DISPOSITION OF PEER REVIEW COMMENTS FOR TOXICOLOGICAL PROFILE FOR LEAD

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Agency for Toxic Substances and Disease Registry

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Peer reviewers for the third pre-public comment draft of the Toxicological Profile for Lead were:

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Comments provided by Peer Reviewer #1

General Comments

COMMENT: I have inserted suggested edits and comments throughout the manuscript using Track Changes and comment balloons.

RESPONSE: *No revisions were suggested. The Peer Reviewer is referring to their annotated comments, which are addressed below under "Annotated Comments."*

COMMENT: Overall, I found that the Profile was fairly comprehensive and did a decent job of trying to organize and describe the enormous volume of scientific literature associated with lead exposure and toxicity.

RESPONSE: *No revisions were suggested.*

COMMENT: The Reviewer commented "However, as is common, in my experience, with an exercise like this, there is an element of "losing the forest for the trees", and a general lack of guidance to the reader on how to interpret the enormous amount of information covered and displayed with respect to overall conclusions as well as how to use the information in a practical way. This is somewhat understandable, since the mandate of these profiles does not include "systematic reviews" and coming to conclusions whether, for example, some relationships are likely to be causal, etc. However, the Profile seems to miss opportunities to come to conclusions when there are resources to do so. For example, with respect to lead and cardiovascular disease, the Profile does a decent job of trying to review and cite the available evidence, but it omits a key paper by an expert panel convened by the CDC that came to the conclusion that the evidence supports a causal connection between lead and hypertension (Navas-Acien et al., Lead Exposure and Cardiovascular Disease—A Systematic Review. Environ Health Perspect 115:472–482 (2007). Similarly, it omits a key paper by that same expert panel that came to the conclusion that the evidence supported a causal connection between lead and adult cognitive declines (Shih et al. Cumulative Lead Dose and Cognitive Function in Adults: A Review of Studies that Measured Both Blood Lead and Bone Lead. Environ Health Perspec 2007;115:483-492. PMID: 17431502."

RESPONSE: *Conclusions of the Navas-Acien et al. (2007) review paper were added to the Section 2.6 (Cardiovascular) as follows:* "A review by Navas-Acien et al. (2007) concluded that that available literature provides evidence that "is sufficient to infer a causal relationship of lead exposure and hypertension" and evidence that "is suggestive but not sufficient to infer a causal relationship of lead exposure with clinical cardiovascular outcomes" (cardiovascular, coronary heart disease, and stroke mortality; and peripheral arterial disease)." *Conclusions of the Shih et al. (2007) review paper were added to the "Measures of Exposure" subsection of Section 2.16 (Neurological) as follows:* "A review by Shih et al. (2007) concluded that negative associations between Pb and cognitive function are stonger for bone Pb (specifically tibia Pb) for environmental exposures and for PbB for occupational exposures."

COMMENT: The Reviewer commented that the Profile also seems to miss the opportunity to cite and discuss a key paper by the same expert panel that provided recommendations on how to monitor and manage adult lead exposure (Kosnett et al., Recommendations for medical management of adult lead exposure. Environ Health Perspec 2007;115:463-471. PMID: 174315002007). Again, this is the type of

article that has practical value and that Profile readers would likely benefit from reading or at least being aware of.

RESPONSE: *A new Section 3.5 on "Methods for Reducing Toxic Effect" has been included in the revised draft that cites the Kosnett et al. (2007) report, CDC (1991, 2002), and other pertinent sources.*

"3.5 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to lead. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to lead. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to lead:

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

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

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

Kosnett MJ. 2001. Lead. In: Clinical toxicology. Ford M, Delaney KA, Ling L, et al., eds). St. Louis: WB Saunders, 723-736.

Kosnett MJ. 2005. Lead. In: Critical care toxicology. Brent J, Wallace KL, Burkhart KK, et al., eds. Philadelphia, PA: Elsevier Mosby, 821-836.

3.5.1 Reducing Absorption Following Exposure

Individuals potentially exposed to lead can prevent inhalation exposure to particles by wearing the appropriate respirator. Lead absorption from the gastrointestinal tract is influenced by nutrition, in particular, calcium and iron status. Although no treatment modalities to reduce lead absorption have yet been developed that make use of these observations, it is recommended that a child's diet contain ample amounts of iron and calcium to reduce the likelihood of increased absorption of lead and that children eat regular meals since more lead is absorbed on an empty stomach (CDC 1991, 2002a). Good sources of iron include liver, fortified cereal, cooked legumes, and spinach, whereas milk, yogurt, cheese, and cooked greens are good sources of calcium (CDC 1991).

General recommendations to reduce absorption of lead following acute exposure include removing the individual from the source of exposure and decontaminating exposed areas of the body. Contaminated skin should be washed with soap and water, and eyes exposed to lead should be thoroughly flushed with water or saline (Stutz and Janusz 1988). Once lead is ingested, it is suggested that syrup of ipecac be administered to induce emesis. Administration of activated charcoal following emesis has not been proven to reduce absorption of any lead remaining in the gastrointestinal system, but is frequently recommended (Kosnett 2004; Stutz and Janusz 1988). Gastric lavage has been used to remove ingested lead compounds. According to anecdotal case reports, whole gut lavage with an osmotically neutral polyethylene glycol electrolyte solution (GO-Lytely®, Co-lyte®) has successfully removed ingested lead-containing pottery glazes. However, this procedure is not universally accepted. Patients who ingest lead foreign objects should be observed for the possible, although rare, development of signs or symptoms of lead poisoning until the ingested object has been proven to have passed through the gut. Surgical excision has been recommended when lead bullets or shrapnel are lodged near joint capsules (reaction with synovial fluid leads to systemic uptake of lead in some cases) (Kosnett 2004). The blood lead level can be monitored and used as an indication for surgical removal of the projectile.

General recommendations proposed by Kosnett et al. (2007) to reduce occupational exposures to Pb include the following: (1) removal of occupational Pb exposure if any PbB measurement exceeds 30 µg/dL or if two successive measurements are ≥20 µg/dL; (2) quarterly monitoring of workers whose PbBs range between 10 and 19 µg/dL; (3) semiannual PbB measurements when sustained PbB is <10 µg/dL; and (4) avoiding occupational exposures that result in PbB >5 ug/dL during pregnancy.

3.5.2 Reducing Body Burden

Lead is initially distributed throughout the body and then redistributed to soft tissues and bone. In human adults and children, approximately 94 and 73% of the total body burden of lead is found in bones, respectively. Lead may be stored in bone for long periods of time, but may be mobilized, thus achieving a steady state of intercompartmental distribution (see Section 3.3.2).

All of the currently available methods to obviate the toxic effects of lead are based on their ability to reduce the body burden of lead by chelation. All of the chelating agents bind inorganic lead, enhance its excretion, and facilitate the transfer of lead from soft tissues to the circulation where it can be excreted. Since the success of chelation therapy depends on excretion of chelated lead via the kidney, caution should be used when treating a patient with renal failure. The standard chelating agents currently in use

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

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

$CaNa_2$-EDTA (or EDTA) works by forming a stable metal-chelate complex that is excreted by the kidney. It increases renal excretion of lead 20–50 times. Numerous adverse effects have been described due to treatment with EDTA including rash, fever, fatigue, thirst, myalgias, chills, and cardiac dysrhythmias. EDTA should be used together with BAL (4 hours after the first dose of BAL) because acute lead encephalopathy may progress if EDTA given alone secondary to lead from soft tissue lead mobilization resulting in increased PbB. Since EDTA chelates zinc, patients with low zinc stores may be adversely affected by EDTA. Since EDTA also chelates other metals, administration of EDTA (or BAL) to persons occupationally exposed to cadmium may result in increased renal excretion of cadmium and renal damage. The dosage recommended for children is 1,000–1,500 mg/m^2/24 hours in 0.5% procaine intramuscularly to avoid fluid overload, although the preferred route of administration of EDTA is intravenously. This dose may be given in up to six divided daily doses. For adults, the recommended dose is 1.5 g/24 hours in two divided doses. The full course for EDTA therapy is 5 days, but the course may be repeated if the patient is still symptomatic or when PbB is >50 μg/dL.

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

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

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

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

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

3. *Chelation therapy is indicated in patients with blood lead levels between 45 and 70 μg/dL. In the absence of clinical symptoms suggesting encephalopathy (e.g., obtundation, headache, and persisting vomiting), patients may be treated with succimer at 30 mg/kg per day for 5 days, followed by 20 mg/day for 14 days. Children may need to be hospitalized for the*

initiation of therapy to monitor for adverse effects and institute environmental abatement. Discharge should be considered only if the safety of the environment after hospitalization can be guaranteed. An alternate regimen would be to use $CaNa_2EDTA$ as inpatient therapy at 25 mg/kg for 5 days. Before chelation with either agent is begun, if an abdominal radiograph shows that enteral lead is present, bowel decontamination may be considered as an adjunct to treatment.

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

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

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

Chelation therapy has been recommended for adults if PbB exceeds 50 µg/dL and overt symptoms of lead toxicity are evident (Kosnett et al. 2007)."

COMMENT: The Reviewer commented that the "As noted in several places in my comments and edits, the Profile also fails to adequately review the literature with respect to the recent important studies of bone lead (a measure of cumulative exposure) and outcomes, mostly because it seems that many of the Tables were compiled strictly looking at epidemiologic results related to blood lead levels---and, in so doing, completely ignored studies that used bone lead levels to signify cumulative exposure. In one case, for example, Weisskopf et al., 2009 was cited in the Table on lead and mortality (as well as the table on lead and cardioavascular outcomes) only for the results that showed no significant association between blood lead levels and cardiovascular mortality, but completely omitted the fact that the main finding of the study was that the bone lead levels were major and highly significant predictors of cardiovascular mortality."

RESPONSE: *New subsections, including summary tables of study results, on associations of bone Pb with health outcomes have been added for the Cardiovascular, Renal, Neurological, and Developmental*

Sections. Results of the bone results from the Weisskopf et al. (2009) study were added to a new table in the cardiovascular section.

To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of µg/dL). Blood Pb concentration reflects both on-going exposure and Pb stores in bone which can be transferred to blood. Becaue of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months andnot necessarily the larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI) which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct noninvasive measurement of bone Pb concentrations have been used as metric of long-term exposure on the basis that most of the absorbed retained in the body will resides in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades.

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 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. 2002b), and mother-child pairs (Zhang et al. 2001). 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 2-1. 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	Al-Saleh et al. 2005; Bost et al. 1999; Bushnik et al. 2014; Cheng et al. 2001; Chu et al. 1999; Den Hond et al. 2002; Elmarsafawy et al. 2006; Faramawi et al. 2015; 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; Martin et al. 2006; Muntner et al. 2005; Nash et al. 2003; Park et al. 2009b; Perlstein et al. 2007; Proctor et al. 1996; Rothenberg et al. 2002b; Schwartz 1995; Scinicariello et al. 2010, 2011; Vupputuri et al. 2003; Wells et al. 2011; Yazbeck et al. 2009; Zhang et al. 2011; Zota et al. 2013
	Atherosclerosis[a]	Ari et al. 2011; Muntner et al. 2005; Navas-Acien et al. 2004;
	Heart disease[b]	Cheng et al. 1998; Eum et al. 2011; Jain et al. 2007; Park et al. 2009a
	Mortality due to cardiovascular disease	Aoki et al. 2016; Khalil et al. 2009; 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; 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]	Poreba et al. 2013
	Mortality due to cardiovascular disease	Lustberg and Silbergeld 2002; Schober et al. 2006

Table 2-1. 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
>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
	Heart disease[b]	Bockelmann et al. 2002; Jain et al. 2007
	Mortality due to cardiovascular disease	Gerhardsson et al. 1995a
>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.

Table 2-2. 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

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

Reference	Population	Blood pressure outcome			
		Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
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	–
Peters et al. 2007	512 men[b]	–	–	–	↑ T (with high stress) ↑ P (with high stress)
Rothenberg et al. 2002b[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; ↓ = negative association; 0 = no association; – = not reported; C = calcaneous 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). 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).

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).

Table 2-3. 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,	–	–	↑ T	Adjudicated delinquency

Table 2-3. Associations Between Bone Pb and Neurological Outcomes in Children

Reference	Population	Neurological outcome			
		Intellectual deficits	Altered neuromotor or neurosensory function	Altered mood or behavior	Outcome measures
	age: 12–18 years				
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; ↓ = negative association; 0 = no association; – = not reported; ADHD = Attention deficit hyperactivity disorder; C = calcaneous bone; MDI = Mental Developmental Index; P = patella; Pb = lead; T = tibia; O = other

Associations Between Bone Pb and Birth Outcome and Post-Natal 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 negatively associated with birth weight (Cantonwine et al. 2010b; Gonzalez-Cossio et al. 1997; 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; Gonzalez-Cossio et al. 1997) or birth length (Hernandez-Avila et al. 2002). Infant weight gain measured at 1 month of age was negatively 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 negatively 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. Taken together, results of these studies

provide evidence that long-term maternal Pb exposure is negatively associated with infant size and post-natal growth.

Table 2-4. 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[b]
Afeiche et al. 2011	Mother-infant pairs (522 boys; 477 girls)	0 T (M, F) 0 P (M, F)	–	–	0 T (M, F)[c] 0 P (M, F)[c]	0 T (M, F) 0 P (M) ↓ P (F)
Cantonwine et al. 2010b	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	–	–
Sanin et al. 2001	329 mother-infant pairs	–	–	–	0 T[d] ↓ P[d]	–

[a]From Mexico City.
[b]Measured at 5 years of age.
[c]Measured from birth to 12 months of age.
[d]Measured at 1 month of age.

↓ = negative 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.

COMMENT: The Reviewer commented that the Profile needs discussion of the fact that in epidemiologic studies of adult outcomes that only include blood lead levels to measure exposure, the blood lead levels may be reflecting outcomes related to acute lead exposure; but it is also possible that the

blood lead levels are a proxy for historical lead exposures that were much higher, with the "source" of the blood lead levels mostly the lead that is mobilized from long-lived bone lead stores. This is an important nuance that deserves discussion in, for example, a preface to the discussion of epidemiologic studies that alerts the reader to what the blood lead levels may really mean. Many of these issues are discussed in another paper published by the expert panel on biomarkers and the epidemiology of lead (Hu et al. Epidemiology of Lead Toxicity in Adults: Measuring Dose and Consideration of Other Methodological Issues. Environ Health Perspec 2007;115:455-462. PMID: 17431499).

RESPONSE: *The concepts regarding bone as a metric of body burden and cumulative exposure have been reinforced in Sections 1.1, 2.1, and 3.3.1. Hu et al. (2007) has been cited in the revised draft.*

"Biomarkers of exposure in practical use today are measurements of total Pb levels in body fluids or tissues, such as blood, bone, or urine. Tetraalkyl Pb compounds may also be measured in the breath. Of these, PbB is the most widely used and is considered to be the most reliable biomarker for general clinical use and public health surveillance. Currently, PbB measurement is the screening test of choice to identify children with elevated PbBs (CDC 2015). Venous sampling of blood is preferable to finger prick sampling, which has a considerable risk of surface Pb contamination from the finger if proper finger cleaning is not carried out. In children, PbBs greater than the blood lead reference values (BLRV) identify high-risk childhood populations and geographic areas most in need of primary prevention (CDC 2012d). In 2012, the BLRV was defined as >5 μg/dL (CDC 2012d).

PbB. Measurement of PbB is the most widely used biomarker of Pb exposure. Elevated PbB (e.g., >5 μg/dL) is an indication of excessive exposure in infants and children (CDC 2012d). The biological exposure index (BEI) for Pb in blood of exposed workers is 30 μg/dL (ACGIH 2001). The National Institute for Occupational Safety and Health (NIOSH) recommended exposure limit (REL) for workers (50 $\mu g/m^3$ air, 8-hour time-weighted average [TWA]) is established to ensure that the PbB does not exceed 60 μg/dL (NIOSH 2016).

The extensive use of PbB as a dose metric reflects mainly the greater feasibility of incorporating PbB measurements into clinical or epidemiological studies, compared to other potential dose indicators, such as Pb in kidney, plasma, or bone. PbB measurements have several limitations as measures of total Pb body burden. Blood comprises <2% of the total Pb burden; most of the Pb burden resides in bone (Barry 1975). Pb is eliminated from blood more rapidly than from bone (Behinaein et al. 2014; Brito et al. 2005; Chamberlain et al. 1978; Griffin et al. 1975; Manton et al. 2001; Nie et al. 2005; Nilsson et al. 1991; Rabinowitz et al. 1976; Rentschler et al. 2012); therefore, the Pb concentration in blood reflects mainly the exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of Pb in bone (Graziano 1994; Lyngbye et al. 1990b). Slow release of Pb from bone can contribute to blood Pb levels long after external exposure has ceased (Fleming et al.

1997; Inskip et al. 1996; Kehoe 1987; McNeill et al. 2000; O'Flaherty et al. 1982; Smith et al. 1996). The relationship between Pb intake and PbB is curvilinear; the increment in PbB per unit of intake decreases with increasing PbB (Ryu et al. 1983; Sherlock and Quinn 1986; Sherlock et al. 1982, 1984). Pb intake-PbB relationships also vary with age as a result of age-dependency of gastrointestinal absorption of Pb, and vary with diet and nutritional status (Mushak 1991). A practical outcome of the above characteristics of PbB is that PbB can change relatively rapidly (e.g., weeks) in response to changes in exposure; thus, PbB can be influenced by short-term variability in exposure that may have only minor effects on total Pb body burden. A single PbB determination cannot distinguish between lower-level intermediate or chronic exposure and higher-level acute exposure. Similarly, a single measurement may fail to detect a higher exposure that occurred (or ended) several months earlier. Time-integrated measurements of PbB (cumulative blood Pb index, CBLI) may provide a means for accounting for some of these factors and thereby provide a better measure of long-term exposure (Armstrong et al. 1992; Behinaein et al. 2014; Chuang et al. 2000; Fleming et al. 1997; Gerhardsson et al. 1993; Healey et al. 2008; Hu et al. 2007; McNeill et al. 2000; Nie et al. 2011a; Roels et al. 1995). The correlation observed between CBLI and tibia bone Pb concentrations provide supporting evidence for this (Hu et al. 2007).

Bone and Tooth Pb Measurements. The development of noninvasive XRF techniques for measuring Pb concentrations in bone has enabled the exploration of bone Pb as a biomarker of Pb exposure in children and in adults (Behinaein et al. 2011; Chettle et al. 2003; Ji et al. 2014; Nie et al. 2011b; Specht et al. 2016; Todd et al. 2000; Hu et al. 2007). Pb in bone is considered a biomarker of cumulative exposure to Pb because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Pb is not distributed uniformly in bone. Pb will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in both cortical and trabecular bone. This suggests that Pb accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Patella, calcaneus, and sternum XRF measurements primarily reflect Pb in trabecular bone, whereas XRF measurements of midtibia, phalanx, or ulna primarily reflect primarily Pb in cortical bone. Pb levels in cortical bone may be a better indicator of long-term cumulative exposure than Pb in trabecular bone, possibly because Pb in trabecular bone may exchange more actively with Pb in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of Pb in cortical bone, compared to trabecular bone (Behinaein et al. 2014; Borjesson et al. 1997; Brito et al. 2005; Nie et al. 2005; Nilsson et al. 1991; Schutz et al. 1987). Longitudinal studies that have repeatedly measured bone Pb (by XRF) over many years have shown more rapid declines in trabeular bone

compared to cortical bone (%) (Kim et al. 1997; Wilker et al. 2011). Estimates of cortical bone Pb elimination half-times (5–50 years) show a dependence on Pb burden, with longer half-times in people who have higher total body burdens (estimated from CBLI) and bone Pb burdens (Behinaein et al. 2014; Brito et al. 2005; Nie et al. 2005). Further evidence that cortical bone Pb measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone Pb measurements have been compared to PbB. Pb levels in trabecular bone (in adults) correlate more highly with contemporary PbB than do levels of Pb in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical bone Pb measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary PbB measurements (Behinaein et al. 2012; Borjesson et al. 1997; Hu et al. 2007; Roels et al. 1994). Bone Pb levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone Pb may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

Standard methods for bone Pb XRF measurements have not been universally accepted, in part, because the technology continues to be improved, and this needs to be considered in comparisons of measurements reported by different laborites and at different times in development of the methodology used. Historically, two XRF methods have seen the most used in bone Pb epidemiology: K-shell and L-shell methods. The K-shell method is the more widely used, although, improvements in L-shell technology continue to be reported (Nie et al. 2011a). One study reported a correlation of 0.65 between bone Pb measurements made with a portable L-shell device and a K-shell method (Nie et al. 2011a). In general, recent advances in K-shell technology have yielded higher sensitivities (approximately 3 μg/g tibia mineral; Behinaein et al. 2011) than L-shell technology (approximately 8 μg/g tibia bone mineral; Nie et al. 2011a). Precision of K-shell XRF bone Pb measurements have been extensively discussed (Behinaein et al. 2014; Todd et al. 2002; Todd et al. 2001; Aro et al. 2000; Todd et al. 2000). Methodological factors can contribute substantially to observed variability in bone Pb measurements in populations (Behinaein et al. 2014). These factors include bone Pb target, radioactive source, measurement time, and data reduction methods (e.g., approach to handling negative values). Measurement uncertainty also appears to contribute by biological factors, such as body mass index and bone mineral content (Behinaein et al. 2014; Berkowitz et al. 2004; Hu et al. 2007a; Theppeang et al. 2008a). The association between BMI and measurement uncertainty may reflect the effect attenuation of the XRF signal by tissue overlaying the target bone site (Behinaein et al. 2014). Bone mineral can be a factor because XRF measures bone Pb fluorescence in relation to fluorescence from bone calcium and the

result is expressed in units of μg Pb per g bone mineral. As a result, variability in bone mineral content can contribute to variability in measured bone Pb. Typically, potential associations between bone density and bone Pb concentration are not evaluated in epidemiologic studies (Berkowitz et al. 2004; Hu et al. 2007; Theppeang et al. 2008a). An important consequence of expressing bone Pb measures relative to bone mineral content is that lower bone mineral density is associated with greater measurement uncertainty in bone Pb. This uncertainty can have important implications for studies in older women for whom low bone mineral density is more common than in other populations including men and younger adults.

Tooth Pb has been considered a potential biomarker for measuring long-term exposure to Pb (e.g., years) because Pb that accumulates in tooth dentin and enamel appears to be retained until the tooth is shed or extracted (Costa de Almeida et al. 2007; Ericson 2001; Fosse et al. 1995; Gomes et al. 2004; Gulson and Wilson 1994: Gulson et al. 1996; Omar et al. 2001; Rabinowitz 1995; Rabinowitz et al. 1989, 1993; Robbins et al. 2010; Steenhout and Pourtois 1987; Tvinnereim et al. 1997). Formation of enamel and primary dentin of deciduous teeth begins *in utero* and is complete prior to the time children begin to crawl. Formation of secondary dentin begins after completion of the tooth root and continues through childhood until the tooth is lost, or otherwise loses vitality. Pb in shed deciduous teeth is not uniformly distributed. Differences in Pb levels and stable isotope signatures of the enamel and dentin suggest that Pb uptake occurs differentially in enamel and dentin (Gulson 1996; Gulson and Wilson 1994). Pb in enamel is thought to reflect primarily Pb exposure that occurs *in utero* and early infancy, prior to tooth eruption. Dentin appears to continue to accumulate Pb after eruption of the tooth; therefore, dentin Pb is thought to reflect exposure that occurs up to the time the teeth are shed or extracted (Gulson 1996; Gulson and Wilson 1994; Rabinowitz 1995; Rabinowitz et al. 1993). The technique of laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) allows measurement of Pb levels in regions of dentin formed at various times during deciduous tooth formation *in utero* and after birth (Arora et al. 2014; Shepherd et al. 2016). Accumulation of Pb in dentin of permanent teeth may continue for the life of the tooth (Steenhout 1982; Steenhout and Pourtois 1981). Because enamel is in direct contact with the external environment, enamel Pb levels may be more influenced than dentin Pb by external Pb levels and tooth wear (Purchase and Fergusson 1986).

An analysis of eight cross-sectional and/or prospective studies that reported tooth Pb and PbBs of the same children found considerable consistency among the studies (Rabinowitz 1995). The mean tooth Pb levels ranged from <3 to >12 μg/g. Dentin Pb was found to be predictive of Pb in tibia, patella, and mean bone Pb in 32 of 63 subjects at follow-up of ≤13 years (Kim et al. 1996b). The authors estimated that a

10 μg/g increase in dentin Pb levels in childhood was predictive of a 1 μg/g increase in tibia Pb levels, a 5 μg/g in patella Pb levels, and a 3 μg/g increase in mean bone Pb among the young adults. Arora et al. (2014) found that Pb levels in primary (prenatal) dentin were more strongly correlated with PbBs at birth (correlation coefficient, r=0.69, n=27), whereas Pb levels in secondary (postnatal) dentin were more strongly correlated with CBLI (r=0.38, n=75). Shepherd et al. (2016) combined LA-ICP-MS with histological determinations of dentin age to reconstruct the history of incorporation of environmental Pb from various sources."

"1.1 OVERVIEW AND U.S. EXPOSURES

Lead (Pb) is an element that is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world. A major source of Pb in the U.S. environment has historically been anthropogenic emissions to the atmosphere from combustion of leaded gasoline, which was phased out of use after 1973 and then banned in 1995 (with the exception of fuels for piston-driven aircraft) (EPA 1996a). Lead continued to be used as an anti-knock agent in NASCAR fuels until it was phased out beginning in 2008. Deteriorating Pb-based paints from weather surfaces in surfaces (which produce highly concentrated Pb debris and dusts) in older housing stock (pre-1978) continues to be a source of childhood Pb poisoning in the United States (CDC 1991, 2012d). The combination of corrosive water and Pb pipes or Pb-soldered joints in either the distribution system or individual houses can create localized zones of high Pb water concentrations (EPA 1989d, 2007a; Hanna-Attisha et al. 2016). Other anthropogenic sources of Pb have included mining and smelting of ore; manufacture of and use of Pb-containing products (e.g., Pb-based paints, pigments, and glazes; electrical shielding; plumbing; storage batteries; solder; and welding fluxes); manufacture and application of Pb-containing pesticides; combustion of coal and oil; and waste incineration."

"Pb does not degrade in the environment, although it can exist in various chemical forms. Particulate matter contaminated with Pb can be transported through air, water, and soil. In general, atmospheric deposition is the largest source of Pb found in soils not impacted by other local non-air sources (e.g., dust from deteriorating leaded paint). Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb. Pb adsorbs strongly to most soils and does not appreciably leach. Soil acidity (pH) and composition are the most important factors affecting solubility, mobility, and phytoavailability of Pb in soil. Other conditions that increase Pb mobility in soil are reducing conditions and high chloride content."

“The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Pb has also been found in a variety of other consumer products including storage batteries, solders, pottery glazes, leaded crystal glassware, cosmetics, hair dyes, jewelry, gun shot and ammunition, relic fishing sinkers, and tire weights. For adults, exposure to levels of Pb beyond background is usually associated with occupational exposures. For children, exposure to high levels of Pb are associated with living in areas contaminated by Pb (e.g., soil or indoor duct in older homes with Pb-based paint). The primary source of Pb exposure to children is from surface dusts (on the ground or entrained) that contain Pb from a variety of sources including deteriorated Pb-based paint (CDC 2009; Lanphear et al. 1998; Succop et al. 1998). Environmental Pb is particularly accessible to children because of their more intensive hand-to-mouth activity and the proximity of the child breathing zone to Pb entrained from surface dusts. Because Pb is transported from soil very slowly, historic sources of deposition of Pb to soil continue to contribute to current exposures (Laidlaw and Filipelli 2008; Laidlaw et al. 2012).”

“PbB has been used as a biomarker of Pb exposure, and periodic surveys of PbB of the U.S. population are conducted by the Centers for Disease Control and Prevention (CDC). Based on data from the National Health and Nutrition Examination Survey (NHANES) (2013–2014, CDC 2017a), the geometric mean PbB in a representative sample of U.S. adults, ≥20 years old, was 0.967 μg/dL (95% confidence interval [CI] 0.921, 1.02). The geometric mean blood PbB of a representative sample of U.S. children, 1–5 years old, was 0.782 μg/dL (95% CI 0.705, 0.869). PbBs in the U.S. have decreased considerably in the last several decades as a result of removal of Pb from gasoline and restrictions placed on the use of Pb in residential paints (Brody et al. 1994; CDC 2011, 2015; Pirkle et al. 1994, 1998; Schwartz and Pitcher 1989).”

“Seasonal variations in blood lead concentration (PbB) levels in children have been observed, with a general trend of increasing PbB during late summer and early fall (Gulson et al. 2008; Johnson and Bretsch 2002; Laidlaw et al. 2005). Seasonal patterns in behavior (e.g., outdoor activities) and weather that promotes re-entrainment and transport of dust Pb (humidity and wind velocity) may contribute to the observed seasonal patterns in PbB (Laidlaw et al. 2005, 2012) and provide additional evidence for surface dusts being a major contributor to child Pb exposure and PbB.”

“1.2 SUMMARY OF HEALTH EFFECTS

The toxicity of Pb to humans has been known for over 2,000 years, and is not disputed. Early epidemiological studies focused on overt toxicity associated with high occupational exposures. However,

during the past few decades, there has been a growing awareness that low-level environmental exposure resulting in PbB <10 µg/dL is associated with adverse effects, particularly in children. As a result, U.S. public health policy has changed to focus on lowering PbB levels to well below 10 µg/dL. Therefore, the primary objective of current research is on health effects associated with PbB ≤10 µg/dL. "

"The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of evidence regarding health effects in humans. Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb. This potentially leaves of the profile discussion of effects that may have been observed in animal models that have not been studied humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics."

"To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of µg/dL). Blood Pb concentration reflects both on-going exposure and Pb stores in bone which can be transferred to blood. Becaue of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months andnot necessarilythe larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI) which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct noninvasive measurement of bone Pb concentrations have been used as metric of long-term exposure on the basis that most of the absorbed retained in the body will resides in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect is typically unknown or highly uncertain."

"Adverse health effects of Pb have been observed in every organ system. This is because the mechanisms that induce toxicity are common to all cell types and because Pb is widely distributed throughout the body. Health effects of Pb have been observed in all organ systems over a wide PbB range (≤10–>50 µg/dL). Exposure thresholds for effects on specific organ systems have not been identified and it is not possible to determine from the epidemiological data which organ systems are the most sensitive (i.e., primary) targets for Pb toxicity. It is also important to note that effects observed in adults, especially older adults, may be due to higher environmental or occupational exposures in the past; therefore, exposure history is an important consideration in epidemiological studies in the effects of Pb."

"The most extensively studied health outcomes, as described below, are neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects. Neurological effects of Pb are of greatest concern because effects are observed in infants and children and may result in life-long decrements in neurological function. Infants are born with a Pb burden derived from maternal transfer in utero and subsequently can continue to absorb maternal Pb from ingestion of breast milk. 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 following briefly summarizes health effects of chronic exposure to Pb observed in humans. More detailed information, including reference citations, is provided in Chapter 2. "

"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 life-time 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)."

COMMENT: The Reviewer commented that the "As noted in several places, some key studies are simply missing, such as those relating lead to other neurological disease endpoints (e.g., Parkinson's; Amyotrophic Laterial Sclerosis)."

RESPONSE: *Studies of associations between blood or bone Pb and Parkinson's and amyotrophic lateral sclerosis are included in the revised draft (Coon et al. 2006; Fang et al. 2010; Kamal et al. 2002; Weisskopf et al. 2010; Weuve et al. 2013).*

"***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 2-5. 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. 2006a, 2006b; 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
	Altered mood and behavior[b]	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
	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. 1996b; Choi et al. 2012; Haenninen et al. 1978; Iwata et al. 2005
	Altered nerve conduction	Araki et al. 1980, 1987, 2000; Chia et al. 1996b; Hirata and Kosaka et al. 1993; Pasternak et al. 1989; Stollery et al. 1989, 1991

Table 2-5. 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; Matte et al. 1989; Valciukas et al. 1978
	Altered mood and behavior[b]	Awad el Karin 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"

"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; 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; 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 (Power et al. 2014; Schwartz et al. 2005; Wang et al. 2007; Weisskopf et al. 2004, 2007; Wright et al. 2003b).

Table 2-6. 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
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 lead workers, age: 20–70 years	↑ P ↑ T	↑ P ↑ T	↑ P ↑ T	Reaction time, executive function, manual dexterity, vibration threshold, depression
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 lead, amyotrophic lateral sclerosis and hemochromatosis gene polymorphisms
Glass et al. 2009	1,001 adults[a], age: 50–70 years	↑ T	↑ T	–	Interaction between lead 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

Table 2-6. 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
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
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 lead workers, age: 56 years (mean)	↑ T	↑ T	–	Memory, executive function, manual dexterity
Schwartz et al. 2001	803 exposed lead 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

Table 2-6. 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
Schwartz et al. 2005	576 exposed lead 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
Stewart et al. 2002	529 lead 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 lead and hemochromatosis gene polymorphisms on learning, memory, executive function
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

Table 2-6. 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
Weuve et al. 2013	101 cases and 50 controls, age: 55–80 years	0 P ↑ T	–	–	Learning, memory (stronger association with lead among Parkinson's disease cases)
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 lead predicted from bone lead.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; C = calcaneous 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 amyotrophic lateral sclerosis (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)."

COMMENT: The Reviewer commented "Finally, it's a bit disconcerting that there is little to nothing related to the treatment of lead toxicity and the potential role of chelation. I realize that this may not be in the purview/mandate of these Profiles, but perhaps the reader can at least be alerted to the references that address these issues, such as monographs by the CDC for childhood lead toxicity, the Kosnett paper regarding lead exposure in adults, etc.?"

RESPONSE: *A new Section 3.5 on "Methods for Reducing Toxic Effect" has been included in the revised draft that cites the Kosnett et al. (2007) report, CDC (1991, 2002), and other pertinent sources.*

"3.5 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to lead. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to lead. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to lead:

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

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

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

Kosnett MJ. 2001. Lead. In: Ford M, Delaney KA, Ling L, et al., eds. Clinical toxicology. St. Louis: WB Saunders, 723-736.

Kosnett MJ. 2005. Lead. In: Brent J, Wallace KL, Burkhart KK, et al., eds. Critical care toxicology. Philadelphia, PA: Elsevier Mosby, 821-836.

3.5.1 Reducing Absorption Following Exposure

Individuals potentially exposed to lead can prevent inhalation exposure to particles by wearing the appropriate respirator. Lead absorption from the gastrointestinal tract is influenced by nutrition, in particular, calcium and iron status. Although no treatment modalities to reduce lead absorption have yet been developed that make use of these observations, it is recommended that a child's diet contain ample amounts of iron and calcium to reduce the likelihood of increased absorption of lead and that children eat regular meals since more lead is absorbed on an empty stomach (CDC 1991, 2002a). Good sources of iron include liver, fortified cereal, cooked legumes, and spinach, whereas milk, yogurt, cheese, and cooked greens are good sources of calcium (CDC 1991).

General recommendations to reduce absorption of lead following acute exposure include removing the individual from the source of exposure and decontaminating exposed areas of the body. Contaminated skin should be washed with soap and water, and eyes exposed to lead should be thoroughly flushed with water or saline (Stutz and Janusz 1988). Once lead is ingested, it is suggested that syrup of ipecac be

administered to induce emesis. Administration of activated charcoal following emesis has not been proven to reduce absorption of any lead remaining in the gastrointestinal system, but is frequently recommended (Kosnett 2004; Stutz and Janusz 1988). Gastric lavage has been used to remove ingested lead compounds. According to anecdotal case reports, whole gut lavage with an osmotically neutral polyethylene glycol electrolyte solution (GO-Lytely®, Co-lyte®) has successfully removed ingested lead-containing pottery glazes. However, this procedure is not universally accepted. Patients who ingest lead foreign objects should be observed for the possible, although rare, development of signs or symptoms of lead poisoning until the ingested object has been proven to have passed through the gut. Surgical excision has been recommended when lead bullets or shrapnel are lodged near joint capsules (reaction with synovial fluid leads to systemic uptake of lead in some cases) (Kosnett 2004). The blood lead level can be monitored and used as an indication for surgical removal of the projectile.

General recommendations proposed by Kosnett et al. (2007) to reduce occupational exposures to Pb include the following: (1) removal of occupational Pb exposure if any PbB measurement exceeds 30 µg/dL or if two successive measurements are ≥20 µg/dL; (2) quarterly monitoring of workers whose PbBs range between 10 and 19 µg/dL; (3) semiannual PbB measurements when sustained PbB is <10 µg/dL; and (4) avoiding occupational exposures that result in PbB >5 ug/dL during pregnancy.

3.5.2 Reducing Body Burden

Lead is initially distributed throughout the body and then redistributed to soft tissues and bone. In human adults and children, approximately 94 and 73% of the total body burden of lead is found in bones, respectively. Lead may be stored in bone for long periods of time, but may be mobilized, thus achieving a steady state of intercompartmental distribution (see Section 3.3.2).

All of the currently available methods to obviate the toxic effects of lead are based on their ability to reduce the body burden of lead by chelation. All of the chelating agents bind inorganic lead, enhance its excretion, and facilitate the transfer of lead from soft tissues to the circulation where it can be excreted. Since the success of chelation therapy depends on excretion of chelated lead via the kidney, caution should be used when treating a patient with renal failure. The standard chelating agents currently in use are dimercaprol (British Anti-Lewisite, or BAL), $CaNa_2$-EDTA (or EDTA), penicillamine, and 2,3-dimercaptosuccinic acid (DMSA; Succimer®). Most of the information below regarding chelators has been extracted from Homan et al. (1998).

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

$CaNa_2$-EDTA (or EDTA) works by forming a stable metal-chelate complex that is excreted by the kidney. It increases renal excretion of lead 20–50 times. Numerous adverse effects have been described due to treatment with EDTA including rash, fever, fatigue, thirst, myalgias, chills, and cardiac dysrhythmias. EDTA should be used together with BAL (4 hours after the first dose of BAL) because acute lead encephalopathy may progress if EDTA given alone secondary to lead from soft tissue lead mobilization resulting in increased PbB. Since EDTA chelates zinc, patients with low zinc stores may be adversely affected by EDTA. Since EDTA also chelates other metals, administration of EDTA (or BAL) to persons occupationally exposed to cadmium may result in increased renal excretion of cadmium and renal damage. The dosage recommended for children is 1,000–1,500 mg/m^2/24 hours in 0.5% procaine intramuscularly to avoid fluid overload, although the preferred route of administration of EDTA is intravenously. This dose may be given in up to six divided daily doses. For adults, the recommended dose is 1.5 g/24 hours in two divided doses. The full course for EDTA therapy is 5 days, but the course may be repeated if the patient is still symptomatic or when PbB is >50 μg/dL.

D-Penicillamine is an orally-administered lead chelator with an unknown mechanism of action that increased urinary excretion of lead. The FDA has not approved the use of d-penicillamine during pregnancy. Administration of d-penicillamine is contraindicated in subjects allergic to penicillin because

of cross-reactivity with the latter. Among the adverse effects are rash, fever, anorexia, nausea, vomiting, leucopenia, thrombocytopenis, eosinophilia, hemolytic anemia, Stevens-Johnson syndrome (severe erythema multiforme), nephrotoxicity, and proteinuria. Furthermore, continued exposure to lead will result in continued absorption of lead at a higher rate. The recommended dose is 10 mg/kg/24 hours for 7 days, but may be increased to 10–15 mg/kg every 12 hours over 2–4 weeks. One way to minimize toxicity is to start medication at ¼ the dosage and gradually increase it to full dosage over 3–4 weeks. The CDC recommends giving children an entire dose on an empty stomach 2 hours before breakfast and giving adults an entire dose in two or three divided doses on an empty stomach 2 hours before meals.

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

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

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

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

4. *Patients with blood lead levels of greater than 70 μg/dL or with clinical symptoms suggesting encephalopathy require inpatient chelation therapy using the most efficacious parenteral agents available. Lead encephalopathy is a life-threatening*

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

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

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

Chelation therapy has been recommended for adults if PbB exceeds 50 µg/dL and overt symptoms of lead toxicity are evident (Kosnett et al. 2007)."

COMMENT: The Reviewer commented "Anyway, I hope this is helpful!!!"

RESPONSE: *No revisions were suggested.*

Annotated Comments

Chapter 1. Relevance to Public Health

COMMENT (Section 1.1): The Reviewer noted that leaded gasoline was phased out of regular commercial gasoline in 1995, but it remained in gasoline used for NASCAR racing until 2008.

RESPONSE: *The phase out of Pb in NASCAR fuels has been noted in the revised draft (Section 1.1).*

"Lead (Pb) is an element that is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world. A major source of Pb in the U.S. environment has historically been anthropogenic emissions to the atmosphere from combustion of leaded gasoline, which was phased out of use after 1973 and then banned in 1995 (with the exception of fuels for piston-driven aircraft) (EPA

1996a). Lead continued to be used as an anti-knock agent in NASCAR fuels until it was phased out beginning in 2008. Deteriorating Pb-based paints from weather surfaces in surfaces (which produce highly concentrated Pb debris and dusts) in older housing stock (pre-1978) continues to be a source of childhood Pb poisoning in the United States (CDC 1991, 2012d). The combination of corrosive water and Pb pipes or Pb-soldered joints in either the distribution system or individual houses can create localized zones of high Pb water concentrations (EPA 1989d, 2007a; Hanna-Attisha et al. 2016). Other anthropogenic sources of Pb have included mining and smelting of ore; manufacture of and use of Pb-containing products (e.g., Pb-based paints, pigments, and glazes; electrical shielding; plumbing; storage batteries; solder; and welding fluxes); manufacture and application of Pb-containing pesticides; combustion of coal and oil; and waste incineration."

COMMENT (Section 1.1): The Reviewer suggested that it would seem advisable (both in terms of exposure science as well as sensitivity to the politics of lead exposure and associated community vulnerabilities) to insert a reference to lead exposure from changes in water sources and treatment, citing the recent incident in Flint.

RESPONSE: *The Hanna-Attisha et al. (2016) reference on Flint, Michigan was added as suggested by the Reviewer.*

"The combination of corrosive water and Pb pipes or Pb-soldered joints in either the distribution system or individual houses can create localized zones of high Pb water concentrations (EPA 1989d, 2007a; Hanna-Attisha et al. 2016). Other anthropogenic sources of Pb have included mining and smelting of ore; manufacture of and use of Pb-containing products (e.g., Pb-based paints, pigments, and glazes; electrical shielding; plumbing; storage batteries; solder; and welding fluxes); manufacture and application of Pb-containing pesticides; combustion of coal and oil; and waste incineration."

COMMENT (page 3, line 21): The Reviewer noted that evidence indicates there are times during the lifecourse when humans have heightened vulnerability to the toxic effects of lead, such as childhood v. adulthood, the 1st trimester of pregnancy v. 2nd or 3rd, etc. and suggested the following editorial change: Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect is typically unknown or highly uncertain.

RESPONSE: *Revised as suggested.* "The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of evidence regarding health effects in humans. Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not

considered for the identification of health effects associated with Pb. This potentially leaves out discussion of effects that may have been observed in animal models that have not been studied in humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics.

To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of μg/dL). Blood Pb concentration reflects both ongoing exposure and Pb stores in bone, which can be transferred to blood. Because of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months and not necessarily the larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI), which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct, noninvasive measurements of bone Pb concentrations have been used as a metric of long-term exposure on the basis that most of the absorbed Pb retained in the body will reside in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect are typically unknown or highly uncertain.

Adverse health effects of Pb have been observed in every organ system. This is because the mechanisms that induce toxicity are common to all cell types and because Pb is widely distributed throughout the body. Health effects of Pb have been observed in all organ systems over a wide PbB range (≤10–>50 μg/dL). Exposure thresholds for effects on specific organ systems have not been identified and it is not possible to determine from the epidemiological data which organ systems are the most sensitive (i.e., primary) targets for Pb toxicity. It is also important to note that effects observed in adults, especially older adults, may be due to higher environmental or occupational exposures in the past; therefore, exposure history is an important consideration in epidemiological studies on the health effects of Pb.

The most extensively studied health outcomes, as described below, are neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects. Neurological effects of Pb are of greatest concern because effects are observed in infants and children and may result in life-long decrements in neurological function. Infants are born with a Pb burden derived from maternal transfer *in utero* and subsequently can continue to absorb maternal Pb from ingestion of breast milk. 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 following briefly summarizes health effects of chronic exposure to Pb observed in humans. More detailed information, including reference citations, is provided in Chapter 2. "

COMMENT (Section 1.2): The Reviewer noted that: "I think you need to insert reference to the recent studies linking lead exposure with amyotrophic lateral sclerosis and Parkinson's Disease", and suggested the following editorial change: Results of a few studies that have followed children to early adulthood show an association between child PbB and behavioral and neuroanatomical changes in adults, suggesting a possible ~~role~~ impact of exposures in childhood ~~to~~ on adult outcomes.

RESPONSE: *The Weuve et al. (2013) study of associations between blood or bone Pb and amyotrophic lateral sclerosis has been included in the revised draft. The editorial change noted above was made.*

"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 (Power et al. 2014; Schwartz et al. 2005; Wang et al. 2007; Weisskopf et al. 2004, 2007; Wright et al. 2003b).

Table 2-7. 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
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 lead workers, age: 20–70 years	↑ P ↑ T	↑ P ↑ T	↑ P ↑ T	Reaction time, executive function, manual dexterity, vibration threshold, depression
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 lead, amyotrophic lateral sclerosis and hemochromatosis gene polymorphisms
Glass et al. 2009	1,001 adults[a], age: 50–70 years	↑ T	↑ T	–	Interaction between lead 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)

Table 2-7. 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
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
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 lead workers, age: 56 years (mean)	↑ T	↑ T	–	Memory, executive function, manual dexterity
Schwartz et al. 2001	803 exposed lead 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 lead workers, age: 41 years (mean)	↑ T	↑ T	↑ T	Executive function, manual dexterity, vibration threshold, depression

Table 2-7. 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
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
Stewart et al. 2002	529 lead 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 lead and hemochromatosis gene polymorphisms on learning, memory, executive function
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 lead among Parkinson's disease cases)

Table 2-7. 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
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 lead predicted from bone lead.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; C = calcaneous 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 amyotrophic lateral sclerosis (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)."

COMMENT (page 7, line 25): The Reviewer noted the following: For example, see: Schaumberg DA, Mendes F, Balaram M, Dana MR, Sparrow D, Hu H. Accumulated lead exposure and risk of age-related cataract in men. JAMA. 2004 Dec 8;292(22):2750-4. Erratum in: JAMA. 2005 Jan 26;293(4):425. PubMed PMID: 15585735, and suggested the following editorial change: *Ocular Effects (Excluding Neurological Effects).* Limited data provide some evidence that exposure to Pb is associated with macular degeneration in adults and increased risk of cataracts.

RESPONSE: *Change made as noted above. The Schaumberg et al. (2004) study was already noted in Section 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)."

Chapter 2. Health Effects

COMMENT (page 10, line 7): The Reviewer noted that "I think this is justifiable EXCEPT for when animal studies suggest an adverse health effect for which human epi studies simply don't exist, such as the multiple publications by Zawia et al. demonstrating that early life lead exposure is a risk factor for upregulation of amyloid precursor protein production and the appearance of plaques on brain pathology in rodents and monkeys--- all very suggestive that early life lead exposure may be a risk factor for Alzheimer's disease.

Given that ATSDR Profiles are often used as comprehensive reference documents on the proven as well as possible adverse impacts of toxicants, this should be seriously considered in my view."

RESPONSE: *Given the large amount of literature on animal toxicology of Pb and the wealth of information on the health effects of Pb in humans, ATSDR has elected to focus the profile on studies of the toxicology and epidemiology of lead in humans. The Reviewer is correct that this decision leaves out discussion of effects that may have been observed in animal models that have not been studied in humans. ATSDR recognizes that these may be important future targets of epidemiology and clinical toxicology. This concept has been included in Section 1.2 of the revised draft (see below). In Section 2.1 (Introduction, Literature Search Strategy), the following statement is included: "For a recent review of studies in animal models, the reader should consult the EPA's Integrated Science Assessment for Lead (EPA 2014c)."*

"The toxicity of Pb to humans has been known for over 2,000 years, and is not disputed. Early epidemiological studies focused on overt toxicity associated with high occupational exposures. However, during the past few decades, there has been a growing awareness that low-level environmental exposure resulting in PbB <10 µg/dL is associated with adverse effects, particularly in children. As a result, U.S. public health policy has changed to focus on lowering PbB levels to well below 10 µg/dL. Therefore, the primary objective of current research is on health effects associated with PbB ≤10 µg/dL.

The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of evidence regarding health effects in humans.

Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb. This potentially leaves of the profile discussion of effects that may have been observed in animal models that have not been studied humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics."

COMMENT (Section 2.1): The Reviewer suggested the following editorial change: However, neither metric offers a confident estimate of exposure duration or of changes in lead exposure over time (including peak exposure periods that may have occurred in the past), and, in general, the complete exposure history is not known.

RESPONSE: *Change made as suggested. See below in quotations.*

"***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 (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 cumulative blood Pb index (CBLI) or bone Pb. However, neither metric offers a confident estimate of exposure duration or of changes in lead 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 cases 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."

COMMENT (Section 2.1): The Reviewer noted that it may be worth mentioning that occupational exposure to organic lead –which still occurs because of the continued use of leaded gasoline in aviation as well as in gas for automobiles in a few remaining countries such as Algeria---may involve dermal absorption as a significant route of exposure.

RESPONSE: *Statement added as noted above. See below in quotations.*

"***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 (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,"

COMMENT (page 11, line 19): The Reviewer noted that the wording of this is odd. The text recognizes that bone lead is a better biological marker of cumulative lead exposure than blood lead. Thus, it is not surprising that numerous studies have been published showing that bone lead is better than blood lead at predicting some adverse outcomes (e.g., hypertension, Parkinson's Disease, etc.). If the point of the ATSDR profile is to highlight health risks associated with lead exposure, why exclude studies using bone lead simply because bone lead measures aren't available widely? In addition, it needs to be emphasized that bone lead can be estimated by the cumulative blood lead index, i.e., by integrating blood lead levels over time. Thus, even if the emphasis is on information that is useful for surveillance, it seems the ATSDR profile could point out the utility of repeated measures of blood lead over time as a means of assessing cumulative lead exposure (without having to obtain bone lead measures). This specific approach was among those recommended by members of a CDC expert panel:

Kosnett MJ, Wedeen RP, Rothenberg SJ, Hipkins KL, Materna BL, Schwartz BS, Hu H, Woolf A. Recommendations for medical management of adult lead exposure. Environ Health Perspect. 2007 Mar;115(3):463-71. Epub 2006 Dec 22. Review. PubMed PMID: 17431500; PubMed Central PMCID: PMC1849937.

RESPONSE: *The concepts regarding bone as a metric of body burden and cumulative exposure have been reinforced in Sections 1.2, 2.1, and 3.2.1. As previously noted, new subsections, including summary tables of study results, on associations of bone Pb with health outcomes have been added for Cardiovascular, Renal, Neurological, and Developmental Sections of Chapter 2.*

"To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of µg/dL). Blood Pb concentration reflects both ongoing exposure and Pb stores in bone, which can be transferred to blood. Because of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months and not necessarily the larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI), which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct, noninvasive measurements of bone Pb concentrations have been used as a metric of long-term exposure on the basis that most of the absorbed Pb retained in the body will reside in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to

Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect are typically unknown or highly uncertain.

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 (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 cumulative blood Pb index (CBLI) or bone Pb. However, neither metric offers a confident estimate of exposure duration or of changes in lead 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 cases 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.

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 life-time 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).

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 lead exposure and blood pressure. Other cardiovascular endpoints (atherosclerosis, cardiac conduction, cardiovascular disease, and mortality due to cardiovascular disease) also show positive and negative 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 lead exposure that, among individuals with high historical lead exposures, typically remains elevated for many years after the PbB declines to ≤10 μg/dL; these cases are noted in the discussions below.

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 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. 2002b), and mother-child pairs (Zhang et al. 2001). 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 2-8. 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

Table 2-8. Associations Between Bone Pb and Blood Pressure Outcomes

Reference	Population	Blood pressure outcome			
		Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
Martin et al. 2006[a]	964 adults	0 T	0 T	–	↑ T
Perlstein et al. 2007	593 men[b]	–	–	↑ T ↑ P	–
Peters et al. 2007	512 men[b]	–	–	–	↑ T (with high stress) ↑ P (with high stress)
Rothenberg et al. 2002b[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; ↓ = negative association; 0 = no association; – = not reported; C = calcaneous 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). 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).

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, 2005c, 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, 2005c) 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). 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 2-9. Associations Between Bone Pb and Renal Function

		Effect					
Reference	Population	SCr	CCr	NAG	RBP	BUN	ESRD
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. 2005c	795 adult Pb workers[b]	↑ T (>40.6 years)	–	–	–	–	–

Table 2-9. Associations Between Bone Pb and Renal Function

Reference	Population	Effect					
		SCr	CCr	NAG	RBP	BUN	ESRD
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)	–
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: >36–46 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; ↓ = negative 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.

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 stonger for bone Pb (specifically tibia Pb) for environmental exposures and for PbB for occupational exposures.

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).

Table 2-10. 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

Table 2-10. 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
Needleman et al. 2002	194 male cases, 145 controls, age: 12–18 years	–	–	↑ T	Adjudicated delinquency
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; ↓ = negative association; 0 = no association; – = not reported; ADHD = Attention deficit hyperactivity disorder; C = calcaneous 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; 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, one of the largest cross-sectional studies analyzed data from NHANES III (1988–1994) and found no associations between PbB and performance 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. Several studies have examined smaller cohorts from longitudinal studies designed to evaluate health in aging populations. Studies of male cohorts of from the Normative Aging Study have found significant ($p \leq 0.05$) associations between increasing blood and/or bone Pb and 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% CL -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% CL -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 negative 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 ($p\leq0.05$) 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 ($p\leq0.05$) in a PbB stratum 4–7 and to >7 µg/dL compared to stratum <4 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. 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.

Associations Between Bone Pb and Birth Outcome and Post-Natal 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 negatively associated with birth weight (Cantonwine et al. 2010b; Gonzalez-Cossio et al. 1997; 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; Gonzalez-Cossio et al. 1997) or birth length (Hernandez-Avila et al. 2002). Infant weight gain measured at 1 month of age was negatively 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 negatively 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. Taken together, results of these studies provide evidence that long-term maternal Pb exposure is negatively associated with infant size and post-natal growth.

Table 2-11. 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[b]
Afeiche et al. 2011	Mother-infant pairs (522 boys; 477 girls)	0 T (M, F) 0 P (M, F)	–	–	0 T (M, F)[c] 0 P (M, F)[c]	0 T (M, F) 0 P (M) ↓ P (F)
Cantonwine et al. 2010b	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	–	–
Sanin et al. 2001	329 mother-infant pairs	–	–	–	0 T[d] ↓ P[d]	–

[a]From Mexico City.
[b]Measured at 5 years of age.
[c]Measured from birth to 12 months of age.
[d]Measured at 1 month of age.

↓ = negative 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.

In addition to pregnancy, other states of increased bone resorption appear to result in release of bone Pb to blood; these include lactation, osteoporosis, and severe weight loss. Analysis of kinetics of changes in the stable isotope signatures of blood Pb in postpartum women as they came into equilibrium with a novel environmental Pb isotope signature indicated that the release of maternal bone Pb to blood appears to accelerate during lactation (Gulson et al. 2002, 2003, 2004). This is consistent with declines in patella bone Pb (measured by XRF) during lactation without calcium supplementation (Henandez-Avila et al. 1996). Similar approaches have detected increased release of bone Pb to blood in women, in association with menopause (Gulson et al. 2002). These observations are consistent with epidemiological studies that have shown increases in PbB after menopause and in association with decreasing bone density in postmenopausal women (Berkowitz et al. 2004; Garrido Latorre et al. 2003; Hernandez-Avila et al. 2000; Korrick et al. 2002; Nash et al. 2004; Popovic et al. 2005; Symanski and Hertz-Picciotto 1995). In a prospective study of women who were scheduled to undergo bilateral oophorectomy for benign conditions, blood and tibia bone Pb (measured by XRF and adjusted for bone mineral density) did not change 6–18 months post-surgery, regardless of whether patients were given estrogen replacement therapy (Berkowitz et al. 2004). Severe weight loss (28% of BMI in 6 months) in women, which increased bone turnover, increased PbB (Riedt et al. 2009)."

COMMENT (page 12, line 24): The Reviewer noted that the evidence is also growing that pediatric lead exposure is a risk factor for criminal behavior/juvenile delinquency.

RESPONSE: *As previously noted, new subsections, including summary tables of study results, on associations of bone Pb with health outcomes have been added for Cardiovascular, Renal, Neurological, and Developmental Sections of Chapter 2. Studies of associations between blood or bone Pb and delinquency are included in the revised profile (Dietrich et al. 2001; Needleman et al. 1996, 2002).*

COMMENT (Section 2.1): The Reviewer suggested the following editorial change:
Musculoskeletal Effects. Bone loss, osteoporosis, dental caries, tooth loss, and periodontitis.

RESPONSE: *Revised as suggested.*

"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 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."

COMMENT (Section 2.1): The Reviewer suggested the to add cataracts to Ocular Effects.
"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 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."

RESPONSE: *Revised as suggested.*

COMMENT (page 18, line 10): The Reviewer noted that as noted elsewhere in this document, a phrase like this implies that if PbB levels were held "constant" at the levels depicted ("<10 ug/dL, >10 ug/dL"), the outcomes described can be expected. However, these are just the blood lead levels measured AT THE TIME OF THE RESEARCH STUDY---not necessarily the previous, average, or even usual blood lead levels experienced by the individuals studied. In addition, the research then reviewed simply concentrates on the results associated with the measured blood lead levels and completely ignores some of the results associated with measures of cumulative exposure that are incorporated in the same papers (such as Weisskopf et al., 2009, for which I also provided a long comment).

RESPONSE: *As previously noted, new subsections, including summary tables of study results, on associations of bone Pb with health outcomes have been added for Cardiovascular, Renal, Neurological, and Developmental Sections of Chapter 2. Concepts regarding bone as a metric of body burden and cumulative exposure have been reinforced in Sections 1.1, 1.2, 2.1, and 3.3.1.*

"Lead (Pb) is an element that is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world. A major source of Pb in the U.S. environment has historically been anthropogenic emissions to the atmosphere from combustion of leaded gasoline, which was phased out of use after 1973 and then banned in 1995 (with the exception of fuels for piston-driven aircraft) (EPA 1996a). Lead continued to be used as an anti-knock agent in NASCAR fuels until it was phased out beginning in 2008. Deteriorating Pb-based paints from weather surfaces in surfaces (which produce highly concentrated Pb debris and dusts) in older housing stock (pre-1978) continues to be a source of childhood Pb poisoning in the United States (CDC 1991, 2012d). The combination of corrosive water and Pb pipes or Pb-soldered joints in either the distribution system or individual houses can create localized zones of high Pb water concentrations (EPA 1989d, 2007a; Hanna-Attisha et al. 2016). Other anthropogenic sources of Pb have included mining and smelting of ore; manufacture of and use of Pb-containing products (e.g., Pb-based paints, pigments, and glazes; electrical shielding; plumbing; storage batteries; solder; and welding fluxes); manufacture and application of Pb-containing pesticides; combustion of coal and oil; and waste incineration.

Pb does not degrade in the environment, although it can exist in various chemical forms. Particulate matter contaminated with Pb can be transported through air, water, and soil. In general, atmospheric deposition is the largest source of Pb found in soils not impacted by other local non-air sources (e.g., dust from deteriorating leaded paint). Pb is transferred continuously between air, water, and soil by natural

chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb. Pb adsorbs strongly to most soils and does not appreciably leach. Soil acidity (pH) and composition are the most important factors affecting solubility, mobility, and phytoavailability of Pb in soil. Other conditions that increase Pb mobility in soil are reducing conditions and high chloride content.

The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Pb has also been found in a variety of other consumer products including storage batteries, solders, pottery glazes, leaded crystal glassware, cosmetics, hair dyes, jewelry, gun shot and ammunition, relic fishing sinkers, and tire weights. For adults, exposure to levels of Pb beyond background is usually associated with occupational exposures. For children, exposure to high levels of Pb are associated with living in areas contaminated by Pb (e.g., soil or indoor duct in older homes with Pb-based paint). The primary source of Pb exposure to children is from surface dusts (on the ground or entrained) that contain Pb from a variety of sources including deteriorated Pb-based paint (CDC 2009; Lanphear et al. 1998; Succop et al. 1998). Environmental Pb is particularly accessible to children because of their more intensive hand-to-mouth activity and the proximity of the child breathing zone to Pb entrained from surface dusts. Because Pb is transported from soil very slowly, historic sources of deposition of Pb to soil continue to contribute to current exposures (Laidlaw and Filipelli 2008; Laidlaw et al. 2012).

PbB has been used as a biomarker of Pb exposure, and periodic surveys of PbB of the U.S. population are conducted by the Centers for Disease Control and Prevention (CDC). Based on data from the National Health and Nutrition Examination Survey (NHANES) (2013–2014, CDC 2017a), the geometric mean PbB in a representative sample of U.S. adults, ≥20 years old, was 0.967 μg/dL (95% confidence interval [CI] 0.921, 1.02). The geometric mean blood PbB of a representative sample of U.S. children, 1–5 years old, was 0.782 μg/dL (95% CI 0.705, 0.869). PbBs in the U.S. have decreased considerably in the last several decades as a result of removal of Pb from gasoline and restrictions placed on the use of Pb in residential paints (Brody et al. 1994; CDC 2011, 2015; Pirkle et al. 1994, 1998; Schwartz and Pitcher 1989).

Seasonal variations in blood lead concentration (PbB) levels in children have been observed, with a general trend of increasing PbB during late summer and early fall (Gulson et al. 2008; Johnson and Bretsch 2002; Laidlaw et al. 2005). Seasonal patterns in behavior (e.g., outdoor activities) and weather that promotes re-entrainment and transport of dust Pb (humidity and wind velocity) may contribute to the

observed seasonal patterns in PbB (Laidlaw et al. 2005, 2012) and provide additional evidence for surface dusts being a major contributor to child Pb exposure and PbB.

1.2 SUMMARY OF HEALTH EFFECTS

The toxicity of Pb to humans has been known for over 2,000 years, and is not disputed. Early epidemiological studies focused on overt toxicity associated with high occupational exposures. However, during the past few decades, there has been a growing awareness that low-level environmental exposure resulting in PbB <10 µg/dL is associated with adverse effects, particularly in children. As a result, U.S. public health policy has changed to focus on lowering PbB levels to well below 10 µg/dL. Therefore, the primary objective of current research is on health effects associated with PbB ≤10 µg/dL.

The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of evidence regarding health effects in humans. Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb. This potentially leaves of the profile discussion of effects that may have been observed in animal models that have not been studied humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics.

To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of µg/dL). Blood Pb concentration reflects both on-going exposure and Pb stores in bone which can be transferred to blood. Becaue of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months andnot necessarilythe larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI) which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct noninvasive measurement of bone Pb concentrations have been used as metric of long-term exposure on the basis that most of the absorbed retained in the body will resides in

bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect is typically unknown or highly uncertain.

Adverse health effects of Pb have been observed in every organ system. This is because the mechanisms that induce toxicity are common to all cell types and because Pb is widely distributed throughout the body. Health effects of Pb have been observed in all organ systems over a wide PbB range (≤10–>50 µg/dL). Exposure thresholds for effects on specific organ systems have not been identified and it is not possible to determine from the epidemiological data which organ systems are the most sensitive (i.e., primary) targets for Pb toxicity. It is also important to note that effects observed in adults, especially older adults, may be due to higher environmental or occupational exposures in the past; therefore, exposure history is an important consideration in epidemiological studies in the effects of Pb.

The most extensively studied health outcomes, as described below, are neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects. Neurological effects of Pb are of greatest concern because effects are observed in infants and children and may result in life-long decrements in neurological function. Infants are born with a Pb burden derived from maternal transfer in utero and subsequently can continue to absorb maternal Pb from ingestion of breast milk. 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 following briefly summarizes health effects of chronic exposure to Pb observed in humans. More detailed information, including reference citations, is provided in Chapter 2."

"***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 (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 cumulative blood Pb index (CBLI) or bone Pb. However, neither metric offers a confident estimate of exposure duration or of changes in lead 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 cases 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 (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 life-time 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).

Time-integrated measurements of PbB (cumulative blood Pb index, CBLI) may provide a means for accounting for some of these factors and thereby provide a better measure of long-term exposure (Armstrong et al. 1992; Behinaein et al. 2014; Chuang et al. 2000; Fleming et al. 1997; Gerhardsson et al. 1993; Healey et al. 2008; Hu et al. 2007; McNeill et al. 2000; Nie et al. 2011a; Roels et al. 1995). The correlation observed between CBLI and tibia bone Pb concentrations provide supporting evidence for this (Hu et al. 2007).

Bone and Tooth Pb Measurements. The development of noninvasive XRF techniques for measuring Pb concentrations in bone has enabled the exploration of bone Pb as a biomarker of Pb exposure in children and in adults (Behinaein et al. 2011; Chettle et al. 2003; Ji et al. 2014; Nie et al. 2011b; Specht et al. 2016; Todd et al. 2000; Hu et al. 2007). Pb in bone is considered a biomarker of cumulative exposure to Pb because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Pb is not distributed uniformly in bone. Pb will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in both cortical and trabecular bone. This suggests that Pb accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Patella, calcaneus, and sternum XRF measurements primarily reflect Pb in trabecular bone, whereas XRF measurements of midtibia, phalanx, or ulna primarily reflect primarily Pb in cortical bone. Pb levels in cortical bone may be a better indicator of long-term cumulative exposure than Pb in trabecular bone, possibly because Pb in trabecular bone may exchange more actively with Pb in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of Pb in cortical bone, compared to trabecular bone (Behinaein et al. 2014; Borjesson et al. 1997; Brito et al. 2005; Nie et al. 2005; Nilsson et al. 1991; Schutz et al. 1987). Longitudinal studies that have repeatedly measured bone Pb (by XRF) over many years have shown more rapid declines in trabeular bone compared to cortical bone (%) (Kim et al. 1997; Wilker et al. 2011). Estimates of cortical bone Pb

elimination half-times (5–50 years) show a dependence on Pb burden, with longer half-times in people who have higher total body burdens (estimated from CBLI) and bone Pb burdens (Behinaein et al. 2014; Brito et al. 2005; Nie et al. 2005). Further evidence that cortical bone Pb measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone Pb measurements have been compared to PbB. Pb levels in trabecular bone (in adults) correlate more highly with contemporary PbB than do levels of Pb in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical bone Pb measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary PbB measurements (Behinaein et al. 2012; Borjesson et al. 1997; Hu et al. 2007; Roels et al. 1994). Bone Pb levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone Pb may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

Standard methods for bone Pb XRF measurements have not been universally accepted, in part, because the technology continues to be improved, and this needs to be considered in comparisons of measurements reported by different laborites and at different times in development of the methodology used. Historically, two XRF methods have seen the most used in bone Pb epidemiology: K-shell and L-shell methods. The K-shell method is the more widely used, although, improvements in L-shell technology continue to be reported (Nie et al. 2011a). One study reported a correlation of 0.65 between bone Pb measurements made with a portable L-shell device and a K-shell method (Nie et al. 2011a). In general, recent advances in K-shell technology have yielded higher sensitivities (approximately 3 μg/g tibia mineral; Behinaein et al. 2011) than L-shell technology (approximately 8 μg/g tibia bone mineral; Nie et al. 2011a). Precision of K-shell XRF bone Pb measurements have been extensively discussed (Behinaein et al. 2014; Todd et al. 2002; Todd et al. 2001; Aro et al. 2000; Todd et al. 2000). Methodological factors can contribute substantially to observed variability in bone Pb measurements in populations (Behinaein et al. 2014). These factors include bone Pb target, radioactive source, measurement time, and data reduction methods (e.g., approach to handling negative values). Measurement uncertainty also appears to contribute by biological factors, such as body mass index and bone mineral content (Behinaein et al. 2014; Berkowitz et al. 2004; Theppeang et al. 2008a; Hu et al. 2007a). The association between BMI and measurement uncertainty may reflect the effect attenuation of the XRF signal by tissue overlaying the target bone site (Behinaein et al. 2014). Bone mineral can be a factor because XRF measures bone Pb fluorescence in relation to fluorescence from bone calcium and the result is expressed in units of μg Pb per g bone mineral. As a result, variability in bone mineral content

can contribute to variability in measured bone Pb. Typically, potential associations between bone density and bone Pb concentration are not evaluated in epidemiologic studies (Berkowitz et al. 2004; Hu et al. 2007; Theppeang et al. 2008a). An important consequence of expressing bone Pb measures relative to bone mineral content is that lower bone mineral density is associated with greater measurement uncertainty in bone Pb. This uncertainty can have important implications for studies in older women for whom low bone mineral density is more common than in other populations including men and younger adults."

COMMENT (Table 2-1): The Reviewer states the following: "Why not insert here, with an asterisk, the results of Weisskopf et al. 2009 with respect to the measured bone lead levels, which showed a very large and highly statistically significant increase in cardiovascular mortality??? To leave these results out simply because the table only focuses on blood lead levels is misleading and a very big disservice to the public health community."

RESPONSE: *Bone Pb results for the Weisskopf et al. (2009) study were added to the new table (Associations between Bone Pb and Cardiac Function, Disease, and Mortality) in Section 2.6 (Cardiovascular). See Table 2-13 below.*

Table 2-12. 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)	–	–
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)	–	–

Table 2-12. Associations Between Bone Pb and Cardiac Function, Disease, and Mortality

		Outcome		
Reference	Population	Function	Disease	Mortality
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; ↓ = negative association; 0 = no association; – = not reported; AV = atrioventricular; 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

COMMENT (page 21, Table 2-1): The Reviewer noted that there is a serious problem throughout this ATSDR Profile that is reflected by how this study is quoted. It is true that Weisskopf et al. did not see an increase in mortality in relation to blood lead levels in this study. However, the most important findings of this prospective study are the very large, highly statistically significant increase in cardiovascular mortality in association with elevations in bone lead level, a marker of cumulative lead exposure. This paper was published in Circulation, one of the highest ranked clinical journals. I could find no reference to these particular results in this ATSDR Profile, which is a huge omission---and reflects the fact that the Profile does a terrible job of understanding, demonstrating and explaining the difference between outcomes resulting from cumulative exposure (which in epi studies are reflected by bone lead levels) v. acute exposures (since blood lead levels are mostly reflective of recent exposure). Moreover, the men in Weisskopf et al. and other studies of adults in the US developed their cumulative lead exposure burdens largely from blood lead levels that were historically much higher than when the blood lead levels were measured in the studies themselves. NHANES data clearly show that adult blood lead levels in the US were around 15 ug/dL around 1975. As currently written, this draft ATSDR profile mixes epi studies of individuals with high cumulative lead exposure (and therefore, high bone lead levels) but low current lead exposure (and therefore, low current blood lead levels), such as the Normative Aging Study subjects studied by Weisskopf et al.---with studies of individuals with high cumulative lead exposure and high current lead exposure (e.g., studies of occupationally-exposed workers). This is misleading. The document needs to clearly explain the importance of understanding secular trends in lead exposure and the importance of distinguishing and separately evaluating the potential impacts of acute v. cumulative lead exposure in the epi studies quoted and reviewed. For assistance, see key papers published by members of the CDC expert panel on adult lead toxicity.

RESPONSE: *As noted in a response to a comment above, significant revisions to the profile has been made to include new subsections for associations between bone Pb and health outcomes. These new subsections, including summary tables of study results, have been added for Cardiovascular, Renal, Neurological, and Developmental Sections. Results of the bone results from the Weisskopf et al. (2009) study was added to a new table* (*Associations between Bone Pb and Cardiovascular Effects) in Section 2.6 (Cardiovascular). Concepts regarding bone as a metric of body burden and cumulative exposure have been reinforced in Sections 1.1, 1.2, 2.1, and 3.3.1.*

“Lead (Pb) is an element that is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world. A major source of Pb in the U.S. environment has historically been anthropogenic emissions to the atmosphere from combustion of leaded gasoline, which was phased out of use after 1973 and then banned in 1995 (with the exception of fuels for piston-driven aircraft) (EPA 1996a). Lead continued to be used as an anti-knock agent in NASCAR fuels until it was phased out beginning in 2008. Deteriorating Pb-based paints from weather surfaces in surfaces (which produce highly concentrated Pb debris and dusts) in older housing stock (pre-1978) continues to be a source of childhood Pb poisoning in the United States (CDC 1991, 2012d). The combination of corrosive water and Pb pipes or Pb-soldered joints in either the distribution system or individual houses can create localized zones of high Pb water concentrations (EPA 1989d, 2007a; Hanna-Attisha et al. 2016). Other anthropogenic sources of Pb have included mining and smelting of ore; manufacture of and use of Pb-containing products (e.g., Pb-based paints, pigments, and glazes; electrical shielding; plumbing; storage batteries; solder; and welding fluxes); manufacture and application of Pb-containing pesticides; combustion of coal and oil; and waste incineration.

Pb does not degrade in the environment, although it can exist in various chemical forms. Particulate matter contaminated with Pb can be transported through air, water, and soil. In general, atmospheric deposition is the largest source of Pb found in soils not impacted by other local non-air sources (e.g., dust from deteriorating leaded paint). Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb. Pb adsorbs strongly to most soils and does not appreciably leach. Soil acidity (pH) and composition are the most important factors affecting solubility, mobility, and phytoavailability of Pb in soil. Other conditions that increase Pb mobility in soil are reducing conditions and high chloride content.

The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Pb has also been found in a variety of other consumer products including storage batteries, solders, pottery glazes, leaded crystal glassware, cosmetics, hair dyes, jewelry, gun shot and ammunition, relic fishing sinkers, and tire weights. For adults, exposure to levels of Pb beyond background is usually associated with occupational exposures. For children, exposure to high levels of Pb are associated with living in areas contaminated by Pb (e.g., soil or indoor duct in older homes with Pb-based paint). The primary source of Pb exposure to children is from surface dusts (on the ground or entrained) that contain Pb from a variety of sources including deteriorated Pb-based paint (CDC 2009; Lanphear et al. 1998; Succop et al. 1998). Environmental Pb is particularly accessible to children because of their more intensive hand-to-

mouth activity and the proximity of the child breathing zone to Pb entrained from surface dusts. Because Pb is transported from soil very slowly, historic sources of deposition of Pb to soil continue to contribute to current exposures (Laidlaw and Filipelli 2008; Laidlaw et al. 2012).

PbB has been used as a biomarker of Pb exposure, and periodic surveys of PbB of the U.S. population are conducted by the Centers for Disease Control and Prevention (CDC). Based on data from the National Health and Nutrition Examination Survey (NHANES) (2013–2014, CDC 2017a), the geometric mean PbB in a representative sample of U.S. adults, ≥20 years old, was 0.967 μg/dL (95% confidence interval [CI] 0.921, 1.02). The geometric mean blood PbB of a representative sample of U.S. children, 1–5 years old, was 0.782 μg/dL (95% CI 0.705, 0.869). PbBs in the U.S. have decreased considerably in the last several decades as a result of removal of Pb from gasoline and restrictions placed on the use of Pb in residential paints (Brody et al. 1994; CDC 2011, 2015; Pirkle et al. 1994, 1998; Schwartz and Pitcher 1989).

Seasonal variations in blood lead concentration (PbB) levels in children have been observed, with a general trend of increasing PbB during late summer and early fall (Gulson et al. 2008; Johnson and Bretsch 2002; Laidlaw et al. 2005). Seasonal patterns in behavior (e.g., outdoor activities) and weather that promotes re-entrainment and transport of dust Pb (humidity and wind velocity) may contribute to the observed seasonal patterns in PbB (Laidlaw et al. 2005, 2012) and provide additional evidence for surface dusts being a major contributor to child Pb exposure and PbB.

1.2 SUMMARY OF HEALTH EFFECTS

The toxicity of Pb to humans has been known for over 2,000 years, and is not disputed. Early epidemiological studies focused on overt toxicity associated with high occupational exposures. However, during the past few decades, there has been a growing awareness that low-level environmental exposure resulting in PbB <10 μg/dL is associated with adverse effects, particularly in children. As a result, U.S. public health policy has changed to focus on lowering PbB levels to well below 10 μg/dL. Therefore, the primary objective of current research is on health effects associated with PbB ≤10 μg/dL.

The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of evidence regarding health effects in humans. Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large

number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb. This potentially leaves of the profile discussion of effects that may have been observed in animal models that have not been studied humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics.

To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of µg/dL). Blood Pb concentration reflects both on-going exposure and Pb stores in bone which can be transferred to blood. Becaue of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months andnot necessarilythe larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI) which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct noninvasive measurement of bone Pb concentrations have been used as metric of long-term exposure on the basis that most of the absorbed retained in the body will resides in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect is typically unknown or highly uncertain.

Adverse health effects of Pb have been observed in every organ system. This is because the mechanisms that induce toxicity are common to all cell types and because Pb is widely distributed throughout the body. Health effects of Pb have been observed in all organ systems over a wide PbB range (≤10–>50 µg/dL). Exposure thresholds for effects on specific organ systems have not been identified and it is not possible to determine from the epidemiological data which organ systems are the most sensitive (i.e., primary) targets for Pb toxicity. It is also important to note that effects observed in adults, especially older adults, may be due to higher environmental or occupational exposures in the past; therefore, exposure history is an important consideration in epidemiological studies in the effects of Pb.

The most extensively studied health outcomes, as described below, are neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects. Neurological effects of Pb are of greatest concern because effects are observed in infants and children and may result in life-long decrements in neurological function. Infants are born with a Pb burden derived from maternal transfer in utero and subsequently can continue to absorb maternal Pb from ingestion of breast milk. 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 following briefly summarizes health effects of chronic exposure to Pb observed in humans. More detailed information, including reference citations, is provided in Chapter 2."

"***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 (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 cumulative blood Pb index (CBLI) or bone Pb. However, neither metric offers a confident estimate of exposure duration or of changes in lead 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 cases 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 (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 life-time 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).

Time-integrated measurements of PbB (cumulative blood Pb index, CBLI) may provide a means for accounting for some of these factors and thereby provide a better measure of long-term exposure (Armstrong et al. 1992; Behinaein et al. 2014; Chuang et al. 2000; Fleming et al. 1997; Gerhardsson et al. 1993; Healey et al. 2008; Hu et al. 2007; McNeill et al. 2000; Nie et al. 2011a; Roels et al. 1995). The correlation observed between CBLI and tibia bone Pb concentrations provide supporting evidence for this (Hu et al. 2007).

Bone and Tooth Pb Measurements. The development of noninvasive XRF techniques for measuring Pb concentrations in bone has enabled the exploration of bone Pb as a biomarker of Pb exposure in children and in adults (Behinaein et al. 2011; Chettle et al. 2003; Ji et al. 2014; Nie et al. 2011b; Specht et al. 2016; Todd et al. 2000; Hu et al. 2007). Pb in bone is considered a biomarker of cumulative exposure to Pb because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Pb is not distributed uniformly in bone. Pb will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in both cortical and trabecular bone. This suggests that Pb accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Patella, calcaneus, and sternum XRF measurements primarily reflect Pb in trabecular bone, whereas XRF measurements of midtibia, phalanx, or ulna primarily reflect primarily Pb in cortical bone. Pb levels in cortical bone may be a better indicator of long-term cumulative exposure than Pb in trabecular bone, possibly because Pb in trabecular bone may exchange more actively with Pb in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of Pb in cortical bone, compared to trabecular bone (Behinaein et al. 2014; Borjesson et al. 1997; Brito et al. 2005; Nie et al. 2005; Nilsson et al. 1991; Schutz et al. 1987). Longitudinal studies that have repeatedly measured bone Pb (by XRF) over many years have shown more rapid declines in trabeular bone compared to cortical bone (%) (Kim et al. 1997; Wilker et al. 2011). Estimates of cortical bone Pb elimination half-times (5–50 years) show a dependence on Pb burden, with longer half-times in people who have higher total body burdens (estimated from CBLI) and bone Pb burdens (Behinaein et al. 2014; Brito et al. 2005; Nie et al. 2005). Further evidence that cortical bone Pb measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone Pb measurements have been compared to PbB. Pb levels in trabecular bone (in adults) correlate more highly with contemporary PbB than do levels of Pb in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical bone Pb measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary PbB measurements (Behinaein et al. 2012; Borjesson et al. 1997; Hu et al. 2007; Roels et al. 1994). Bone Pb levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone Pb may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

Standard methods for bone Pb XRF measurements have not been universally accepted, in part, because the technology continues to be improved, and this needs to be considered in comparisons of measurements reported by different laborites and at different times in development of the methodology used. Historically, two XRF methods have seen the most used in bone Pb epidemiology: K-shell and L-shell methods. The K-shell method is the more widely used, although, improvements in L-shell technology continue to be reported (Nie et al. 2011a). One study reported a correlation of 0.65 between bone Pb measurements made with a portable L-shell device and a K-shell method (Nie et al. 2011a). In general, recent advances in K-shell technology have yielded higher sensitivities (approximately 3 µg/g tibia mineral; Behinaein et al. 2011) than L-shell technology (approximately 8 µg/g tibia bone mineral; Nie et al. 2011a). Precision of K-shell XRF bone Pb measurements have been extensively discussed (Behinaein et al. 2014; Todd et al. 2002; Todd et al. 2001; Aro et al. 2000; Todd et al. 2000). Methodological factors can contribute substantially to observed variability in bone Pb measurements in populations (Behinaein et al. 2014). These factors include bone Pb target, radioactive source, measurement time, and data reduction methods (e.g., approach to handling negative values). Measurement uncertainty also appears to contribute by biological factors, such as body mass index and bone mineral content (Behinaein et al. 2014; Berkowitz et al. 2004; Theppeang et al. 2008a; Hu et al. 2007a). The association between BMI and measurement uncertainty may reflect the effect attenuation of the XRF signal by tissue overlaying the target bone site (Behinaein et al. 2014). Bone mineral can be a factor because XRF measures bone Pb fluorescence in relation to fluorescence from bone calcium and the result is expressed in units of µg Pb per g bone mineral. As a result, variability in bone mineral content can contribute to variability in measured bone Pb. Typically, potential associations between bone density and bone Pb concentration are not evaluated in epidemiologic studies (Berkowitz et al. 2004; Hu et al. 2007; Theppeang et al. 2008a). An important consequence of expressing bone Pb measures relative to bone mineral content is that lower bone mineral density is associated with greater measurement uncertainty in bone Pb. This uncertainty can have important implications for studies in older women for whom low bone mineral density is more common than in other populations including men and younger adults."

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;	–	–

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

Reference	Population	Outcome		
		Function	Disease	Mortality
		AV block; IV block) ↑ P (QT and QRS intervals) 0 P (AV block; IV block)		
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; ↓ = negative association; 0 = no association; – = not reported; AV = atrioventricular; 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

COMMENT (Section 2.6): The Reviewer suggested the following editorial change: In some cases, although no associations between PbB and cardiovascular outcomes were observed, associations were observed for bone Pb, a biomarker of cumulative lead exposure that, among individuals with high historical lead exposures, typically remains elevated for many years after the blood lead levels decline to ~~concentrations at concomitant PbB~~ ≤10 µg/dL; these cases are noted in the discussions below.

RESPONSE: *Revised as suggested.*

*"**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 lead exposure and blood pressure. Other cardiovascular endpoints (atherosclerosis,

cardiac conduction, cardiovascular disease, and mortality due to cardiovascular disease) also show positive and negative 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 lead exposure that, among individuals with high historical lead exposures, typically remains elevated for many years after the PbB declines to ≤10 µg/dL; these cases are noted in the discussions below."

COMMENT (page 45, line 17): The Reviewer noted that Weisskopf et al. 2009 is a study of middle-aged to elderly adults (not children)

RESPONSE: *Weisskopf et al. (2009) was deleted from the paragraph discussing associations between PbB and cardiovascular function in children in section 2.6.*

"Several studies have evaluated associations between PbB and cardiovascular function in children (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."

COMMENT (Section 2.6): The Reviewer noted the following: "In Weisskopf et al., no effect was seen with respect to blood lead; however, bone lead was a major, significant predictor or cardiovascular mortality. Again, this document has to do a better job of discussing the different biological markers of lead dose, what they mean with respect to acute vs. cumulative exposure, and for studies that used both blood and bone lead biomarkers, reporting the results of each."

RESPONSE: *As noted in responses above, the profile has been revised to include subsections on associations between bone Pb and health outcomes. Results of the Weisskopf et al. (2007) paper for associations between bone Pb and cardiovascular mortality have been added this the new subsection of Section 2.6 (Cardiovascular). However, in this publication, there was no significant association between bone Pb and cardiovascular mortality, based on 95% confidence intervals and p-values. Concepts regarding bone as a metric of body burden and cumulative exposure have been reinforced in Sections 1.1, 1.2, 2.1, and 3.3.1.*

"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; Menke et al. 2006; Schober et al. 2006). Aoki et al.

(2016) and Menke et al. (2006) observed positive associations of mortality due to cardiovascular disease, including 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)."

"Lead (Pb) is an element that is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world. A major source of Pb in the U.S. environment has historically been anthropogenic emissions to the atmosphere from combustion of leaded gasoline, which was phased out of use after 1973 and then banned in 1995 (with the exception of fuels for piston-driven aircraft) (EPA 1996a). Lead continued to be used as an anti-knock agent in NASCAR fuels until it was phased out beginning in 2008. Deteriorating Pb-based paints from weather surfaces in surfaces (which produce highly concentrated Pb debris and dusts) in older housing stock (pre-1978) continues to be a source of childhood Pb poisoning in the United States (CDC 1991, 2012d). The combination of corrosive water and Pb pipes or Pb-soldered joints in either the distribution system or individual houses can create localized zones of high Pb water concentrations (EPA 1989d, 2007a; Hanna-Attisha et al. 2016). Other anthropogenic sources of Pb have included mining and smelting of ore; manufacture of and use of Pb-containing products (e.g., Pb-based paints, pigments, and glazes; electrical shielding; plumbing; storage batteries; solder; and welding fluxes); manufacture and application of Pb-containing pesticides; combustion of coal and oil; and waste incineration.

Pb does not degrade in the environment, although it can exist in various chemical forms. Particulate matter contaminated with Pb can be transported through air, water, and soil. In general, atmospheric deposition is the largest source of Pb found in soils not impacted by other local non-air sources (e.g., dust from deteriorating leaded paint). Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb. Pb adsorbs strongly to most soils and does not appreciably leach. Soil acidity (pH) and composition are the most important factors affecting solubility, mobility, and phytoavailability of Pb in soil. Other conditions that increase Pb mobility in soil are reducing conditions and high chloride content.

The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Pb has also been found in a variety of other consumer products including storage batteries, solders, pottery glazes, leaded crystal glassware, cosmetics, hair dyes, jewelry, gun shot and ammunition, relic fishing sinkers, and tire weights. For adults, exposure to levels of Pb beyond background is usually associated with occupational exposures. For children, exposure to high levels of Pb are associated with living in areas contaminated by Pb (e.g., soil or indoor duct in older homes with Pb-based paint). The primary source of Pb exposure to children is from surface dusts (on the ground or entrained) that contain Pb from a variety of sources including deteriorated Pb-based paint (CDC 2009; Lanphear et al. 1998; Succop et al. 1998). Environmental Pb is particularly accessible to children because of their more intensive hand-to-mouth activity and the proximity of the child breathing zone to Pb entrained from surface dusts. Because Pb is transported from soil very slowly, historic sources of deposition of Pb to soil continue to contribute to current exposures (Laidlaw and Filipelli 2008; Laidlaw et al. 2012).

PbB has been used as a biomarker of Pb exposure, and periodic surveys of PbB of the U.S. population are conducted by the Centers for Disease Control and Prevention (CDC). Based on data from the National Health and Nutrition Examination Survey (NHANES) (2013–2014, CDC 2017a), the geometric mean PbB in a representative sample of U.S. adults, ≥20 years old, was 0.967 μg/dL (95% confidence interval [CI] 0.921, 1.02). The geometric mean blood PbB of a representative sample of U.S. children, 1–5 years old, was 0.782 μg/dL (95% CI 0.705, 0.869). PbBs in the U.S. have decreased considerably in the last several decades as a result of removal of Pb from gasoline and restrictions placed on the use of Pb in residential paints (Brody et al. 1994; CDC 2011, 2015; Pirkle et al. 1994, 1998; Schwartz and Pitcher 1989).

Seasonal variations in blood lead concentration (PbB) levels in children have been observed, with a general trend of increasing PbB during late summer and early fall (Gulson et al. 2008; Johnson and Bretsch 2002; Laidlaw et al. 2005). Seasonal patterns in behavior (e.g., outdoor activities) and weather that promotes re-entrainment and transport of dust Pb (humidity and wind velocity) may contribute to the observed seasonal patterns in PbB (Laidlaw et al. 2005, 2012) and provide additional evidence for surface dusts being a major contributor to child Pb exposure and PbB.

1.2 SUMMARY OF HEALTH EFFECTS

The toxicity of Pb to humans has been known for over 2,000 years, and is not disputed. Early epidemiological studies focused on overt toxicity associated with high occupational exposures. However,

during the past few decades, there has been a growing awareness that low-level environmental exposure resulting in PbB <10 µg/dL is associated with adverse effects, particularly in children. As a result, U.S. public health policy has changed to focus on lowering PbB levels to well below 10 µg/dL. Therefore, the primary objective of current research is on health effects associated with PbB ≤10 µg/dL.

The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of evidence regarding health effects in humans. Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb. This potentially leaves of the profile discussion of effects that may have been observed in animal models that have not been studied humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics.

To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of µg/dL). Blood Pb concentration reflects both on-going exposure and Pb stores in bone which can be transferred to blood. Becaue of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months andnot necessarilythe larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI) which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct noninvasive measurement of bone Pb concentrations have been used as metric of long-term exposure on the basis that most of the absorbed retained in the body will resides in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect is typically unknown or highly uncertain.

Adverse health effects of Pb have been observed in every organ system. This is because the mechanisms that induce toxicity are common to all cell types and because Pb is widely distributed throughout the body. Health effects of Pb have been observed in all organ systems over a wide PbB range (≤10–>50 µg/dL). Exposure thresholds for effects on specific organ systems have not been identified and it is not possible to determine from the epidemiological data which organ systems are the most sensitive (i.e., primary) targets for Pb toxicity. It is also important to note that effects observed in adults, especially older adults, may be due to higher environmental or occupational exposures in the past; therefore, exposure history is an important consideration in epidemiological studies in the effects of Pb.

The most extensively studied health outcomes, as described below, are neurological, renal, cardiovascular, hematological, immunological, reproductive, and developmental effects. Neurological effects of Pb are of greatest concern because effects are observed in infants and children and may result in life-long decrements in neurological function. Infants are born with a Pb burden derived from maternal transfer in utero and subsequently can continue to absorb maternal Pb from ingestion of breast milk. 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 following briefly summarizes health effects of chronic exposure to Pb observed in humans. More detailed information, including reference citations, is provided in Chapter 2."

"***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 (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 cumulative blood Pb index (CBLI) or bone Pb. However, neither metric offers a confident estimate of exposure duration or of changes in lead 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 cases 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 (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 life-time 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). “

". Time-integrated measurements of PbB (cumulative blood Pb index, CBLI) may provide a means for accounting for some of these factors and thereby provide a better measure of long-term exposure (Armstrong et al. 1992; Behinaein et al. 2014; Chuang et al. 2000; Fleming et al. 1997; Gerhardsson et al. 1993; Healey et al. 2008; Hu et al. 2007; McNeill et al. 2000; Nie et al. 2011a; Roels et al. 1995). The correlation observed between CBLI and tibia bone Pb concentrations provide supporting evidence for this (Hu et al. 2007).

Bone and Tooth Pb Measurements. The development of noninvasive XRF techniques for measuring Pb concentrations in bone has enabled the exploration of bone Pb as a biomarker of Pb exposure in children and in adults (Behinaein et al. 2011; Chettle et al. 2003; Ji et al. 2014; Nie et al. 2011b; Specht et al. 2016; Todd et al. 2000; Hu et al. 2007). Pb in bone is considered a biomarker of cumulative exposure to Pb because Pb accumulates in bone over the lifetime and most of the Pb body burden resides in bone. Pb is not distributed uniformly in bone. Pb will accumulate in those regions of bone undergoing the most active calcification at the time of exposure. During infancy and childhood, bone calcification is most active in trabecular bone, whereas in adulthood, calcification occurs at sites of remodeling in both cortical and trabecular bone. This suggests that Pb accumulation will occur predominantly in trabecular bone during childhood, and in both cortical and trabecular bone in adulthood (Aufderheide and Wittmers 1992). Patella, calcaneus, and sternum XRF measurements primarily reflect Pb in trabecular bone, whereas XRF measurements of midtibia, phalanx, or ulna primarily reflect primarily Pb in cortical bone. Pb levels in cortical bone may be a better indicator of long-term cumulative exposure than Pb in trabecular bone, possibly because Pb in trabecular bone may exchange more actively with Pb in blood than does cortical bone. This is consistent with estimates of a longer elimination half-time of Pb in cortical bone, compared to trabecular bone (Behinaein et al. 2014; Borjesson et al. 1997; Brito et al. 2005; Nie et al. 2005; Nilsson et al. 1991; Schutz et al. 1987). Longitudinal studies that have repeatedly measured bone Pb (by XRF) over many years have shown more rapid declines in trabeular bone compared to cortical bone (%) (Kim et al. 1997; Wilker et al. 2011). Estimates of cortical bone Pb elimination half-times (5–50 years) show a dependence on Pb burden, with longer half-times in people who have higher total body burdens (estimated from CBLI) and bone Pb burdens (Behinaein et al. 2014; Brito et al. 2005; Nie et al. 2005). Further evidence that cortical bone Pb measurements may provide a better reflection of long-term exposure than do measurements of trabecular bone comes from studies in which cortical and trabecular bone Pb measurements have been compared to PbB. Pb levels in trabecular bone (in adults) correlate more highly with contemporary PbB than do levels of Pb in cortical bone (Erkkila et al. 1992; Hernandez-Avila et al. 1996; Hu et al. 1996b, 1998; Watanabe et al. 1994). Cortical

bone Pb measurements correlate well with time-integrated PbB measurements, which would be expected to be a better reflection of cumulative exposure than contemporary PbB measurements (Behinaein et al. 2012; Borjesson et al. 1997; Hu et al. 2007; Roels et al. 1994). Bone Pb levels tend to increase with age (Hu et al. 1996b; Kosnett et al. 1994; Roy et al. 1997), although the relationship between age and bone Pb may be stronger after adolescence (Hoppin et al. 1997). These observations are consistent with cortical bone reflecting cumulative exposures over the lifetime.

Standard methods for bone Pb XRF measurements have not been universally accepted, in part, because the technology continues to be improved, and this needs to be considered in comparisons of measurements reported by different laborites and at different times in development of the methodology used. Historically, two XRF methods have seen the most used in bone Pb epidemiology: K-shell and L-shell methods. The K-shell method is the more widely used, although, improvements in L-shell technology continue to be reported (Nie et al. 2011a). One study reported a correlation of 0.65 between bone Pb measurements made with a portable L-shell device and a K-shell method (Nie et al. 2011a). In general, recent advances in K-shell technology have yielded higher sensitivities (approximately 3 μg/g tibia mineral; Behinaein et al. 2011) than L-shell technology (approximately 8 μg/g tibia bone mineral; Nie et al. 2011a). Precision of K-shell XRF bone Pb measurements have been extensively discussed (Behinaein et al. 2014; Todd et al. 2002; Todd et al. 2001; Aro et al. 2000; Todd et al. 2000). Methodological factors can contribute substantially to observed variability in bone Pb measurements in populations (Behinaein et al. 2014). These factors include bone Pb target, radioactive source, measurement time, and data reduction methods (e.g., approach to handling negative values). Measurement uncertainty also appears to contribute by biological factors, such as body mass index and bone mineral content (Behinaein et al. 2014; Berkowitz et al. 2004; Hu et al. 2007a; Theppeang et al. 2008a). The association between BMI and measurement uncertainty may reflect the effect attenuation of the XRF signal by tissue overlaying the target bone site (Behinaein et al. 2014). Bone mineral can be a factor because XRF measures bone Pb fluorescence in relation to fluorescence from bone calcium and the result is expressed in units of μg Pb per g bone mineral. As a result, variability in bone mineral content can contribute to variability in measured bone Pb. Typically, potential associations between bone density and bone Pb concentration are not evaluated in epidemiologic studies (Berkowitz et al. 2004; Hu et al. 2007a; Theppeang et al. 2008a). An important consequence of expressing bone Pb measures relative to bone mineral content is that lower bone mineral density is associated with greater measurement uncertainty in bone Pb. This uncertainty can have important implications for studies in older women for whom low bone mineral density is more common than in other populations including men and younger adults."

Table 2-14. Associations Between Bone Pb and Cardiac Function, Disease, and Mortality

Reference	Population	Outcome		
		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)	–	–
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; ↓ = negative association; 0 = no association; – = not reported; AV = atrioventricular; 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

COMMENT (Section 2.6): The Reviewer suggested the following text inclusion: The association between cumulative lead exposure (as reflected by bone lead levels) and elevations in pulse pressure (Perlstein et al., 2007; Zhang et al., 2010) also suggests that lead's effects on cardiovascular function may be exerted in part through loss of arterial elasticity.

RESPONSE: *The above statement was added to the new subsection (Associations between Bone Pb and Cardiovascular Effects) in Section 2.6 (Cardiovascular).*

*"**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 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. 2002b), and mother-child pairs (Zhang et al. 2001). 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. "

COMMENT (page 65, line 8): The Reviewer noted that the following should be included in the profile:

- Perlstein T, Weuve J, Schwartz J, Sparrow D, Wright R, Litonjua A, Nie H, Hu H. Bone and blood lead levels in relation to pulse pressure in community-exposed men: the Normative Aging Study. Environ Health Perspec 2007 Dec;115(12):1696-700. PMID: 18087585
- Zhang A, Park SK, Wright RO, Weisskopf MG, Mukherjee B, Nie H, Sparrow D, Hu H. HFE H63D polymorphism as a modifier of the effect of cumulative lead exposure on pulse pressure: the Normative Aging Study. Environ Health Perspect. 2010 Sep;118(9):1261-6. Epub 2010 May 14. PubMed PMID: 20478760; PubMed Central PMCID: PMC2944087.

RESPONSE: *Perlstein et al. (2007) and Zhang et al. (2010) have been added to the new subsection (Associations between Bone Pb and Cardiovascular Effects) in Section 2.6 (Cardiovascular).*

"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 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. 2002b), and mother-child pairs (Zhang et al. 2001). 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 2-15. 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

Table 2-15. Associations Between Bone Pb and Blood Pressure Outcomes

Reference	Population	Blood pressure outcome			
		Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
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	–
Peters et al. 2007	512 men[b]	–	–	–	↑ T (with high stress) ↑ P (with high stress)
Rothenberg et al. 2002b[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	–

Table 2-15. Associations Between Bone Pb and Blood Pressure Outcomes

Reference	Population	Blood pressure outcome			
		Systolic blood pressure	Diastolic blood pressure	Pulse pressure	Hypertension
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; ↓ = negative association; 0 = no association; – = not reported; C = calcaneous 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). 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)."

COMMENT (Table 2-28): Reviewer suggested the following text inclusion: Weisskopf et al., 2010 Lead exposure and Parkinson's Disease; also Gorrell et al., etc.

RESPONSE: *Studies of associations between blood or bone Pb and Parkinson's are included in the revised draft (Coon et al. 2006; Weisskopf et al. 2010). The Gorrell et al. (1999) study was not included because it did not examine associations with blood or bone Pb; it examined associations between years of occupation exposure and Parkinson's Disease.*

“

Table 2-16. 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 lead workers, age: 20–70 years	↑ P ↑ T	↑ P ↑ T	↑ P ↑ T	Reaction time, executive function, manual dexterity, vibration threshold, depression
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 lead, amyotrophic lateral sclerosis and hemochromatosis gene polymorphisms
Glass et al. 2009	1,001 adults[a], age: 50–70 years	↑ T	↑ T	–	Interaction between lead 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

Table 2-16. 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
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
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 lead workers, age: 56 years (mean)	↑ T	↑ T	–	Memory, executive function, manual dexterity
Schwartz et al. 2001	803 exposed lead 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

Table 2-16. 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
Schwartz et al. 2005	576 exposed lead 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
Stewart et al. 2002	529 lead 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 lead and hemochromatosis gene polymorphisms on learning, memory, executive function
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

Table 2-16. 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
Weuve et al. 2013	101 cases and 50 controls, age: 55–80 years	0 P ↑ T	–	–	Learning, memory (stronger association with lead among Parkinson's disease cases)
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 lead predicted from bone lead.

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

COMMENT (page 161, Table 2-28): The Reviewer noted the following: Weisskopf MG, Weuve J, Nie H, Saint-Hilaire M-H, Sudarsky L, Simon DK, Hersh B, Schwartz J, Wright RO, Hu H. Association of Cumulative Lead Exposure with Parkinson's Disease. *Environ Health Perspec 2010; 118:1609–1613, PMID: 20807691; PMCID: PMC2974701

RESPONSE: *Studies of associations between blood or bone Pb and Parkinson's are included in the revised draft (Coon et al. 2006; Weisskopf et al. 2010).*

*"**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; 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; 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 (Power et al. 2014; Schwartz et al. 2005; Wang et al. 2007; Weisskopf et al. 2004, 2007; Wright et al. 2003b).

Table 2-17. 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 lead workers, age: 20–70 years	↑ P ↑ T	↑ P ↑ T	↑ P ↑ T	Reaction time, executive function, manual dexterity, vibration threshold, depression
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 lead, amyotrophic lateral sclerosis and hemochromatosis gene polymorphisms

Table 2-17. 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
Glass et al. 2009	1,001 adults[a], age: 50–70 years	↑ T	↑ T	–	Interaction between lead 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
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

Table 2-17. 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
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 lead workers, age: 56 years (mean)	↑ T	↑ T	–	Memory, executive function, manual dexterity
Schwartz et al. 2001	803 exposed lead 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 lead 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
Stewart et al. 2002	529 lead 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 lead and hemochromatosis gene polymorphisms on learning, memory, executive function

Table 2-17. 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
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 lead among Parkinson's disease cases)
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 lead predicted from bone lead.

↑ = positive association; ↓ = negative association; 0 = no association; – = not reported; C = calcaneous 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 amyotrophic lateral sclerosis (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)."

COMMENT (page 235, line 4): The Reviewer noted the following: Why not cite the primary studies, as this monograph does in most other cases, rather than the EPA review?

RESPONSE: *Typically, when literature is extensive, ATSDR prefers to rely on authoritative reviews as the main source for describing mechanisms. This is the case for epigenetic mechanisms. Rather than attempting to review and cite the numerous studies on the subject, ATSDR has elected to rely on authoritative reviews.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

COMMENT (page 285, line 7): The Reviewer noted the following: "I don't agree. I think this monograph needs to go over recent studies of HFE as a modifier of lead and cognition and cardiovascular effects, which appear fairly consistent in demonstrating that the HFE variants are associated with worse impacts of lead."

RESPONSE: *This sentence indicated above was deleted and replaced with the following: "HFE polymorphisms have been shown to enhance Pb-induced cognitive impairment (Want et al. 2007) and the HFE H63D polymorphism appears to enhance positive associations between bone Pb and pulse pressure (Zhang et al. 2010)."*

COMMENT (page 285, line 23): The Reviewer noted the following: Roy A, Hu H, Bellinger DC, Mukherjee B, Modali R, Nasaruddin K, Schwartz J, Wright RO, Ettinger AS, Palaniapan K, Balakrishnan K. Hemoglobin, Lead Exposure, and Intelligence Quotient: Effect Modification by the DRD2 Taq IA Polymorphism. Environ Health Perspect. 2011 Jan;119(1):144-9. PubMed PMID: 21205584.

RESPONSE: *The reference noted in the comment was added as suggested.*

COMMENT (page 287, line 7): The Reviewer noted the following: "I don't agree with this. Given that biomarkers need to be thought of both for clinical utility as well as value in epidemiologic studies, I think the ideal "situation" is being able to have separate biomarkers of total Pb body burden (fairly equivalent to cumulative Pb burden), which is well-reflected by non-invasively measured KXRF bone lead levels; recent or acute lead exposure (so that a clinician will know to look for current lead exposures that can be mitigated), as well-reflected by blood lead levels; and lead exposure that may have occurred at certain sensitive time periods during the life course, such as prenatally. The latter is now being well-served in epidemiologic studies by the method of measuring lead in shed deciduous teeth developed by Arora et al. (Arora M, Austin C, Sarrafpour B, Hernández-Ávila M, Hu H, Wright RO, Tellez-Rojo MM. Determining prenatal, early childhood and cumulative long-term lead exposure using micro-spatial deciduous dentine levels. PLoS One. 2014 May 19;9(5):e97805. doi: 10.1371/journal.pone.0097805. eCollection 2014. PubMed PMID: 24841926; PubMed Central PMCID: PMC4026445.)"

RESPONSE: *The statement "The ideal biomarker of Pb exposure would be a measurement of total Pb body burden." has been deleted. Studies of micro-spatial measurement of dentine Pb are cited in the revised draft (Arora et al. 2014; Shepherd et al. 2016).*

"Tooth Pb has been considered a potential biomarker for measuring long-term exposure to Pb (e.g., years) because Pb that accumulates in tooth dentin and enamel appears to be retained until the tooth is shed or extracted (Costa de Almeida et al. 2007; Ericson 2001; Fosse et al. 1995; Gomes et al. 2004; Gulson and Wilson 1994: Gulson et al. 1996; Omar et al. 2001; Rabinowitz 1995; Rabinowitz et al. 1989, 1993; Robbins et al. 2010; Steenhout and Pourtois 1987; Tvinnereim et al. 1997). Formation of enamel and primary dentin of deciduous teeth begins *in utero* and is complete prior to the time children begin to crawl. Formation of secondary dentin begins after completion of the tooth root and continues through childhood until the tooth is lost, or otherwise loses vitality. Pb in shed deciduous teeth is not uniformly distributed. Differences in Pb levels and stable isotope signatures of the enamel and dentin suggest that Pb uptake occurs differentially in enamel and dentin (Gulson 1996; Gulson and Wilson 1994). Pb in enamel is thought to reflect primarily Pb exposure that occurs *in utero* and early infancy, prior to tooth eruption. Dentin appears to continue to accumulate Pb after eruption of the tooth; therefore, dentin Pb is thought to reflect exposure that occurs up to the time the teeth are shed or extracted (Gulson 1996; Gulson and Wilson 1994; Rabinowitz 1995; Rabinowitz et al. 1993). The technique of laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS) allows measurement of Pb levels in regions of dentin formed at various times during deciduous tooth formation *in utero* and after birth (Arora et al. 2014; Shepherd et al. 2016). Accumulation of Pb in dentin of permanent teeth may continue for the life of the tooth (Steenhout 1982; Steenhout and Pourtois 1981). Because enamel is in direct contact with the external environment, enamel Pb levels may be more influenced than dentin Pb by external Pb levels and tooth wear (Purchase and Fergusson 1986).

An analysis of eight cross-sectional and/or prospective studies that reported tooth Pb and PbBs of the same children found considerable consistency among the studies (Rabinowitz 1995). The mean tooth Pb levels ranged from <3 to >12 μg/g. Dentin Pb was found to be predictive of Pb in tibia, patella, and mean bone Pb in 32 of 63 subjects at follow-up of ≤13 years (Kim et al. 1996b). The authors estimated that a 10 μg/g increase in dentin Pb levels in childhood was predictive of a 1 μg/g increase in tibia Pb levels, a 5 μg/g in patella Pb levels, and a 3 μg/g increase in mean bone Pb among the young adults. Arora et al. (2014) found that Pb levels in primary (prenatal) dentin were more strongly correlated with PbBs at birth (correlation coefficient, r=0.69, n=27), whereas Pb levels in secondary (postnatal) dentin were more strongly correlated with CBLI (r=0.38, n=75). Shepherd et al. (2016) combined LA-ICP-MS with

histological determinations of dentin age to reconstruct the history of incorporation of environmental Pb from various sources. “

COMMENT (Section 3.3.1): The Reviewer suggested the following text inclusion: It is generally recognized as mostly reflecting acute exposure (i.e., exposure over weeks to months).

RESPONSE: *ATSDR has elected not to make this statement in this introductory section of “Section 3.3.1 Biomarkers of Exposure” because blood Pb is a more complex function of recent and past exposure (e.g., contribution of bone Pb to blood Pb). However, the general intent of the Reviewer’s comment is addressed in the subsection, “PbB,” where it is stated that* “Pb is eliminated from blood more rapidly than from bone (Behinaein et al. 2014; Brito et al. 2005; Chamberlain et al. 1978; Griffin et al. 1975; Manton et al. 2001; Nie et al. 2005; Nilsson et al. 1991; Rabinowitz et al. 1976; Rentschler et al. 2012); therefore, the Pb concentration in blood reflects mainly the exposure history of the previous few months and does not necessarily reflect the larger burden and much slower elimination kinetics of Pb in bone (Graziano 1994; Lyngbye et al. 1990b). S”

Chapter 6. Adequacy of the Database

COMMENT (page 385, line 26): The Reviewer noted that it has to be acknowledged that this is just a small sampling of on-going studies of lead based on studies that are currently funded by NIH to specifically study lead (as reflected by search the NIH reporter data base for “lead” in the abstract, presumably). However, there are many other ongoing studies of lead that are continuing WITHOUT such NIH funding specifically for lead---such as our research group’s work, which developed large early life as well as adult longitudinal cohort studies that were initially funded by NIH to study lead; but that are now funded by NIH to study other toxicants and outcomes. However, with archived data on lead exposure in our subjects, we are still publishing new research on lead, particularly as we measure new outcomes. I believe this is true for other investigators; in addition, there are plenty of other studies of lead that are funded by sources other than NIH (particularly, international studies).

RESPONSE: *The following statement was added to Section 6.3: “Note that the studies listed below are funded by the National Institute of Health (NIH) and do not include ongoing studies that are funded by other sources.”*

Comments provided by Peer Reviewer #2:

Chapter 1. Relevance to Public Health

COMMENT (Section 1.1): The Reviewer noted: Might want to be more specific here or provide context. For example, at battery recycling yards, atmospheric deposition is not the largest source of Pb found in soils. Similarly, around the foundation of houses or lighthouses, atmospheric deposition is not the largest source.

RESPONSE: *The text has been revised to read "In general, atmospheric deposition is the largest source of Pb found in soils not impacted by other local non-air sources (e.g., dusts from deteriorating leaded paint)."*

COMMENT (Section 1.1): The Reviewer suggested the following editorial change: New paragraph and it might fit better below the following paragraph.

RESPONSE: *The paragraph noted in the comment was split into two paragraphs, and the new paragraph was moved to the suggested location.*

"1.1 OVERVIEW AND U.S. EXPOSURES

Lead (Pb) is an element that is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world. A major source of Pb in the U.S. environment has historically been anthropogenic emissions to the atmosphere from combustion of leaded gasoline, which was phased out of use after 1973 and then banned in 1995 (with the exception of fuels for piston-driven aircraft) (EPA 1996a). Lead continued to be used as an anti-knock agent in National Association for Stock Car Auto Racing (NASCAR) fuels until it was phased out beginning in 2008. Deteriorating Pb-based paints from weathered surfaces (which produce highly concentrated Pb debris and dusts) in older housing stock (pre-1978) continues to be a source of childhood Pb poisoning in the United States (CDC 1991, 2012d). The combination of corrosive water and Pb pipes or Pb-soldered joints in either the distribution system or individual houses can create localized zones of high Pb water concentrations (EPA 1989d, 2007a; Hanna-Attisha et al. 2016). Other anthropogenic sources of Pb have included mining and smelting of ore; manufacture of and use of Pb-containing products (e.g., Pb-based paints, pigments, and glazes; electrical shielding; plumbing; storage batteries; solder; and welding fluxes); manufacture and application of Pb-containing pesticides; combustion of coal and oil; and waste incineration.

Pb does not degrade in the environment, although it can exist in various chemical forms. Particulate matter contaminated with Pb can be transported through air, water, and soil. In general, atmospheric deposition is the largest source of Pb found in soils not impacted by other local non-air sources (e.g., dust

from deteriorating leaded paint). Pb is transferred continuously between air, water, and soil by natural chemical and physical processes such as weathering, runoff, precipitation, dry deposition of dust, and stream/river flow; however, soil and sediments appear to be important sinks for Pb. Pb adsorbs strongly to most soils and does not appreciably leach. Soil acidity (pH) and composition are the most important factors affecting solubility, mobility, and phytoavailability of Pb in soil. Other conditions that increase Pb mobility in soil are reducing conditions and high chloride content.

The general population may be exposed to Pb in ambient air, foods, drinking water, soil, and dust. Pb has also been found in a variety of other consumer products including storage batteries, solders, pottery glazes, leaded crystal glassware, cosmetics, hair dyes, jewelry, gun shot and ammunition, relic fishing sinkers, and tire weights. For adults, exposure to levels of Pb beyond background is usually associated with occupational exposures. For children, exposure to high levels of Pb is associated with living in areas contaminated by Pb (e.g., soil or indoor dust in older homes with Pb-based paint). The primary source of Pb exposure to children is from surface dusts (on the ground or entrained) that contain Pb from a variety of sources including deteriorated Pb-based paint (CDC 2009; Lanphear et al. 1998; Succop et al. 1998). Environmental Pb is particularly accessible to children because of their more intensive hand-to-mouth activity and the proximity of the child breathing zone to Pb entrained from surface dusts. Because Pb is transported from soil very slowly, historic sources of deposition of Pb to soil continue to contribute to current exposures (Laidlaw and Filipelli 2008; Laidlaw et al. 2012).

Blood lead (PbB) has been used as a biomarker of Pb exposure, and periodic surveys of PbB of the U.S. population are conducted by the Centers for Disease Control and Prevention (CDC). Based on data from the National Health and Nutrition Examination Survey (NHANES) (2015–2016, CDC 2018a), the geometric mean PbB in a representative sample of U.S. adults, ≥20 years old, was 0.920 μg/dL (95% confidence interval [CI] 0.862, 0.982). The geometric mean blood PbB of a representative sample of U.S. children, 1–5 years old, was 0.758 μg/dL (95% CI 0.675, 0.850). PbBs in the U.S. have decreased considerably in the last several decades as a result of removal of Pb from gasoline and restrictions placed on the use of Pb in residential paints (Brody et al. 1994; CDC 2011, 2018a; Pirkle et al. 1994, 1998; Schwartz and Pitcher 1989).

Seasonal variations in blood lead concentration (PbB) levels in children have been observed, with a general trend of increasing PbB during late summer and early fall (Gulson et al. 2008; Johnson and Bretsch 2002; Laidlaw et al. 2005). Seasonal patterns in behavior (e.g., outdoor activities) and weather that promotes re-entrainment and transport of dust Pb (humidity and wind velocity) may contribute to the

observed seasonal patterns in PbB (Laidlaw et al. 2005, 2012) and provide additional evidence for surface dusts being a major contributor to child Pb exposure and PbB."

COMMENT (Section 1.2): The Reviewer suggested the following editorial change: The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of ~~epidemiological~~ evidence regarding health effects in humans.

RESPONSE: *Revised as suggested.*

"The literature evaluating the health effects of Pb is enormous, and includes an extensive database in humans, including children and infants. Information on health effects reviewed below is taken from epidemiological studies that identify the major lines of evidence regarding health effects in humans. "

COMMENT (Section 1.2): The Reviewer was not in complete agreement – it is in part related the contemporary exposures relative to historical accumulation – there are instances where PB/PK models suggest the PbB concentration can be quite elevated due to release from historical stores, particularly at older ages where bone mass loss becomes more dominant], particularly when you simulate a relatively low current day environmental exposure [perhaps I have too much faith in some of the PB/PK models (O'Flaherty, IEUBK], but some caution is perhaps warranted for your statement, and some of the work by Gulson supports this [isotope studies]

RESPONSE: *The revised draft states that blood Pb concentration reflects both ongoing exposure and Pb stores in bone, which can be transferred to blood.*

"To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of µg/dL). Blood Pb concentration reflects both ongoing exposure and Pb stores in bone, which can be transferred to blood. Because of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months and not necessarily the larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI), which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct, noninvasive measurements of bone Pb concentrations have been used as a metric of long-term exposure on the basis that most of the absorbed Pb retained in the body will reside in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect are typically unknown or highly uncertain."

COMMENT (Section 1.2): The Reviewer ask is this last sentence an assumption? The Reviewer agreed PbB lacks power regarding the complex history of exposure, but bone lead is an internal metric that does

provide more insight, particularly cortical bone, and the contrasting of bone versus blood concentrations can be valuable.

RESPONSE: *The statement has been deleted.*

"To quantify exposure, epidemiological studies on the toxicity of Pb rely on internal exposure metrics, rather than measurements of external exposures (e.g., concentration of Pb in water or air) or ingested dose. The most common internal dose metric for Pb is the concentration of Pb in blood (PbB, typically expressed in terms of µg/dL). Blood Pb concentration reflects both on-going exposure and Pb stores in bone which can be transferred to blood. Becaue of the relatively rapid elimination of Pb from blood compared to bone, blood Pb will reflect mainly the exposure history of the previous few months andnot necessarilythe larger burden of Pb in bone (see Section 3.1). As a result, a single PbB measurement may not be a reliable metric for Pb body burden or cumulative exposure. Longitudinal measurements of PbB can be used to construct a cumulative blood Pb index (CBLI) which may be a better reflection of exposure history; however, the CBLI will not capture shorter-term variation in exposure that may occur between measurements. Direct noninvasive measurement of bone Pb concentrations have been used as metric of long-term exposure on the basis that most of the absorbed retained in the body will resides in bone (see Section 3.1). The health effects of Pb are the same, regardless of the route of exposure (e.g., inhalation or ingestion). Given that exposure is quantified by internal exposure metrics (e.g., PbB, bone Pb), epidemiological studies do not attempt to define the route of exposure. Environmental exposure to Pb occurs continuously over a lifetime and Pb is retained in the body for decades. Because internal dose metrics cannot define the complete history of exposure, the exposure duration and timing that correlates most strongly with the observed health effect is typically unknown or highly uncertain. ~~Therefore, health effects are considered to be associated with chronic exposures, rather than to shorter exposures~~."

COMMENT (Section 1.2): The Reviewer commented that it may be worth discussing infants and breast milk transfer as a key pathway/route of exposure.

RESPONSE: *The following statement has been included in the revised draft: "Infants are born with a Pb burden derived from maternal transfer in utero and subsequently can continue to absorb maternal Pb from ingestion of breast milk."*

COMMENT (Section 1.2): The Reviewer commented that the effect of early onset of menopause, demonstrated in epidemiology studies, should be included (such as Popovic et al, 2005 (Environ Health Perspect 113(4), 478-484); Eum et al 2014 (Environ Health Perspect 122(3) 229-234).

RESPONSE: *The finding of decreased age at the onset of menopause was added to the Section 1.2, Reproductive Effects in Females. In addition, results of the Popovic et al. (2005) and Eum et al. (2014) studies were also included in Section 2.17 (Reproductive)*

"**Reproductive Effects in Females.** Compared to studies of male reproductive effects, the epidemiologic literature database for effects of Pb on the female reproductive system is smaller, with most epidemiological studies conducted in populations with mean PbB ≤10 μg/dL. Studies provide some evidence of alterations in serum reproductive hormone levels (estradiol, LH, and FSH), decreased fertility, increased spontaneous abortion, increased preterm birth, and decreased age at onset of menopause. However, results are inconsistent, with several studies reporting no association between PbB and female reproductive effects. "

Table 2-18. 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; Krieg et al. 2007
	Decreased fertility	Chang et al. 2006
	Increased spontaneous abortion	Yin et al. 2008
	Increased preterm birth	Rabito et al. 2014
	Decreased 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 day	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

"*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 a negative 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 lower 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."

Chapter 2. Health Effects

COMMENT (Section 2.1): The Reviewer noted: Again, comment about early onset of menopause in women.

RESPONSE: *Revised as suggested.*

"**Reproductive Effects in Females.** Compared to studies of male reproductive effects, the epidemiologic literature database for effects of Pb on the female reproductive system is smaller, with most epidemiological studies conducted in populations with mean PbB ≤10 µg/dL. Studies provide some evidence of alterations in serum reproductive hormone levels (estradiol, LH, and FSH), decreased fertility, increased spontaneous abortion, increased preterm birth, and decreased age at onset of menopause. However, results are inconsistent, with several studies reporting no association between PbB and female reproductive effects. "

COMMENT (Section 2.2): The Reviewer suggested the following text change: 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.

RESPONSE: *Revised as suggested.*

- "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."

COMMENT (Section 2.2): The Reviewer commented that they are also susceptible due to increased exposure potential compared to adults.

RESPONSE: *Revised as suggested.*

"***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 potential compared to adults."

COMMENT (Section 2.3): The Reviewer suggested the following text change: Numerous confounding 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).

RESPONSE: *Revised as suggested.*

"***Confounding Factors.*** Numerous confounding 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). "

COMMENT (Section 2.5, Table 2-5): The Reviewer suggested the following editorial change: HR ~~B~~black

RESPONSE: *Revised as suggested.*

Table 2-19. 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]
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***
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*
		Atrioventribular 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**

Table 2-19. 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]
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)*

[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]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; HR = hazard ratio; IQR = intraquartile range; IVCD = intraventricular conduction defect; OR = odds ratio; Pb = lead; SD = standard deviation

COMMENT (Section 2.5, Table 2-10): The Reviewer noted: "Not sure you need to list (95% CI) here as you have it in the definitions below (unless otherwise specified…), same, same and same again in Table 2-11."

RESPONSE: *Revised as suggested in Tables 2-10 and 2-11.*

Table 2-20. 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]
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***
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*
		Atrioventribular 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**

Table 2-20. 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]
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)*

[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]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; HR = hazard ratio; IQR = intraquartile range; IVCD = intraventricular conduction defect; OR = odds ratio; Pb = lead; SD = standard deviation

Table 2-21. 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*
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.
[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

COMMENT (Section 2.8): The Reviewer suggested the following text change: Thus, data are not adequate to establish, or not, an exposure-response relationship for decreased hemoglobin at PbB ≤10 µg/dL.

RESPONSE: *Revised as suggested.*

"***Effect at Blood Pb Levels ≤10 µg/dL.*** Epidemiological studies evaluating hematological effects of PbB ≤10 µg/dL are summarized in Table 2-14, 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 negative 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 children with mean PbB of 6.9–9.0 µg/dL, there was a negative 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 population were small (n=50–189) (Olivero-Verbel et al. 2007; Zentner et al. 2006). Thus, data are not adequate to establish, or not, an exposure-response relationship for decreased hemoglobin at PbB ≤10 µg/dL. "

COMMENT (Section 2.16): The Reviewer suggested the following editorial change: The wide C~~I~~Ls for this study may indicate that findings are unstable due to the small number of controls.

RESPONSE: *Sentence was deleted.*

"). 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). 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% CL 1.4, 2.6) for a 1 µg/dL increase in PbB (Kamel et al. 2002). ~~The wide CLIs for this study may indicate that findings are unstable due to the small number of controls."~~

COMMENT (Section 2.16): The Reviewer noted that this could be said for multiple studies in this document. Not sure why it got particular mentioning here.

RESPONSE: *The statement has been deleted.*

"). 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). 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% CL 1.4, 2.6) for a 1 µg/dL increase in PbB (Kamel et al. 2002). ~~The wide CLIs for this study may indicate that findings are unstable due to the small number of controls."~~

COMMENT (Section 2.17): The Reviewer suggested adding the following: "…as is the disruption of calcium homeostasis."

RESPONSE: *Revised as suggested.*

"***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 homeostatsis. "

COMMENT (Section 2.17): The Reviewer suggested the following editorial change: altered release of pituitary hormones i~~n~~s due.

RESPONSE: *The sentence was revised as follows: "…altered release of pituitary hormones is ~~in~~ due to interference with cation-dependent second messenger systems;"*

COMMENT (Section 2.18): The Reviewer suggested the following editorial change: 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 ~~effects~~ exposure on the fetus. The Reviewer also noted: toxicodynamics being more related to effect and interaction with tissue.

RESPONSE: *Revised as suggested.*

"***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."

COMMENT (Section 2.18, Table 2-39): The Reviewer noted: NHAA OR: [missing value?] (0.42, 0.97); p<0.05*; NHAA OR: 0.62 (0.41, 0.96); P<0.05 [should these be bolded?]; OR for T2: 0.48 (0.25, 0.92)* [not sure I agree this is a clear association with PbB that should be bolded; same with menarche] – what were the p values?

RESPONSE: *The missing OR was added as noted above. Bolding was added to the ORs listed above. p-Values were not reported in the Wu et al. (2003b) study. Results of this study are in bold font based on confidence intervals; therefore, no change was made to this entry.*

“

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)***
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

[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]Asterick indicates association with Pb; unless otherwise specified, values in parenthesis are 95% CIs.

CI = confidence interval; MA = Mexican Americans; NHW = Non-Hispanic whites; NHAA = Non-Hispanic African Americans; NS = not statistically significant; OR = odds ratio; Pb = lead; PR = prevalence ratio; SE = standard error

COMMENT (Section 2.20): The Reviewer suggested the following text change: Thus, plasma levels of Pb are far lower (at least two orders of magnitude lower) than the concentrations examined in in vitro studies in human cell lines.

RESPONSE: *Revised as suggested.*

"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)."

COMMENT (Section 2.20): The Reviewer noted the following: equivalent to approximately 2.3 to 23 µg/dL [might be of value to put concentrations into compatible PbB units, while acknowledging that ultimately these would be comparable to the soluble proportion of Pb in plasma – hard for many members of the public to shift between units]

RESPONSE: *Equivalent units were added as suggested.*

"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). "

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

COMMENT (Section 3.1.1): The Reviewer suggested the following text change: Dietary calcium intake ~~appears to~~ affects Pb absorption.

RESPONSE: *Revised as suggested.*

"Dietary calcium intake affects Pb absorption. An inverse relationship has been observed between dietary calcium intake and PbBs in children, suggesting that children who are calcium-deficient may absorb more Pb than calcium-replete children (Elias et al. 2007; Mahaffey et al. 1986; Schell et al. 2004; Ziegler et al. 1978). An effect of calcium on Pb absorption is also evident in adults. "

COMMENT (Section 3.1.1): The Reviewer suggested the following editorial change: The value reported for fasted subjects (26%) was approximately half that reported for soluble Pb ingested by fasting adults, or approximately 60% (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980).

RESPONSE: *Revised as suggested.*

"Adult subjects who ingested soil (particle size <250 μm) collected from the Bunker Hill National Priorities List (NPL) site absorbed 26% of the resulting 250 μg/70 kg body weight Pb dose when the soil was ingested in the fasted state, and 2.5% when the same soil Pb dose was ingested with a meal (Maddaloni et al. 1998). The value reported for fasted subjects (26%) was approximately half that reported for soluble Pb ingested by fasting adults, or approximately 60% (Blake et al. 1983; Heard and Chamberlain 1983; James et al. 1985; Rabinowitz et al. 1980)."

COMMENT (Section 3.1.1): The Reviewer noted that it might be worth mentioning that these percentages of doses recovered are underestimates as they exclude distribution to other tissues as well as fecal excretion.

RESPONSE: *The following statement has been included in the revised text: "The estimates for percent of dose excreted underestimate actual absorption as these estimates do not account for the Pb retained in bone and other tissues."*

COMMENT (Section 3.3): The Reviewer noted the following: Do you mean pathway or media? It is possible to distinguish between different sources (e.g., leaded gasoline versus a galena source) – this is one of the unique powerful aspects of isotopic ratio comparisons] – it really depends on exposure history, but certainly they have to power to identify source in some instances.

RESPONSE: *The statement in Section 3.3 has been revised to: "Pb isotope studies can be used to identify sources of Pb contributing to exposure."*

Chapter 6. Adequacy of the Database

COMMENT (Section 6.2): The Reviewer suggested the following editorial change: Increased awareness of the potential adverse consequences of low environmental exposures to Pb has led...

***RESPONSE**: Revised as suggested.*

"Increased awareness of the potential adverse consequences of low environmental exposures to Pb has led to changes in U.S. public health policy, with a focus on lowering PbB levels to well below 10 µg/dL (CDC 2012d; EPA 2016b). In 2012, the CDC concluded that the 97.5th percentile of the U.S. PbB distribution (based on NHANES data) should be considered a reference value for identifying children who have "elevated" PbB (CDC 2012d). "

COMMENT (Section 6.2): The Reviewer suggested the following editorial change: Comparative Toxicokinetics [maybe just Comparative Bioavailability?]

***RESPONSE**: No change has been made because this section is intended to highlight important data needs related to Comparative Toxicokinetics, not just bioavailability. The need for studies that would compare relative bioavailability (RBA) of lead in soil in humans and animals are noted in this section because: (1) bioavailability is an important factor in assessing health risk from exposure to Pb in different environmental media; and (2) estimates of relative bioavailability of Pb in soil are currently derived from animal models that have not been evaluated for how well the models predict RBA in humans. ATSDR did not identify important data needs for other aspects of comparative toxicokinetics.*

Comments provided by Peer Reviewer #3

General Comments

COMMENT: The Reviewer noted: "I wish to express my appreciation for the opportunity of taking part of the Peer Reviewers of this Profile and I hope that this report can be helpful."

RESPONSE: *No revisions were suggested.*

COMMENT: The Reviewer noted that the present document ASDR´S LEAD TOXICOLOGY PROFILE is structured according to the standard format for the ATSDR profiles, and includes introductory standard language in some sections (in bold), and tables, figures, headings as described in the guidelines. It gives an updated information that is summarized in the Chapter 1 and then it has an exhaustive review of the available toxicological and epidemiological studies, biokinetics, biomarkers, lead production and environmental regulations among other subjects. As expected, this new document includes a complete and updated information for the topics of each chapter.

RESPONSE: *No revisions were suggested.*

COMMENT: The Reviewer noted: "During my peer reviewing process, I found several and positive differences in the structure of chapters compared with that of 2007 edition, but also some unnecessary repeated concepts or not well harmonized within the chapters. In this new version, for example the "Analytical Methods" chapter was not included and I could not find the supporting reasons why this relevant issue was skipped. As you mentioned, "the principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public". However, these ATSDR Profiles are extensively used and referred worldwide. Then in my opinion, health professionals, laboratory personnel and health policy-makers would hope to find the updated information about recommended analytical methods, their advantages and disadvantages and their application in several screening campaigns related to human exposure to lead as there is a permanent need of information about the newest technologies and analytical methodologies requested to obtain lower detection limits and/or to improve accuracy and precision in order to ensure the technical competence needed for the quality of lab results assurance. Epidemiological studies reviewed on the toxicity of Pb rely on internal exposure metric mainly the biomarker PbB, the concentration of lead in blood so, the importance of the good quality analytical results should be highlighted. Results of lead levels in other biological fluids and matrix, are also referred in this Profile, so I would suggest to include this chapter again if possible, or in a separate document."

RESPONSE: *ATSDR recently revised the Toxicological Profile template and excluded discussions of analytical methods in new Toxicological Profiles. However, the Reviewer's comment will be considered in future discussion of the Toxicological Profile template.*

COMMENT: The Reviewer noted: "In the same analytical line, I noticed that there are diversity of units to express results of PbB, for example, not all the reviewed studies describe the PbB results in µg /dL but in µ/L or µmol/L so there´s a need to harmonize those results in a single unit or give the corresponding conversion of measurement units. Also, I found some mistakes when transcribing study results (eg. Chapter 2, pg 173, lines 11- 12: "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" instead of µg/dL); pg 251 line 5-7 " ..Pb binding to ALAD is saturable; the binding capacity has been estimated to be approximately 850 µg/dL red blood cells…", instead of 850 µg/L as reported in Bergdahl et al. 1998."

RESPONSE: *The profile was searched for all PbB values to ensure that all PbB values are reported in units of µg/dL.*

COMMENT: The Reviewer noted: "Other issues that called my attention were some unnecessary repeated concepts in different chapters and the non-consistency with regard to the reference to health effects studies in animals. An example are the anthropogenic sources of lead in the environment and human lead exposure sources which are markedly repeated and it could be better referred in tables and figures. The other example is that both items 1.2 SUMMARY OF HEALTH EFFECTS and in B1 LITERATURE SEARCH AND SCREEN "……specifically clarify that there is large number of studies available in humans, so results of animal studies were not considered for the identification of health effects associated with Pb or were not included in this Profile. However with a quick overview of the whole document, several animal studies are referred in the Chapter 2 as well. Then I suggest to explain this clearer if possible."

RESPONSE: *The topic of anthropogenic sources of Pb is discussed in several different contexts: Overview (Section 1), Potential for Human Exposure (5.1), Releases to the Environment (5.3), Environmental Fate (5.4.2), and Levels in the Environment (5.5.3). This organization of the profile does result in some redundancy; however, it also provides a more complete discussion of the information pertinent to each topic. The Reviewer's comment will be considered in future discussion of the Toxicological Profile template.*

The statement in Section 1.2 has been revised to: "Although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb. This potentially leaves out discussion of effects that may have been observed in animal models that have not been studied humans and that may be future targets of human epidemiology and clinical toxicology studies. Animal studies were included in discussion of mechanisms of toxicity of Pb and toxicokinetics." This statement has been included in Section B1.

COMMENT: The Reviewer noted: "In relation to the acronyms, many times throughout the document, the meaning of acronyms appears in the tables for the first time, so I suggest that they can also be included in the text when they are mentioned for the first time (e.g. Blood Parameters). In addition, some acronyms are missing in the appendix list (Eg. RR, RBA, IVBA)."

RESPONSE: *Acronyms are defined when first used in the document. Thus, if an acronym is defined for the first time in Chapter 1, it is not redefined in other chapters. In some cases, acronyms defined in a table are not used in the text. The acronyms RR, RBA, and IVBA were added to the list in Appendix F.*

COMMENT: The Reviewer noted that regarding the glossary, it would be important to highlight the meaning of some additional terms, in the context of the ATSDR profiles so as not to generate confusion in the understanding (eg bioavailability and bioaccessibility).

RESPONSE: *The following definitions were added to the glossary:*

- *"Absolute bioavailability (ABA): Amount of Pb absorbed expressed as a fraction or percent of ingested."*
- *"Relative bioavailability (RBA): ABA of Pb in a test material (e.g., soil) expressed as a fraction or percent of the ABA for a reference material (e.g., lead acetate)."*
- *"Bioaccessibility: Fraction or percent of Pb in a medium (e.g., soil) that is released from the medium in gastrointestinal tract so that it can be available to absorptive transport mechanisms (e.g., transcellular carriers or channels, paracellular diffusion)."*
- *"In vitro bioaccessibility (IVBA): Bioaccessibility predicted from an in vitro extraction assay."*

COMMENT: The Reviewer noted: "In addition to my previous comments on this Lead Toxicology Profile, in the guidelines, you mentioned the "Supplemental Document" that contains detailed descriptions of studies that provide no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) but this document was not included in the emailing or in this Profile version. By the other side, there is another document which is referred several times in this Profile to look for additional information, that is the "Supporting Document for Epidemiological Studies for Lead" which is not available neither in the Profile you sent, nor in the web or is not linked to."

RESPONSE: *The Supplemental Document will be publicly available when the profile is finalized and posted on ATSDR's website.*

ATSDR Charge Questions and Responses

Chapter 1. Relevance to Public Health

QUESTION: Do you agree with those effects known to occur in humans as reported in the text? If not, provide a copy of additional references you would cite and indicate where (in the text) these references should be included.

COMMENT: The Reviewer noted: "YES. In fact, Health Effects is the most extensive chapter of the document and includes the review of numerous studies focused on the adverse effects of different organs, tissues and systems and its association with lead exposure."

RESPONSE: *No revisions were suggested.*

QUESTION: Are the effects only observed in animals likely to be of concern to humans? Why or why not? If you do not agree, please explain.

COMMENT: The Reviewer noted: "NO, the priority for health effects of reviewed studies are in human population while animal studies are not being considered for the identification of health effects associated with Pb in this Profile. However, studies are frequently described or included to explain probable mechanisms of action."

RESPONSE: *No revisions were suggested.*

QUESTION: Have exposure conditions been adequately described? If you disagree, please explain.

COMMENT: The Reviewer noted: "YES, I agree."

RESPONSE: *No revisions were suggested.*

QUESTION: If MRLs have been derived, are the values justifiable? If no MRLs have been derived, do you agree that the data do not support such a derivation?

COMMENT: The Reviewer noted: "YES, I agree."

RESPONSE: *No revisions were suggested.*

Chapter 2. Health Effects

QUESTION: Were adequately designed human studies identified in the text (i.e., good exposure data, sufficiently long period of exposure to account for observed health effects, adequate control for confounding factors)? Were the major study limitations sufficiently described in the text without going into lengthy discussions? If study limitations were not adequately addressed, please suggest appropriate changes.

COMMENT: The Reviewer noted: "YES, as referred in this chapter, the number of studies that evaluate the health effects of Pb is huge, comprising extensive database in humans including children. The reviewed information from health effects studies was focused on those effects associated PbB $\leq$10 µg/dL. Confounding factors, such as age, diet, nutritional factors, alcohol use, and potential exposure to other chemicals were highlighted as main limitations in several studies."

RESPONSE: *No revisions were suggested.*

QUESTION: Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the profile? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)? Please suggest appropriate changes.

COMMENT: The Reviewer noted: "YES, the selection of the epidemiological evidence from Lead studies was taken into account in a very thorough way by the authors of this chapter. In those cases where few epidemiological studies were available for punctual health effect (e.g., hepatic), the discussion of the results and conclusions has been also very accurate. Since a large number of epidemiologic studies including recent advances in the evaluation of multiple health effects was reviewed (a total of 540 epidemiological studies –table 2-1), in my opinion, the authors were very objective and critical in evaluating those studies considering the various limitations that can arose in order to arrive at conclusive evidences."

RESPONSE: *No revisions were suggested.*

QUESTION: Were all appropriate NOAELs and/or LOAELs identified for each study? If not, did the text provide adequate justification for excluding NOAELs/LOAELs including, but not limited to, citing study limitations? Please suggest appropriate changes.

COMMENT: The Reviewer noted: "NO, some specific health effects identified in both human and animal studies were reported by kind of health effect but NOAEL and LOAEL were not specifically identified in the whole document."

RESPONSE: *NOAELs and LOAELs were not identified in this profile. Epidemiological studies identified adverse effects at the lowest PbB evaluated. Therefore, it is not appropriate to identify NOAEL and LOAEL values.*

QUESTION: Were the appropriate statistical tests used in the studies? Would other statistical tests have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE:** As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.

COMMENT: The Reviewer noted: "N/A. Appropriate statistical tests were not specifically described as a topic itself in this document. When necessary, you have to look into each study. In Chapter 6 it is referred that "Additional details on studies with PbB $\leq$10 μg/dL, including statistical analyses and assessment of confounding factors, are provided in the "Supporting Document for Epidemiological Studies for Lead" which was not available for my review."

RESPONSE: *Statistical methods are described in the "Supporting Document for Epidemiological Studies for Lead." The Supplemental Document will be publicly available when the profile is finalized and posted on ATSDR's website.*

QUESTION: Are you aware of other studies which may be important in evaluating the toxicity of the substance? Please provide a copy of each study and indicate where in the text each study should be included.

COMMENT: The Reviewer noted: "The reviewed studies in the profile were very illustrative and representative of the current situation concerning health effects of lead at low levels of exposure. Besides, the references give a wide variety of recent studies and updated reviews on health effects so I am not aware to provide any other contribution by now."

RESPONSE: *No revisions were suggested.*

QUESTION: For the health effects in humans exposed tables, are the study details and author conclusions presented accurately?

COMMENT: The Reviewer noted: "YES, the tables are very clear and illustrative of the studies referred to. Epidemiological studies tables comprise more than 50% of all the tables included in this Profile."

RESPONSE: *No revisions were suggested.*

QUESTION: Were adequately designed animal studies identified in the text (i.e., adequate number of animals, good animal care, accounting for competing causes of death, sufficient number of dose groups, and sufficient magnitude of dose levels)? If not, does the inadequate design negate the utility of the study? Please explain.

COMMENT: The Reviewer noted: "In this Profile, it was mentioned that "although the literature on adverse effects of Pb in laboratory animals also is extensive, due to the large number of available epidemiological studies, results of animal studies were not considered for the identification of health effects associated with Pb"."

Animal studies were only briefly described to explain some mechanism of action and this was not the main objective of the chapter. In other cases, Animal Studies are referred to EPA (2014c). Then, the following questions may be not applicable (N/A).

RESPONSE: *No revisions were suggested.*

QUESTION: Were the animal species appropriate for the most significant toxicological endpoint of the study? If not, which animal species would be more appropriate and why?

COMMENT: The Reviewer noted: "N/A"

RESPONSE: *No revisions were suggested.*

QUESTION: Were the conclusions drawn by the authors of the studies appropriate and accurately reflected in the text? If not, did the text provide adequate justification for including the study (e.g., citing study limitations)?

COMMENT: The Reviewer noted: "N/A"

RESPONSE: *No revisions were suggested.*

QUESTION: Were all appropriate NOAELs and LOAELs identified for each study? Were all appropriate toxicological effects identified for the studies? If not, please explain.

COMMENT: The Reviewer noted: "N/A. There were not any NOAELs or LOAELs identified in the reported human data and the "Supplemental Document" was not available in this Profile."

RESPONSE: *No revisions were suggested. However, as noted above, epidemiological studies identified adverse effects at the lowest PbB evaluated. Therefore, it is not appropriate to identify NOAEL and LOAEL values.*

QUESTION: If appropriate, is there a discussion of the toxicities of the various forms of the substance? If not, please give examples of toxicological effects that might be important for forms of the substance.

COMMENT: The Reviewer noted: "YES, the Profile distinguishes health effects between organic and inorganic lead forms but in Human health effects assessment."

RESPONSE: *No revisions were suggested.*

QUESTION: Were the appropriate statistical tests used in the interpretation of the studies? If not, which statistical tests would have been more appropriate? Were statistical test results of study data evaluated properly? **NOTE:** As a rule, statistical values are not reported in the text, but proper statistical analyses contribute to the reliability of the data.

COMMENT: The Reviewer noted: "This was responded for the Human Toxicity studies."

RESPONSE: *As noted above, statistical methods are described in the "Supporting Document for Epidemiological Studies for Lead." The Supplemental Document will be publicly available when the profile is finalized and posted on ATSDR's website.*

QUESTION: Are you aware of other studies that may be important in evaluating the toxicity of the substance? If you are citing a new reference, please provide a copy and indicate where (in the text) it should be included.

COMMENT: The Reviewer noted: "N/A"

RESPONSE: *No revisions were suggested.*

QUESTION: Are the LSE tables and figures complete and self-explanatory? Does the "Users Guide" explain clearly how to use them? Are exposure levels (units, dose) accurately presented for the route of exposure? Please offer suggestions to improve the effectiveness of the LSE tables and figures and the "User's Guide."

COMMENT: The Reviewer noted: "N/A"

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the categorization of "less serious" or "serious" for the effects cited in the LSE tables?

COMMENT: The Reviewer noted: "N/A"

RESPONSE: *No revisions were suggested.*

QUESTION: Have the major limitations of the studies been adequately and accurately discussed? How might discussions be changed to improve or more accurately reflect the proper interpretation of the studies?

COMMENT: The Reviewer noted: "This was briefly explained above."

RESPONSE: *No revisions were suggested.*

QUESTION: Has the effect, or key endpoint, been critically evaluated for its relevance in both humans and animals?

COMMENT: The Reviewer noted: “This was briefly explained above.”

RESPONSE: *No revisions were suggested.*

QUESTION: Have "bottom-line" statements been made regarding the relevance of the endpoint for human health?

COMMENT: The Reviewer noted: “This was briefly explained above.”

RESPONSE: *No revisions were suggested.*

QUESTION: Are the conclusions appropriate given the overall database? If not, please discuss your own conclusions based on the data provided and other data provided to you but not presented in the text.

COMMENT: The Reviewer noted: “This was briefly explained above.”

RESPONSE: *No revisions were suggested.*

QUESTION: Has adequate attention been paid to dose-response relationships for both human and animal data? Please explain.

COMMENT: The Reviewer noted: “This was briefly explained above.”

RESPONSE: *No revisions were suggested.*

QUESTION: Has the animal data been used to draw support for any known human effects? If so, critique the validity of the support.

COMMENT: The Reviewer noted: “This was briefly explained above.”

RESPONSE: *No revisions were suggested.*

QUESTION: Have all possible mechanisms of action been discussed within their relevant health effect section? If not, please explain.

COMMENT: The Reviewer noted: “YES, each health effect category has a very exhaustive review of possible mechanisms of action.”

RESPONSE: *No revisions were suggested.*

QUESTION: Are the hazard identifications clear and justifiable based on ATSDR’s SR process? (In other words, if you follow ATSDR’s SR protocol from start to finish, would you come to the same hazard identification conclusions?) If not, discuss where in the process there was a deviation from the protocol.

COMMENT: The Reviewer noted: "N/A. My experience in ATSDR's SR protocol is very limited."

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the selection of endpoints that was carried forward through the SR process? If not, please indicate which endpoints you think should or should not have been included and why.

COMMENT: The Reviewer noted: "YES, although my experience in ATSDR´s SR protocol is limited as I mentioned before, I fully agree with the selection of endpoints that was carried forward through the SR process because since the last 2007 Toxicological Profile on Lead, several epidemiological studies were developed growing attention to multiple adverse health effects of Pb exposures that result in blood Pb concentrations (PbB) below the level of concern <10 µg/dL as mentioned in this Profile. In addition, many countries follow CDC`s recommendations and the awareness of the potential adverse effects demonstrated by all those studies as a consequence of Pb low level exposures, leading also, to changes in health policies lowering reference PbB levels for children."

RESPONSE: *No revisions were suggested.*

QUESTION: Do you agree with the SR framework as presented in Appendix B? Are there any steps that need to be revised? Please offer any suggestions to improve the utility, effectiveness, or clarity of the SR Framework.

COMMENT: The Reviewer noted: "YES, I agree."

RESPONSE: *No revisions were suggested.*

Chapter 3. Toxicokinetics, Susceptible Populations, Biomarkers, Chemical Interactions

QUESTION: Is there adequate discussion of absorption, distribution, metabolism, and excretion of the substance? If not, suggest ways to improve the text.

COMMENT: The Reviewer noted: "YES. The discussion is very complete as toxicokinetics of Pb in humans have been extensively studied and some reviewed studies in experimental animals provide additional evidence of lead ADME. I suggest including an introductory sub-title as "Excretion and routes of exposure" into the section 3.1.4. Excretion, in order to clear up the items that refers to the excretion according to the routes of exposure."

RESPONSE: *Revised as suggested.*

"3.1.4 Excretion

Independent of the route of exposure, absorbed Pb is excreted primarily in urine and feces; sweat, saliva, hair and nails, breast milk, and seminal fluids are minor routes of excretion (Chamberlain et al. 1978; Griffin et al. 1975; Hernandez-Ochoa et al. 2005; Hursh and Suomela 1968; Hursh et al. 1969; Kehoe

1987; Rabinowitz et al. 1976; Sears et al. 2012; Stauber et al. 1994). Fecal excretion accounts for approximately one-third of total excretion of absorbed Pb (fecal/urinary excretion ratio of approximately 0.5), based on intravenous injection studies conducted in humans (Chamberlain et al. 1978). A similar value for fecal/urinary excretion ratio, approximately 0.5, has been observed following inhalation of submicron Pb particles (Chamberlain et al. 1978; Hursh et al. 1969). Contributors to fecal excretion may include secretion into the bile, gastric fluid, and saliva (Rabinowitz et al. 1976). Biliary excretion of Pb has been observed in the dog, rat, and rabbit (Klaassen and Shoeman 1974; O'Flaherty 1993).

Mechanisms by which inorganic Pb is excreted in urine have not been fully characterized. Such studies have been hampered by the difficulties associated with measuring ultrafilterable Pb in plasma and thereby in measuring the GFR of Pb. Renal plasma clearance was approximately 20–30 mL/minute in a subject who received a single intravenous injection of a ^{203}Pb chloride tracer (Chamberlain et al. 1978). Urinary Pb excretion is strongly correlated with the GFR of Pb (Araki et al. 1986) and plasma Pb concentration (Bergdahl et al. 1997b; Rentschler et al. 2012) (i.e., urinary excretion is proportional to GFR x plasma Pb concentration). Estimates of plasma-to-urine clearance of Pb range from 13 to 22 L/day, with a mean of 18 L/day (Araki et al. 1986; Manton and Cook 1984; Manton and Malloy 1983; Chamberlain et al. 1978). The rate of urinary excretion of Pb was less than GFR of ultrafilterable Pb, suggesting renal tubular reabsorption of Pb from the glomerular filtrate (Araki et al. 1986, 1990). Measurement of the renal clearance of ultrafilterable Pb in plasma indicates that in dogs, Pb undergoes glomerular filtration and net tubular reabsorption (Araki et al. 1986, 1990; Vander et al. 1977; Victery et al. 1979). Net tubular secretion of Pb has been demonstrated in dogs made alkalotic by infusions of bicarbonate (Victery et al. 1979). Renal clearance of blood Pb increases with increasing PbBs >25 µg/dL (Chamberlain 1983). The mechanism for this has not been elucidated and could involve a shift in the distribution of Pb in blood towards a fraction having a higher GFR (e.g., lower molecular weight complex), a capacity-limited mechanism in the tubular reabsorption of Pb, or the effects of Pb-induced nephrotoxicity on Pb reabsorption.

Excretion and Routes of Exposure

Inhalation Exposure “

QUESTION: Have the major organs, tissues, etc. in which the substance is stored been identified? If not, suggest ways to improve the text.

COMMENT: The Reviewer noted: "YES, major organs, tissues, have been identified. Lead exposure can be associated with adverse effects of every organ system."

The Reviewer suggested including in Glossary the definitions of Bioavailability and Bioaccessibility that are missing.

RESPONSE: *The following definitions were added to the glossary:*

- *"Absolute bioavailability (ABA): Amount of Pb absorbed expressed as a fraction or percent of ingested."*
- *"Relative bioavailability (RBA): ABA of Pb in a test material (e.g., soil) expressed as a fraction or percent of the ABA for a reference material (e.g., lead acetate)."*
- *"Bioaccessibility: Fraction or percent of Pb in a medium (e.g., soil) that is released from the medium in gastrointestinal tract (GIT) so that it can be available to absorptive transport mechanisms (e.g., transcellular carriers or channels, paracellular diffusion)."*
- *"In vitro bioaccessibility (IVBA): Bioaccessibility predicted from an in vitro extraction assay."*

QUESTION: Have all applicable metabolic parameters been presented? Have all available pharmacokinetic/pharmacodynamic models and supporting data been presented? If not, please explain.

COMMENT: The Reviewer noted: "YES, several models of Pb pharmacokinetics have been described in 3.1.5 (Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models)."

RESPONSE: *No revisions were suggested.*

QUESTION: Is there adequate discussion of the differences in toxicokinetics between humans and animals? What other observations should be made?

COMMENT: The Reviewer noted: "NO, there are plenty human studies that support the discussion of Lead Toxicokinetics. The animals toxicokinetics studies are complementary to the conclusions arrived on studies in human, and "in vitro" studies as well."

RESPONSE: *No revisions were suggested.*

QUESTION: Is there an adequate discussion of the relevance of animal toxicokinetic information for humans? If not, please explain.

COMMENT: The Reviewer noted: "NO, as mentioned before, animal studies were complementary to those in human and in vitro tests."

RESPONSE: *No revisions were suggested.*

QUESTION: If applicable, is there a discussion of the toxicokinetics of different forms of the substance (e.g., inorganic vs. organic mercury)?

COMMENT: The Reviewer noted: "YES, inorganic Lead and organic lead have different toxicokinetics behavior."

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any data relevant to child health and developmental effects that have not been discussed in the profile and should be?

COMMENT: The Reviewer noted: "NO, Generally, the child health and developmental effects associated with lead exposure has been well identified, discussed and supported in this Profile."

RESPONSE: *No revisions were suggested.*

QUESTION: Are there any general issues relevant to child health that have not been discussed in the profile and should be?

COMMENT: The Reviewer noted: "NO, most relevant issues concerning lead exposure including low levels associated with health effects, were taken into account in this Profile as far as I know."

RESPONSE: *No revisions were suggested.*

QUESTION: If you answer yes to either of the above questions, please provide any relevant references.

COMMENT: The Reviewer noted: "N/A"

RESPONSE: *No revisions were suggested.*

QUESTION: Is there a discussion of populations at higher risk because of biological differences that make them more susceptible? Do you agree with the choices of populations? Why or why not? Are you aware of additional studies in this area?

COMMENT: The Reviewer noted: "N/A"

RESPONSE: *No revisions were suggested.*

QUESTION: Are the biomarkers of exposure specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?

COMMENT: The Reviewer noted: "YES, the biomarkers of lead exposure are specific. The concentration of Lead in blood (PbB) is the most widely used and is considered to be the most reliable biomarker for general clinical use and public health surveillance as described in 3.3.1 Biomarkers of exposure."

RESPONSE: *No revisions were suggested.*

QUESTION: Are there valid tests to measure the biomarker of exposure? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.

COMMENT: The Reviewer noted: "Although there are several analytical methods for measuring lead in blood (PbB) or in other biological samples, this analytical topic has not being approached in this new version of Lead Toxicology Profile as it was in 2007 edition, within the chapter "Analytical Methods""

RESPONSE: *The analytical methods section of the profile is no longer included in the new format for the profiles.*

QUESTION: Are the biomarkers of effect specific for the substance or are they for a class of substances? If they are not specific, how would you change the text?

COMMENT: The Reviewer noted: "Several biomarkers of effect are described and associated with PbB, but most of them are not necessary specific or sensitive enough for low levels of lead exposure."

RESPONSE: *No revisions were suggested.*

QUESTION: Are there valid tests to measure the biomarker of effect? Is this consistent with statements made in other sections of the text? If not, please indicate where inconsistencies exist.

COMMENT: The Reviewer noted: "YES, there are valid methodologies to measure lead biomarkers of effect but as it was mentioned above, the Analytical Methods section was not included in this Profile"

RESPONSE:
The analytical methods section of the profile is no longer included in the new format for the profiles.

QUESTION: Is there adequate discussion of the interactive effects with other substances? Does the discussion concentrate on those effects that might occur at hazardous waste sites? If not, please clarify and add additional references.

COMMENT: The Reviewer noted: "YES, the Interactions between Pb and other chemicals were classified into two categories: interactions with contaminants that are commonly found together with Pb at hazardous waste sites, and interactions with essential elements.

However, the effects that might occur at hazardous waste sites owing to multiple metals exposure was not exhaustively discussed in this Section. The included table was taken from ATSDR 2004a,b ; 2006 and several interactions with chemicals were mentioned in Chapter 2 as possible co-founders.

I understand that although it is not expressly indicated or referred, the information on this topic need to be complemented with other documents like EPA 2014c (Integrated science assessment for lead. Contains errata sheet created 5/12/2014.) which should be referred into the description of the section.

Another aspect to remark, from my "chemist" point of view is that, metals and metalloids (or non-metals) are named together "toxic metals" in Toxicology disciplines but it would be advisable, not to categorize arsenic and selenium as metals, because it is chemically incorrect."

RESPONSE: *ATSDR has not discussed confounding in Section 3.4 because ATSDR does not consider confounding in an epidemiology study to be evidence for an interaction.*

Studies that have examined interactions between Pb and other co-contaminants (ATSDR 2004a, 2004b, 2006) identify specific endpoints that were the basis for the classification; however, this information alone is not necessarily predictive of dose-response relationships for those effects in humans that result from interactions; in particular in association with PbB <10 µg/dL. Some interactions are likely to have a toxicokinetic mechanism (e.g., absorption), in which case, the interaction would be expected to be relevant to all effects associated with Pb exposure.

A citation to EPA (2014c) has been included in the revised draft of Section 3.4.

The term "metalloid" has been included in the revised draft of Section 3.4.

QUESTION: If interactive effects with other substances are known, does the text discuss the mechanisms of these interactions? If not, please clarify and provide any appropriate references.

COMMENT: The Reviewer noted: "Lead interactions with essential elements as Calcium, iron and Zinc are briefly discussed in this section as full details were presented in Section 3.1, Toxicokinetics"

RESPONSE: *No revisions were suggested.*

Chapter 4. Chemical and Physical Information

QUESTION: Are you aware of any information or values that are wrong or missing in the chemical and physical properties tables? Please provide appropriate references for your additions or changes.

QUESTION: Is information provided on the various forms of the substance? If not, please explain.

COMMENT: The Reviewer noted: "The information is adequate not only for the physical properties but also chemical forms and the corresponding properties. I have some concerns about the "rare" condition of Lead. This is not validated by the Chemistry reference literature and although lead is present in less than 0.0015% of the earth's crust cannot be considered to be a rare element since it is easily mined and refined. I would suggest to skip the term "rare element" for Lead in this chapter."

RESPONSE: *The term "rare" was removed from the statement.*

"Pb is a naturally occurring element with an abundance of 0.0016% in the earth's crust (Davidson et al. 2014). It is a member of Group 14 (IVA) of the periodic table. Natural Pb is a mixture of four stable isotopes: ^{204}Pb (1.4%), ^{206}Pb (24.1%), ^{207}Pb (22.1%), and ^{208}Pb (52.4%). The Pb isotopes ^{206}Pb, ^{207}Pb, and ^{208}Pb are the stable decay product of the naturally occurring decay series of uranium, actinium, and thorium, respectively (Haynes 2014).

Pb is found in concentrated and easily accessible Pb ore deposits that are widely distributed throughout the world (King et al. 2014). Its properties, such as corrosion resistance, density, and low melting point,

make it a familiar metal in pipes, solder, weights, and storage batteries. The chemical identities of Pb and several of its compounds are provided in Table 4-1."

Chapter 5. Potential for Human Exposure

QUESTION: Are you aware of any information that is wrong or missing? If so, please provide copies of the references and indicate where (in the text) the references should be included.

COMMENT: The Reviewer noted: "The large information detailed in this section corresponds to USA, so I'm not aware as to provide additional information or references."

RESPONSE: *No revisions were suggested.*

QUESTION: Has the text appropriately traced the substance from its point of release to the environment until it reaches the receptor population? Does the text provide sufficient and technically sound information regarding the extent of occurrence at NPL sites? Do you know of other relevant information? Please provide references for added information.

COMMENT: The Reviewer noted: "YES, On Section 5.3 Releases to the Environment there is an exhaustive review of studies reported by EPA contemplating all these aspects and sub-sections specially dedicated to different media: Air, water, soil and paint."

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text cover pertinent information relative to transport, partitioning, transformation, and degradation of the substance in all media? Do you know of other relevant information? Please provide references for added information.

COMMENT: The Reviewer noted: "YES, on Section 5.4: Environmental Fate, there is enough and pertinent information about the referred subjects."

RESPONSE: *No revisions were suggested.*

QUESTION: Does the text provide information on levels monitored or estimated in the environment, including background levels? Are proper units used for each medium? Does the information include the form of the substance measured? Is there an adequate discussion of the quality of the information? Do you know of other relevant information? Please provide references for added information.

COMMENT: The Reviewer noted: "YES, the Section 5.5: Levels in the Environment, provides full information of lead levels in different media and main emphasis is placed on the importance of the quality of analytical methods with low levels of detection. Tables include different references to the limit of detection obtained but few information about the methodologies."

RESPONSE: *No revisions were suggested. The analytical methods section of the profile is no longer included in the new format for the profiles.*

QUESTION: Does the text describe sources and pathways of exposure for the general population and occupations involved in the handling of the substance, as well as populations with potentially high exposures? Do you agree with the selection of these populations? If not, why? Which additional populations should be included in this section?

COMMENT: The Reviewer noted: "YES, Section 5.6; GENERAL POPULATION EXPOSURE describes different sources and pathways of exposure for the general and occupationally exposed population and many relevant studies involving sources and exposure risks assessment are presented. In this case, there also are many human studies available with different populations so I can agree with the selection of the studies as they are representative of the respective lead sources.

I could add to this Chapter that Table 5-1. Lowest Limit of Detection for Lead Based on Standards has old data from literature (NIOSH 1994), so I propose to update the table with updated data (e.g. CLSI C40-42 Measurement Procedures for the Determination of Lead Concentrations in Blood and Urine, 2nd Edition, 2013)

On the other side I also add, to pay attention of the toys (new and old ones) as another source of lead exposure to children. Studies may be not available, but preventive actions to protect children from exposure from toys, should be taken into account as well."

RESPONSE: No change was made to the cited detection limits. ATSDR does not routinely rely CLSI for citing standards. However, the Agency will consider the reviewers suggestion in future discussions of procedures for developing Toxicological Profiles.

Regarding the suggestion to include information on the potential for Pb-containing toys as a source of child exposure, the following *sentence in Section 5.6 was revised to include toys (revision in bold),*

> *Exposure to infants and children can occur from mouthing of leaded jewelry and* ***toys*** *containing Pb or painted with leaded paint (CDC 2018c).*

Chapter 6. Adequacy of the Database

QUESTION: Do you know of other studies that may fill a data gap? If so, please provide the reference.

COMMENT: The Reviewer noted: "This section does not have Figure 6-1 with those data. It refers to the epidemiological studies included in Chapter 2 that were selected to identify health effects associated to the exposure of humans to Pb and the findings are highlighted by referring to the figure 2-1 in Chapter 2 and several.

From my point of view, and after an exhaustive reading of Chapter 2, comprising a great review of selected studies on different health effects, I am not able to suggest other studies to fill data gaps for evaluation of post-exposure health effects by this moment."

RESPONSE: *No change suggested.*

QUESTION: Are the data needs presented in a neutral, non-judgmental fashion? Please note where the text shows bias.

QUESTION: Do you agree with the identified data needs? If not, please explain your response and support your conclusions with appropriate references.

QUESTION: Does the text indicate whether any information on the data need(s) exist(s)?

QUESTION: Does the text adequately justify why further development of the data need(s) would be desirable; or, conversely, justify the "inappropriateness" of developing the data need(s) at present? If not, how can this justification be improved.

COMMENT: The Reviewer noted: "I agree with most of the identified data needs but once again, and considering all the proposed studies, there´s a need for Laboratories to be able to quantify and report very low PbB results so I disagree with "No data needs were identified regarding analytical methods".

For illustrating this, on the recent manuscript of Caldwell, Kathleen L. et al. "Laboratory Measurement Implications of Decreasing Childhood Blood Lead Levels." Pediatrics 140.2 (2017) it was reported about the analytical laboratory and clinical interpretation challenges of blood lead measurements ≤ 5 μg/dL. They reviewed five years of results for target blood lead values < 11 μg/dL for U.S. clinical laboratories participating in CDC's voluntary Lead and Multi-Element Proficiency (LAMP) quality assurance program and it showed 40% laboratories unable to quantify and reported a non-detectable result at a target blood lead value of 1.48 μg/dL compared 5.5 % at a target blood lead of 4.60 μg/dL. http://doi.org/10.1542/peds.2017-0272.

I recommend the inclusion of a section for updated information on lead analysis performance in body fluids and other matrix since this topic was not well addressed in the whole profile."

RESPONSE:
The analytical methods section of the profile is no longer included in the new format for the profiles. The statement regarding analytical methods was deleted from the profile.

"**Exposures of Children.** Since an important variable in estimating Pb intakes from measurements of surface dust Pb levels is the rate of surface dust ingestion, improved estimates of soil ingestion would increase confidence in predictions of Pb intakes associated with exposures to Pb in surface dusts. In some contexts, exposure to surface dust Pb is measured in terms of Pb loading (μg/Pb/cm^2 of surface area available for contact); however, Pb loading measurements do not provide a direct way of estimating Pb ingestion without corresponding estimates of dust loading and surface dust ingestion rates. Improved methods for translating measurements of Pb loading into estimates of surface dust Pb concentration or surface dust Pb intake would be helpful for improving models for predicting exposure-Pb relationships in children.

~~**Analytical Methods.** No data needs were identified regarding analytical methods."~~

Chapter 7. Regulations and Guidelines

QUESTION: Are you aware of other regulations or guidelines that may be appropriate for the table? If so, please provide a copy of the reference.

COMMENT: The Reviewer noted: "As the large information detailed in this section corresponds to USA, I'm not aware as to provide additional information or references. I can suggest, to include references of International Guidelines as those from WHO, but perhaps this is out of the scope of ATSDR Profiles."

RESPONSE: *No revisions have been made. The focus of Chapter 7 (Regulations and Guidelines) of ATSDR profiles is on U.S. regulations and selected International Guidelines (e.g., IARC) that universally apply.*

Chapter 8. References

QUESTION: Are there additional references that provide new data or are there better studies than those already in the text? If so, please provide a copy of each additional reference.

COMMENT: The Reviewer noted: "NO, this is a very complete list of references that support all the studies and discussions developed throughout the document profile."

RESPONSE: *No change suggested.*