.4, 2.6) for a 1 µg/dL increase in PbB (Kamel et al. 2002).

Associations Between Bone Pb and Neurological Effects in Adults. Decrements in neurological function in adults have also been associated with bone Pb (Table 2-33). In general, these studies provide further support for associations between Pb exposure and neurobehavioral function, including decrements

in cognitive function, altered neuromotor and neurosensory function, and altered behavior and mood. Most of these studies are of cohorts from longitudinal health studies: Boston Memory Study (Bandeen-Roche et al. 2009; Glass et al. 2009; Shih et al. 2006), Nurses' Health Study (Power et al. 2014; Weuve et al. 2009), or Normative Aging Study (Eum et al. 2013; Farooqui et al. 2017; Grashow et al. 2013a, 2013b, 2015; Ji et al. 2015; Park et al. 2010; Payton et al. 1998; Power et al. 2014; Rajan et al. 2007, 2008; Rhodes et al. 2003; Schwartz et al. 2005; Wang et al. 2007, 2018; Weisskopf et al. 2004, 2007; Wright et al. 2003b). These studies have provided both cross-sectional and longitudinal assessments of associations between bone Pb (and PbB) and neurological function in adult populations. Longitudinal designs are particularly important because they allow age-related declines in cognitive function to be assessed. Longitudinal studies have found that associations between bone Pb and cognitive function (learning, memory) persist when adjustments are made for age (Bandeen-Roche et al. 2009; Dorsey et al. 2006; Eum et al. 2013; Grashow et al. 2013a; Khalil et al. 2009; Payton et al. 1998; Power et al. 2014; Rajan et al. 2008; Schwartz et al. 2005; Seegal et al. 2013; Shih et al. 2006; Stewart et al. 2002; van Wijngaarden et al. 2009; Weisskopf et al. 2007; Weuve et al. 2009, 2013; Wright et al. 2003b). Rates of decrement in cognitive function with age have been found to be more severe in association with increasing bone Pb (Farooqui et al. 2017; Power et al. 2014; Schwartz et al. 2005; Wang et al. 2007; Weisskopf et al. 2004, 2007; Wright et al. 2003b).

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Bandeen-Roche et al. 2009	965 adults, age: 50–70 years[a]	↑ T	–	–	Learning, memory, executive function, eye-hand coordination
Coon et al. 2006	121 adult cases, 414 controls, age: 50–>80 years	–	↑ 0[d]	–	Parkinson's disease
Dorsey et al. 2006	652 adult Pb workers, age: 20–70 years	↑ P ↑ T	↑ P ↑ T	↑ P ↑ T	Reaction time, executive function, manual dexterity, vibration threshold, depression

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Eum et al. 2013	789 adult males[b], age: 68 years (median)	↑ P ↑ T	–	–	Memory, verbal and written skills, executive function
Eum et al. 2015	100 adult cases, 194 controls, age: 60 years (mean)	–	↑ P ↑ T	–	Interaction between Pb, amyotrophic lateral sclerosis and hemochromatosis gene polymorphisms
Farooqui et al. 2017	741 males, age: 68 years (mean)	↑ P 0 T	–	–	Memory, visuospatial ability, attention, language, orientation
Glass et al. 2009	1,001 adults[a], age: 50–70 years	↑ T	↑ T	–	Interaction between Pb and psychosocial hazard scale for eye-hand coordination, executive function, language
Grashow et al. 2013a	51 adult males[b], age: 75 years (mean)	↑ P 0 T	–	–	Fear conditioning
Grashow et al. 2013b	362 adult males[b], age: 69 years (mean)	–	↑ P ↑ T	–	Manual dexterity
Grashow et al. 2015	164 adult males[b], age: 80 years (mean)	–	0 P ↑ T	–	Olfactory function
Ji et al. 2015	672 adult males[b], age: 50–98 years	–	0 P 0 T	–	Tremor (no association in adjusted models)
Kamel et al. 2002	109 adult cases, 256 controls, age: 30–80 years	–	0 P 0 T	–	Amyotrophic lateral sclerosis (no association in adjusted models)
Khalil et al. 2009	83 adult workers and 51 controls, age: >55 years	↑ T	–	–	Learning, memory

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Park et al. 2010	448 adult males[b], age: 65 years (mean)	–	↑ P ↑ T	–	Hearing function
Payton et al. 1998	141 adult males[b], age: 67 years (mean)	↑ T	–	–	Memory, visual-spatial performance
Power et al. 2014	584 adult females[c], age: 60–74 years	0 P 0 T	–	–	Learning, memory, executive function
Rajan et al. 2007	1,075 adult males[b], age: 48–94 years	–	–	↑ P ↑ T	Psychiatric symptoms
Rajan et al. 2008	982 adult males[b], age: 49–>72 years	0 P ↑ T	–	–	Visual-spatial performance
Rhodes et al. 2003	536 adult males[b], age: 48–70 years	–	–	↑ P ↑ T	Anxiety
Schwartz et al. 2000b	535 Pb workers, age: 56 years (mean)	↑ T	↑ T	–	Memory, executive function, manual dexterity
Schwartz et al. 2001	803 exposed Pb workers and 135 controls, age: 40 years (mean)	0 T	0 T	0 T	Learning, memory, executive function, manual dexterity, grip strength, mood and depression
Schwartz et al. 2005	576 exposed Pb workers, age: 41 years (mean)	↑ T	↑ T	↑ T	Executive function, manual dexterity, vibration threshold, depression
Seegal et al. 2013	241 capacitor workers, age: 64 years (mean)	↑ T	↑ T	–	Learning, memory, executive function, manual dexterity
Shih et al. 2006	991 adults[a], age: 50–70 years	↑ T	↑ T	–	Learning, memory, executive function, manual dexterity

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Stewart et al. 2002	529 Pb workers, age: 40–>70 years	↑ T	↑ T	–	Learning, memory, executive function, reaction time, manual dexterity
van Wijngaarden et al. 2009	47 adults, age: 55–67 years	↑ C	–	–	Learning, memory
Wang et al. 2007	358 adult males[b], age: 67 years (median)	↑ T	–	–	Interaction between Pb and hemochromatosis gene polymorphisms on learning, memory, executive function
Wang et al. 2018	634 males, age: 67 years (mean)	–	↑ P ↑ T	–	Glaucoma
Weisskopf et al. 2004	466 adult males[b], age: 68 years (mean)	↑ P	–	–	Memory, verbal and written skills, executive function
Weisskopf et al. 2007	761 adult males[b], age: 69 years (mean)	↑ P ↑ T	–	–	Memory, visual-spatial performance
Weisskopf et al. 2010	330 adult cases and 308 controls, age: 67 years (mean)	–	↑ T	–	Parkinson's disease
Weuve et al. 2009	587 adult females[c], age: 47–74 years	0 P ↑ T	–	–	Learning, memory
Weuve et al. 2013	101 cases and 50 controls, age: 55–80 years	0 P ↑ T	–	–	Learning, memory (stronger association with Pb among Parkinson's disease cases)

Table 2-33. Associations Between Bone Pb and Neurological Outcomes in Adults

		Neurological outcome			
Reference	Population	Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
Wright et al. 2003b	736 adult males[b], age: 68 years (mean)	↑ P ↑ T	–	–	Memory, verbal and written skills, executive function

[a]Boston Memory Study.
[b]Normative Aging Study.
[c]Nurses Health Study.
[d]Whole-body Pb predicted from bone Pb.

↑ = positive association; ↓ = inverse association; 0 = no association; – = not reported; C = calcaneus bone; P = patella; Pb = lead; T = tibia; O = other

Bone Pb has been associated with declines in neuromotor and neurosensory function. Neuromotor outcomes that have been associated with bone Pb include tremor, Parkinson's disease, and ALS (Coon et al. 2006; Eum et al. 2015; Weisskopf et al. 2010; Weuve et al. 2013). Neurosensory outcomes include decrements in olfactory and hearing function, vibration threshold, and manual dexterity (Dorsey et al. 2006; Grashow et al. 2013b, 2015; Park et al. 2010; Schwartz et al. 2000b; 2005; Shih et al. 2006; Stewart et al. 2002). Bone Pb has also been associated with increased risk or odds of psychiatric symptoms such as anxiety and depression (Dorsey et al. 2006; Rajan et al. 2007; Rhodes et al. 2003; Schwartz et al. 2005).

Mechanisms of Action. Numerous cellular mechanisms are likely involved in Pb-induced alterations in neurological function. Pb disrupts cellular function through diverse mechanisms, including displacement of metal ion co-factors from protein, enzyme inhibition, inhibition of ion transport, disruption of cell and mitochondrial membrane potentials, disruption of intracellular calcium homeostasis oxidative stress, and inflammation and endocrine disruption (see Section 2.21). All of these Pb mechanisms have been demonstrated in neuronal tissues, although there is no consensus on which mechanisms dominate. Evidence for various mechanisms that may participate in Pb neurotoxicity are summarized in this section. The reader is referred to references cited therein for more detailed information (Bouton and Pevsner 2000; Bressler et al. 1999; Cory-Slechta 1995, 2003; EPA 2014c; Gilbert and Lasley 2002; Lasley and Gilbert 2000; Mitra et al. 2017; Nihei and Guilarte 2002; Suszkiw 2004; Toscano and Guilarte 2005; Zawia et al. 2000; Zhang et al. 2015).

Pb can affect the nervous system by multiple mechanisms, one of the most important of which is by mimicking calcium action and/or disruption of calcium homeostasis. Because calcium is involved as a cofactor in many cellular processes, it is not surprising that many cell-signaling pathways are affected by Pb. One pathway that has been studied in more detail is the activation of protein kinase C (PKC). PKC is a serine/threonine protein kinase involved in many processes important for synaptic transmission such as the synthesis of neurotransmitters, ligand-receptor interactions, conductance of ionic channels, and dendritic branching. The PKC family is made up of 12 isozymes, each with different enzymatic cofactor requirements, tissue expression, and cellular distributions. The γ-isoform is one of several calcium-dependent forms of PKC and is a likely target for Pb neurotoxicity; it is neuron-specific and is involved in long-term potentiation (see below), spatial learning, and memory processes. Pb has the capacity to both activate and inhibit PKCs. Studies have shown that micromolar concentrations of Pb can activate PKC-dependent phosphorylation in cultured brain microvessels, whereas picomolar concentrations of Pb activate preparations of PKC *in vitro*. Interestingly, studies in rats exposed to low Pb levels have shown few significant changes in PKC activity or expression, suggesting that the whole animal may be able to compensate for Pb PKC-mediated effects compared to a system *in vitro*. PKC induces the formation of the AP-1 transcriptional regulatory complex, which regulates the expression of a large number of target genes via AP-1 promoter elements. A gene regulated by Pb via AP-1 promoters is the glial fibrillary acidic protein (GFAP), an astrocytic intermediate filament protein that is induced during periods of reactive astrocytic gliosis. Astrocytes, along with endothelial cells, make up the blood-brain barrier. Studies in rats exposed chronically to low Pb levels have reported alterations in the normal pattern of GFAP gene expression in the brain, and the most marked long-lasting effects occurred when the rats were exposed during the developmental period. In immature brain microvessels, most of the protein kinase C is in the cytosol, whereas in mature brain microvessels, this enzyme is membrane-bound. Activation of protein kinase C in other systems is known to result in a change in distribution from cytosol to membrane, and has been observed with exposure of immature brain microvessels to Pb. An inhibition of microvascular formation has been observed with Pb concentrations that are effective in activating PKC. Thus, it appears that premature activation of PKC by Pb may impair brain microvascular formation and function, and at high levels of Pb exposure, may account for gross defects in the blood-brain barrier that contribute to acute Pb encephalopathy. The blood-brain barrier normally excludes plasma proteins and many organic molecules, and limits the passage of ions. With disruption of this barrier, molecules such as albumin freely enter the brain, and ions and water follow. Because the brain lacks a well-developed lymphatic system, clearance of plasma constituents is slow, edema occurs, and intracranial pressure rises. The particular vulnerability of the fetus and infant to the neurotoxicity of Pb may be due in part to

immature brain microvessels, which affect the blood brain barrier, and to the lack of the high-affinity Pb-binding protein in astroglia, which sequester Pb.

Another enzyme altered by Pb is calmodulin, a major intracellular receptor for calcium in eukaryotes. Normally, calcium induces a conformational change in calmodulin that converts the protein to an active form; Pb improperly activates the enzyme. Some studies suggest that activation of calmodulin by Pb results in protein phosphorylation in the rat brain and brain membrane preparations and can alter proper functioning of cAMP messenger pathways. It has been shown that calmodulin can mediate gene expression via calmodulin-dependent kinases. The effects of Pb on gene expression via activation of calmodulin are not as marked as those via PKC because activation of calmodulin requires 100-fold more Pb than activation of PKC.

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

Pb affects virtually every neurotransmitter system in the brain, but most information on changes is available on the glutamatergic, dopaminergic, cholinergic, and gamma-aminobutyric acid (GABA) systems. Of these, special attention has been paid to the glutamatergic system and its role in hippocampal long-term potentiation (LTP). Hippocampal LTP is a cellular model of learning and memory characterized by a persistent increase in synaptic efficacy following delivery of brief tetanic stimulation (high-frequency stimulation). LTP provides a neurophysiological substrate for learning and storing information and is thought to utilize the same synaptic mechanisms as the learning process. LTP is established only with complex patterns of stimulation but not with single pulse stimulation. While it has

been studied primarily in the hippocampal subregions CA1 and dentate gyrus, it can also be evoked in cortical areas. Exposure of intact animals or tissue slices to Pb diminishes LTP by a combination of three actions: increasing the threshold for induction, reducing the magnitude of potentiation, and shortening its duration by accelerating its rate of decay. This effect on LTP involves actions of Pb on glutamate release (presynaptic effects) and on the N-methyl-D-aspartate (NMDA) receptor function. Pb exposure inhibits release of glutamine from pre-synaptic endings, which may be mediated, in part, by altered pre-synaptic vesicle formation or activation. Studies have shown that the effects of Pb vary as a function of the developmental exposure period and that Pb exposure early in life is critical for production of impaired LTP in adult animals. LTP is more readily affected by Pb during early development, but exposure initiated after weaning also affects synaptic plasticity. Studies also have shown that both LTP magnitude and threshold exhibit a U-shape type response with increasing Pb doses. While LTP is primarily a glutamatergic phenomenon, it can be modulated through input from extrahippocampal sources including noradrenergic, dopaminergic, and cholinergic sources.

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

The findings regarding the effects of Pb on postsynaptic glutamatergic function have been inconsistent across laboratories, but a direct inhibitory action of Pb on the NMDA receptor is unlikely at environmentally relevant exposure levels. Some studies have shown that continuous exposure of rats

from gestation to adulthood results in a significant increase in NMDA receptor numbers in cortical areas, hippocampus, and forebrain. This was observed in the forebrain at PbB of 14 μg/dL. Other studies, however, have reported changes in the opposite direction and the reason for the discrepancy in results may be due to the different exposure protocols used. From a functional point of view, it seems plausible that a Pb-induced reduction in presynaptic transmitter release be compensated by a postsynaptic increase in number or density of receptors in order to maintain a viable function.

The dopaminergic system also has a role in aspects of cognitive function since lesions of dopaminergic neurons impair behavior in various types of learning and cognitive tasks. Also, individuals who suffer from Parkinson's disease, a disease associated with dopamine depletion in the striatum, sometimes show difficulties in cognitive functions. Most of the evidence available suggests that Pb may impair regulation of dopamine synthesis and release, indicating a presynaptic site of action. Studies in animals often report opposing effects of Pb on nigrostriatal and mesolimbic dopamine systems regarding receptor binding, dopamine synthesis, turnover, and uptake. Postweaning exposure of rats to Pb resulted in supersensitivity of D1 and D2 dopamine receptors, which can be interpreted as a compensatory response to decreased synthesis and/or release of dopamine. Lesions to the nucleus accumbens (a terminal dopamine projection area) and the frontal cortex resulted in perseverative deficits, suggesting that the mesolimbic system is preferentially involved in the effects of Pb. Results of studies using dopaminergic compounds seem to indicate that changes in dopamine systems do not play a role in the effects of Pb on learning. Instead, it has been suggested that changes in dopaminergic systems may play a role in the altered response rates on Fixed-Interval (FI) schedules of reinforcement that have been observed in animals exposed to Pb. This type of change has been thought to represent a failure to inhibit inappropriate responding.

It is widely accepted that the cholinergic system plays a role in learning and memory processes. Some cognitive deficits observed in patients with Alzheimer's disease have been attributed to impaired cholinergic function in the cortex and hippocampus. Exposure to Pb induces numerous changes in cholinergic system function, but the results, in general, have been inconsistently detected, or are of opposite direction in different studies, which may be attributed to the different exposure protocols used in the different studies. However, it is clear that Pb blocks evoked release of acetylcholine and diminishes cholinergic function. This has been demonstrated in central and peripheral synapses. Studies with the neuromuscular junction showed that Pb reduces acetylcholine release by blocking calcium entry into the terminal. At the same time, Pb prevents sequestration of intracellular calcium by organelles, which results in increased spontaneous release of the neurotransmitter. Studies *in vitro* show that Pb can block nicotinic cholinergic receptors, but it is unclear whether such effects occur *in vivo* or whether Pb alters the

expression of nicotinic cholinergic receptors in the developing brain. Evidence for an involvement in Pb-induced behavioral deficits has been presented based on the observation that intrahippocampal transplants of cholinergic-rich septal and nucleus basalis tissue improve the deficits and that treatment with nicotinic agonists can improve learning and memory impairments following perinatal Pb treatment of rats. Chronic exposure of rats to Pb has resulted in decreased muscarinic-receptor expression in the hippocampus. Whether or not Pb exposure during development alters muscarinic receptor sensitivity is unclear as there are reports with opposite results. The preponderance of the binding data suggests that Pb does not directly affect muscarinic receptors with the exception of the visual cortex, where Pb may have a direct inhibitory effect on muscarinic receptors from rods and bipolar cells of the retina.

Pb exposure decreases spontaneous and evoked release of GABA in rats and in hippocampal cultures and brain slices. In general, GABA functions in the brain as a post-synaptic inhibitory transmitter. The role of changes in GABA release in the neurotoxicity of Pb has not been firmly established.

Various other mechanisms may also contribute to Pb neurotoxicity. Exposure to Pb has also been shown to stimulate inflammation in a variety of tissues, including neuronal tissue (see Section 2.21). Contributing mechanisms include alterations in levels of ROS, activation of nuclear activation factor NFκβ, cytokine release, and alterations in prostaglandin metabolism. Pb exposure has been shown to alter neuronal nitric oxide signaling (NOS) and the hormone levels regulated by the hypothalamic-pituitary-thyroid axis.

2.17 REPRODUCTIVE

Overview. Numerous epidemiological studies have evaluated effects of Pb on male and female reproductive function. In males, most exposures were occupational, with mean PbB >10 µg/dL. In general, studies in males show consistent evidence of reproductive effects on sperm (production, motility, viability, and morphology), semen quantity and composition, serum reproductive hormone levels, and fertility, with severity of effects increasing with increasing PbB. In contrast to exposure of males, most exposures of females were non-occupational, with mean PbB ≤10 µg/dL. Studies investigating effects on serum reproductive hormone levels, fertility, spontaneous abortion, and preterm birth provide mixed results; thus, dose-dependence of effects in females is difficult to assess.

The following reproductive effects in males have been associated with PbB:

- ≤10 µg/dL:
  - Increased serum testosterone; evaluated in a few studies with mixed results.
  - Effects on sperm (decreased sperm count, concentration, motility, and viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm); evaluated in a few studies with mixed results.
- >10 µg/dL:
  - Altered serum concentrations of reproductive hormones (testosterone, FSH, LH); evaluated in several studies with mixed results.
  - Effects on sperm (decreased sperm count, concentration, motility, viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm); corroborated in several studies.
  - Alterations in semen quality (decreased semen volume and altered composition of seminal fluid); evaluated in a few studies.
  - Decreased fertility; evaluated in a few studies.
  - Histopathological changes to the testes (peritubular fibrosis, oligospermia, and vacuolization of Sertoli cells); evaluated in a few studies.

The following reproductive effects in females have been associated with PbB:

- ≤10 µg/dL:
  - Increased serum levels of estradiol, FSH, and LH; studies have mixed results.
  - Decreased fertility; studies have mixed results.
  - Increased spontaneous abortion; studies have mixed results.
  - Increased preterm birth; studies have mixed results.
  - Earlier age at onset of menopause; demonstrated in a few studies.
- >10 µg/dL:
  - Decreased fertility; studies have mixed results.
  - Increased preterm birth; studies have mixed results.

Measures of Exposure. Most studies evaluating effects on male and female reproductive systems used PbB as the biomarker for exposure. More recent studies in men have explored the relationship between the concentration of Pb in semen or spermatozoa and adverse effects (Table 2-34). It has been suggested

that semen levels of Pb may be a better biomarker for assessment of male reproductive effects, particularly at low PbB, because no relationship between PbB and Pb levels in semen or spermatozoa has been observed (Hernandez-Ochoa et al. 2005; Mendiola et al. 2011). In women, other biomarkers of exposure include concentration of Pb in plasma (Lamadrid-Figueroa et al. 2007), red blood cells (Perkins et al. 2014), placenta (Gundacker et al. 2010), and plasma/blood ratio (Lamadrid-Figueroa et al. 2007).

Confounding Factors and Effect Modifiers. Numerous factors may add uncertainty in the interpretation of studies examining associations between PbB and reproductive effects, including overall health, body weight, nutrition, and SES. Exposures to other substances, including recreational drugs, alcohol, therapeutic agents, industrial chemicals, insecticides, and pesticides, also may affect fertility (Foster and Gray 2008). Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome. Some studies examining effects on sperm (discussed below) were conducted on samples obtained at fertility clinics; therefore, other causes for sperm effects could be effect modifiers (additional details are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 11). In addition, because sperm counts can vary by geographical location, it is important that control and exposed groups are matched for geographic location.

Characterization of Effects in Males. General trends regarding the relationship between PbB and male reproductive effects are shown in Table 2-34. Overall, the dose-effect pattern suggests an increasing severity of toxicity associated with increasing PbB, with effects on sperm at ≤10 µg/dL (discussed in more detail below). At increasing PbB, effects become more severe, with decreased fertility observed at PbB >10 µg/dL and histopathological changes of the testes at PbB of approximately 30 µg/dL. Effects on sperm, including decreased sperm count, concentration, motility, viability, and increased immature sperm concentration and percentage of morphologically abnormal sperm, have been observed at PbB of ≤10–>50 µg/dL (Alexander et al. 1998a; Assennato et al. 1987; Bonde et al. 2002; Cullen et al. 1984; Famurewa and Ugwuja 2017; Hernández-Ochoa et al. 2005; Kasperczyk et al. 2008; Lancranjan et al. 1975; Lerda 1992; Li et al. 2015; Meeker et al. 2008; Moran-Martinez et al. 2013; Telisman et al. 2007; Wildt et al. 1983). However, a few studies showed no association between PbB and adverse effects on sperm (Lancranjan et al. 1975; Mendiola et al. 2011). The significance of the observed changes to sperm on fertility is uncertain. Decreased semen volume and altered composition of seminal fluid have been observed at PbB >10 µg/dL (Bonde et al. 2002; Naha and Chowdhury 2006; Telisman et al. 2000; Wildt et al. 1983). Decreased fertility has been reported in association with PbB >10–>50 µg/dL (Sallmén et al. 2000; Shiau et al. 2004), although no effect on fertility was observed in one study of workers with PbB

>40 µg/dL (Coste et al. 1991). Histopathological assessment of biopsied testicular tissue from Pb workers (mean PbB: 29.0 µg/dL) showed peritubular fibrosis, oligospermia, and vacuolization of Sertoli cells (Braunstein et al. 1978). Evaluations of associations between PbB and serum levels of reproductive hormones show inconsistent results (Table 2-35). At PbB ≤10 µg/dL, positive associations between PbB and serum testosterone levels have been observed (Kresovich et al. 2015; Lewis and Meeker 2015; Meeker et al. 2010; Telisman et al. 2007), whereas inverse associations or no effects were reported at PbB >10 µg/dL. No effects on FSH or LH were reported at PbB ≤10 µg/dL, and inconsistent results were observed at PbB >10 µg/dL. Changes in serum levels of reproductive hormones may indicate disruption of the hypothalamic-pituitary-gonadal axis; however, due to inconsistent findings, an association between PbB and endocrine disruption in males has not been firmly established.

Table 2-34. Overview of Effects on the Male Reproductive System Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Effects on sperm (decreased sperm concentration, motility, and viability; increased morphologic abnormalities)	Famurewa and Ugwuja 2017; Hernández-Ochoa et al. 2005; Li et al. 2015; Meeker et al. 2008; Telisman et al. 2007
	Effects on hormones (increased serum levels of testosterone, estradiol, LH, FSH, and SHBG; decreased serum prolactin and SHBG	Chen et al. 2016; Kresovich et al. 2015; Lewis and Meeker 2015; Meeker et al. 2010; Telisman et al. 2007
>10–30	Effects on sperm (decreased sperm count, concentration, density, motility, viability; morphologic abnormalities)	Alexander et al. 1998a; Bonde et al. 2002; Moran-Martinez et al. 2013
	Effects on semen (decreased volume)	Bonde et al. 2002
	Decreased fertility	Sallmén et al. 2000
>30–50	Effects on sperm (decreased count, concentration, motility, viability; morphologic abnormalities)	Hsu et al. 2009; Lancranjan et al. 1975; Lerda 1992; Telisman et al. 2000
	Effects on composition of seminal fluid	Telisman et al. 2000
	Effects on hormones (increased estradiol, LH, FSH; decreased testosterone)	Braunstein et al. 1978; Ng et al. 1991; Telisman et al. 2000
	Histopathological changes to testes (peritubular fibrosis, oligospermia, vacuolization of Sertoli cells)	Braunstein et al. 1978
	Decreased fertility	Sallmén et al. 2000; Shiau et al. 2004

Table 2-34. Overview of Effects on the Male Reproductive System Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
>50	Effects on sperm (decreased count, concentration, motility, viability; morphologic abnormalities)	Assennato et al. 1987; Cullen et al. 1984; Kasperczyk et al. 2008; Lancranjan et al. 1975; Lerda 1992; Naha and Chowdhury 2006; Wildt et al. 1983
	Effects on semen (decreased volume; altered composition)	Naha and Chowdhury 2006; Wildt et al. 1983
	Effects on hormones (altered serum levels of testosterone, FSH, LH, prolactin)	Assennato et al. 1987; Rodamilans et al. 1988
	Decreased fertility	Sallmén et al. 2000

FSH = follicle-stimulating hormone; LH = luteinizing hormone; SHBG = sex hormone binding globulin

Table 2-35. Effects on Reproductive Hormones Associated with Chronic Exposure to Lead (Pb) in Males

PbB (µg/dL)	Hormone							Reference
	T	FSH	LH	E	P	A	SHBG	
≤10	↑	0	–	–	–	0	0	Kresovich et al. 2015
	↑	0	0	–	–	–	0	Meeker et al. 2010
	↑	–	–	↑	0	–	–	Telisman et al. 2007
	↑	–	–	–	–	–	–	Lewis and Meeker 2015
	↑	↑	↑	0	–	–	↑	Chen et al. 2016
	0	0	0	–	–	–	–	Mendiola e al. 2011
10–30	0	0	0	–	–	–	–	Hsieh et al. 2009
	0	0	0	–		–	–	Alexander et al. 1998a
30–50	↓	0	0	–	0	–	–	Braunstein et al. 1978
	0	0	0	–	0	–	–	Erfurth et al. 2001
	0	↓	↓	–	–	–	–	Gustafson et al. 1989
	0	↑	↑	–	–	–	–	McGregor and Mason 1990
	↓	↑	↑		0	–	–	Ng et al. 1991
				↑	–	–	–	Telisman et al. 2000
	0	0	0	0	–	–	–	Sadeghnaiit Haghighi et al. 2013
	↓	–	–	–	–	–	–	Rodamilans et al. 1988

0 = no effect; ↑ = increased serum level; ↓ = decreased serum level; – = not evaluated; A = androstenedione; E = estradiol; FSH = follicle stimulating hormone; LH = luteinizing hormone; P = prolactin; SHBG = sex hormone binding globulin; T = testosterone

Effects in Males at Blood Pb Levels ≤10 µg/dL. Cross-sectional studies evaluating adverse effects of non-occupational exposures to Pb on the male reproductive system show that damage to sperm, decreased semen volume, and increased serum testosterone are associated with mean PbB ≤10 µg/dL or with Pb concentrations in semen or spermatozoa when PbBs are ≤10 µg/dL. Results are summarized in Table 2-36, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 11. None of the studies evaluated associations between PbB and male fertility parameters (i.e., pregnancy). Three studies assessed larger populations, including two studies using NHANES data (Kresovich et al. 2015; Lewis and Meeker 2015) and one study of a Chinese population (Chen et al. 2016). However, in general, study populations were small (n=61–240). In addition, for a few studies, participants were selected from infertility clinics and it is unclear how this may have biased study results (Meeker et al. 2008, 2010; Mendiola et al. 2011). Despite these limitations, taken together, results of non-occupational exposure studies support that adverse effects to the male reproductive system occur at PbB ≤10 µg/L.

Sperm and semen. A significant association between an increase in PbB ≤10 µg/dL and increasing percentages of morphologically abnormal sperm, wide sperm, and round sperm was observed in a population of Croatian men (Telisman et al. 2007). The mean PbB was 4.92 µg/dL; although the maximum PbB value in this study was 14.9 µg/dL, over 90% of participants had PbB <10 µg/dL. Li et al. (2015) found small, but significant inverse associations between PbB and sperm count, sperm concentration, motile sperm, and morphologically normal sperm in 154 men from a reproductive clinic in Taiwan. The median PbB was 2.78 µg/dL (SD 1.85); range and percentiles were not reported. Sperm count was associated with PbB in a small population of infertile men with mean PbB 1.71–2.05 µg/dL (Famurewa and Ugwuja 2017). Other studies have shown associations between Pb levels in semen and/or spermatozoa and increased percentages of morphologically abnormal sperm and decreased sperm motility and viability, although no associations were observed between PbB and these outcomes (Hernandez-Ochoa et al. 2005; Mendiola et al. 2011); mean PbB levels were 9.3 µg/dL in the Hernandez-Ochoa et al. (2005) study and 2.8 µg/dL in the Mendiola et al. (2011) study. No associations were observed between PbB and sperm concentration, motility, or morphologic abnormalities in men at a median PbB of 1.5 µg/dL (Meeker et al. 2008). Semen volume (mL) was inversely associated with PbB at a mean PbB of 9.3 µg/dL; however, 48% of participants had PbB >10 µg/dL (Hernandez-Ochoa et al. 2005).

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Effects on serum hormone levels			
Chen et al. 2016 Cross-sectional study; n=2,286	Median (IQR): 4.40 (2.90–6.23) Quartiles: • Q1: <2.9 (n=558) • Q2: 2.9–4.39 (n=572) • Q3: 4.4–6.2 (n=585) • Q4: >6.2 (n=571)	Testosterone	**β coefficient (SE) Q4: 0.033 (0.010); p<0.01***
		FSH	**β coefficient (SE) Q4: 0.030 (0.015); p<0.05***
		LH	**β coefficient (SE) Q4: 0.028 (0.013); p<0.05***
		E	β coefficient (SE) Q4: -0.003 (0.017)
		SHBG	**β coefficient (SE) Q4: 0.038 (0.012); p<0.01***
Kresovich et al. 2015 Cross-sectional study; n=869	Median:2.0 Quartiles: • Q1: ≤1.4 (reference) • Q2: 1.4–2.1 • Q3: 2.10–3.20 • Q4: >3.20	Testosterone	• **β coefficient ng/mL per µg/dL (SE)** • **Q3: 0.54 (0.21); p<0.05*** • **Q4: 0.79 (0.22); p<0.05*; p-trend=0.00268***
Lewis and Meeker 2015 Cross-sectional study; n=484	Gmean:1.06 Quartiles: • Q1: <0.71 • Q2: 0.71–1.00 • Q3: 1.00–1.59 • Q4: 1.59–33.67	Testosterone	• **Percent change in serum testosterone concentration associated with a doubling (100% increase) in PbB: 6.65% (2.09, 11.41); p<0.004)*; p-trend across quartiles=0.003***

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Meeker et al. 2010 Cross-sectional study; n=219	Median:1.5 Quartiles • Q1: <1.1 (reference) • Q2: 1.1–1.5 • Q3: 1.5–2.0 • Q4: >2.0–16.2	Testosterone	**Regression coefficient Q4 (ng/dL per µg/dL): 39.9 (3.32, 76.4)***
		FSH	Regression coefficient Q4 (mIU/mL per µg/dL): 0.07 (-0.18, 0.31)
		LH	Regression coefficient Q4 (mIU/m per µg/dL): 0.08 (-0.14, 0.29)
		Inhibin B	Regression coefficient Q4 (pg/mL per µg/dL): -7.79 (-29.0, 13.4)
		SHBG	Regression coefficient Q4 (nmol/L per µg/dL): 0.07 (-0.10, 0.23)
		FAI	Regression coefficient Q4 (per µg/dL): 0.08 (-0.05, 0.21)
Mendiola et al. 2011 Case-control study; n=61	Gmean: 2.8	Testosterone	β coefficient (ng/mL per µg/L): -0.12 (-0.40, 0.14)
		FSH	β coefficient (IU/L per µg/L): -0.20 (-0.64, 0.25)
		LH	β coefficient (IU/L per µg/L): -0.07 (-0.49, 0.31)
Telisman et al. 2007 Cross-sectional study; n=240	Median: 4.92	Testosterone	**β coefficient (nmol/L per µg/L): 0.21; p<0.003***
		Estradiol	**β coefficient (nmol/L per µg/L): 0.22; p<0.0008***
		Prolactin	β coefficient (µg per µg/L): -0.18; p<0.007
Sperm and semen quality			
Famurewa and Ugwuja 2017 Cross-sectional study; n=75 men with infertility	**PbB:** Mean • Normospermic: 1.49 • Azoospermic: 1.71 • Oligospermic: 2.05	Semen volume	Pearson correlation R value: -0.132; p=0.27
		Sperm count	**Pearson correlation R value: -0.280; p=0.02***
		Sperm motility	Pearson correlation R value: -0.092; p=0.44
		Sperm morphology	Pearson correlation R value: -0.081; p=0.50

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Hernandez-Ochoa et al. 2005 Cross-sectional study; n=68	Mean: 9.3 SPZ Pb: 0.047 ng/10^6 cells SF Pb: 2.02 µg/L	Log sperm concentration	**β coefficient SPZ Pb (10^6 cells/mL per ng/10^6 cells): -17.17 (p<0.05)***
		Sperm motility	β coefficient PbB (% per µg/dL): -0.006 **β coefficient SPZ Pb: (% per ng/10^6 cells): -2.12 (p<0.05)***
		Sperm morphology (abnormal)	β coefficient PbB (% per µg/dL): -0.001 **β coefficient SPZ Pb (% per ng/10^6 cells): -1.42 (p<0.05)***
		Sperm viability	β coefficient PbB (% per µg/dL): -0.095 **β coefficient SPZ Pb (% per ng/10^6 cells): -0.130 (p<0.05)***
		Semen volume	β coefficient PbB (mL per µg/dL): -0.043 **β coefficient SF Pb (mL per µg/L): -0.183 mL; p<0.05***
Li et al. 2015 Cross-sectional study; n=154	Mean: All participants: 2.78 Low-quality semen group: 3.43 High-quality semen group: 2.38	Low quality sperm	**OR: 1.040 (1.011, 1.069); p=0.0061***
		Decreased sperm concentration	**OR: 1.046 (1.015, 1.078); p=0.0032***
		Decreased sperm number	**OR: 1.041 (1.012, 1.071); p=0.0048***
		Decreased motile sperm	**OR: 1.057 (1.026, 1.089; p=0.0003***
		Decreased morphologically normal sperm	**OR: 1.071 (1.025, 1.118; p=0.0021***
Meeker et al. 2008 Cross-sectional study; n=219	Median:1.50 • Quartiles (Q): o Q1: <1.10 o Q2: 1.10–1.50 o Q3: 1.50–2.00 o Q4: 2.00–16.2	Sperm concentration	Regression coefficient (10^6/mL per µg/dL) Q4: 0.02 (-0.39, 0.43)
		Sperm motility	Regression coefficient (% per µg/dL) Q4: 1.10 (-4.56, 6.75)
		Sperm morphology	Regression coefficient (% per µg/dL) Q4: -0.16 (-1.58, 1.26)
		Semen volume	Regression coefficient (mL per µg/dL) Q4: 0.17 (-0.41, 0.74)

Table 2-36. Summary of Epidemiological Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Mendiola et al. 2011 Case-control study; n=61	Gmean: 2.8 Median: 2.9	Sperm concentration	β coefficient (10^6/mL per µg/L): 0.08 (-4.1, 5.2)
		Immobile sperm	β coefficient (% per µg/L): -0.49 (-1.8, 0.62)
		morphologically normal sperm	β coefficient(% per µg/L): -0.8 (-3.5, 3.4)
Telisman et al. 2007 Cross-sectional study; n=240	Median: 4.92	Immature sperm	β coefficient (10^6/mL per µg/L): 0.13 (p<0.07)
		Pathologic sperm	**β coefficient (% per µg/L): 0.31 (p<0.0002)***
		Wide sperm	**β coefficient (% per µg/L): 0.32 (p<0.0001)***
		Round sperm	**β coefficient (% per µ: 0.16 (p<0.03)***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 11 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterisk and **bold** indicate association with PB; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

CI = confidence interval; E = estradiol; FAI = free androgen index; FSH = follicle-stimulating hormone; Gmean = geometric mean; Inhibin B = gonadal dimeric polypeptide hormone; IQR = interquartile range; LH = luteinizing hormone; OR = odds ratio; Pb = lead; SE = standard error; SF = seminal fluid; SHBG = sex hormone-binding globulin; SPZ = spermatozoa

Serum testosterone levels. Significant associations have also been observed between PbB ≤10 µg/dL and increased serum testosterone levels (Table 2-34). Studies using NHANES data found significant positive associations between PbB and serum testosterone levels (Kresovich et al. 2015; Lewis and Meeker 2015). Examined by PbB quartiles, Kresovich et al. (2015) observed significant positive associations between PbB and serum testosterone (ng/L) for PbBs of 2.10–3.20 and >3.2 µg/dL; the median PbB of the study population was 2.0 µg/dL. A doubling of PbB was positively associated with a 6.65% change in serum testosterone; the mean PbB of the study population was 1.06 µg/dL (Lewis and Meeker 2015). The toxicological significance of the observed associations between PbB and serum testosterone has not been established.

Characterization of Effects in Females. As noted above, most epidemiological studies evaluated effects at PbB ≤10 µg/dL, with few studies of PbB >10 µg/dL. Studies of PbB ≤10 µg/dL are discussed in detail in the section below. General trends for studies showing a relationship between PbB ≤10–50 µg/dL and female reproductive effects are shown in Table 2-37. Effects associated with PbB include increased serum levels of estradiol, FSH, and LH at PbB ≤10 µg/dL (Chang et al. 2006; Krieg 2007), decreased fertility at PbB ≤10 µg/dL (Chang et al. 2006), increased time to pregnancy at PbB >30–40 µg/dL (Sallmén et al. 1995), increased spontaneous abortion at PbB ≤10–30 µg/dL (Borja-Aburto et al. 1999; Yin et al. 2008), decreased number of gestational days at PbB >10–40 µg/dL (Jelliffe-Pawlowski et al. 2006), and increased preterm birth at PbB ≤10–50 µg/dL (McMichael et al. 1986; Jelliffe-Pawlowski et al. 2006; Rabito et al. 2014). Although epidemiological studies demonstrate effects on reproductive function, results are inconsistent, with several studies reporting no association between PbB and female reproductive effects (Baghurst et al. 1987; Bloom et al. 2010, 2011, 2015; Garcia-Esquinas et al. 2014; Jackson et al. 2007; Murphy et al. 1990; Perkins et al. 2014; Pollack et al. 2011; Sallmén et al. 1995; Taylor et al. 2015; Vigeh et al. 2010). Dose-dependence has not been firmly established within the relatively narrow range of PbB (≤10 µg/dL) in most studies.

Table 2-37. Overview of Effects on the Female Reproductive System and Pregnancy Outcomes Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Increased serum hormones (estradiol, FSH, LH)	Chang et al. 2006; Chen et al. 2016; Krieg 2007
	Decreased fertility	Chang et al. 2006
	Increased spontaneous abortion	Yin et al. 2008
	Increased preterm birth	Li et al. 2017b; Rabito et al. 2014
	Earlier age at menopause	Eum et al. 2014; Popovic et al. 2005
>10–30	Increased spontaneous abortion	Borja-Aburto et al. 1999
	Decreased number of gestational days	Jelliffe-Pawlowski et al. 2006
	Increased preterm birth	McMichael et al. 1986
>30–40	Increased time to pregnancy	Sallmén et al. 1995
	Decreased number of gestational days	Jelliffe-Pawlowski et al. 2006
	Increased preterm birth	Jelliffe-Pawlowski et al. 2006
>40–50	Increased preterm birth	Jelliffe-Pawlowski et al. 2006

FSH = follicle-stimulating hormone; LH = luteinizing hormone

Effects in Females at Blood Pb Levels ≤10 µg/dL. As discussed above, most epidemiology studies evaluating adverse effects of Pb on female reproductive function reported mean PbB ≤10 µg/dL. Although some studies provide evidence showing associations between PbB ≤10 µg/dL and effects on serum reproductive hormones (Chang et al. 2006; Chen et al. 2016; Krieg 2007), fertility (Chang et al. 2006), spontaneous abortion (Lamadrid-Figueroa et al. 2007; Yin et al. 2008), and preterm birth (Li et al. 2017b; Rabito et al. 2014; Taylor et al. 2015; Vigeh et al. 2011), many studies show no associations between PbB and these outcomes. In general, most studies are limited by small sample sizes, although, as discussed below, some studies were of larger populations. The basis for differences in study outcomes in not readily apparent, although several factors may contribute, including low samples size, timing of evaluations in menstrual and life cycles, and inclusion of study participants identified from fertility clinics. Results are summarized in Table 2-38, with study details provided in the *Supporting Document for Epidemiological Studies for Lead* Table 12.

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Effects on serum hormone levels			
Chang et al. 2006 Case control study; n=147	Mean: 3.55	Estradiol	**β coefficient pg/mL per µg/dL (SE): 1.18 (0.60); p=0.049***
Chen et al. 2016 Cross-sectional study; n=1,571 postmenopausal women	Median: 4.1 • Q1: <2.7 (n=558) • Q2: 2.7–4.09 (n=572) • Q3: 4.1–5.98 (n=585) • Q4: >5.98 (n=571)	FSH	**β coefficients (SE)** • **Q3: 0.047 (0.015); p<0.01*** • **Q4: 0.046 (0.016); p<0.01***
		LH	**β coefficients (SE), Q4: 0.037 (0.016); p<0.05***
		Estradiol	β coefficients (SE), Q4: -0.021 (0.020)
		Testosterone	β coefficients (SE), Q4: -0.016 (0.020)
		Sex hormone binding globulin	**β coefficients (SE), Q4: 0.048 (0.016); p<0.01***
Jackson et al. 2011 Longitudinal cohort study; n=252	Mean: 0.87	FSH	β coefficient (IU/L per µg/dL): -2.5 (-11.2, 7.0)
		LH	β coefficient (mg/L per µg/dL): 2.5 (-12.3, 19.9)
		Estradiol	β coefficient (pg/mL per µg/dL): 4.9 (-5.0, 15.9)
		Progesterone	β coefficient (ng/mL per µg/dL): 4.6 (-12.2, 24.6)
Krieg 2007 Cross-sectional study; n=3,375	Gmean: 2.2	FSH	• **Slope pre-menopausal (IU/L per µg/dL): 8.3 (2.2); 95% CI 3.8, 12.7; p=0.0006*** • **Slope post-menopausal (IU/L per µg/dL): 22.2 (4.3); 95% CI 13.5, 30.8; p=0.0000*** • **Slope both ovaries removed (IU/L per µg/dL): 32.6 (11.2); 95% CI 10.1, 55.1; p=0.0054***
		LH	• Slope pre-menopausal (IU/L per µg/dL): 1.7 (1.2); 95% CI -0.6, 4.1; p=0.1486 • **Slope post-menopausal (IU/L per µg/dL): 6.2 (1.6); 95% C: 3.0, 9.5; p=0.0003***

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
			• **Slope both ovaries removed (IU/L per µg/dL): 10.0 (4.4); 95% CI 1.1, 18.9; p=0.0279***
Pollack et al. 2011 Longitudinal cohort study; n=252	Mean: 0.93	Estradiol	β coefficient (pg/mL per µg/dL): 0.03 (-0.05, 0.11)
		FSH	β coefficient (mIU/mL per µg/dL): -0.01 (-0.07, 0.06)
		LH	β coefficient (ng/mL per µg/dL): 0.02 (-0.06, 0.10)
		Progesterone	β coefficient (ng/mL per µg/dL): 0.06 (-0.04, 0.17)
Fertility			
Bloom et al. 2010 Longitudinal cohort study; n=15	Mean: 0.82	Oocyte fertilization (*in vitro*)	RR: 1.09 (0.72, 1.65).
Bloom et al. 2011 Longitudinal cohort study; n=80	Mean: 1.54	Achieving pregnancy over 12 menstrual cycles	β coefficient (probability of pregnancy per µg/dL): -0.031 (95% CI -1.066, 1.004); p=0.954
Chang et al. 2006 Case control study; n=147	Mean: • All: 3.12 • Controls: 2.78 • Cases: 3.55	Infertility	**OR for PbB >2.5 versus ≤2.5 µg/dL: 2.94 (95% CI 1.18, 7.34); p=0.021***
Pregnancy outcome			
Bloom et al. 2015 Case control study; n=235	Mean: 0.71 Tertiles (mean): • T1: not reported • T2: 0.55 • T3: 0.73	Duration of gestation	Regression coefficient gestational age per µg/dL) T3: 0.14 (-0.81, 1.09)

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Garcia-Esquinas et al. 2014 Birth cohort study; n=100	Gmean: 1.83	Duration of gestation	Mean difference in gestational age (weeks) per 2-fold increase in PbB: 0.02 (95% CI -0.44, 0.47)
Gundacker et al. 2010 Cross-sectional study; n=30	Median PbB: 2.5 Median Pb (placenta): 25.8 µg/kg	Spontaneous abortion	**Placenta Pb concentration in women with a history of miscarriage was higher (n=8; p=0.039) than in women with no history of miscarriage (n=22)***
Lamadrid-Figueroa et al. 2007 Cross-sectional study; n=207	Mean PbB: 6.24 (4.48) Mean plasma Pb: 0.014 Mean plasma/blood Pb ratio: 0.22% (tertile values not reported)	Spontaneous abortion	IRR PbB: 0.93; p=0.56 IRR Plasma Pb: 1.12; p=0.22 **Plasma/blood Pb ratio: 1.18; p=0.02*** IRR for T2 plasma/blood Pb ratio: 1.161; p=0.612 **IRR for T3 plasma/blood Pb ratio: 1.903; p=0.015***
Li et al. 2017b Birth cohort study; n=3,125	Mean (range): 1.5 (0.02-5.46) Stratified: • Low: <1.18 • Medium: 1.18–1.70 • High: ≥1.71	Preterm birth	• **OR Medium PbB: 2.33 (1.49, 3.65); p<0.001*** • **OR High PbB: 3.09 (2.01, 4.76); p<0.001***
Perkins et al. 2014 Birth cohort; n=949	Estimated mean PbB: 0.4 Mean RBC: 1.22 µg/dL Quartile RBC (µg/dL): • Q1: 0.65 • Q2: 0.96 • Q3: 1.27 • Q4: 2.02	Duration of gestation	β coefficient Q4 gestational age (weeks) per µg/dL: -0.17 (-0.51, 0.16)
Rabito et al. 2014 Birth cohort; n=98	Second trimester mean: 0.42 Third trimester mean: 0.45	Preterm birth	**OR second trimester: 1.66 (1.23, 2.23); p<0.01*** **OR third trimester: 1.24 (1.01, 1.52); p=0.04***

Table 2-38. Summary of Epidemiological Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)	Outcome evaluated	Result[c]
Taylor et al. 2013, 2015 Longitudinal cohort study; n=3,870	Mean: 3.67 Median: 3.42	Preterm birth	**OR for PbB ≥5.0: 2.0 (1.35, 3.00); p=0.001***
Vigeh et al. 2010 Longitudinal cohort study; n=351	Mean: 3.8	Spontaneous abortion	OR (log PbB): 0.331 (0.011, 10.096); p=0.53
Vigeh et al. 2011 Longitudinal cohort study; n=44 women with preterm birth; n=304 women with term birth	Mean: • Term birth: 3.72 • Preterm birth: 4.52	Preterm birth	**OR: 1.41 (1.08, 1.84)***
Yin et al. 2008 Case-control study; n=80	Control (term birth): 4.5 Spontaneous abortion: 5.3	Spontaneous abortion	**PbB was higher in cases of anembryonic pregnancy during gestational weeks 8–13 compared to controls with term births (p=0.03).***
Zhu et al. 2010 Retrospective cohort; n=43,288 mother-infant pairs (n=3,519 preterm birth; n=39,769 term birth)	**PbB** Mean: 2.1 Quartiles: • Q1: ≤1.0 • Q2: 1.1–2.0 • Q3: 2.1–3.0 • Q4: 3.1–9.9	Preterm birth	Adjusted ORs did not show an increased risk of preterm birth for any quartile. Q4: 1.04 (0.89, 1.22)

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 12 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Asterisk and **bold** indicate association with PB; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

CI = confidence interval; FSH = follicle-stimulating hormone; Gmean = geometric mean; IRR = incidence rate ratio; LH = luteinizing hormone; OR = odds ratio; Pb = lead; PbPl = Pb concentration in placenta (µg/kg); RBC = red blood cell; RR = relative risk; SE = standard error

Serum hormone levels and estrus cycle. Results of epidemiological studies on associations between PbB ≤10 μg/dL and serum hormone levels show conflicting results (Table 2-38). The strongest evidence showing that chronic Pb exposure alters serum hormone levels is from a large cross-sectional study (mean PbB: 2.2 μg/dL) participating in the NHANES III study (Krieg 2007). Serum levels of FSH (IU/L) increased with PbB in both pre-menopausal and post-menopausal women. Serum levels of LH increased with PbB in post-menopausal women, but not pre-menopausal women. The lowest PbBs associated with a significant increase in FSH in pre- and post-menopausal women were 4.1 μg/dL and 2.4 μg/dL, respectively. The lowest PbB associated with a significant increase in FSH in post-menopausal women was 2.8 μg/dL (slope±SE 8.6±3.3; 95% CI 2.1, 15.2; p=0.0109). Increases in serum FSH and LH were also observed in women who had total ovariectomy, indicating that increased hormone levels may be related to effects on the hypothalamus or pituitary (Krieg 2007). A large cross-sectional study of postmenopausal Chinese women also found that elevated serum hormones levels were positively associated with PbB. Increased FSH was observed in the two highest PbB quartiles (4.1–5.9 and >5.9 μg/dL), with LH increased in the highest quartile (Chen et al. 2016). SHBG was also increased in the highest quartile. No associations were observed between Pb and serum levels of FSH, LH, estradiol, or progesterone or menstrual cycle length in a smaller study of pre-menopausal women with a mean PbB of 0.87 μg/dL (Jackson et al. 2011). In this same study population, when PbB was examined by tertiles, increased serum progesterone levels were observed in the second PbB tertile (0.73–1.10 μg/dL) compared to the lowest tertile (0.30–0.72 μg/dL), but no effects were observed in the highest PbB tertile (1.11–6.20 μg/dL) compared to the lowest (Pollack et al. 2011). In this study population, no association was observed between PbB and anovulation. In a case-control study of women attending a fertility clinic, a significant association was observed between PbB and serum estradiol concentrations (Chang et al. 2006).

Fertility. Little epidemiological information is available on the effects of PbB ≤10 μg/dL on female fertility. A prospective cohort study with a mean Pb of 1.5 μg/dL showed no effect on achieving pregnancy over 12 menstrual cycles (Bloom et al. 2011). A case-control study of women from a fertility clinic showed a 2.9-fold risk of infertility for PbB >2.5 μg/dL compared to PbB ≤2.5 μg/dL (Chang et al. 2006). In a study of women undergoing *in vitro* fertilization, no association was observed between PbB and oocyte fertilization; however, only 15 women were included in this study. Available epidemiological studies on the effects of PbB ≤10 μg/dL on fertility are limited due to small numbers of participants and study populations of women undergoing fertility treatment; thus, data are not sufficient to determine if fertility in women is affected at PbB ≤10 μg/dL.

Spontaneous abortion. Few epidemiological studies have evaluated associations between PbB ≤10 μg/dL and spontaneous abortion (Table 2-38). Although studies provide some evidence suggesting associations between PbB ≤10 μg/dL or plasma/blood Pb ratio and spontaneous abortion, results are inconsistent. In a case-control study, PbB was significantly higher in cases of spontaneous abortion (PbB 5.3 μg/dL; p=0.03) during weeks 8–13, compared to women with term birth (PbB 4.5 μg/dL) (Yin et al. 2008). A cross-sectional study reported that the risk of miscarriage per 1 SD increase of plasma/blood Pb ratio [mean plasma/blood Pb ratio±SD (%): 0.22±0.14] was associated with an 18% greater incidence of spontaneous abortion, although the association between risk of spontaneous abortion and PbB (mean 6.24) was not significant (Lamadrid-Figueroa et al. 2007). In contrast, results of a longitudinal cohort study showed no association between PbB and spontaneous abortion during gestational weeks 13–19 (Vigeh et al. 2010).

Preterm birth. Several studies have evaluated associations between PbB ≤10 μg/dL and preterm birth (<37 weeks of gestation), including three studies of larger study populations (n=705–3,870) (Li et al. 2017b; Perkins et al. 2014; Taylor et al. 2015). Results of these studies are mixed (Table 2-38). The strongest evidence showing that chronic Pb exposure is associated with preterm birth is from two large, cohort studies (Li et al. 2017b; Taylor et al. 2013, 2015). Taylor et al. (2013, 2015) reported that when stratified into groups of PbB <5 and ≥5.0 μg/dL, there was a 2-fold increase in the risk of preterm birth for PbB ≥5.0 μg/dL compared to PbB <5 μg/dL. In the PbB ≥5.0 μg/dL group, the maximum PbB was 19.14 μg/dL, although very few PbBs were >10 μg/dL; however, the group mean PbB was not reported. In a large cohort study, the risk of preterm birth was increased in women with PbBs of 1.18–1.70 and 1.71–5.46 μg/dL, relative to women with PbBs of 0.02–1.18 μg/dL (Li et al. 2017b). The risk of preterm birth also was increased in a longitudinal cohort study (Vigeh et al. 2011). Mean PbB in women with preterm birth was significantly higher than in women with term birth (preterm PbB: 4.52 μg/dL; term birth PbB: 3.72 μg/dL). A cohort study showed increased odds of preterm birth associated with PbB measured in the 2nd (mean: 0.42 μg/dL) and 3rd (mean: 0.45 μg/dL) trimesters (Rabito et al. 2014). ORs for risks of preterm birth were 1.66 (p<0.01) and 1.24 (p=0.04) for 2nd and 3rd trimester PbB, respectively. Other studies reported no associations between PbB and preterm birth at mean PbB of 0.71–5.70 μg/dL (Bloom et al. 2015; Perkins et al. 2014; Zhu et al. 2010), including a large retrospective cohort study (Zhu et al. 2010) and a large case-control study (Perkins et al. 2014).

Age at menopause. A few studies had evaluated associations between Pb exposure and age at menopause (Eum et al. 2014; Popovic et al. 2005). Eum et al. (2014) found an inverse association between tibia Pb and age at onset of natural menopause (e.g., non-surgical) in a population of 434 participants in the

Nurses Health Study cohort. In the highest tibia Pb tertile, the age at onset of menopause was 1.21 years earlier than controls. However, no associations were observed between PbB (mean PbB: <5 μg/dL) or patella Pb. In a study of 108 former smelters (mean PbB: 2.73 μg/dL), the age at onset of combined natural and surgical menopause was earlier by 7 years (p=0.001) compared to controls (n=99; PbB: 1.25 μg/dL) (Popovic et al. 2005). No difference was observed between the age at onset and natural menopause between the exposed and control groups.

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in the development of toxicity to male and female reproductive systems. Oxidative stress through ROS is a plausible mechanism for reproductive effects, as is the disruption of calcium homeostasis. Mechanisms for alterations in circulating hormone levels have been not been established. However, EPA (2014c) and NRC (2012) noted several possible mechanisms that may be involved in alterations of serum hormones, including direct inhibition of LH secretion; reduced expression of steroidogenic acute regulatory protein (a protein required in maintaining gonadotropin-stimulated steroidogenesis); altered release of pituitary hormones due to interference with cation-dependent second messenger systems; and altered binding of hormones to receptors. Pb is distributed to, and has been measured in, semen, spermatozoa, the fetus, umbilical cord blood, placenta, and follicular fluid (see Section 3.1.2, Toxicokinetics, Distribution), providing a toxicokinetic mechanism for direct effects to reproductive tissues.

2.18 DEVELOPMENTAL

This section discusses developmental effects of Pb other than neurodevelopmental defects. Neurodevelopmental effects are discussed in Section 2.16 (Neurological Effects). The term "developmental" used in the discussion that follows refers to effects other than neurodevelopmental.

Overview. Numerous epidemiological studies have evaluated developmental effects (birth outcomes, birth defect, neural tube defects, decreased anthropometric measures in children, and delayed puberty) associated with Pb exposure, with the database for developmental effects dominated by environmental exposure studies with PbB ≤10 μg/dL. In general, studies provide mixed evidence for effects on birth outcomes (e.g., infant size) and anthropometric measures in children, but more consistent evidence for delayed puberty. Although studies provide evidence of associations between PbB and developmental outcomes, results are inconsistent, and several studies, including prospective studies, with PbB ≤10 μg/dL show no associations with developmental outcomes.

The following developmental effects have been associated with PbB:

- ≤10 µg/dL:
  - Effects on birth outcomes (decreased birth weight, head circumference, and crown-heel length); results are mixed when compared across studies.
  - Decreased anthropometric measures in children (weight, height, head circumference, trunk length, leg length, arm length, BMI); results are mixed when compared across studies.
  - Delayed puberty in females (breast development, pubic hair development, onset of menarche); corroborated in multiple studies.
  - Delayed puberty in males (testicular volume, genitalia development, pubic hair development); a few studies with equivocal results.
- >10 µg/dL (based on few studies):
  - Effects on birth outcomes (low birth weight).
  - Decreased anthropometric measures in children (decreased weight, height, head circumference, chest circumference).
  - Delayed puberty in females (breast development).
  - Delayed puberty in males (decreased testicular size, delayed pubic hair development, delayed penile development).

Measures of Exposure. Most studies evaluating developmental effects used maternal PbB and/or cord, infant, or child PbB as the biomarker for exposure. In some studies, Pb concentrations in red blood cells (Perkins et al. 2014), maternal bone (Afeiche et al. 2011; Cantonwine et al. 2010; Hernandez-Avila et al. 2002; Kordas et al. 2009), or hair (Sanín et al. 2001; Sanna and Vallascas 2011) were used as biomarkers.

Confounding Factors and Effect Modifiers. Numerous complicating factors may add uncertainty in the interpretation of studies examining associations between PbB and developmental effects. These factors include nutrition during pregnancy, prenatal care, adequate nutrition during infancy and childhood, SES, intercurrent diseases, alcohol consumption, smoking status, and potential exposure to other chemicals. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of the effect of the variable on the outcome.

Characterization of Effects. As noted above, most epidemiological studies evaluated developmental effects at PbB ≤10 µg/dL, with few studies of PbB >10 µg/dL. Studies of PbB ≤10 µg/dL are discussed

in detail in the section below. General trends for studies showing a relationship between PbB ≤10–50 µg/dL and developmental effects are shown in Table 2-39. Effects on birth outcomes, including decreased birth weight, head circumference, and crown-heel length have been observed at maternal PbBs of ≤10–50 µg/dL. Decreased anthropometric measures in infants and children, including decreased weight, height, head circumference, trunk length, leg length, arm length, and BMI, have been observed over the PbB range of ≤10–30 µg/dL. Delayed onset of puberty in males and females was observed over the PbB range of ≤10–30 µg/dL. Very little data are available regarding *in utero* exposure to Pb and birth defects. Two studies that examined neural tube defects did not find associations with Pb exposure at mean blood levels over for PbB means ranging from 2.4 to 24 µg/dL (Brender et al. 2006; Zeyrek et al. 2009). As discussed below, although epidemiological studies demonstrate developmental effects of Pb, results across studies are inconsistent, with several studies reporting no association between PbB and developmental effects. For example, results of effects on birth outcomes in study populations with maternal PbB ≤10 µg/dL are equivocal (see Tables 2-40 and 2-41). For studies with maternal PbB >10 µg/dL, equivocal results also were observed for associations between PbB and birth weight and length (Factor-Litvak et al. 1991; Hernandez-Avila et al. 2002; McMichael et al. 1986; Murphy et al. 1990). Dose-dependence has not been firmly established within the relatively narrow range of PbB (≤10 µg/dL) in most studies.

Table 2-39. Overview of Developmental Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
≤10	Effects on birth outcome (decreased birth weight, crown-heel length, head circumference)	Bornschein et al. 1989; González - Cossío et al. 1997; Nishioka et al. 2014; Odland et al. 1999; Taylor et al. 2013, 2015; Wang et al. 2017b, 2017b; Xie et al. 2013; Zhu et al. 2010
	Minor congenital anomalies	Needleman et al. 1984
	Decreased anthropometric measures in children (decreased weight, height, head circumference, waist circumference, trunk length, leg length, arm length, body mass index, body fat)	Afeiche et al. 2011; Alvarez-Ortega et al. 2019; Dallaire et al. 2014; Deierlein et al. 2019; Hauser et al. 2008; Hong et al. 2014; Ignasiak et al. 2006; Little et al. 2009; Min et al. 2008b; Olivero-Verbel et al. 2007; Raihan et al. 2018; Schell et al. 2009; Yang et al. 2013a
	Delayed puberty in females (breast development, pubic hair development, onset of menarche)	Denham et al. 2005; Den Hond et al. 2011; Gollenberg et al. 2010; Naicker et al. 2010; Selevan et al. 2003; Wu et al. 2003b

Table 2-39. Overview of Developmental Effects Associated with Chronic Exposure to Lead (Pb)

Mean blood lead concentration (PbB) (µg/dL)	Effects associated with Pb exposure	References
	Delayed puberty in males (testicular volume, genitalia development, pubic hair development)	Hauser et al. 2008; Williams et al. 2010, 2019
>10–30	Effects on birth outcome (decreased birth weight)	Chen et al. 2006; Hernandez-Avila et al. 2002
	Decreased anthropometric measures in children (decreased weight, height, head circumference, chest circumference)	Frisancho and Ryan 1991; Kerr et al. 2019; Tomoum et al. 2010
	Delayed puberty in females (breast development)	Liu et al. 2019b; Tomoum et al. 2010
	Delayed puberty in males (decreased testicular size, delayed pubic hair development; delayed penile development)	Tomoum et al. 2010
>30–50	Effects on birth outcome (low birth weight)	Jelliffe-Pawlowski et al. 2006

Table 2-40. Effects on Birth Outcomes at Blood Lead Concentration (PbB) ≤10 µg/dL

	Birth outcome			
Reference (population size)	Birth weight	Height or C-H length	SGA	Head circumference
Al-Saleh et al. 2014 (n=1,577)	0[a]	0	0	0
Bloom et al. 2015 (n=235)	0[a]	0	−	0
Bornschein et al. 1989 (n=202)	↓[a]	↓	−	0
Garcia-Esquinas et al. 2014 (n=97)	0[a]	0	−	−
González-Cossío et al. 1997 (n=272)	0[b]	−	−	−
Kim et al. 2017b (n=280)	0[b]	↑ (M), 0 (F)	−	0
Nishioka et al. 2014 (n=386)	↓[b]	−	−	−
Odland et al. 1999 (n=50)	↓[a,b]	−	−	−
Perkins et al. 2014 (n=949)	0[a,b]	0	−	0
Rabito et al. 2014 (n=98)	0[a]	−	−	−
Rodosthenous et al. 2017 (n=946)	−	−	0	−
Taylor et al. 2015 (n=4,285)	↓[b]	↓	−	↓
Thomas et al. 2015 (n=1,835)	−	−	0	−
Wang et al. 2017b	↓	0	↓	0
Wang et al. 2017c	↑ (M), 0 (F)	0 (F)	−	0

Table 2-40. Effects on Birth Outcomes at Blood Lead Concentration (PbB) ≤10 µg/dL

	Birth outcome			
Reference (population size)	Birth weight	Height or C-H length	SGA	Head circumference
Xie et al. 2013 (n=252)	↓[b]	0	−	0
Zhu et al. 2010 (n=43,288)	↓[b]	−	0	−

[a]Birth weight not adjusted for gestational age
[b]Birth weight adjusted for gestational age

↓ = decrease in outcome measure; ↑ = increase in outcome measure; 0 = no effect on outcome measure; − = not assessed; C-H = crown-heel; F = female; M = male; SGA = small for gestational age

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Al-Saleh et al. 2014 Cross-sectional study; n=1578 mother-infant pairs	Maternal PbB mean: 2.897	Birth weight	OR: 1.107 (0.797, 1.538); p=0.545
		Birth height	OR: 1.299 (0.945, 1.786); p=0.107
		Crown-heel length	OR: 1.061 (0.795, 1.415); p=0.689
		SGA	OR: 1.168 (0.837, 1.631); p=0.362
		Head circumference	OR: 1.007 (0.724,1.400); p=0.968
		Apgar	OR: 1.027 (0.787, 1.341); p=0.842
Bloom et al. 2015 Case-control study; n=235 mother-infant pairs	Maternal PbB mean: 0.71 Tertiles: • T1: <0.55 (reference) • T2: 0.55–<0.73 • T3: 0.73–2.23	Birth weight	Linear regression coefficient (g per µg/dL) T3: -34.85 (-97.76, 128.06); p-trend=0.202
		Birth length	Linear regression coefficient (cm per µg/dL) T3: 0.14 (-0.81, 1.09); p-trend:0.671
		Head circumference	Linear regression coefficient (cm per µg/dL) T3: -0.33 (-1.07, 0.41); p-trend: 0.132
Bornschein et al. 1989 Prospective study; n=202 mother-infant pairs	**PbB:** Mean (SD): 7.5	Birth weight	**Regression coefficient (g per ln µg/dL) for all births: -114; p<0.001*.** **Regression coefficient (g per ln µg/dL) with significant interaction with maternal age (p=0.0073)*:** **maternal age 18 years: -58*** **maternal age 30 years: -601***
		Birth length	**Regression coefficient (cm per ln µg/dL): -2.5; p=0.019***
		Head circumference	Regression coefficient (cm per ln PbB µg/dL): 0.0 p=0.97

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Garcia-Esquinas et al. 2014 Birth cohort study; n=100 mother-infant pairs	Maternal PbB Gmean: 1.83	Birth weight	Adjusted mean difference in grams for a 2-fold increase in PbB (µg/L): 62.4 (-73.1, 197.8)
		Birth length	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/L): 0.17 (-0.56, 0.91)
		Abdominal diameter	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/d): 0.31 (-0.52, 1.15)
		Cephalic diameter	Adjusted mean difference in cm for a 2-fold increase in PbB (µg/L): 0.15 (-0.21, 0.51)
González-Cossío et al. 1997 Birth cohort study; n=272 mother-infant pairs	**PbB:** • Maternal o Mean (SD): 8.9 (4.1) o Quartiles: ▪ Q1: ≤5.8 ▪ Q2: 5.9–8.0 ▪ Q3: 8.1–11.0 ▪ Q4: ≥11.1 • Umbilical cord o Mean (SD): 7.1 (3.5) o Quartiles ▪ Q1: ≤4.6 ▪ Q2: 4.7–6.1 ▪ Q3: 6.2–8.5 ▪ Q4: ≥8.6	Birth weight	Regression coefficient: • Maternal PbB for Q4: -98.30 (59.55); p=0.100 • Umbilical cord PbB for Q4: -41.74 (64.04); p=0.514

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Kim et al. 2017b Prospective longitudinal study; n=280 mother-infant pairs	**PbB:** Umbilical cord, mean (SE) • All: 1.31 (0.06) • Boys: 1.39 (0.09) • Girls: 1.21 (0.07)	Birth weight	Regression coefficient: • Boys: 0.010 (-0.014, 0.034); p=0.403 • Girls: 0.001 (-0.025, 0.027); p=0.950
		Birth length	Regression coefficient: • **Boys: 0.017 (0.003, 0.031); p=0.019*** • Girls: 0.007 (-0.010, 0.025); p=0.410
		Head circumference	Regression coefficient: • Boys: 0.010 (-0.001, 0.022); p=0.083 • Girls: -0.007 (-0.016, 0.002); p=0.148
		Ponderal index	Regression coefficient: • **Boys: -0.055 (-0.103, -0.006); p=0.027*** • Girls: -0.009 (-0.062, 0.045); p=0.748
Nishioka et al. 2014 Cohort study; n=386 mother-infant pairs	Maternal PbB mean at gestational weeks: • 12 weeks: 0.98 • 25 weeks: 0.92 • 36 weeks: 0.99	Birth weight	Regression coefficient based on log µg/dL: • **Infant males: -0.151 (p<0.05)*** • Infant females: -0.098 (p>0.05)
Odland et al. 1999 Cohort study; n=262 mother-infant pairs	Maternal, mean (range); p-values compare Russian and Norwegian cohorts • Russian cohort: 2.9 (0.83–13.5) • Norwegian cohort: 2.3 (0.41–3.9); p<0.001	Birth weight	Regression coefficient, combined Russian and Norwegian cohorts [g per µmol/L (g per 20.7 µg/dL)]: **-1,068 (95% CI -2,134, -2); p<0.05***

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Perkins et al. 2014 Birth cohort study; n=829 mother-infant pairs	Maternal RBC Pb concentration (µg/dL) mean: 1.22 Quartiles for RBC Pb; mean: • Q1: 0.65 • Q2: 0.96 • Q3: 1.27 • Q4: 2.02 Estimated maternal PbB mean: 0.4	Birth weight	Linear regression β coefficient for RBC (µg/dL) Q4: -47 (-128, 35); p-trend: 0.27
		Birth length	Linear regression β coefficient for RBC (µg/dL) Q4: -0.15 (-0.54, 0.23); p-trend: 0.37
		Head circumference	Linear regression β coefficient for RBC (µg/dL) Q4: -0.08 (-0.33, 0.16); p-trend: 0.56
Rabito et al. 2014 Birth cohort study; n=98 mother-infant pairs	Maternal 2nd trimester PbB mean: 0.42 Maternal 3rd trimester PbB mean: 0.45	Birth weight	Linear regression β coefficient, g per µg/dL maternal: • 2nd trimester: -43.21 (-88.6, 2.18); p=0.06 • 3rd trimester: β not reported; p=0.68 • Delivery: β not reported; p=0.83
Rodosthenous et al. 2017 Prospective cohort study; n=944 mother-infant pairs	Maternal 2nd trimester PbB: 3.7 • Quartiles: o Q1: <1.93 o Q2: 1.93–2.79 o Q3: 2.80–4.53 o Q4: >4.53	Birthweight-for-gestational age z-score	• Linear regression β for a doubling for PbB: -0.06 (-0.13, 0.003); p=0.06
		SGA	Logistic regression OR Q4: 1.62 (0.99–2.65)
Taylor et al. 2013, 2015 Longitudinal cohort study; n=4,285 mother-infant pairs	Maternal PbB mean: 3.67 Population stratified by PbB <5.0 and ≥5.0	Birth weight	**β coefficient (g per µg/dL): -13.23 (-23.75, -2.70); p=0.014***
		Head circumference	**β coefficient (cm per µg/dL): -0.04 (-0.07, -0.06)[e]; p=0.021***
		Crown-heel length	**β coefficient (cm per µg/dL): -0.05 (-0.10, -0.00); p=0.034***

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Thomas et al. 2015 Prospective cohort; n=1,835 mother-infant pairs	Maternal PbB median: 0.59 Tertiles: • T1: <0.52 • T2: 0.52–1.04 • T3: >1.04–4.04	SGA	Adjusted RR for T3 (95% CI): 1.19 (0.65, 2.18)
Wang et al. 2017b Prospective cohort study; n=3,125 mother-infant pairs	Maternal serum Pb mean: 1.50 Tertiles: • T1: <1.18 • T2: 1.18–1.70 • T3: ≥1.71	Birth weight	**Regression coefficient β: -2.74 (-5.17, -0.31); p=0.03***
		Birth length	Regression coefficient β: -0.013 (-0.026, 0.001); p=0.06
		Head circumference	Regression coefficient β: -0.008 (-0.019, 0.004); p=0.18
		Chest circumference	Regression coefficient β: -0.008 (-0.018, 0.002); p=0.13
		SGA	• **OR T2: 1.45 (1.04, 2.02); p=0.03*** • **OR T3: 1.69 (1.22, 2.34); p=0.002***
Wang et al. 2017c Cross-sectional study; n=1,009 mother-infant pairs	**PbB:** Cord PbB, Gmean (95% CI) All: 4.07 (3.98, 4.17) Infant boys: 4.07 (3.89, 4.17) Infant girls: 4.17 (3.98, 4.36)	Birth weight	Regression coefficient β (95%), per 1-unit increase in log_{10}-transformed PbB: • All: 60.78 (-66.30, 187.85); p=0.35 • **Boys: 182.32 (15.24. 349.39); p=0.03*** • Girls: -96.06 (-289.23, 97.10); p=0.33
		Birth length	Regression coefficient β (95%), per 1-unit increase in log_{10}-transformed PbB: • All: 0.32 (-0.18, 0.82); p=0.21 • Boys: not reported • Girls: 0.30 (-0.46, 1.05); p=0.44

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
		Head circumference	Regression coefficient β (95%), per 1-unit increase in log_{10}-transformed PbB: • All: -0.36 (-0.78, 0.06); p=0.09 • Boys: -0.50 (-1.09, 0.09); p=0.10 • Girls: -0.32 (-0.91, 0.27); p=0.29
		Ponderal index	Regression coefficient β (95%), per 1-unit increase in log_{10}-transformed PbB: • All: -0.01(-0.10, 0.09); p=0.94 • Boys: 0.10 (-0.03, 0.23); p=0.12 • **Girls: -0.17 (-0.31, -0.02); p=0.02***
Xie et al. 2013 Birth cohort study; n=252 mother-infant pairs	Maternal PbB mean: 3.53	Birth weight	**β coefficient (g per square root µg/dL): -148.99 (-286.33, -11.66); p=0.03***
		Birth length	β coefficient (cm per square root µg/dL): -0.46 (-1.25, 0.34); p=0.26
		Head circumference	β coefficients (cm per square root µg/dL): -0.37 (-0.78, 0.19); p=0.24

Table 2-41. Summary of Epidemiological Studies Evaluating Birth Outcomes Effects of Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Zhu et al. 2010 Retrospective cohort study; n=43,288 mother-infant pairs	Maternal PbB mean: 2.1	Birth weight	**β coefficient g per µg/dL (95% CI):** 0: reference **1: -27.4 (-17.1, -37.8)*** **2: -38.8 (-24.1, -53.4)*** **3: -47.5 (-29.6, -65.4)*** **4: -54.8 (-34.2, -75.5)*** **5: -61.3 (-38.2, -84.4)*** **6: -67.2 (-41.8, -92.5)*** **7: -72.5 (-45.2, -99.9)*** **8: -77.6 (-48.3, -106.8)*** **9: -82.3 (-51.2, -113.3)*** **10: -86.7 (-54.0, -119.4)***
		SGA	Adjusted OR for Q4: 1.07 (0.93, 1.23)

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 13 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Values are for maternal PbB, unless otherwise specified.
[d]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[e]Values are reported; the value for the β coefficient is outside of the 95% CI.

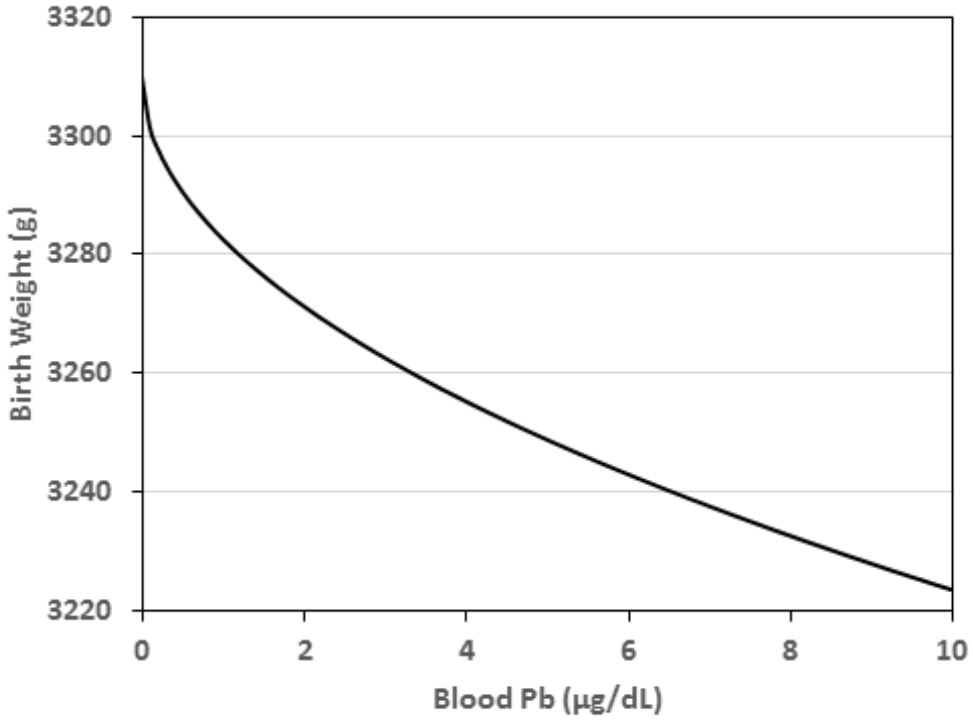
CI = confidence interval; Gmean = geometric mean; OR = odds ratio; Pb = lead; RBC = red blood cell; RR = relative risk; SD = standard deviation; SE = standard error; SGA = small for gestational age

Effect at Blood Pb Levels ≤10 µg/dL. Epidemiology studies have reported developmental effects, including birth outcomes, birth defects, anthropometric measures in children, and delayed onset of puberty, at mean PbB ≤10 µg/dL. Study details are provided in *Supporting Document for Epidemiological Studies for Lead*, Table 13. Results of studies on associations between PbB and adverse effects on birth outcomes and anthropometric measures are mixed when compared across studies. Delayed onset of puberty in females has been corroborated in several studies. Fewer studies are available regarding effects of Pb on onset of puberty in males, with equivocal results. Exposure to Pb has not been shown to cause birth defects in humans. Neural tube defects have not been associated with Pb exposure and findings of a single study showing minor anomalies have not been corroborated.

Birth outcomes. An overview of results of studies that evaluated associations between Pb exposure and birth outcomes (infant weight, height or crown-heel length, small for gestation age [SGA], head circumference, and ponderal index) at maternal PbB ≤10 µg/dL is shown in Table 2-40, with more detailed results in Table 2-41. Studies include two prospective studies (Bornschein et al. 1989; Thomas et al. 2015), several studies of large populations (n=829–43,288) (Al-Saleh et al. 2014; Perkins et al. 2014; Rodosthenouse et al. 2017; Taylor et al. 2015; Thomas et al. 2015; Wang et al. 2017b, 2017b; Zhu et al. 2010), and cohort and case-control studies of smaller (n=98–386) populations (Bloom et al. 2015; Garcia-Esquinas et al. 2014; González-Cossío et al. 1997; Kim et al. 2017b; Nishioka et al. 2014; Rabito et al. 2014). As shown in Table 2-41, results of most studies show either decreases or no change in birth outcomes. Some positive associations between PbB and birth outcomes have been reported. A large cross-sectional study (n=1,009) reported a positive association between umbilical cord PbB (mean: 4.07 g/dL) and birth weight in male infants, but no change for female infants (PbB mean: 4.17 µg/dL) (Wang et al. 2017c). A longitudinal study showed a positive association between umbilical cord PbB in infant boys (mean: 1.39 µg/dL) and birth length, but an inverse association for ponderal index (calculated relationship between body mass and height); no associations were observed for infant girls (PbB mean: 1.21 µg/dL) (Kim et al. 2017b). In a small (n=202) prospective study, Bornschein et al. (1989) reported associations between maternal PbB (mean 7.5 µg/dL) and decreased birth weight and length. The size of the effect of PbB varied with maternal age ($p<0.007$), with a 58 g per lnPbB decrease for pregnancies at age 18 years and a 601 g decrease per ln PbB (µg/dL) for pregnancies at age 30 years. In the complete birth cohort from this study, which included mothers who declined participation in the infant follow-up (n=861), the decline in birth weight was -114 g per ln PbB. Results of the largest cohort study, a retrospective study of >43,000 participants (mean PbB: 2.1 µg/dL), showed an inverse association between PbB and birth weight (Zhu et al. 2010). The best fitting model was a linear change in birth weight with square root of PbB (Figure 2-7). The model predicts a 34 g decrease in birth weight for an

increase in PbB from 1 to 5 µg/dL and a 59 g decrease for an increase in PbB from 1 to 10 µg/dL (adjusted for confounders).

Figure 2-7. Relationship Between Blood Lead Concentration (PbB) and Birth Weight at PbB ≤10 µg/dL



Source: Zhu et al. 2010

Results of a longitudinal cohort study of 4,285 mother-infant pairs (maternal PbB mean: 2.1 µg/dL; range 0.42–19.14) showed inverse associations between birth weight, crown-heel length, and head circumference for participants with PbB ≥5 µg/dL compared to PbB <5 µg/dL (Taylor et al. 2015). A prospective cohort study of 3,125 mother infant pairs observed an inverse association between maternal serum Pb (mean: 1.50 µg/dL) and birth weight and SGA (Wang et al. 2017b). Other smaller cohort studies also showed associations between maternal PbB ≤10 µg/dL and decreased birth weight (Nisioka et al. 2014; Odland et al. 1999). In contrast, other studies, including a prospective study and cohort studies of large populations, did not find associations between PbB and birth outcome measures. A prospective study of 1,835 mother-infant pairs did not find an association between PbB and SGA, with PbB data stratified by tertiles (range for highest tertile: 1.04–4.04 µg/dL) (Thomas et al. 2015). Similarly, no associations between maternal PbB and decreased birth weight, length, or head circumference were

observed in a cohort study of 829 participants (estimated PbB mean of 0.4 μg/dL) (Perkins et al. 2014), or in a cross-sectional study of 1,578 participants (Al-Saleh et al. 2014). Smaller cohort studies also report no associations between PbB and adverse birth outcome measures (Bloom et al. 2015; Garcia-Esquinas et al. 2014; González-Cossío et al. 1997; Rabito et al. 2014). Equivocal findings for birth outcomes in studies examining effects at maternal PbB ≤10 μg/dL are not surprising, given that prospective studies at maternal PbB >10 μg/dL also have reported conflicting results for adverse effects on birth outcomes (Factor-Litvak et al. 1991; Hernandez-Avila et al. 2002; McMichael et al. 1986; Murphy et al. 1990). For example, two prospective studies found no associations between PbB and birth weight in birth cohorts that had mean maternal PbBs >10 μg/dL (Factor-Litvak et al. 1991; McMichael et al. 1986).

Birth defects. Few studies have evaluated associations between *in utero* exposure to Pb and birth defects. Details of studies evaluating PbB ≤10 μg/dL are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 13. No association was observed between PbB and neural tube defects in a case-control study (n=409) with mean maternal PbB of 2.5 μg/dL (Brender et al. 2006). Other epidemiological studies that have reported associations between Pb in exposure media (e.g., water, soil) and neural tube defects are limited by the lack of PbB measurement (Bound et al. 1997; Huang et al. 2011; Irgens et al. 1998). An early cross-sectional study of birth outcomes examined associations between PbB and congenital anomalies using hospital records on 5,183 deliveries in Boston, Massachusetts (Needleman et al. 1984). The RR of an anomaly increased with increasing cord PbB; the RR (relative to PbB 0.7 μg/dL) was 1.87 (95% CI 1.44, 2.42) for PbB of 6.3 μg/dL and increased to 2.39 (95% CI 1.66, 3.43) at 15 μg/dL and 2.73 (95% CI 1.80, 4.16) at 24 μg/dL. The anomalies were considered to be minor (hemangiomas, lymphangiomas, hydrocele, minor skin anomalies, undescended testicle) and no specific anomaly was associated with PbB. Limitations of this study are that it was a cross-sectional study of a convenience sample with outcomes obtained from hospital records. Associations between PbB and congenital anomalies have not been corroborated. A case-control study of 97 cases and 201 controls did not find an increased risk for congenital heart defects (Liu et al. 2018a). For the highest umbilical cord PbB tertile (≥0.826 μg/dL), the OR (95% CI) for congenital heart defects was 1.67 (0.88, 3.17).

Anthropometric measures in children. An overview of results of studies evaluating associations between Pb exposure and growth of infants and children (aged 0.5–15 years) at maternal and/or offspring PbB ≤10 μg/dL is shown in Table 2-42, with more detailed results in Table 2-43. Studies include five prospective studies (Dallaire et al. 2014; Deierlein et al. 2019; Lamb et al. 2008 Kim et al. 2017b; Renzetti et al. 2017), cross-sectional studies of large (n=899–1,050) populations (Afeiche et al. 2011;

Hong et al. 2014; Ignasiak et al. 2006), and several smaller (n=108–729) cohort and cross-sectional studies (Alvarez-Ortega et al. 2019; Hauser et al. 2008; Little et al. 2009; Min et al. 2008b; Olivero-Verbel et al. 2007; Raihan et al. 2018; Schell et al. 2009; Yang et al. 2013a). Most studies report inverse associations between Pb exposure and height, with mixed results for weight and BMI (Table 2-42). In a prospective longitudinal study of girls (n=692; mean PbB: 1.16 µg/dL), height, BMI, waist circumference, and percent body fat were decreased in participants with PbB ≥1 µg/dL, compared to participants with PbB <1 µg/dL; decreases were observed at yearly assessments at ages 7–14 years (Deierlein et al. 2019). The Renzetti et al. (2017) prospective study (n=513 mothers) reported inverse associations between 3rd pregnancy trimester maternal PbB (mean: 3.1 µg/dL) and weight-for-age and height-for-age, but no associations for BMI or percentage body fat. No associations were observed between 2nd trimester PbB or cord PbB. In contrast, a prospective study of 280 children (18–27 months) observed positive associations between umbilical cord PbB (mean: 1.31 µg/dL) and weight and BMI, but not height; no associations were observed at 18 or 27 months (Kim et al. 2017b). A small (n=290) prospective study showed an association between cord PbB (mean 4.8 µg/dL) and small decreases in height and head circumference, but not for weight or BMI (Dallaire et al. 2014). Similarly, Lamb et al. (2008) did not find an association between maternal PbB and height or BMI at maternal PbB means of 5.60–20.56 µg/dL (means for different geographic locations). In contrast, results of large case-control studies showed inverse associations between maternal bone Pb and weight (Afeiche et al. 2011), maternal PbB and weight and height (Hong et al. 2014), and child PbB and several growth measures, including weight, height, and BMI (Ignasiak et al. 2006). The largest inverse association for decreased weight was observed for maternal bone Pb in females assessed at 2–5 years of age; the mean PbB in children was 3.8 µg/dL (Afeiche et al. 2011). At the 5-year assessment, body weight in females was decreased by approximately 172 g for each 1-SD increase in maternal bone Pb. Smaller case-control and cohort studies reported consistent inverse associations between PbB and height, with equivocal findings for weight, and no associations for BMI.

Table 2-42. Overview of Decreased Anthropometric Measures in Children at Blood Lead Concentration (PbB) ≤10 µg/dL

Reference	Age at time of assessment (years)	Anthropometric measurements		
		Weight	Height	BMI
Afeiche et al. 2011	1–5	↓ (F); 0 (M)	–	–
Alvarez-Ortega et al. 2019	5–16	↓ (F); 0 (M)	↓ (F); 0 (M)	↓ (F); 0 (M)
	5–11	0	0	0
	12–16	↓	↓	↓
Dallaire et al. 2014	8–14	0	↓	0
Deierlein et al. 2019	7–14	↓	↓	↓

Table 2-42. Overview of Decreased Anthropometric Measures in Children at Blood Lead Concentration (PbB) ≤10 µg/dL

Reference	Age at time of assessment (years)	Anthropometric measurements		
		Weight	Height	BMI
Hauser et al. 2008	8–9	0	↓	0
Hong et al. 2014	0.5–2	↓	↓	−
Ignasiak et al. 2006	7–15	↓ (F); 0 (M)	↓ (F); 0 (M)	↓
Kim et al. 2017b	2.25	0	0	0
Lamb et al. 2008	1–10	0	0	0
Little et al. 2009	2–12	↓	−	−
Min et al. 2008b	5–13	0	↓	−
Olivero-Verbel et al. 2007	5–9	0	↓	−
Raihan et al. 2018	<2	↓[a]	↓[a]	0
Renzetti et al. 2017	4–6	↓	↓	−
Schell et al. 2009	0.5−1	0	↓	−
Yang et al. 2013a	3–9	↓	↓	0

[a]Assessments were underweight (defined as weight-for-age z-score <-2) and "stunting" (defined as length-for-age z-score <-2).

↓ = decrease in outcome measure; 0 = no effect on outcome measure; − = not assessed; BMI = body mass index; F = females; M = males

Delayed puberty. Results of studies that evaluated associations between Pb exposure and sexual maturation in boys and girls at child PbB ≤10 µg/dL are summarized in Table 2-44. In girls, delayed onset of puberty, as measured by breast development, pubic hair development, and attainment of menarche, has been corroborated in multiple cross-sectional studies (Den Hond et al. 2011; Denham et al. 2005; Gollenberg et al. 2010; Naicker et al. 2010; Selevan et al. 2003; Wu et al. 2003b). Mean PbB in these studies ranged from 0.49 to 4.9 µg/dL. Delays in the predicted attainment of menarche ranged from 3.6 to 10.6 months (Denham et al. 2005; Selevan et al. 2003). Fewer studies examining associations between Pb exposure and sexual maturation in boys at child PbB ≤10 µg/dL are available. Results of these studies are equivocal. Delayed sexual maturation (time to onset to puberty and sexual maturity), measured by genitalia development, testicular volume, and pubic hair development, was observed in three cross-sectional studies of the same study population of 481–489 boys; the median child PbB was 3 µg/dL at the time of study enrollment (Hauser et al. 2008; Williams et al. 2010, 2019). However, no association between PbB and the onset of puberty was observed in a cross-sectional study of 887 boys with a median PbB of 2.5 µg/dL (Den Hond et al. 2011).

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Afeiche et al. 2011 Cross-sectional study; n=999 mother-child pairs	• Child PbB mean: 3.8 • Maternal bone Pb (patella) mean (µg/g): 10.4	Weight (females)	Associations between a 1-SD increase in maternal bone Pb (µg/g) and child weight (g) for children aged: • 12 months: -70.9 (-147.9, 6.0) • **24 months: -96.1 (-170.4, -21.8)*** • **36 months: -121.3 (-200.0, -42.6)*** • **48 months: -146.4 (-235.5, -57.4)*** • **60 months: -171.6 (-275.2, -68.0)***
		Weight (males)	Associations between a 1-SD increase in maternal bone Pb (µg/g) and child weight (g) for children aged: • 12 months: 29.4 (-42.1, 100.8) • 24 months: 27.8 (-43.5, 99.1) • 36 months: 7.9 (-67.3, 83.1) • 48 months: -13.6 (-97.9, 70.8) • 60 months: -35.0 (-132.4, 62.3)
Alvarez-Ortega et al. 2019 Cross-sectional study; n=554 children (ages 5–16 years)	Mean (SE): 3.5 (0.2) Median: 1.9 Range: 0.1–50.1	Weight	Spearman correlations: • **All participants: -0.152; p<0.001*** • **Females: -0.226; p<0.001*** • Males: -0.056; p=0.380 • **Age 5–11 years: -0.069; p=0.010*** • **Age 12–16 years: -0.385; p<0.001***
		Height	Spearman correlations: • All **participants: -0.101; p=0.019*** • **Females: -0.153; p=0.009*** • Males: -0.037; p=0.567 • Age 5–11 years: -0.137; p=0.418 • **Age 12–16 years: -0.206; p=0.009***

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
		BMI	Spearman correlations: • **All participants: -0.172; p<0.001*** • **Females: -0.273; p<0.001*** • Males: -0.040; p=0.536 • Age 5–11 years: -0.056; p=0.295 • **Age 12–16 years: -0.384; p<0.001***
Dallaire et al. 2014 Prospective cohort study; n=290 children (aged 8–14 years)	• Cord PbB mean: 4.8 • Child PbB mean: 2.7	Height	**β coefficients (cm per µg/dL cord): -1.57; p=0.004***
		Head circumference	**β coefficients (cm per µg/dL cord): -0.005; p=0.04***
		Weight	β coefficients (kg per µg/dL cord): β not reported; p=0.70
		BMI	β coefficients (kg/m^2 per µg/dL cord): 0.07; p=0.23
Deierlein et al. 2019 Prospective longitudinal study; n=of 683 girls (enrolled at ages 6–8 years)	• Mean (SD): 1.16 (0.67) • Range: 0.18–5.40	Height	**Predicted mean differences (cm) for PbB ≥1 µg/dL compared to <1 µg/dL:** • **Age 7: -2.0 (-3.0, -1.0); p<0.001*** • **Age 14: -1.5 (-2.5, -0.4): p=0.01***
		BMI	**Predicted mean differences (kg/m^2) for PbB ≥1 µg/dL compared to <1 µg/dL:** • **Age 7: -0.7 (-1.2, -0.2); p=0.005*** • **Age 14: -0.8 (-1.5, -0.02); p=0.05***
		Waist circumference	**Predicted mean differences (cm) for PbB ≥1 µg/dL compared to <1 µg/dL:** • **Age 7: -2.2 (-3.8, -0.6); p=0.01*** • **Age 14: -2.9 (-4.8, -0.9); p=0.005***
		Body fat	**Predicted mean differences (%) for PbB ≥1 µg/dL compared to <1 µg/dL:** • **Age 7: -1.8 (-3.2, -0.4); p=0.01*** • **Age 14: -1.7 (-3.1, -0.4); p=0.01***

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Hauser et al. 2008 Cross-sectional study n=489 children (aged 8–9 years)	Child PbB, mean: 3	Height	**Regression coefficient (cm per µg/dL): -1.439 (-2.25, -0.63); p<0.001***
		Weight	Regression coefficient (kg per µg/dL): -0.761 (-1.54, 0.02); p=0.067
		BMI	Regression coefficient (kg/m^2 per µg/dL): -0.107 (-0.44, 0.23); p=0.53
Hong et al. 2014 Cross-sectional study; n=1,150 infants (aged 6–24 months)	Maternal PbB mean: 1.25	Weight	**Weight z score: -0.28 (-0.48, -0.09); p<0.05***
		Height	**Height z score: -0.28 (-0.49, -0.06); p<0.05***
Ignasiak et al. 2006 Cross-section study; n=899 children (aged 7–15 years)	Child PbB mean: 7.7	Weight	• Slope boys(kg per $\log_{10}$ µg/dL): 4.00 (2.45); p=0.10 • **Slope girls (kg per $\log_{10}$ µg/dL): -6.59 (2.09); p=0.001***
		Height	• Slope boys (cm per $\log_{10}$ µg/dL): -6.26 (1.40); p=0.002 • **Slope girls (cm per $\log_{10}$ µg/dL): -5.54 (2.05); p=0.007***
		BMI	• Slope boys (kg/m^2 per $\log_{10}$ µg/dL): -0.39 (0.82); p=NS • **Slope girls (kg/m^2 per log µg/dL): -1.86 (0.75); p=0.01***
		Trunk length	• **Slope boys (cm per $\log_{10}$ µg/dL): -2.21 (0.97); p=0.02*** • Slope girls (cm per log µg/dL): -1.47 (1.00); p=NS

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
		Leg length	• **Slope boys (cm per log_{10} µg/dL): -4.05 (1.27); p=0.002*** • **Slope girls (cm per log_{10} µg/dL): -4.08 (1.27) p=0.0001***
		Arm length	• **Slope boys (cm per µg/dL): -3.20 (0.97); p=0.0001*** • **Slope girls (cm per log_{10} µg/dL): -2.61 (0.98); p=0.008***
		Trunk-length ratio	• **Slope boys (per log_{10} µg/dL): 0.71 (0.34): p=0.04*** • **Slope girls (per log_{10} µg/dL): 1.03 (0.34); p=0.003***
Lamb et al. 2008 Population-based prospective cohort; n=309 children (aged 1–10) years	Maternal PbB mean for towns of: • Pristina: 5.60 • Mitrovica: 20.56	Height/BMI	Pristina (β coefficients per log µg/dL): • Age 1 year: -0.61 (-2.24, 1.03) • Age 10 years: -0.09 (-3.69, 3.52) Mitrovica (β coefficients per log µg/dL): • Age 1 year: -0.30 (-2.55, 1.96) • Age 10 years: -2.87 (-6.21, 0.47)
Little et al. 2009 Cross-sectional study; n=360 children (aged 2–12 years)	Child PbB mean • 1980 cohort: 23.6 • 2002 cohort: 1.6 • Pooled cohort PbB mean not reported	Height	**β coefficient (cm per10 µg/dL PbB decrease): 2.1 (1.9, 2.3); p<0.0001***
		Weight	**β coefficient (kg per 10 µg/dL PbB decrease): 1.9 (1.7, 2.1); p<0.0001***
		BMI	**β coefficient (kg/m^2 per 10 µg/dL PbB decrease): 0.5 (0.4, 0.7); p<0.0001***

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Kim et al. 2017b Prospective longitudinal study; n=280 children (18–27 months)	Umbilical cord, mean: 1.31 • All: 1.31 (0.06) • Boys: 1.39 (0.09) • Girls: 1.21 (0.07)	Weight	Regression coefficient β: • 18 months: 0.897 (-0.171, 1.965); p=0.092 • **24 months: 0.717 (0.195, 1.239); p=0.009*** • 27 months: 0.316 (-0.345, 0.977); p=0.333
		Height	Regression coefficient β: • 18 months: 0.909 (-0.222, 2.040); p=0.101 • 24 months: 0.138 (-0.530, 0.806); p=0.675 • 27 months: 0.354 (-0.497, 1.205); p=0.394
		BMI	Regression coefficient β: • 18 months: 0.157 (-1.266, 1.580) p=0.806 • **24 months: 0.695 (0.077, 1.313); p=0.029*** • 27 months: 0.409 (-0.398, 1.216); p=0.300
Min et al. 2008b Cross-sectional study; n=108 children (aged 5–13 years)	Child PbB mean: 2.4	Height	**Regression coefficient cm per µg/dL (SE): -1.449 (0.639); p=0.026***
		Weight	Regression coefficient kg per µg/dL (SE): -0.646 (0.718); 0.370
		BMI	Regression coefficient kg/m^2 per µg/dL (SE): -0.006 (0.272); p=0.982
		Arm length	**Regression coefficient cm per µg/dL (SE): -1.804 (0.702); p=0.012***
Olivero-Verbel et al. 2007 Cross-sectional study; n=189 children (aged 5–9 years)	Child PbB mean: 5.53	Height	**Correlation coefficient: -0.224; p=0.002***
		Weight	Correlation coefficient: -0.126; p=0.087
Raihan et al. 2018 Cross-sectional study; n=729 children (<2 years of age)	Mean (SD): 8.25 (3.64) 95% CI: 7.98, 8.51 “Normal” PbB: <5 “Elevated” PbB: ≥5	Stunting[e]	**OR for PbB ≥5 µg/dL (compared to PbB <5 µg/dL): 1.78 (1.07, 2.99); p=0.028***
		Wasting[e]	OR for PbB ≥5 µg/dL (compared to PbB <5 µg/dL): 1.18 (0.64, 2.19); p=0.581
		Underweight[e]	**OR for PbB ≥5 µg/dL (compared to PbB <5 µg/dL): 1.63 (1.02, 2.61); p=0.043***

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Renzetti et al. 2017 Prospective study; n=513 mothers (children assessed at ages 4–6 years)	Maternal PbB (Gmean) • 2nd trimester: 3.0 (0.8–17.8) • 3rd trimester: 3.1 (0.3–28.3) • At delivery: 3.5 (0.7–21.9) • Umbilical cord: 2.8 (0.4–18.5)	BMI z-score	β coefficient for: • 2nd trimester: 0.04 (-0.07, 0.15); p=0.51 • 3rd trimester: -0.01 (-0.12, 0.10); p=0.81 • At delivery: -0.03 (-0.08, 0.14); p=0.58 • Cord PbB: 0.05 (-0.08, 0.17); p=0.46
		Percentage body fat	β coefficient for: • 2nd trimester: -0.13 (-0.75, 0.49); p=0.68 • 3rd trimester: -0.21 (-0.82, 0.41); p=0.52 • At delivery: -0.12 (-0.74, 0.50); p=0.70 • Cord PbB: 0.31 (-0.37, 0.99); p=0.37
		Weight-for-age z-score	β coefficient for: • 2nd trimester: -0.02 (-0.13, 0.09); p=0.68 • **3rd trimester: -0.11 (-0.22, -0.003); p=0.04*** • At delivery: -0.03 (-0.13, 0.08); p=0.58 • Cord PbB: -0.03 (-0.15, 0.09); p=0.64
		Height-for-age z-score	β coefficient for: • 2nd trimester: -0.04 (-0.13, 0.04); p=0.32 • **3rd trimester: -0.10 (-0.19, -0.01); p=0.03*** • At delivery: -0.04 (-0.13, 0.05); p=0.39 • Cord PbB: -0.04 (-0.14, 0.06); p=0.39
Schell et al. 2009 Longitudinal cohort study; n=244 children (aged 3–12 months)	Maternal PbB mean: 2.8	Length	Regression coefficients (SE): • **6 months (cm per log µg/dL): 0.149 (0.076); p=0.05*** • 12 months (cm per log µg/dL): 0.073 (0.083); p=0.38
		Weight-for-age	Regression coefficients (SE): • 6 months (kg per µg/dL): 0.013 (0.098); p=0.89 • 12 months (kg per µg/dL): 0.124 (0.107); p=0.25

Table 2-43. Summary of Epidemiological Studies Evaluating Anthropometric Measurements in Infants and Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
		Weight for length	Regression coefficients (SE): • 6 months(per µg/dL): -0.158 (0.111); p=0.16 • 12 months (per µg/dL): 0.084 (0.111); p=0.45
		Head circumference	Regression coefficients (SE): • **6 months (cm per µg/dL): -0.242 (0.094); p=0.01*** • **12 months (cm per µg/dL): -0.220 (0.109); p=0.05***
		Upper arm circumference	Regression coefficients (SE): • 12 months (cm per µg/dL):-0.132 (0.114); p=0.25
Yang et al. 2013a Cross sectional study; n=246 children (aged 3–8 years)	Child PbB mean: 7.30	Height	**β coefficient(cm per µg/dL): -0.10; p=0.02***
		Weight	**β coefficient (kg per µg/dL): -0.14; p=0.01***
		BMI	β coefficient (kg/m^2 per µg/dL): -0.08;p=0.24

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 13 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Values are for maternal PbB, unless otherwise specified.
[d]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.
[e]Stunting (defined as length-for-age z score <-2), wasting (defined as weight-for-length z-score <-2), and underweight (defined as weight-for-age z-score <-2)

BMI = body mass index; CI = confidence interval; Gmean = geometric mean; NS = not statistically significant; OR = odds ratio; Pb = lead; SD = standard deviation; SE = standard error

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty in Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Onset of puberty in females			
Den Hond et al. 2011 Cross-sectional study; n=792 girls (aged 14–15 years)	Median: 1.81	Pubic hair development	**OR: 0.65 (0.45, 0.93); p=0.020***
Denham et al. 2005 Cross-sectional study; n=138 girls (aged 10–16.9 years)	Mean: 0.49	Attainment of menarche	**β coefficient (SE) predicting likelihood of attaining menarche (per ln µg/dL): -1.29 (0.494); p=0.01***
Gollenberg et al. 2010 Cross-sectional study; n=705 girls (aged 6–11 years)	Median: 2.5 Tertiles • T1: <1.0 • T2: 1–4.99 • T3: ≥5.00	Inhibin B pubertal cutoff value	**OR for exceeding pubertal cutoff value:** • **T2 (OR): 0.38 (0.12, 1.15)*** • **T3 (OR): 0.26 (0.11, 0.60)***
Naicker et al. 2010 Cross-sectional, longitudinal study; n=682 girls (aged 13 years)	Mean: 4.9	Breast development	**Trend analysis over ages 8–16 years: p<0.001***
		Pubic hair development	**Trend analysis over ages 8–16 years: p<0.001***
		Attainment of menarche	**Trend analysis over ages 8–16 years: p<0.001***

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty in Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Selevan et al. 2003 Cross-sectional study; n=2,186 girls (aged 8–18 years)	Gmean • NHW: 1.4 • NHAA: 2.1 • MA: 1.7	Breast development	• NHW OR: 0.82 (0.47, 1.42) • **NHAA OR: 0.64 (0.42, 0.97); p<0.05*** • **MA OR**: **0.76 (0.63, 0.91); p<0.05***
		Pubic hair development	• NHW OR: 0.75 (0.37, 1.51) • **NHAA OR: 0.62 (0.41, 0.96); P<0.05** • **MA OR: 0.70 (0.54, 0.91); p<0.05**
		Age of menarche	• NHW HR: 0.74 (0.55, 1.002) • **NHAA HR: 0.78 (0.63, 0.98); p<0.05 (age at menarche delayed 3.6 months)*** • MA HR: 0.90 (0.73, 1.11)
Wolff et al. 2008 Cross-sectional study; n=192 girls (aged 9 years)	Median: 2.4	Breast development	PR for breast stage ≥2 versus stage 1: 1.01 (0.79,1.30)
		Pubic hair development	PR for pubic hair stage ≥2 versus stage 1: 1.25 (0.83, 1.88)
Wu et al. 2003b Cross-sectional study; n=1,706 girls (aged 8–16 years)	Mean: 2.5 Tertiles: • T1: 0.7–2.0 (reference) • T2: 2.1–4.9 • T3: 5.0–21.7	Breast development	• OR for T2: 1.51 (0.90, 2.53) • OR for T3: 1.20 (0.51, 2.85)
		Pubic hair development	• **OR for T2: 0.48 (0.25, 0.92)*** • **OR for T3: 0.27 (0.08, 0.93)***
		Attainment of menarche	• **OR for T2: 0.42 (0.18, 0.97)*** • **OR for T3: 0.19 (0.08, 0.43)***

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty in Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Onset of puberty in males			
Den Hond et al. 2011 Cross-sectional study; n=887 boys (aged 12–15 years)	Median: 2.50	Onset of puberty	No association between PbB and the onset of puberty (specific data not reported)
Hauser et al. 2008 Cross-sectional study; n=489 peripubertal boys (aged 8–9 years)	Median: 3	Genitalia development	**OR for having entered genitalia stage G2 for PbB ≥5 compared to PbB <5: 0.57 (0.34, 0.95); p=0.03***
Williams et al. 2010 Longitudinal cohort; n=489 peripubertal boys (aged 8–9 years)	Median: 3	Testicular volume	**HR for testicular volume <3 mL for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.73 (0.55, 0.97); p=0.03***
		Genitalia stage	**HR for having entered genitalia stage G2 for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.76 (0.59, 0.98); p=0.04***
		Pubic hair stage	HR for having entered pubic hair stage G2 for PbB ≥5 µg/dL compared to PbB <5 µg/dL: 0.69 (0.44, 1.07); p=0.10

Table 2-44. Summary of Epidemiological Studies Evaluating the Onset of Puberty in Children with Mean Blood Lead Concentration (PbB) ≤10 µg/dL[a]

Reference and study population[b]	PbB (µg/dL)[c]	Outcome evaluated	Result[d]
Williams et al. 2019 Longitudinal cohort; n=481 boys (enrolled at ages 8–9 years)	Median: 3	Onset of puberty	**Difference in age (shift in mean age in months) (95% CI) for PbB ≥5 µg/dL compared to PbB, based on:** • **Genitalia: 8.40 (3.70, 13.10); p<0.001*** • **Pubic hair: 8.12(3.46, 12.78); p<0.001*** • **Testicular volume: 7.68 (3.46, 11.90); p<0.001***
		Onset of sexual maturity	**Difference in age (shift in mean age in months) (95% CI) for PbB ≥5 µg/dL compared to PbB, based on:** • **Genitalia: 4.20 (0.56, 7.84); p=0.024*** • Pubic hair: 4.23 (-0.31, 8.77); p=0.068 • **Testicular volume: 5.14 (1.70, 8.58); p=0.003***

[a]See the *Supporting Document for Epidemiological Studies for Lead,* Table 13 for more detailed descriptions of studies.
[b]Participants had no known occupational exposure to Pb.
[c]Values are for maternal PbB, unless otherwise specified.
[d]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table

CI = confidence interval; Gmean = geometric mean; HR = hazard ratio; MA = Mexican Americans; NHW = Non-Hispanic whites; NHAA = Non-Hispanic African Americans; OR = odds ratio; Pb = lead; PR = prevalence ratio; SE = standard error

Associations Between Bone Pb and Birth Outcome and Postnatal Growth. Studies evaluating associations between maternal bone Pb and birth outcome (birth weight and length, head circumference) and postnatal growth (infant and child weight gain) are summarized in Table 2-45. Studies were conducted in mother-infant/child pairs residing in Mexico City. Maternal tibia Pb was inversely associated with birth weight (Cantonwine et al. 2010; González-Cossío; Kordas et al. 2009), birth length (Hernandez-Avila et al. 2002), and head circumference (Hernandez-Avila et al. 2002; Kordas et al. 2009). Maternal patella Pb was associated with decreased head circumference (Hernandez-Avila et al. 2002), but not birth weight (Afeiche et al. 2011; González-Cossío) or birth length (Hernandez-Avila et al. 2002). Infant weight gain measured at 1 month of age was inversely associated with maternal patella Pb, but not maternal tibia Pb (Sanin et al. 2001); no associations between maternal tibia or patella Pb were observed from birth to 12 months of age (Afeiche et al. 2011). Maternal patella Pb was inversely associated with weight gain in girls, but not boys, at 5 years of age; however, no associations were observed for maternal tibia Pb for boys or girls. In contrast, no associations were observed in a prospective study examining the relationships between maternal patella or tibia Pb (measured 1 month postpartum) and BMI, percent body fat, weight-for-age score, or height-for-age score in children ages 4–6 years (Renzetti et al. 2017). Taken together, results of these studies provide evidence that long-term maternal Pb exposure is inversely associated with infant size and post-natal growth.

Table 2-45. Associations Between Maternal Bone Pb and Birth Outcome and Postnatal Growth

		Effect				
Reference	Population[a]	Birth weight	Birth length	Head circumference	Infant weight gain	Child weight gain
Afeiche et al. 2011	Mother-infant pairs (522 boys; 477 girls)	0 T (M, F) 0 P (M, F)	–	–	0 T (M, F)[b] 0 P (M, F)[b]	0 T (M, F) 0 P (M) ↓ P (F)[c]
Cantonwine et al. 2010	538 mother-infant pairs	↓ T	–	–	–	–
Gonzalez-Cossio et al. 1997	272 mother-infant pairs	↓ T 0 P	–	–	–	–
Hernandez-Avila et al. 2002	223 mother-infant pairs	–	↓ T 0 P	↓ T ↓ P	–	–
Kordas et al. 2009	474 mother-infant pairs	↓ T	0 T	↓ T	–	–

Table 2-45. Associations Between Maternal Bone Pb and Birth Outcome and Postnatal Growth

		Effect				
Reference	Population[a]	Birth weight	Birth length	Head circumference	Infant weight gain	Child weight gain
Renzetti et al. 2017	424 (P) and 430 (T) mother-child pairs	–	–	–	–	0 T[d] 0 P[d]
Sanin et al. 2001	329 mother-infant pairs	–	–	–	0 T[e] ↓ P[e]	–

[a]From Mexico City.
[b]Measured from birth to 12 months of age.
[c]Measured at 5 years of age.
[d]Measured at 4–6 years; assessments included BMI, percentage body fat, weight-for-age, and height-for-age. No associations between maternal Pb and any of the assessments were observed.
[e]Measured at 1 month of age.

↓ = inverse association; 0 = no association; – = not reported; F = female; M = male; P = patella; Pb = lead; T = tibia

Mechanisms of Action. General mechanisms of toxicity of Pb (reviewed in Section 2.21) are likely involved in adverse development effects. EPA (2014c) specifically noted that delayed puberty may result from alterations in pulsatile release of sex hormones and that insulin-like growth factor 1 (IGF-1) may play a role in this effect. Pb is distributed to the fetus and has been measured in umbilical cord blood, placenta, and follicular fluid (See Section 3.1.2, Toxicokinetics, Distribution), providing a toxicokinetic mechanism for direct exposure of the fetus.

2.19 CANCER

Overview. Numerous epidemiological studies have investigated associations between Pb exposure and cancer. Studies include exposure of workers and general populations, with many studies reporting PbB. In most studies, mean PbBs in these studies are <10 µg/dL. Although studies provide limited evidence of carcinogenicity of Pb in humans, results are inconsistent and interpretation may be limited due to confounding factors.

Many studies of occupational cohorts and cancer risks do not report PbB data. These studies have reported associations between occupational exposure to Pb and cancer, including overall cancer mortality and cancers of the lung, brain, stomach, kidney, and bladder. However, results are inconsistent and interpretation may be limited due to confounding factors.

The following cancers have been associated with PbB:

- ≤10 µg/dL:
  - Increased risk of all cancer; evaluated in multiple studies with mixed results.
  - Increased risk of lung cancer; evaluated in multiple studies with mixed results.
- >10 µg/dL:
  - Increased risk of all cancer; evaluated in multiple studies with mixed results.
  - Increased risk of respiratory tract cancers (bronchus, trachea, lung); evaluated in multiple studies with mixed results.
  - Increased risk of stomach cancer; evaluated in multiple studies with mixed results.
  - Increased risk of intestinal cancer.
  - Increased risk of cancer of the larynx.
  - Increased risk of glioma.

Carcinogenicity Classifications of Pb and Pb Compounds. IARC has classified inorganic Pb compounds as probably carcinogenic to humans (Group 2A) based on sufficient evidence in animals and limited evidence in humans; evidence for organic Pb compounds was considered to be inadequate in humans and animals (IARC 2006). The National Toxicology Program 14th Report on Carcinogens classified Pb and Pb compounds as reasonably anticipated to be human carcinogens (NTP 2016). As the basis of the Group 2A classification for inorganic Pb compounds, IARC (2006) cited multiple animal studies showing kidney cancer following chronic oral and parenteral exposure (Azar et al. 1973; Balo et al. 1965; Fears et al. 1989; Kasprzak et al. 1985; Koller et al. 1985; Van Esch and Kroes 1969; Zawirska 1981; Zollinger 1953), renal tubular adenoma in offspring of mice exposed during gestation and lactation (Waalkes et al. 1995), and brain gliomas following oral exposure of rats (Zawirska 1981; Zawirska and Medras 1972). For epidemiological studies of occupational cohorts, IARC (2006) noted limited evidence of carcinogenicity of the lung, stomach, kidney, and brain/nervous system, although studies yielded inconsistent results, and interpretation of results was compromised due to potential confounding factors (e.g., smoking, occupational exposure to other carcinogens such as arsenic).

Confounding Factors and Effect Modifiers. Numerous factors can influence results of epidemiological studies evaluating associations between Pb exposure and cancer, including smoking status, family history of cancer, and co-exposure to other carcinogens. Failure to account for these factors may attenuate or strengthen the apparent associations between Pb exposure and the outcome, depending on the direction of

the effect of the variable on the outcome. For example, many occupational studies include smelters where exposure to arsenic and other carcinogenic metals (e.g., cadmium) can be correlated with exposure to Pb. Exposures to Pb occur throughout the lifetime and a cross-sectional evaluation of PbB may not adequately represent the exposure history of the individual.

Measures of Exposure. Numerous studies evaluating cancer in general populations and Pb-exposed workers report PbB as a measure of exposure. A few studies measured exposure by bone Pb concentrations, cumulative blood Pb index, or cumulative exposure (Bhatti et al. 2009; Englyst et al. 2001; Ionescu et al. 2007; Rajaraman et al. 2006); however, these studies did not report PbB.

Characterization of Effects. Numerous epidemiological studies have assessed associations between PbB and cancer. Studies of general populations and workers are briefly summarized in Table 2-46. Studies of general populations include large cross-sectional studies (n=5,482–13,946) of NHANES participants (Cheung et al. 2013; Jemal et al. 2002; Menke et al. 2013; Schober et al. 2006). Mean PbBs in most studies are <10 µg/dL, although in some studies that stratify by PbB, the highest exposure categories are >10 µg/dL (Jemal et al. 2002; Kelly et al. 2013; Schober et al. 2006). Results of two studies with PbB <10 µg/dL show increased risks of all cancer and of lung cancer (Cheung et al. 2013; Schober et al. 2006), although other studies show no increases in cancer risk (Jemal et al. 2002; Khalil et al. 2009; Kelly et al. 2013; Menke et al. 2013; Santibanez et al. 2008; Wiesskopf et al. 2009). Results of occupational exposure studies are mixed and do not establish a pattern of effects of exposure-response relationships. PbBs in these studies generally are >40 µg/dL. Studies have reported associations between PbB and all cancers (Anttila et al. 1995; Lundstrom et al. 1997; Lustberg and Silbergeld 2002; McElvenny et al. 2015; Wong and Harris et al. 2000), cancers of the bronchus, trachea, and lung (Anttila et al. 1995; Barry and Steenland 2019; Chowdhury et al. 2014; Kim et al. 2015; Lundstrom et al. 1997; McElvenny et al. 2015; Steenland and Boffetta 2000; Steenland et al. 2017, 2019), cancer of the larynx (Barry and Steenland 2019; Chowdhury et al. 2014; Steenland et al. 2019), esophageal cancer (Steenland et al. 2019), stomach cancer (Cooper et al. 1985; Steenland and Boffetta 2000; Steenland et al. 2017, 2019; Wong and Harris et al. 2000), intestinal or rectal cancer (Kim et al. 2015; Steenland et al. 2019), bladder cancer (Steenland et al. 2017), and gliomas (Anttila et al. 1996).

Many studies of occupational cohorts with high exposure to Pb and cancer risks do not report PbB data (Bertazzi and Zocchetti 1980; Bhatti et al. 2009; Cocco et al. 1994, 1997, 1998a, 1998b, 1999a, 1999b; Davies 1984a, 1984b; Dingwall-Fordyce and Lane 1963; Fayerweather et al. 1997; Hu et al. 1999; Jones et al. 2007; Kauppinen et al. 1992; Lin et al. 2009; McElroy et al. 2008; Michaels et al. 1991; Pan et al.

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
General population			
Cheung et al. 2013 Cross-sectional study; n=3,482 (NHANES III)	Mean (SE): 4.44 (0.14)	All cancer	**OR: 1.071 (1.036, 1.106)***
		Lung cancer	**OR: 1.090 (1.054, 1.127)***
Jemal et al. 2002 Cross-sectional study; n=3,592 (NHANES II, age 6 months–74 years)	Quartiles: • Q1: ≤9.8 • Q2: 9.9–12.9 • Q3: 13.0–16.9 • Q4: ≥17.0	All cancer	Adjusted RR Q4: 1.50 (0.75, 3.01)
Khalil et al. 2009 Prospective cohort study; n=532 women (age 65–87 years)	Mean: 5.3 <8 (n=453) ≥8 (n=79)	All cancer	Adjusted HR PbB ≥8 (versus <8): 1.64 (0.73, 3.71)
Kelly et al. 2013 Nested case-control study; n=194 cases NHL; 76 cases MM; and 270 controls (mean age 53.08 years)	Mean (range) • Males: 6.18 (1.54, 67.2) • Females: 5.27 (1.1, 40.1) Quartiles • Q1: 1.5423–3.986 • Q2: 3.9504–5.8763 • Q3: 5.8832–8.7218 • Q4: 8.7531–40.0843	NHL	OR Q4: 0.93 (0.43, 2.02) p-trend=0.849
		MM	OR Q4: 1.63 (0.45, 5.94) p-trend=0.533
Menke et al. 2006 Cross-sectional study; n=13,946 (NHANES 1988–1994; mean age 44.4 years)	Mean: 2.58 Tertiles: • T1: <1.93 • T2: 1.94–3.62 • T3: ≥3.62	All cancer	Adjusted OR • T2: 0.72 (0.46, 1.12); p-trend=0.130 • T3: 1.10 (0.82, 1.47); p-trend=0.101
Santibanez et al. 2008 Case-control study; n=185 esophageal cancer patients; 285 controls (age 30–80 years)	Low: ≤4.9 High: >4.9	Esophageal	Adjusted OR • Low: 0.79 (0.43, 1.46) • High: 1.69 (0.57, 5.03)

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Schober et al. 2006 Cross-sectional study; n=9,757 (NHANES III; age ≥40 years)	Tertiles • T1: <5 (mean 2.6) • T2: 5–9 (mean 6.3) • T3: >10 (mean 11.8)	All cancer	Adjusted RR • **T2: 1.44 (1.12, 1.86)*** • **T3: 1.69 (1.14, 2.52)*** • **p-trend<0.01***
Weisskopf et al. 2009 Prospective study; n=868 men (Normative Aging Study; age 21–80 years)	Mean (SD): 5.6 (3.4) Tertiles: • T1: <4 • T2: 4–6 • T3: >6	All cancer	**Adjusted HR T3: 0.48 (0.25–0.91)*; p-trend=0.02**
Workers			
Anttila et al. 1995 Cross-sectional study; n=20,700 workers (age 30–74 years)	Tertiles: • T1: 0–18.6 • T2: 20.7–39.4 • T3: 41.1–161.6	All cancer	**SMR T2: 1.4 (1.1, 1.8)*** SMR T3: 1.2 (0.9, 1.8)
		Lung, trachea	**SMR T2: 2.0 (1.2, 3.2)*** SMR T3: 1.5 (0.8, 2.1)
Anttila et al. 1996 Cross-sectional study; n=20,741 workers (age 18–74 years)	Tertiles: • T1: 2.1–14.5 • T2: 16.6–26.9 • T3: 29.0–89.1	All nervous system cancers	Adjusted OR T3: 2.2 (0.7, 6.6) p-trend=0.17
		Glioma	**Adjusted OR T3: 11 (1.0, 626)*** **p-trend: 0.037**

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Barry and Steenland 2019 Retrospective study; n=58,368 male workers (follow-up of Chowdhury et al. 2014)	Quartiles • Q1: 0–<5 • Q2: 5–<25 • Q3: 25–<40 • Q4: ≥40	Colon	HR Q4: 1.19 (0.54, 2.61)
		Esophagus	HR Q4: 0.97 (0.43, 2.20)
		Kidney	HR Q4: 0.92 (0.32, 2.58)
		Liver	HR Q4: 1.53 (0.79, 2.99)
		Lung	**HR Q2: 1.61 (1.04, 2.48)* HR Q3: 2.03 (1.34, 3.10)* HR Q4: 2.92 (1.91, 4.46)* p-trend: <0.01***
		Stomach	HR Q4: 0.64 (0.22, 1.82)
	Tertiles: • T1: 0–<25 • T2: 25–<40 • T4: ≥40	Brain	HR Q4: 1.49 (0.71, 3.12)
		Bladder	HR Q4: 1.71 (0.83, 3.55)
		Larynx	**HR Q4: 3.42 (1.29, 9.09)***
		Non-Hodgkin's lymphoma	HR Q4: 1.60 (0.85, 3.01)
		Pancreas	HR Q4: 1.15 (0.72, 1.85)
		Rectal	HR Q4: 2.06 (0.87, 4.84)
Chowdhury et al. 2014 Survey study/cross-sectional study; n=58,368 male workers (mean age 38.9 years)	Quartiles • Q1: 0–<5 • Q2: 5–<25 • Q3: 25–<40 • Q4: ≥40	Lung	**SMR Q4: 1.20 (1.03, 1.39)***
		Brain	SMR Q4: 0.83 (0.41, 1.49)
		Kidney	SMR Q4: 0.72 (0.33, 1.37)
		Stomach	SMR Q4: 0.92 (0.44, 1.69)
		Esophagus	SMR Q4: 0.65 (0.32, 1.16)
		Larynx	**SMR Q4: 2.11 (1.05, 3.77)***
		Bladder	SMR Q4: 0.70 (0.28, 1.45)
Cooper et al. 1985 Cohort study; n=4,519 battery workers; 2,300 smelters	Mean • Battery (n=1,326): 62.7 • Smelters (n=537): 79.7	All cancer	Battery PMR: 1.06 (0.96, 1.16) Smelters PMR: 1.02 (0.87, 1.19)
		Stomach	**Battery PMR: 1.54 (1.11, 2.15)*** Smelters PMR: 1.03 (0.75, 1.42)
		Large intestine	Battery PMR: 0.98 (0.69, 1.40) Smelters PMR: 1.19 (0.62, 2.28)

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
		Larynx	Battery PMR: 1.19 (0.54, 2.65) Smelters PMR (95% CI): 1.06 (0.27, 4.21)
		Bronchus, trachea, lung	Battery PMR: 1.16 (0.97, 1.39) Smelters PMR: 1.13 (0.84, 1.51)
		Brain and other CNS	Battery PMR: 1.09 (0.55, 2.18) Smelters PMR: 0.97 (0.32, 3.01)
Kim et al. 2015 Cross-sectional study; n=81,067 inorganic Pb workers (54,788 males; 26,279 females; age 20–≤50 years)	Mean (SD) • Males: 8.8 (8.5) • Females 5.8 (5.4) Tertiles: • T1: <10 • T2: 10–20 • T3: >20	All cancer	Males: RR T3: 0.95 (0.56, 1.61) Females RR T3: 1.68 (0.40, 7.13)
		Stomach	Males: RR T3: 0.80 (0.23, 2.71) Females RR T2: 1.82 (0.20, 16.36) Females T3: no cases
		Colo-rectal	Males: RR T3: 1.86 (0.35, 9.79) **Females RR T2: 13.42 (1.21, 149.4)*; p<0.05** Females T3: no cases
		Liver	Males: RR T3: 1.72 (0.72, 4.14) Females T2 RR: 0.83 (0.10, 6.56) Females T3: no cases
		Bronchus, lung	Males: RR T3: 0.46 (0.10, 2.01) **Females RR T2: 10.45 (1.74, 62.93)*; p<0.05** **Females RR T3: 12.68 (1.69, 147.86)*; p<0.05**
Lundstrom et al. 1997 Cross-sectional study; n=3979 workers	Mean: • In 1950: 62.2 • In 1987: 33.2	All cancer	**SMR: 1.2 (1.0, 1.5)***
		Lung	**SMR: 2.8 (2.0, 3.8)***
Lundstrom et al. 2006 Nested case-referent study; 3,979 smelter workers	Peak: Cases (n=40): 49.7 Referents (n=114): 55.9	Lung	OR: 0.93 (0.60, 1.44)

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Lustberg and Silbergeld 2002 Cross-sectional study; n=4,292; age 30–74 years (NHANES II)	Tertiles: • T1 (n=818): <10 • T2 (n=2,735): 10–19 • T3 (n=637): 20–29	All cancer (rate ratio)	RR T2: 1.46 (0.87, 2.48) **RR T3: 1.68 (1.02, 2.78)***
McElvenny et al. 2015 Cohort study; n=9,122 workers; mean age 29.2 years	Mean (SD): 44.3 (22.7) Range: 2.3–321.5	All cancer	**SMR: 1.13 (1.07, 1.20)***
		Esophagus	SMR: 1.05 (0.78, 13.8)
		Stomach	SMR: 1.11 (0.86, 1.43)
		Colon	SMR: 0.98 (0.77, 1.26)
		Kidney	SMR: 1.30 (0.91, 1.86)
		Bladder	SMR: 0.95 (0.67, 1.35)
		Bronchus, trachea, lung	**SMR: 1.42 (1.29, 1.57)***
		Brain	SMR: 0.92 (0.61, 1.38)
Selevan et al. 1985 Retrospective cohort study; n=1,987 male workers	Mean: 56.3	All cancer	SMR: 0.95 (0.78, 1.14)
		Digestive organs	SMR: 0.77 (0.52, 1.10)
		Respiratory system	SMR: 1.11 (0.80, 1.51)
		Kidney	SMR: 2.04 (0.75, 4.44)
		Bladder	SMR: 1.44 (0.53, 3.14)
Steenland and Boffetta 2000 Meta-analysis; data from eight studies on Pb workers; n=36,027 workers	Range of study means: 26–80	Lung	**RR: 1.14 (1.04, 1.25)***
		Stomach	**RR: 1.34 (1.14, 1.57)***
		Brain	RR: 1.06 (0.81, 1.40)
Steenland et al. 1992 Cohort study (same cohort as Selevan et al. 1985); n=1,990 male smelter workers	Mean: 56.3	All Cancer	SMR: 0.98 (0.84, 1.12)
		Colon	SMR: 0.48 (0.22, 0.90)
		Lung	SMR: 1.18 (0.92, 1.48)
		Kidney	SMR: 1.93 (0.88, 3.67)

Table 2-46. Summary of Epidemiological Studies Evaluating Cancer Endpoints and Blood Lead Concentration (PbB)

Reference and study population	PbB (µg/dL)	Cancer outcomes	Effects[a]
Steenland et al. 2017 Cohort study; n=88,000 Pb workers	Median: 26	Bladder (>40 µg/dL)	**HR: 1.86 (1.04, 3.33)***
		Kidney (>40 µg/dL)	HR: 1.21 (0.74, 1.97)
		Larynx (>40 µg/dL)	**HR: 2.69 (1.07, 6.76)***
		Lung (20–<30 µg/dL)	**HR: 1.39 (1.19, 1.64)***
		Stomach (20–<40 µg/dL)	**HR: 1.62 (1.13, 2.32)***
Steenland et al. 2019 Cohort study; n=29,874 Pb workers	Median: 29	Brain (>40 µg/dL)	HR: 1.71 (0.94, 3.12)
		Bladder (>40 µg/dL)	HR: 1.24 (0.87, 1,75)
		Esophagus (30–39 µg/dL)	**HR: 2.00 (1.08, 3.71)***
		Kidney (>40 µg/dL)	HR: 1.00 (0.66, 1.51)
		Larynx (>40 µg/dL)	HR: 1.92 (0.94, 3.91)
		Lung (20–29 µg/dL)	**HR: 1.39 (1.17, 1.65)***
		Rectum (>40 µg/dL)	**HR: 1.49 (1.03, 2.17)***
		Stomach (20–29 µg/dL)	**HR: 1.55 (1.10, 2.18)***
Wong and Harris et al. 2000 Cohort study; n=4,519 battery workers; 2,300 smelters (same cohort as Cooper et al. 1985)	Mean: • All workers: 64.0 • Battery workers: 62.7 • Smelters: 79.7	All cancer	**SMR: 1.045 (1.012, 1.080)***
		Stomach	**SMR: 1.474 (1.125, 1.898)***
		Large intestine	SMR: 0.994 (0.789, 1.235)
		Bronchus, trachea, lung	SMR: 1.164 (1.039, 1.299)
		Kidney	SMR: 0.636 (0.339, 1.087)
		CNS	SMR: 0.748 (0.419, 1.234)

[a]Asterisk and **bold** indicate association with Pb; unless otherwise specified, values in parenthesis are 95% CIs; p-values <0.05 unless otherwise noted in the table.

CI = confidence interval; CNS = central nervous system; HR = hazard ratio; MM = multiple myeloma; NHANES = National Health and Nutrition Examination Survey; NHL = non-Hodgkin's lymphoma; OR = odds ratio; Pb = lead; PMR = proportionate mortality ratio; RR = rate ratio or relative ratio; SD = standard deviation; SE = standard error; SMR = standard mortality ratio

2011; Partanen et al. 1991; Pesch et al. 2000; Rajaraman et al. 2006; Risch et al. 1988; Rousseau et al. 2007; Sankila et al. 1990; Sheffet et al. 1982; Siemiatycki 1991; Sweeney et al. 1986; van Wijngaarden and Dosemeci 2006; Wingren and Englander 1990). Although results of these studies are mixed and interpretation may be limited due to confounding factors, associations have been reported between occupational exposure to Pb and cancer, including overall cancer mortality and cancers of the lung, brain, stomach, kidney, and bladder.

Mechanisms of Action. Numerous mechanisms for Pb-induced carcinogenicity have been proposed (EPA 2014c); however, it is likely that a combination of mechanisms, rather than a single mechanism, is involved. Although Pb is considered to be only weakly mutagenic, it has been shown to produce DNA damage (single and double strand breaks), sister chromatid exchanges (SCEs), chromosome aberrations, micronuclei (MN) formation, and cytogenetic damage. Epigenetic mechanisms (e.g., changes in gene expression in the absence of changes to DNA), post-translational alterations to protein structure, and immune modulation of tumorigenesis in response to Pb-induced ROS oxidative damage and inflammation have also been proposed as possible mechanisms involved in Pb-induced carcinogenesis.

2.20 GENOTOXICITY

The genotoxicity of Pb has been studied in Pb workers and the general population, in *in vivo* animal models, and *in vitro* cultures of microorganisms and mammalian cells. For the following discussions, data from epidemiological studies on genotoxicity were obtained from the primary literature. Information on *in vitro* studies and *in vivo* animal studies was taken from comprehensive reviews of Pb genotoxicity (EPA 2014c; Garcia-Leston et al. 2010; IARC 2006; NTP 2003).

Epidemiological Studies

Overview. Epidemiological studies have examined genotoxic effects associated with Pb exposure in adults (general populations and workers) and children. Most studies were conducted in small populations of workers. Numerous studies with PbB ≥10 µg/dL report associations for exposure to Pb and genotoxic endpoints (gene mutation, DNA damage, SCE, MN formation, and DNA methylation), although some inverse associations have been reported. Few epidemiology studies have evaluated genotoxicity at PbB ≤10 µg/dL.

The following genotoxic effects have been associated with PbB:

- ≤10 µg/dL:
  - Gene mutation.
  - DNA damage; evaluated in a few studies with mixed results.
  - DNA methylation; positive results, corroborated in a few studies.
- >10 µg/dL:
  - DNA damage; corroborated in numerous studies.
  - Decreased telomere length.
  - Chromosomal aberrations; evaluated in numerous studies with mainly positive results.
  - Sister chromatid exchange; evaluated in numerous studies with mainly positive results.
  - Micronuclei formation; evaluated in numerous studies with mainly positive results.
  - DNA methylation.

Measures of Exposure. Studies evaluating the association between genotoxic effects and Pb exposure typically evaluate exposure by measurement of PbB.

Confounding Factors and Effect Modifiers. Most epidemiological studies evaluating genotoxic effects were conducted in worker populations. Therefore, potential co-exposure to other genotoxic compounds (such as arsenic) could occur, complicating interpretation of results. In addition, many studies were conducted in small populations (n<100). Variable outcomes of genotoxicity studies in human populations may derive from the influence of experimental variables that may act as confounders, such as duration and route of Pb exposure, cell culturing time following the exposure, smoking habits, and simultaneous exposure to other toxic agents that could act by modifying the genotoxic response of the cells to Pb exposure and similarly, modifying the results of the studies (García-Lestón et al. 2010).

Characterization of Effects. General trends for studies demonstrating associations between PbB and genotoxic effects are shown in Table 2-47. Additional study details are provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 14. Although few studies have evaluated genotoxic effects at PbB ≤10 µg/dL (see discussion below), numerous studies in adult workers with mean PbBs ranging from 20 to >50 µg/dL provide evidence of increased DNA damage, chromosomal aberrations, SCEs, and MN. One study reported decreased telomere length in workers (Pawlas et al. 2016). A few studies in workers reported negative findings for chromosomal aberrations (Anwar and Kamal 1988; Bulsma and DeFrance 1976; Mäki-Paakkanen et al. 1981; Schwanitz et al. 1975) and SCEs

(Grandjean et al. 1983; Mäki-Paakkanen et al. 1981); however, positive results for these endpoints were reported in other studies at similar PbBs.

Table 2-47. Overview of Epidemiology Studies Evaluating Genotoxicity Associated with Chronic Exposure to Lead (Pb)

Mean PbB (µg/dL)	Effects associated with Pb exposure	References
≤10	Gene mutation	Van Larebeke et al. 2004
	DNA damage/repair	Akram et al. 2019; Jasso-Pineda et al. 2012;
	Decreased telomere length	Pawlas et al. 2015
	MN	Mielzynska et al. 2006; Wu et al. 2017
	DNA methylation	Hanna et al. 2012; Li et al. 2016b; Pilsner et al. 2009
>10–30	DNA damage/repair	Chinde et al. 2014; Danadevi et al. 2003; Dobrakowski et al. 2017; Jannuzzi and Alpertunga 2016; Kašuba et al. 2012; Kayaalti et al. 2015b; Méndez-Gómez et al. 2008; Shaik and Jamil 2009
	Chromosomal aberrations	Pinto et al. 2000
	SCE	Anwar and Kamal 1988; Pinto et al. 2000
	MN	Chinde et al. 2014; Khan et al. 2010b; Kašuba et al. 2012;Nordenson et al. 1978; Pinto et al. 2000
>30–50	DNA damage/repair	Dobrakowski et al. 2017; Fracasso et al. 2002; Grover et al. 2010; Pawlas et al. 2017
	Decreased telomere length	Pawlas et al. 2016
	Chromosomal aberrations	Forni et al. 1976; Grover et al. 2010; Schwanitz et al. 1970
	SCE	Duydu et al. 2001, 2005; Wiwanitkit et al. 2008; Wu et al. 2002
	MN	Grover et al. 2010; Hamurcu et al. 2001; Minozzo et al. 2004
	DNA methylation	Devoz et al. 2017
>50	DNA damage/repair	de Restrepo et al. 2000
	Chromosomal aberrations	Al-Hakkak et al. 1986; Forni et al. 1976; Huang et al. 1988; Nordenson et al. 1978; Schwanitz et al. 1970
	SCE	Huang et al. 1988
	MN	Shaik and Jamil 2009; Singh et al. 2013; Vaglenov et al. 1998, 2001

DNA = deoxyribonucleic acid; MN = micronuclei; PbB = blood lead concentration; SCE = sister chromatid exchange

Results of genotoxicity studies conducted in small populations of children (n=12–103) are inconsistent; for study details, see the *Supporting Document for Epidemiological Studies for Lead,* Table 14. Mixed results were observed for studies on DNA damage, with positive associations at mean PbBs of 7.3 and 28.5 µg/dL (Méndez-Gómez et al. 2008; Jasso-Pineda et al. 2012) and no associations at a mean PbB of 19.5 µg/dL (Méndez-Gómez et al. 2008). No associations were observed for chromosome aberrations at

a PbB range of 12–33 µg/dL (Bauchinger et al. 1977) and for SCE at mean PbBs of 7.69 and 62.7 µg/dL (Dalpra et al. 1983; Mielzynska et al. 2006). MN formation was positively associated with a mean PbB of 7.69 µg/dL (Mielzynska et al. 2006), and altered DNA methylation was found in newborns at mean umbilical cord PbB of 6.6 µg/dL (Pilsner et al. 2009) and mean prenatal maternal RBC Pb of 1.2 µg/dL (Wu et al. 2017).

Effect at Blood Pb Levels ≤10 µg/dL. Results of studies evaluating genotoxic effects of PbB ≤10 µg/dL are summarized in Table 2-48, with study details provided in the *Supporting Document for Epidemiological Studies for Lead*, Table 14. Few studies have evaluated genotoxicity at PbB ≤10 µg/dL. Some endpoints were only evaluated in a single study; therefore, it is difficult to draw conclusions. With the exception of a large study conducted in NHANES participants (Zota et al. 2015), genotoxic effects were evaluated in small study populations (n=12–103). Gene mutations were observed in a single study of Finnish women at a PbB range of 1.6–5.2 µg/dL (Van Larebeke et al. 2004). Results of studies on DNA damage are mixed, with no associations in adult workers at PbB means of 2.1–4.4 µg/dL (Al Bakheet et al. 2013; Hengstler et al. 2003), and positive associations in a small study of children with a mean PbB of 7.3 µg/dL (Jasso-Pineda et al. 2012). No effect on telomere length was observed in a large NHANES study of adults with a mean PbB of 1.67 µg/dL (Zota et al. 2015). No associations were observed for SCE in a single study in workers with a mean PbB of 9.3 µg/dL and for MN in children with a mean PbB of 7.69 µg/dL (Mielzyńska et al. 2006; Wu et al. 2002). Studies on DNA methylation showed positive associations in adult women undergoing *in vitro* fertilization (median PbB 2.88 µg/dL), in children (mean PbB: 1.36 µg/dL), and in newborns (mean umbilical cord PbB 6.6 µg/dL or prenatal maternal RBC Pb 1.2 µg/dL) (Hanna et al. 2012; Li et al. 2016b; Pilsner et al. 2009; Wu et al. 2017).

***In Vivo* Animal Models and I*n Vitro* Cultures of Mammalian Cells and Microorganisms.** Numerous studies have investigated the genotoxicity of Pb using *in vivo* animal models and cultured mammalian cells and microorganisms. Rather than reviewing these numerous studies, an overview of findings is summarized below. This information was taken from the following reviews: EPA 2006, 2014c; IARC 2006; NTP 2016.

In vivo studies in animals. DNA damage has been observed in several *in vivo* exposure studies in rodents. DNA damage (single strand breaks), as measured in comet assays, was observed in various organ systems, bone marrow, leukocytes, and spermatozoa of mice and rats following repeated inhalation or oral exposures to Pb or Pb acetate. Many of these studies administered Pb by parenteral routes (intravenous, intraperitoneal). Narayana and Al-Bader (2011) and Narayana and Raghupathy (2012) did

Table 2-48. Results of Genotoxicity Studies at Blood Lead Concentration (PbB) ≤10 µg/dL

PbB or range (µg/dL)	Population (n)	Gene mutation	DNA damage	Telomere length	SCE	MN	DNA methylation	Reference
1.6–5.2	Women (99)	↑	NA	NA	NA	NA	NA	Van Larebeke et al. 2004
2.1	Men (40)	NA	0	NA	NA	NA	NA	Al Bakheet et al. 2013
3.28	Children (99)	NA	NA	↓	NA	NA	NA	Pawlas et al. 2015
4.4	Workers (78)	NA	0	NA	NA	NA	NA	Hengstler et al. 2003
7.3	Children (12)	NA	↑	NA	NA	NA	NA	Jasso-Pineda et al. 2012
1.67	Adults (6,796)[a]	NA	NA	0	NA	NA	NA	Zota et al. 2015
9.3	Workers (34)	NA	NA	NA	0	NA	NA	Wu et al. 2002
7.69	Children	NA	NA	NA	NA	0	NA	Mielzyńska et al. 2006
>0.73	Women (43)	NA	NA	NA	NA	NA	↓	Hanna et al. 2012
1.45	Adults (78)[b]	NA	NA	NA	NA	NA	↓	Li et al. 2016b
6.6[c]	Newborns (103)	NA	NA	NA	NA	NA	↑↓	Pilsner et al. 2009
8	Workers (100)	NA	↑	NA	NA	NA	NA	Akram et al. 2019
1.2[d]	Newborns (268)	NA	NA	NA	NA		↓	Wu et al. 2017

[a]NHANES participants.
[b]Prospective study; genotoxicity assessed in adults and evaluated against PbB obtained during childhood (birth–78 months).
[c]Umbilical cord PbB.
[d]Maternal RBC lead at gestation week 28.

↑ = increase observed for specific effect; ↓ = decrease observed for specific effect; ↑↓ = decreased DNA methylations at some differentially methylated regions, and increased DNA methylation at other regions; 0 = no effect observed; DNA = deoxyribonucleic acid; MN = micronuclei; NA = not assessed; NHANES = National Health and Nutrition Examination Survey; RBC = red blood cell; SCE = sister chromatid exchange

not find DNA damage in rats that received oral doses of lead nitrate at levels that produced necrotic changes in the liver. Global hypomethylation in hepatic DNA of rats was observed following single intravenous injection of Pb nitrate; hypomethylation was associated with an increase in cell proliferation. Exposure to Pb compounds is correlated with increased DNA synthesis and cell proliferation in the mammalian liver following intravenous injection. Numerous studies have assessed Pb compounds for chromosomal damage. Chromosomal aberrations were observed in bone marrow cells and spermatocytes of mice and rats following single or repeated exposure (intraperitoneal, gavage, dietary); however, the increase in aberrations did not consistently demonstrate dose-dependence.

Exposure to Pb compounds has been associated with SCEs in bone marrow of mice and rats following intravenous exposure. Studies assessing Pb compounds for MN formation in bone marrow erythrocytes of rats and mice were positive for multiple exposure routes (gavage, drinking water, intraperitoneal).

In vitro studies in human cell lines. *In vitro* studies in human cells lines have yielded mixed results. Pb acetate was weakly mutagenic in keratinocytes in the presence of 6-thioguanine, but not mutagenic in human foreskin, fibroblasts, or lung carcinoma cells. Results of assays assessing Pb compounds for DNA damage in human cell cultures were inconsistent. Double or single DNA strand breaks have been observed in peripheral blood lymphocytes, endothelial cells, hTERT-immortalized human skin fibroblasts, and HepG2 cells, but not in HeLa cells. DNA-protein crosslinks were observed in lymphoma cells exposed to 100 µM Pb acetate, although cross-links were not observed for Pb nitrate at concentrations up to 10,000 µM. Studies investigating SCEs and MN formation in human lymphocytes were positive following exposure to Pb nitrate and Pb chloride; however, no SCEs were observed in human lung cells or primary lymphocytes exposed to Pb. Interpretation of *in vitro* studies is challenging because concentrations used in these studies typically are very high and are not relevant to environmental or occupational exposures. As discussed in Section 3.1.2 (Toxicokinetics, Distribution), >99% of Pb in blood is bound to erythrocytes, leaving <1% available in plasma. Thus, plasma levels of Pb are far lower (at least two orders of magnitude) than the concentrations examined in *in vitro* studies in human cell lines. This leads to the introduction of considerable bias when interpreting study results (Bannon and Williams 2017).

In vitro studies in prokaryotic and mammalian cells. Mutagenicity tests of Pb compounds in prokaryotic organisms have mostly yielded negative results. Studies assessed gene mutation and DNA damage in *Salmonella typhimurium, Escherichia coli,* and *Bacillus subtilis* and gene conversion and mitotic recombination in *Saccharomyces cerevisiae* in the presence or absence of metabolic activation. The only

Pb compound that yielded positive results for gene mutation in *S. typhimurium* and *E. coli* was Pb bromide. Results of *in vitro* studies in mammalian cells for Pb compounds are mixed. Mutagenicity assays (hypoxanthine phosphorybosyl transferase [HPRT] and glutamate pyruvate transaminase [gpt] assays) were mutagenic in Chinese hamster ovary (CHO) and CHV79 cells at higher concentrations (>100 µM) and negative at lower concentrations (<100 µM). Pb chloride was the only Pb compound that was consistently mutagenic (gpt assay) in CHO cells at low concentrations (0.1–1.1 µM; equivalent to 2.3–23 µg/dL). Comet assays assessing Pb acetate for DNA damage (single strand breaks) in undifferentiated PC12 cells and mouse bone marrow mesenchymal stem cells were positive. Concentration-dependent increases in DNA-protein crosslinks were observed in hepatoma cells exposed to Pb nitrate, although Pb acetate did not induce single or double DNA strand breaks or DNA crosslinks in CHV79 cells. Exposure to Pb nitrate or Pb glutamate did not induce chromosomal aberrations in CHO cells. Assays assessing Pb compounds for SCEs in CHV79 cells were negative when fewer cells per concentrations were utilized (25–30 cells), but were positive when the number of cells per concentration was increased (100 cells). Conflicting results were reported for MN formation in Chinese hamster cells.

Mechanisms of Action. Several mechanisms of action are likely involved in the genotoxic effects of Pb (EPA 2014c; IARC 2006; NTP 2016). Studies in occupationally exposed populations have found significant correlations between DNA breaks, decreased glutathione levels in the lymphocytes, and increased production of ROS, which may indicate oxidative stress as a possible mechanism for this response. The production of ROS after Pb exposure is a multi-pathway process, which results from oxidation of ALA, membrane and lipid oxidation, NAD(P)H oxidase activation, and antioxidant enzyme depletion. Disruption of functional metal ions that form enzymes (superoxide dismutase [SOD], catalase [CAT], and glutathione peroxidase [GPx]) may occur as part of this process.

2.21 GENERAL CELLULAR MECHANISMS OF ACTION

2.21.1 Perturbation of Ion Homeostasis

Pb exerts many of its adverse effects by perturbing ion homeostasis. This perturbation occurs when Pb displaces other metal ions such as iron, calcium, zinc, magnesium, selenium, and manganese, interfering with the critical biological processes mediated by the ions themselves or by enzymes and proteins that require these ions (reviewed by EPA 2014c; Flora et al. 2012). Among the biological processes that Pb has been shown to affect via its impact on ion homeostasis are: calcium homeostasis; transportation of

ions across cell membranes; cellular energetics; and the functioning of numerous proteins involved in cell signaling, growth and differentiation, gene expression, energy metabolism, and biosynthetic pathways.

Calcium Homeostasis. Many of Pb's adverse effects can be traced back to its ability to displace calcium, leading to perturbations of numerous calcium-dependent cellular functions, including energy metabolism, apoptosis, cellular motility, signal transduction, and hormonal regulation (reviewed by EPA 2014c). In addition, intracellular migration of Pb has been shown in several cell lines (HEK293, HeLa, and PC12) to occur via calcium channels; higher Pb permeation correlated with lower calcium concentrations, suggesting that Pb competed with calcium for the channel binding sites.

Ion Transport. Pb has been shown to disrupt the transportation of critical cations across the cell membrane by decreasing the activity of ATPases (including Na+/K+-, Ca2+, and Mg2+-ATPases; reviewed by EPA 2014c). Pb-induced inhibition of ATPase activities has been shown in the kidneys, livers, erythrocytes, and brain synaptosomes of rats exposed to Pb in drinking water; in testes of rat pups exposed during lactation and postweaning; in primary cerebellar granule neuronal cultures of rat pups exposed pre- and postnatally; in rabbit kidney membranes and sarcoplasmic reticulum exposed *in vitro*; and in human erythrocyte ghosts. Furthermore, blood or hair Pb levels were inversely correlated with ATPase activities in erythrocytes in several human epidemiological studies.

In addition to ATPases, Pb's action on ion transport includes competitive inhibition of voltage-gated calcium channels (reviewed by EPA 2014c). A number of *in vitro* studies have demonstrated inhibition of calcium transport via voltage gated channels in cultured neurons and neuroblastoma cells, bovine adrenal chromaffin cells, and human embryonic kidney cells. Inhibition of calcium transportation via voltage-gated channels can disrupt release of neurotransmitters, and impaired neurotransmitter release has, in fact, been shown with Pb exposure at low *in vitro* levels. In addition to inhibiting calcium-dependent neurotransmitter release, Pb may mimic calcium, thereby increasing neurotransmitter release in some circumstances. For example, Pb exposure *in vitro* has been shown to induce the spontaneous release of norepinephrine from bovine adrenal chromaffin cells and increase the release of catecholamine from PC12 cells. It has been suggested that Pb may trigger spontaneous neurotransmitter release via activation of calcium/calmodulin-dependent protein kinase II-dependent phosphorylation of synapsin I, or by directly activating synaptotagmin I (a calcium-sensing protein that regulates neurotransmitter release). Intracellular migration of Pb has been shown to occur via calcium channels; higher Pb permeation in several cell lines (HEK293, HeLa, and PC12) correlated with lower calcium concentrations, suggesting that Pb competed with calcium for the channel binding sites.

Pb also disrupts the activity of calcium-dependent potassium channels, as shown by increased efflux of potassium from inverted erythrocyte vesicles, and alterations in potassium channel activation in erythrocytes exposed to Pb (reviewed by EPA 2014c). The nature of the effect on potassium channels is dose-dependent; at low Pb concentrations (<10 μM), potassium channels are activated, while inhibition of the channels is seen at higher Pb concentrations. As with calcium channels, alterations in potassium channel activity may also disrupt neurotransmitter release. In rats exposed to Pb *in utero* and postnatally, potassium-stimulated release of hippocampal GABA was decreased at low exposure levels, but enhanced GABA release was observed at higher exposures (in the absence of calcium).

Cellular Energetics. Evidence indicating that Pb exposure perturbs mitochondrial function and cellular energy metabolism is abundant (as reviewed by EPA 2014c). In rats exposed to Pb via diet or drinking water, renal tubular and epididymal mitochondria exhibited swelling, rupture of the outer membrane, distorted cristae or loss of cristae, vacuolization, inclusion bodies, and fusion with nearby mitochondria. As discussed further in Section 2.21.6, Apoptosis, Pb exposure has been shown to open the mitochondrial transmembrane pore, initiating the apoptotic caspase cascade. Evidence for Pb's effect on energy metabolism includes decreased ATP levels and/or adenylate energy charge (AEC) (along with increased ADP, AMP, and/or adenosine levels) in forebrain synaptosomes from rats exposed via drinking water, in cerebellar granule neuronal cultures from rats exposed by drinking water, in PC-12 cells exposed *in vitro*, and in isolated mitochondria exposed *in vitro*. In osteoblasts exposed *in vitro*, Pb inhibited both coupled and uncoupled respiratory oxygen use in mitochondria. Pb has been proposed to behave as a classic chemical uncoupler of respiration, abolishing the proton gradient necessary for oxidative phosphorylation. In the muscles of rats exposed to Pb in drinking water, decreased activities of the enzymes of complex I and IV of the respiratory chain were observed. However, in forebrain synaptosomes from rats exposed to Pb *in vivo*, oxidative phosphorylation was not inhibited, despite the fact that ATP levels were decreased.

Pb may affect cellular energetics via perturbation of the glycolysis pathway. Decreased glycolysis was observed in osteoblasts and erythrocytes exposed to Pb *in vitro* (reviewed by EPA 2014c). However, increased levels of glycolytic enzymes were noted in workers with higher blood Pb levels, when compared with workers with lower blood Pb, suggesting that Pb may activate anaerobic glycolysis.

Depletion of cellular nucleotide pools required for ATP synthesis has also been observed after Pb exposure of human erythrocytes *in vitro* and in rats exposed via drinking water (reviewed by EPA 2014c). This effect may be mediated by Pb-induced inhibition of enzymes involved in nucleotide biosynthesis in

erythrocytes, including adenine phosphoribosyltransferase (see Impaired Protein Function below) and NAD synthetase (which depends on magnesium for activity). In support of the latter mechanism, in humans exposed to Pb, PbB levels were inversely correlated with NAD synthetase activity.

Impaired Protein Function. Pb impairs the functions of numerous proteins, with concomitant effects on signaling, growth and differentiation, gene expression, energy metabolism, and biosynthetic pathways. The mechanisms by which Pb alters protein activity are by displacing metal cofactors or binding to sulfhydryl groups (reviewed by EPA 2014c). Table 2-49 shows proteins known to be bound to or otherwise altered by Pb, along with their functions and brief summaries of the evidence for Pb-induced alterations. As the table suggests, Pb-induced alterations in proteins may play a role in its adverse effects on the neurological, hematological, cardiovascular, and skeletal systems.

Through its displacement of calcium, Pb perturbs the function of several calcium-dependent proteins, including protein kinase C, calmodulin, osteocalcin, the mitochondrial transmembrane pore, and NAD(P)H oxidase (reviewed by EPA 2014c). The protein kinase C family of enzymes is important to cell signaling, growth, and differentiation. Pb exposure has been shown to activate PKC in a number of cell types tested *in vitro* (see table), and to decrease its activity in mouse macrophages and rat brain cortex. Pb stimulates calmodulin activity, as shown by increased activity of several calmodulin-dependent enzymes, and increased binding of calmodulin to brain membranes. In experiments testing the affinity of metal cations to bind calmodulin, Pb was more potent than mercury, cadmium, iron, and even calcium. Pb binding to calmodulin has been postulated as a mechanism for its stimulatory effect on Ca^{2+}/Mg^{2+} ATPase. Calmodulin plays an essential role in maintaining calcium homeostasis and regulating calcium-dependent cell signaling important to structural integrity, gene expression, and maintaining membrane potential (reviewed by EPA 2014c).

Skeletal effects of Pb may be mediated in part by Pb's interference with another calcium-dependent protein: osteocalcin (reviewed by EPA 2014c). The binding of Pb to osteocalcin is much stronger than binding of calcium, and Pb binding alters the structure of osteocalcin. The conformational change in osteocalcin induced by Pb has been postulated as the mechanism by which Pb exposure diminishes the adsorption of osteocalcin to hydroxyapatite.

Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Calcium-dependent proteins		
Calcium binding proteins (CABPs I and II)	Regulation of calcium signaling, especially in neuronal cells	No data -Ca^{2+} displacement shown *in vitro*.
Ca^{2+}-dependent K^+ channel	Ion transport; activation of channels regulates neuron firing and neurotransmitter release	Activates or inhibits channel -Pb promoted efflux of K^+ from inverted red blood cell vesicles. -Pb induced activation of K^+ channel in erythrocytes at low Pb concentrations and inhibited activity at high concentrations.
Calmodulin	Cell signaling, including structural integrity, gene expression, and maintenance of membrane potential	Amplifies calmodulin activity -Pb activated calmodulin-dependent phosphodiesterase and cyclic nucleotide phosphodiesterase activities. -Pb stimulated brain membrane phosphorylation. -Pb increased binding of calmodulin to brain membranes.
Mitochondrial transmembrane pore (MTMP)	Triggers mitochondrial apoptosis cascade when open	Opens MTMP, triggering apoptosis -Pb increased mitochondria-regulated apoptotic indicators (cytochrome c, caspases) in rat retinal rod cells and hepatic oval cells *in vitro*.
NAD(P)H oxidase	Inflammatory mediator; triggers oxidative burst (via production of superoxide) in response to infection	Increases activity, leading to ROS generation -Pb increased protein levels of glycosylated subunit of NAD(P)H oxidase in brain, heart, and renal cortex of rats exposed via drinking water and in human coronary artery endothelial cells *in vitro*.
Osteocalcin	Bone resorption, osteoclast differentiation, and bone growth	Alters binding of osteocalcin to hydroxyapatite -Pb exposure has been shown to both increase and decrease binding of osteocalcin to hydroxyapatite.
Parvalbumin	Unclear; may buffer Ca^{2+} levels; expressed at high levels in interneurons	No data -Ca^{2+} displacement shown *in vitro*.
Phospholipase A_2	Hydrolyze fatty acids from membrane phospholipids; released fatty acids are metabolized to bioactive lipid mediators	No data -Ca^{2+} displacement shown *in vitro*.

Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Protein kinase C (PKC)	Cell signaling, especially growth and differentiation	Increases or decreases activity -Pb shown to activate PKC *in vitro* in bovine adrenal chromaffin cells, rat brain microvessels, human erythrocytes, and rabbit mesenteric arteries. -Pb decreased PKC activity in mouse macrophages and rat brain cortex.
Synaptotagmin I	Ca^{2+} sensor regulating neurotransmitter release	No data -Ca^{2+} displacement shown *in vitro*.
Troponin C	Ca^{2+} sensor regulating muscle contraction	No data -Ca^{2+} displacement shown *in vitro*.
Heme-dependent proteins		
Catalase	Antioxidant; scavenger of hydrogen peroxide	Increases or decreases activity -Pb shown to increase activity in some studies and decrease activity in others, possibly due to differences in species, exposure duration, dose, or other study design variations.
Guanylate cyclase	Catalyzes synthesis of cGMP, which stimulates vasorelaxation in vascular tissues	Impairs production of cGMP -Pb reduced cGMP in plasma and urine of rats exposed by drinking water. -Pb decreased protein levels of soluble guanylate cyclase in vascular tissue.
Hemoglobin	Oxygen transportation	Impairs heme production needed for synthesis of hemoglobin -Pb binding to hemoglobin demonstrated in human blood.
Magnesium-dependent proteins		
Adenine and hypoxanthine/guanine phosphoribosyltransferases	Recycling of nucleotides	Inhibits activity -Pb inhibited phosphoribosyltransferase activities in erythrocytes of rats exposed via drinking water and in human erythrocytes *in vitro*.
NAD synthetase (Mg)	Nucleotide biosynthesis	Decreases activity -Blood Pb was inversely correlated with NAD synthetase activity in humans.
Pyrimidine 5'-nucleotidase	Dephosphorylates pyrimidine nucleotides in erythrocytes, preserving purine nucleotides (e.g., ATP, ADP) necessary for energy	Alters protein conformation and amino acid positioning at active site, possibly by occupying active site -Pb binding and protein conformation changes observed *in vitro*. -Pyrimidine nucleotide accumulation in erythrocytes is seen in Pb poisoning.

Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Zinc-dependent proteins		
δ-ALA (δ-ALAD or porphobilinogen synthase)	Heme biosynthesis (converts δ-ALA to porphobilinogen)	Depletes δ-ALAD, preventing heme biosynthesis and leading to accumulation of δ-ALA. - δ-ALAD shown to be major binding target of Pb in erythrocytes.
GATA zinc finger proteins	Activation/suppression of DNA transcription	Decreases ability of GATA proteins to bind to DNA and regulate transcription -Pb binding to cysteine residues and displacement of Zn from GATA proteins observed *in vitro*. -Pb-bound GATA proteins exhibited reduced DNA binding.
Transcription factors TFIIIA, Sp1, and Erg-1	Activation/suppression of DNA transcription	Decreases ability of TFIIIA, Sp1, and Erg-1 to bind to DNA and regulate transcription -Pb exposure caused dissociation of TFIIIA-DNA adducts. -Pb exposure altered DNA binding profile of Sp-1 and Erg-1 in rat pups exposed via lactation, leading to changes in gene expression.
Proteins altered by lead interaction with other cations or sulfhydryl groups		
ATPases (Ca^{2+}-, Mg^{2+}-, and Na^{+}/K^{+}-)	Ion transport	Decreases activity -Pb decreased ATPase activities in brain, kidneys, liver, testes, and erythrocytes (cells or tissues).
cGMP phosphodiesterase (Zn, Mg)	Hydrolysis of cGMP	Inhibits activity -Decreased activity observed in homogenized bovine retinas exposed to Pb *in vitro*.
Ferrochelatase (Fe)	Heme biosynthesis; incorporates Fe^{2+} into protoporphyrin IX to form heme	Inhibits insertion of Fe into protoporphyrin ring, leading to substitution by Zn -Zn-protoporphyrin levels correlated with blood Pb levels in humans.
Glutathione peroxidase and glutathione S-transferase (Se)	Antioxidants	Reduces uptake of Se and depletes cellular GSH and protein thiols, resulting in altered GST and GPx enzyme activities -Decreased activity, often with compensatory upregulation of the enzymes, seen in Pb-exposed animals and humans.

Table 2-49. Effects of Lead (Pb) on Function of Various Proteins

Protein	General function	Effect of Pb; summary of evidence
Metallothionein (Zn, Cu)	Trace element homeostasis; free radical scavenging	Sequestered by metallothionein, providing protective effect -Pb toxicity is seen at lower blood Pb levels in humans with low expression of metallothionein or low Pb binding to metallothionein. -Pb induced production of metallothionein in mice exposed via intraperitoneal or intravenous injection and in rats exposed via intraperitoneal injection, but not in rats exposed via drinking water. -Presence of zinc metallothionein reduced effect of Pb on membrane integrity in hepatocytes exposed *in vitro*. -Pb nephrotoxicity and preneoplastic and neoplastic lesions in the testes, bladder, and kidneys were more severe or seen at increased incidences in metallothionein-null mice compared with wild-type.
Superoxide dismutase	Antioxidant; catalyzes conversion of superoxide to hydrogen peroxide; inhibits oxidative inactivation of nitric oxide	Increased or decreased activity -Pb shown to increase activity in several studies and decrease activity in others, possibly due to differences in species, exposure duration, dose, or other study design variations.
Thymosin β-4	Actin regulation; exerts angiogenic, anti-inflammatory, and cardioprotective effects on the heart	No data -Pb binding observed *in vitro.*

ADP = adenosine diphosphate; δ-ALA = aminolevulinic acid; δ-ALAD = aminolevulinic acid dehydratase; ATP = adenosine triphosphate; ATPase = family of phosphatase enzymes that breakdown ATP and ADP; cGMP = cyclic guanosine monophosphate; DNA = deoxyribonucleic acid; Erg-1 = early growth response protein 1; GST = glutathione S-transferase; GSH = glutathione; GPx = glutathione peroxidase; NAD = nicotinamide adenine dinucleotide; NAD(P)H = the reduced form of nicotinamide adenine dinucleotide phosphate; ROS = reactive oxygen species; Sp1 = Transcription factor specificity protein 1; TFIIIA = transcription factor IIIA

Sources: EPA 2014c; Ahamed and Siddiqui 2007; Flora et al. 2012; Gonick 2011

Other calcium-dependent proteins bound to or impaired by Pb include parvalbumin, phospholipase A2, synaptotagmin I (see *Ion Transport* above), troponin C, the mitochondrial transmembrane pore (see Section 2.21.6, Apoptosis), and NAD(P)H oxidase (see Section 2.21.3, Oxidative Stress) (reviewed by EPA 2014c).

Pb also displaces zinc in a number of critical proteins, including ALAD, GATA proteins, and several zinc-binding transcription factors (TFIIIA, Sp1, and Erg-1) (reviewed by EPA 2014c). Section 2.8 provides a detailed discussion of Pb's effects on ALAD and heme biosynthesis. Binding of Pb to zinc-binding domains in GATA proteins and transcription factors inhibits their binding to DNA and impairs their ability to regulate gene expression (see Section 2.21.5, *Epigenetic Effects*, below for further detail).

Through competitive inhibition of magnesium-dependent proteins, Pb also affects the activities of adenine and hypoxanthine/guanine phosphoribosyltransferases, cyclic guanosine monophosphate (cGMP) phosphodiesterase, and pyrimidine 5'-nucleotidase (reviewed by EPA 2014c). In erythrocytes, adenine phosphoribosyltransferase catalyzes the synthesis of nucleotides via the adenine salvage pathway; Pb exposure has been shown to decrease nucleotide pools in human erythrocytes *in vitro* and in erythrocytes from rats exposed via drinking water. Inhibition of cGMP phosphodiesterase, a magnesium-dependent enzyme regulating cGMP signaling in smooth muscle contraction and relaxation, has been observed in homogenized bovine retinas cultured with Pb. Pb inhibits magnesium binding in pyrimidine 5'-nucleotidase, inhibiting its activity by changing its active site conformation. Pyrimidine 5'-nucleotidase occurs at high levels in erythrocytes, where it dephosphorylates pyrimidine nucleotides while leaving purine nucleotides (used as an energy source in erythrocytes, as they lack mitochondria), intact. Basophilic stippling of erythrocytes, a common feature of Pb poisoning, is also seen in individuals with inherited pyrimidine-5'-nucleotidase deficiency (Rees et al. 2003), providing supporting evidence that Pb inactivates the enzyme.

2.21.2 Protein Binding/Sequestration

A number of low molecular-weight proteins, including metallothionein, have been shown to bind (through thiol residues) to Pb, forming inclusion bodies in the kidney, liver, lung, and glial cells (reviewed by EPA 2014c; Gonick 2011). In the case of metallothionein, the effect of the binding is to sequester Pb, protecting the exposed cells and tissues. The strongest evidence for the protective effect of metallothionein comes from studies of metallothionein-null mice, which exhibit more severe Pb-induced renal toxicity, as well as increased incidences of neoplastic and nonneoplastic lesions in the testes,

bladder, and kidneys, compared with wild-type mice. Supporting this finding is the observation that higher blood Pb levels, as well as more pronounced Pb-induced effects on systolic blood pressure and kidney function, were observed in exposed workers with a metallothionein mutation (compared with those exhibiting a normal metallothionein genotype). Metallothionein levels have been shown to be induced by Pb exposure in mice and in rats pretreated with zinc.

In erythrocytes, the major Pb-binding protein is ALAD; hemoglobin also binds Pb (reviewed by EPA 2014c; Gonick 2011). In exposed humans, polymorphisms in the ALAD gene that increase the Pb-binding capacity of its protein product (e.g., ALAD-2) were observed to decrease blood Pb levels and biomarkers for Pb toxicity, including plasma levulinic acid, zinc protoporphyrin, cortical bone Pb levels, and dimercaptosuccinic acid-chelatable Pb levels. Other proteins that bind Pb in erythrocytes include pyrimidine 5'-nucleotidase and acyl-coenzyme A binding protein.

In rat kidneys, inclusion bodies consisting of Pb-bound proteins have been observed in a number of studies (reviewed by EPA 2014c; Gonick 2011). These inclusion bodies are initially observed in the cytosol, but appear to translocate to the nucleus, as they disappear concomitantly with the appearance of intranuclear inclusion bodies. The primary Pb-bound protein in the kidney (a 32 kDa protein with an isoelectric point of 6.3, named p32/6.3) has not been identified, but has been shown to be enriched in the brain and is highly conserved across species (rats, mice, dogs, chickens, and humans). Studies in rats exposed by food or drinking water showed that p32/6.3 is not found in the kidneys of untreated rats but rather is induced by Pb exposure. Other Pb-binding proteins identified in the kidneys of rats or humans include acyl-CoA binding protein and thymosin β-4 (the latter is involved in actin regulation).

2.21.3 Oxidative Stress

Pb exposure has resulted in oxidative damage in several tissues in humans and rats, including the brain, kidneys, reproductive organs, heart, and erythrocytes (reviewed by EPA 2014c; Ahamed and Siddiqui 2007). Oxidative damage may play a role in Pb-induced toxicity in these tissues, including neurological effects, hypertension and other cardiovascular effects, and diminished fertility. Pb induces oxidative stress through several mechanisms, including increased production of ROS via inhibition of heme biosynthesis and activation of NAD(P)H oxidase; stimulation of lipid peroxidation and alteration of lipids enhancing their susceptibility to lipid peroxidation; and inactivation and/or depletion of antioxidant enzymes. Through the increased production of ROS, which sequesters nitric oxide, Pb exposure also leads to perturbation of nitric oxide signaling that is critical to vasodilation.

Exposure to Pb triggers increased production of ROS via its effects on heme biosynthesis. In erythrocytes, Pb has been shown to bind to δ-ALAD as well as to inhibit its activity by interfering with the zinc ions the enzyme requires for heme biosynthesis; in fact, inhibition of δ-ALAD activity is inversely correlated with PbB levels in humans (reviewed by EPA 2014c; Ahamed and Siddiqui 2007). δ-ALAD catalyzes the conversion of δ-ALA to porphobilinogen; thus, its inhibition results in accumulation of δ-ALA in blood and in urine. In these environments, δ-ALA undergoes autoxidation, yielding superoxide and hydroxyl radicals, as well as hydrogen peroxide and an ALA radical. In addition, through subsequent reduction of ferricytochrome c and transfer of electrons from oxyhemoglobin, methemoglobin, and ferric and ferrous iron complexes, oxidized δ-ALA also produces ROS.

Pb may also increase intracellular ROS by upregulating expression of NAD(P)H oxidase, an enzyme that produces superoxide anion via reaction of NAD(P)H and molecular oxygen, but data are limited (reviewed by EPA 2014c). Increased protein expression of the glycosylated subunit of NAD(P)H oxidase was observed in tissues of rats exposed to Pb in drinking water, and in human endothelial cells *in vitro*.

ROS produced via Pb effects on δ-ALA and/or NAD(P)H oxidase can damage membrane lipids through peroxidation. In addition, however, Pb has been shown to catalyze ferrous ion-initiated lipid peroxidation (reviewed by EPA 2014c). Furthermore, there is evidence that Pb exerts effects on membrane lipids that render them more vulnerable to peroxidation (reviewed by EPA 2014c; Ahamed and Siddiqui 2007). For example, Pb has been shown to alter the composition of fatty acids in chicks exposed by drinking water, such that a higher fraction of longer fatty acids (such as arachidonic acid) and lower fraction of shorter fatty acids (compared with controls) were observed. Oxidative potential of fatty acids is correlated with both length and desaturation (i.e., the number of double bonds; the hydrogen on a double bond is easier to remove). It has been proposed that Pb may stimulate both elongation and desaturation of fatty acids, increasing their susceptibility to peroxidation. Alterations in lipid composition may also affect membrane permeability and functions, including the activity of membrane-associated enzymes, solute transport functions, endo- and exocytosis, and signal transduction.

Increased circulating ROS (specifically, superoxide anion) can inactivate nitric oxide, an endogenously produced molecule that plays an important role in vasodilation (reviewed by EPA 2014c). Depletion of nitric oxide has been observed in animals exposed to Pb, as well as in human and animal immune cells treated *in vitro*. In addition, nitric oxide depletion is believed to be the mechanism behind Pb-induced upregulation of nitric oxide synthases seen in vascular tissues after Pb exposure. Nitric oxide depletion

occurs when it reacts with superoxide anion to form the highly reactive peroxynitrite anion, which itself damages DNA and proteins. Levels of nitrotyrosine, which results from peroxynitrite-induced nitration of tyrosine residues in proteins, were increased in plasma and other tissues after *in vivo* exposure to Pb. In vascular tissues, nitric oxide induces vasorelaxation via cGMP signaling (reviewed by EPA 2014c). Exposure of rats to Pb in drinking water for 1–3 months markedly reduced cGMP levels in both blood and urine. Synthesis of cGMP is catalyzed by soluble guanylate cyclase, a heme-dependent enzyme. Pb exposure has been shown to reduce protein levels of soluble guanylate cyclase in vascular tissues; alleviation of this effect by antioxidant treatment (ascorbic acid) demonstrated that this finding was mediated, at least in part, by increased oxidative stress.

In human epidemiological studies, the ratio of oxidized glutathione (glutathione disulfide or GSSG) to reduced glutathione (GSH), a measure of oxidative stress, was positively correlated with blood Pb levels (reviewed by EPA 2014c; Ahamed and Siddiqui 2007; Flora et al. 2012). The effects of Pb on oxidative stress levels may occur through depletion of antioxidant levels in addition to stimulation of ROS, as oxidative stress occurs when the antioxidant capacity of the body is exceeded. Pb forms covalent bonds with sulfhydryl groups in antioxidant enzymes such as GSH, glutathione reductase (GR), and glutathione S-transferase (GST) (reviewed by EPA 2014c; Ahamed and Siddiqui 2007; Flora et al. 2012). In humans, animals, and *in vitro* studies, decreased GSH in blood and organs has been associated with Pb exposure. After long-term exposure to Pb, increased GSH levels, attributed to compensatory upregulation of GSH biosynthesis, have been reported. Like GSH, GR (which reduces GSSG back to GSH) and GST also have disulfides at their active site that could be bound by Pb. Studies examining GR and GST activity after Pb exposure used varying study designs and showed both increases and decreases; it is not clear whether the differences in results reflect species, strain, dose, or duration differences.

Pb's capacity to compete with cations and its interference with heme biosynthesis have also been suggested as potential mechanisms for its ability to alter levels of SOD, CAT, GPx, and GST (reviewed by EPA 2014c; Flora et al. 2012; Ahamed and Siddiqui 2007). SOD forms require copper, zinc, or manganese, cations that Pb may displace, while catalase is a heme-dependent enzyme. Several studies in humans and animals have shown alterations in SOD and CAT activity, with some evidence for a nonlinear dose-response relationship. EPA (2014c) suggested that increased SOD and CAT may occur at low doses as a result of ROS generation by Pb, while at higher doses, Pb may inactivate the enzymes. Pb exposure also alters activities of GPx and GST, potentially by reducing the uptake of selenium (required by GPx) and/or disrupting protein thiols (necessary for GST function). Decreased GPx and GST

activities have been observed, along with compensatory upregulation of these enzymes, in Pb-exposed humans and animals.

2.21.4 Inflammation

Increasing oxidative stress through ROS generation and depletion of antioxidant enzymes may be one mechanism by which Pb induces an inflammatory response (reviewed by EPA 2014c). Inflammation, considered a hallmark of Pb exposure (EPA 2014c), may also be triggered by pro-inflammatory signaling and cytokine production. Inflammation has been seen after Pb exposure in many different cell types, as well as in the kidneys of rats exposed to Pb in drinking water.

Oxidative stress is known to activate the pro-inflammatory nuclear transcription factor kappa B (NFκB). In the rat kidney, Pb-induced inflammation was accompanied by activation of NFκB as well as lymphocyte and macrophage infiltration (reviewed by EPA 2014c). Pb has been shown to stimulate the expression of pro-inflammatory signal mediators including NFκB, activator protein-1 (AP-1), and c-Jun, and to stimulate phosphorylation of the Erk/MAPK pathway. In addition, exposure to Pb is associated with increased production of prostaglandins, which also mediate pro-inflammatory messaging. Increases in arachidonic acid production, leading to increases in prostaglandins E2 and F2 and thromboxane levels, have been seen in Pb-exposed workers as well as in animals and in cultured cells systems exposed to Pb. In vascular smooth muscle cells, Pb has been shown to activate phospholipase A2, which may explain its ability to stimulate the release of arachidonic acid.

In both human epidemiological and laboratory animal studies, Pb exposure has been demonstrated to increase cytokine production (reviewed by EPA 2014c). In these studies, a fairly consistent picture of decreasing Th-1 cytokines and increasing Th-2 cytokines has emerged. EPA (2014c) outlined three modes by which Pb influences cytokine production: (1) direct action on macrophages to increase pro-inflammatory cytokines such as TNF-α and interleukin 6 (IL-6); (2) skew the ratio of IL-12 to IL-10, leading to suppression of Th-1 cell responses and stimulation of Th-2 cell responses; and (3) during acquired immune response occurring after Pb exposure, production of cytokines by Th-1 lymphocytes is suppressed, and Th-2 cytokines are increased. The net result of these changes is consistent with the pro-inflammatory picture seen with Pb exposure.

Human epidemiological studies have provided evidence that Pb exposure skews immune responses toward Th-2 pro-inflammatory responses (reviewed by EPA 2014c). Higher blood Pb levels in children

were associated with increased serum levels of Il-4 (which induces differentiation of Th0 cells to the Th-2 phenotype) and lower levels of interferon gamma (IFN-γ). In adult students in Korea, higher blood Pb levels were positively associated with increased TNF-α and IL-6; a 1 μg/dL increase in blood Pb was associated with a 23% increase in log TNF-α and a 26% increase in IL-6. Finally, in occupationally-exposed workers, higher blood Pb levels were associated with increases in IL-2, IL-10, IL-6, TNF-α, and granulocyte colony stimulating factor (G-CSF), and, in one study, lower levels of Th-1 cytokines IL-1β and IFN-γ. Similar effects were seen in mice exposed to Pb in feed; blood levels of Th-1 cytokines (IL-2 and IFN-γ) were decreased at low dietary doses, while increases in IL-4 were seen as the Pb dose increased. Based on these data, EPA (2014c) suggested that the immune system response to Pb may exhibit nonlinearities at low doses. In rats exposed to Pb via intraperitoneal injection, increased levels of TNF-α were seen in the hippocampus, and increased IL-6 was noted in the forebrain. *In vitro* data have also shown alterations in cytokine production after exposure to Pb.

2.21.5 Epigenetic Effects

In a small number of studies, Pb has been shown to induce epigenetic effects, including perturbations in DNA methylation as well as alterations in mitogenesis (reviewed by EPA 2014c; Bakulski et al. 2012). In human studies, maternal blood Pb was correlated with decreased DNA methylation of Alu retrotransposable elements in umbilical cord blood, and bone Pb levels were correlated with decreased DNA methylation of LINE-1 retrotransposons in elderly men, while higher blood Pb was associated with increased methylation of p16 tumor suppressor gene promoters in occupationally exposed individuals. Other evidence for effects of Pb on DNA methylation include a study in primates in which the activity of DNA methyltransferase 1 was decreased by early life Pb exposure, and *in vitro* data showing decreased global DNA methylation in rat pheochromocytoma cells. Hypomethylation of DNA has been shown to trigger changes in gene expression that may lead to alterations in tissue differentiation.

Pb exposure also induces effects on mitogenesis, including both increases in cell proliferation and decreases in some systems (reviewed by EPA 2014c). Increased cell proliferation and/or DNA synthesis have been reported in workers exposed to Pb, in hepatocytes of rats exposed by intravenous injection of Pb nitrate, and in mouse lung after exposure to Pb acetate via inhalation. In *in vitro* studies, results were mixed: in some cases cell proliferation was decreased, as Pb exposure resulted in cell cycle arrest. Effects of Pb exposure on gene expression have been demonstrated in several studies (reviewed by EPA 2014c). Although the exact mechanisms by which Pb alters gene expression have not been elucidated, Pb is known to interfere with GATA proteins and several transcription factors (TFIIIA, Sp1, and Erg-1)

through its interaction with zinc-binding domains, reducing the ability of these proteins to bind to DNA and exert their transcriptional regulation functions. *In vivo* and *in vitro* studies have shown that Pb alters the transcription of genes for metabolic enzymes including GST-P and GST-Ya, CYPs 1A1 and 1A2, and NAD(P)H:quinone oxidoreductase, as well as genes involved in the pentose phosphate pathway and amino acid metabolism.

2.21.6 Apoptosis

As discussed earlier, Pb is capable of opening the mitochondrial transmembrane pore (MTMP, the first step in the mitochondrial apoptosis cascade), possibly by displacing calcium on the matrix side of the pore (reviewed by EPA 2014c). Evidence for this effect includes observations of mitochondrial swelling and decreased membrane potential in rat primary cerebellar granule neuronal cultures, astroglia, proximal tubule cells, and retinal rod photoreceptor cells. In addition, release of cytochrome c and activation of caspases 3 and 9 were observed in rat retinal rod cells and hepatic oval cells exposed to Pb *in vitro*. In lymphocytes of Pb-exposed humans, increased apoptosis, karyorrhexis, and karyolysis (early indicators of apoptosis) were observed. Other tissues have also exhibited increased apoptosis after Pb exposure, including liver, fibroblasts, and alveolar macrophages.