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Integrated Science Assessment for Lead

Appendix 9: Effects on Other Organ Systems and Mortality

External Review Draft

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Health and Environmental Effects Assessment Division
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DOCUMENT GUIDE

This Document Guide is intended to orient readers to the organization of the Lead (Pb) Integrated Science Assessment (ISA) in its entirety and to the sub-section of the ISA at hand (indicated in bold). The ISA consists of the Front Matter (list of authors, contributors, reviewers, and acronyms), Executive Summary, Integrated Synthesis, and 12 appendices, which can all be found at https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=357282.

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ACRONYMS AND ABBREVIATIONS

AAS	atomic absorption spectrometry
AD	Alzheimer's disease
ALAD	δ-aminolevulenic acid dehydratase
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMD	age-related macular degeneration
AOPP	advanced oxidation protein products
AQCD	Air Quality Criteria Document
ARCA	Automobile Racing Clube of America
AST	aspartate aminotransferase
AV/TV	adipocyte volume/total volume
BLL	blood lead (Pb) level
BMD	bone mineral density
BMI	body mass index
BMP	bone morphogenic protein
BV/TV	bone volume to total volume
C2C	serum cleavage neoepitope of type II collagen
Ca^{2+}	calcium ions
CAT	catalase
C-R	concentration-response
CAR	cortisol awakening response
Cd	cadmium
CHEER	Children's Health and Environment Research
CHF	congestive heart failure
CI	confidence interval
CK18	cytokeratin 18
COMP	cartilage oligomeric matrix protein
CPII	carboxypropeptide of type II collagen
CRP	C-reactive protein
CVD	cardiovascular disease
CYP	Cytochrome P450
d	day(s)
DBP	diastolic blood pressure
DMFT	decayed, missing, and filled teeth
DXA	Dual-energy X-ray absorptiometry
ECRHS	European Community Respiratory Health Survey
EGF	epidermal growth factor
eGFR	estimated glomerular filtration rate
ELEMENT	Early Life Exposures in Mexico to Environmental Toxicants
ER	endoplasmic reticulum
ERSD	end-stage renal disease
F#	filial generation
FBG	fasting blood glucose
FEV1	forced expiratory volume in one second
FIB-4	fibrosis-4
FT3	free triiodothyronine
FT4	free thyroxine
FVC	forced vital capacity
GADA	glutamic acid decarboxylase antibodies
GD	gestational day
GDM	gestational
GFAAS	graphite furnace atomic absorption spectrometry
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GH	growth hormone
GI	gastrointestinal
GM	geometric mean
GPx	glutathione peroxidase
GSH	glutathione
GSH-PX	glutathione peroxidase
Hb	hemoglobin
HDL	high-density lipoprotein
HDL-C	high-density lipoprotein cholesterol
HF	hepatic fibrosis
HOMA- β	HOMA of β-cell function
HOMA-IR	Homeostatic Model Assessment for Insulin Resistance
HR	hazard ratio
HS	hepatic steatosis
ICP-MS	inductively coupled plasma mass spectrometry
IHC	immunohistochemistry
IHD	ischemic heart disease
i.p.	intraperitoneal
IOP	intraocular pressure
ISA	Integrated Science Assessment
KARE	Korean Association Resource
KNHANES	Korean National Health and Nutrition Examination Survey
K-XRF	K-Shell X-Ray Fluorescence
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LOD	limit of detection
mo	month(s)
MDA	malondialdehyde
MetS	metabolic syndrome

METS	Modeling the Epidemiologic Transition Study
MI	myocardial infarction
microCT	micro-computed tomography
mRNA	messenger ribonucleic acid
NAAQS	National Ambient Air Quality Standards
NAFLD	nonalcoholic fatty liver disease
NANC	noncholinergic
NAS	Normative Aging Study
NASCAR	National Association for Stock Car Auto Racing
NHANES	National Health and Nutrition Examination Survey
NF-κB	nuclear factor kappa B
NP	nanoparticle
OA	osteoarthritis
OLD	obstructive lung disease
OLF	obstructive lung function
OR	odds ratio
Pb	lead
PbO	lead oxide
PCNA	proliferating cell nuclear antigen
PCR	polymerase chain reaction
PD	Potential difference
PECOS	Population, Exposure, Comparison, Outcome, and Study
PIR	poverty-income-ratio
PM	particulate matter
PND	postnatal day
PROGRESS	Programming Research in Obesity, Growth Environment and Social Stress
PTH	parathyroid hormone
PTHrP	parathyroid hormone-related protein
qRT-PCR	real-time quantitative reverse transcription-polymerase chain reaction
RBC	red blood cell
RR	risk ratio
RT-PCR	reverse transcription-polymerase chain reaction
SBP	systolic blood pressue
SBEHC	Shiwha and Banwol Environmental Health Cohort
SD	standard deviation
SE	standard error
SES	socioeconomic status
SNP	single nucleotide polymorphisms
SOD	superoxide dismutase
SPECT	single photon emission computed tomography
SSBI	sugar sweetened beverage intake
T-SOD	total superoxide dismutase
T	tertile
TB	total bilirubin
TBARS	thiobarbituric acid reactive substance
TC	total cholesterol
TEM	transmission electron microscopy
Tg	thyroglobulin
TGAb	thyroglobulin antibodies
TGF-β1	transforming growth factor-beta 1
TNF	tumor necrosis factor
TSH	thyroid stimulating hormone
TPOAb	thyroid peroxidade antibody
Q	quartile
wk	week(s)
yr	year(s)

APPENDIX 9 EFFECTS ON OTHER ORGAN SYSTEMS AND MORTALITY

Summary of Causality Determinations for Pb Exposure and Effects on Other Organ Systems

This appendix characterizes the scientific evidence that supports causality determinations for lead (Pb) exposure and hepatic effects, metabolic effects, gastrointestinal effects, endocrine system effects, effects on bone and teeth, effects on ocular health, and respiratory effects. The types of studies evaluated within this appendix are consistent with the overall scope of the ISA as detailed in the Process Appendix (see Section 12.4). In assessing the overall evidence, strengths and limitations of individual studies were evaluated based on scientific considerations detailed in the Table 12-5 of the Process Appendix (Section 12.6.1). More details on the causal framework used to reach these conclusions are included in the Preamble to the ISA (U.S. EPA, 2015). The evidence presented throughout this appendix supports the following causality conclusions:

Outcome Group	Causality Determination
Hepatic Effects	Suggestive
Metabolic Effects	Inadequate
Gastrointestinal Effects	Inadequate
Endocrine System Effects	Inadequate
Musculoskeletal Effects	Likely to be Causal
Effects on Ocular Health	Inadequate
Respiratory Effects	Inadequate
Mortality	Likely to be Causal

The Executive Summary, Integrated Synthesis, and all other appendices of this Pb ISA can be found at https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=357282.

9.1 Effects on the Hepatic System

9.1.1 Introduction, Summary of the 2013 ISA, and Scope of the Current Review

The 2013 Lead Integrated Science Assessment (2013 Pb ISA) concluded that "because of the insufficient quality of studies, the available evidence was inadequate to determine if there is a causal relationship between Pb exposure and hepatic effects" (U.S. EPA, 2013). Epidemiologic evidence from a limited number of occupational studies demonstrated impaired liver function in Pb-exposed workers. However, the internal validity and generalizability of these studies was limited by cross-sectional study designs, lack of consideration for potential confounders, and notably higher blood Pb levels (BLLs) (>29 µg/dL) than the general population. Similarly, toxicological studies observed changes in liver function enzymes and other markers of liver health in animals exposed to Pb, but the use of bolus injections as a common route of exposure and high BLLs (>30 µg/dL) introduced uncertainty regarding their relevance to human exposures.

9.1.2 Scope

The scope of this section is defined by Population, Exposure, Comparison, Outcome, and Study Design (PECOS) statements. The PECOS statement defines the objectives of the review and establishes study inclusion criteria, thereby facilitating identification of the most relevant literature to inform the Pb ISA.[1] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies included in the 2013 Pb ISA, including many that do not meet the current PECOS criteria, are discussed in this appendix to establish the state of the evidence prior to this assessment. Except for supporting evidence used to demonstrate the biological plausibility of Pb-

[1] The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

associated effects on the hepatic system, recent studies were only included if they satisfied all the components of the following discipline-specific PECOS statements:

Epidemiologic Studies:

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect.

Exposure: Exposure to Pb[1] as indicated by biological measurements of Pb in the body – with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure;[2] or intervention groups in randomized trials and quasi-experimental studies.

Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles).

Outcome: Effects on the hepatic system.

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

Experimental Studies:

Population: Laboratory nonhuman mammalian animal species (e.g., mouse, rat, guinea pig, minipig, rabbit, cat, dog) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).

Exposure: Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a BLL of 30 µg/dL or below.[3,4]

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[1] Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area of particular relevance to the National Ambient Air Quality Standards (NAAQS) review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[2] Studies that estimate Pb exposure by measuring Pb concentrations in particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm^3 (PM_{10}) and particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm^3 ($PM_{2.5}$) ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure (Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with blood Pb levels (BLLs) are lacking.

[3] Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.

[4] This level represents an order of magnitude above the upper end of the distribution of U.S. young children's BLL. The 95th percentile of the 2011–2016 National Health and Nutrition Examination Survey (NHANES) distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (Egan et al., 2021) and the proportion of individuals with BLL that exceed this concentration varies depending on factors including (but not limited to) housing age, geographic region, and a child's age, sex, and nutritional status.

Comparators: A concurrent control group exposed to vehicle-only treatment or untreated control.

Outcomes: Effects on the hepatic system.

Study design: Controlled exposure studies of animals in vivo.

9.1.3 Epidemiologic Studies on the Hepatic System

Epidemiologic evidence evaluated in the 2013 Pb ISA (U.S. EPA, 2013) was limited to a small number of occupational studies that demonstrated impaired liver function in Pb-exposed workers. However, the internal validity and generalizability of these studies was limited by cross-sectional study designs, lack of consideration for potential confounders, and notably higher BLLs (>29 μg/dL) than the general population. Recent epidemiologic studies of the hepatic system generally examine one of three groups of endpoints: (1) direct evaluation of liver injury (e.g., nonalcoholic fatty liver disease [NAFLD] and hepatic fibrosis); (2) serum biomarkers of liver function (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], and gamma-glutamyl transferase [GGT]); and (3) serum lipids (e.g., fatty acids, lipids, and cholesterol). Results from recent studies provide inconsistent evidence of an association between BLLs and direct or indirect measures of liver damage. Recent studies evaluating hepatic effects are generally limited to cross-sectional analyses, which are unable to establish temporality between exposure and outcome. Additionally, with BLL, it is difficult to characterize the specific timing, duration, frequency, and level of Pb exposure that contributed to associations observed with liver function. This uncertainty may apply particularly to assessments of BLLs, which in nonoccupationally-exposed adults, reflect both current exposures and cumulative Pb stores in bone that are mobilized during bone remodeling. Measures of central tendency for Pb biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 9-4. An overview of the recent evidence is provided below.

9.1.3.1 Direct Evaluation of Liver Injury

A limited number of recent cross-sectional studies examined the association between BLLs and liver injury, including NAFLD and fibrosis (Chung et al., 2020; Reja et al., 2020; Werder et al., 2020; Zhai et al., 2017). These studies, which use a variety of diagnostic tools, provide inconsistent evidence of an association between BLLs and NAFLD and fibrosis. Liver biopsy is the gold standard for evaluating NAFLD and liver fibrosis, but it is an invasive and cost prohibitive procedure. Therefore, epidemiologic studies often rely on alternative measurement techniques, including imaging, biomarkers, and biomarker-based prediction models. Imaging – either ultrasonic or magnetic resonance – generally has greater sensitivity and specificity than reliance on biomarkers.

A recent cross-sectional study of adults in the Yangtze River Delta in China examined the relationship between BLLs and NAFLD measured by ultrasound (Zhai et al., 2017). In addition to using ultrasonic imaging, this study included a large number of participants (n = 2,011). In sex-stratified models, Zhai et al. (2017) reported increases in the odds of NAFLD associated with increasing BLL quartiles after adjusting for a range of demographic and hepatic and metabolic health factors. The observed associations were stronger in magnitude among men (odds ratio [OR] = 2.168 [95% CI: 0.989, 4.751] quartile 4 versus quartile 1) compared with women (OR = 1.613 [95% CI: 1.082, 2.405] quartile 4 versus quartile 1); however, the effect estimates in men were much less precise due to a smaller sample of men in the study population. Given the imprecise estimates for men (i.e., wide 95% CIs), it is difficult to draw conclusions on sex-specific comparisons.

Results from other recent cross-sectional studies are inconsistent. In a small exploratory analysis of oil spill response workers with low BLLs (mean = 1.82 µg/dL), Werder et al. (2020) evaluated the association between BLLs and cytokeratin 18 (CK18), a serologic biomarker of hepatocyte death that has been used as a marker for NAFLD. The authors observed an association between BLLs and caspase-cleaved fragment CK18 (CK18 M30), but not whole protein CK18 (CK18 M65). Notably, CK18 M65 has performed better as a measure of NAFLD than CK18 M30 (Lee et al., 2020), adding further ambiguity to the observed results. Additionally, Werder et al. (2020) examined a range of heavy metals and markers of inflammation and did not adjust for multiple testing, which increases the likelihood of chance findings and may explain the inconsistent results. In addition to this weak evidence of an association between BLLs and markers of NAFLD, (Chung et al., 2020) analyzed data from the Korean National Health and Nutrition Examination Survey (KNHANES) and reported null or negative sex-specific associations between BLLs and scores on the Hepatic Steatosis Index, a validated biomarker-based prediction model of NAFLD. The authors also observed negative associations between BLLs and Fibrosis 4 Index, a similarly validated model for fibrosis. This larger analysis (n = 4,420) reported similar mean BLLs (1.81 µg/dL) as those reported in Werder et al. (2020).

In addition to studies examining NAFLD and fibrosis separately, (Reja et al., 2020) used a biomarker-based index to estimate fibrosis level in National Health and Nutrition Examination Survey (NHANES) participants with NAFLD. In this case, fibrosis level was used as an indicator of NAFLD severity. Reja et al. (2020) reported large, but imprecise associations between BLL quartiles and advanced liver fibrosis. For example, the authors noted that participants in the highest quartile of BLLs (>1.62 µg/dL) had a 493% increase in the odds of advanced liver fibrosis (95% CI: 188%, 1,124%) compared to participants in the lowest quartile (<0.64 µg/dL). Despite having a large sample size, the authors only examined severe liver fibrosis, which likely resulted in a small number of cases (total cases not reported), which would have decreased the statistical power of the study. Limited statistical power resulting from a small sample size simultaneously reduces the likelihood of detecting a true effect and the likelihood that an observed result reflects a true effect.

9.1.3.2 Serum Biomarkers of Liver Function

Serum biomarkers can be used as indirect evidence of liver damage. For example, elevated levels of ALT or AST can indicate the presence of necrosis in the liver, and elevated levels of bilirubin, ALP, or GGT can be associated with cholestasis. However, changes in serum biomarker levels are also related to effects on other biological systems. Elevated GGT can also occur with chronic heart failure, and elevated ALP can be used to detect bone disorders. Therefore, studies evaluating these biomarkers in combination are more likely to provide evidence of abnormal liver function relative to studies evaluating a single biomarker.

There have been a limited number of recent epidemiologic studies that evaluated serum biomarkers of liver function, including a longitudinal study (Pollack et al., 2015) and a few cross-sectional analyses (Chen et al., 2019; Obeng-Gyasi, 2019; Christensen et al., 2013). Recent studies, which adjust for a wide range of potential confounders, provide some evidence of an association between BLLs and serum biomarkers, but results are not entirely consistent, and the implications of some associations are unclear. Specifically, a small prospective cohort study of premenopausal women evaluated the percent change in AST, ALT, ALP, and bilirubin over the course of an 8-week follow-up (Pollack et al., 2015). The authors reported imprecise increases in AST (5.02% [95% CI: −1.36%, 11.41%]), ALT (6.39% [95% CI: 3.07%, 9.72%]), and ALP (2.14% [95% CI: −5.05%, 9.33%]) per 1 µg/dL increase in BLLs measured at baseline (mean = 1.03 µg/dL), but no change in bilirubin (−0.20% [95% CI: −7.50%, 7.11%]). The clinical relevance of these findings is uncertain given the majority of the study population fell well within the normal ranges of each of the biomarkers. A recent cross-sectional study of adults living near an e-waste facility in China better addresses clinical relevance by examining the association between BLLs and abnormal liver function, defined as having two or more transaminases (AST, ALT, GGT) elevated above the normal range, or having one transaminase at least twice as high as the upper bound of the normal range (Chen et al., 2019). In this study, which had notably higher median BLLs (5.1 to 8.7 µg/dL across study locations), a 1 µg/dL increase in BLL was associated with a large, but imprecise increase in the odds of abnormal liver function (OR = 1.94 [95% CI: 1.00, 3.73]).

Results from recent large cross-sectional NHANES analyses examining a single serum biomarker of liver function were inconsistent. In an analysis of 2003–2004 NHANES participant's ages 12 years and older, Christensen et al. (2013) reported null associations between increasing BLL quartiles and ALT levels. An analysis restricted to adult participants of more recent NHANES survey cycles (2011–2016) observed an increase in the odds of GGT levels above the study population median (18 U/L) associated with a 1 µg/dL increase in BLLs (OR = 1.94 [95% CI: 1.652, 2.28] for young adults and 1.34 [95% CI: 1.14, 1.58] for middle-aged adults) (Obeng-Gyasi, 2019). Similar to the Pollack et al. (2015) study, the median GGT levels in this study were within the normal range, making it difficult to interpret the clinical relevance of the results.

9.1.3.3 Serum Lipids

Many fatty acids, lipids, and cholesterol are synthesized and eliminated in the liver; the relationships among them and their relevance to other aspects of human health, including metabolic effects (Section 9.2) and cardiovascular effects (Appendix 4), are complex. Although increases or decreases in serum or liver cholesterol levels may be associated with liver damage, it can be challenging to determine whether the changes are a consequence of said damage or a contributing factor in disease progression (Arguello et al., 2015; Chrostek et al., 2014). Recent epidemiologic studies of serum lipids have been conducted in populations of adults and children and include a mix of prospective cohorts and cross-sectional designs. Recent studies also account for a range of potential confounders, including demographics and socioeconomic status (SES) factors, medical history, and medication use. Associations between BLLs and serum lipids have been largely inconsistent across both lifestages.

In a recent study including a subset of the Veterans Affairs Normative Aging Study (NAS) cohort with healthy older adults, Peters et al. (2012) examined the associations between BLLs at baseline and serum lipid levels after three to four years of follow-up. The authors reported increased odds of clinically elevated total cholesterol associated with an increase in BLLs (OR = 1.08 [95%: 0.99, 1.19] per 1 μg/dL increase in BLL). Associations with clinical cut points for other serum lipids were either null (elevated triglycerides and low-density lipoprotein [LDL] cholesterol) or negative (low high-density lipoprotein [HDL] cholesterol). Cross-sectional studies of adult populations, including analyses of nationally representative health survey data (Xu et al., 2021; Lee and Kim, 2016) and a small analysis of adults of African descent (Ettinger et al., 2014), are also inconsistent. Results across these studies (see Table 9-2) provide no discernable pattern of associations between BLLs and triglycerides, LDL cholesterol, or HDL cholesterol. BLL measures of central tendency were low across the evaluated studies (<5 μg/dL) and do not appear to explain the inconsistencies.

Results from studies in children are similarly inconsistent. Two recent studies of serum lipids analyzed data from separate birth cohorts in Mexico – the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) study (Liu et al., 2020) and the Programming Research in Obesity, Growth Environment and Social Stress (PROGRESS) birth study (Kupsco et al., 2019). In children ages 4 to 6, Kupsco et al. (2019) reported null associations between prenatal BLLs and serum triglycerides and non-HDL cholesterol. In contrast, in an analysis including older children and teens, Liu et al. (2020) observed an increase in triglyceride Z-scores in children with prenatal BLLs ≥5 μg/dL compared to those with BLLs less than 5 μg/dL (0.58 [95% CI: −0.05, 1.20]). The authors observed negative associations between prenatal BLLs and cholesterol Z-scores (total, LDL, and HDL). A large cross-sectional analysis of NHANES participants ages 12 to 19 noted a 2.3% (95% CI: 0.3%, 4.2%) increase in LDL cholesterol and a 0.6% (95% CI: −0.1%, 1.3%) increase in total cholesterol per 1 μg/dL increase in BLL (Xu et al., 2017). The authors observed null (total cholesterol and HDL cholesterol) or negative (triglycerides) associations between BLLs and other serum lipids.

9.1.4 Toxicological Studies on the Hepatic System

As described in the 2013 Pb ISA, evidence from toxicological studies indicates exposure to Pb can result in altered liver function and hepatic oxidative stress (U.S. EPA, 2013). A few studies reported Pb-induced decreases in cytochrome P450 (CYP) enzymes (Phase I xenobiotic metabolism), as well as Pb-induced decreases in serum protein and albumin levels and increased AST, ALT, ALP, and GGT activities (indicators of decreased liver function), increased oxidative stress, and decreased antioxidant status. A number of recent studies have corroborated findings of Pb exposure and decreased liver function (Barkaoui et al., 2020; Dumková et al., 2020b; Gao et al., 2020; Andjelkovic et al., 2019; Laamech et al., 2017; Long et al., 2016; Liu et al., 2013; Berrahal et al., 2011). While impaired lipid metabolism was reported in the 2013 Pb ISA, results from recent studies of cholesterol have been inconsistent. Laamech et al. (2017) found an increase in total cholesterol in mice given Pb acetate in their drinking water (BLL: 18 µg/dL). Conversely, Dumková et al. (2020a) found lower levels of total cholesterol in rats that were given Pb oxide nanoparticles by inhalation (BLLs: 3.1–8.5 µg/dL); however, the latter group did report an increase in lipid droplets by liver histology [BLLs: 3.1–17.8 µg/dL; (Dumková et al., 2020a; Dumková et al., 2020b; Dumková et al., 2017)]. Observation of Pb-associated increases in hepatic oxidative stress, as indicated by a decrease in glutathione (GSH) levels and catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx) activities has been found in additional recent studies of oral Pb exposure [drinking water: 21.4–29.0 µg/dL (Barkaoui et al., 2020; Andjelkovic et al., 2019; Long et al., 2016); oral gavage: 18.5–30.2 µg/dL (Gao et al., 2020; Laamech et al., 2017; Li et al., 2017)].

Since the 2013 Pb ISA, several recent studies have reported perturbations related to oxidative stress in addition to the endpoints noted above. For example, Andjelkovic et al. (2019) found changes in multiple parameters of oxidative stress in liver and kidney tissue in male rats, indicative of an oxidative stress response to Pb exposure (BLL: 29.0 µg/dL). Long et al. (2016) also reported several markers of oxidative damage and response, in mouse liver tissue. They showed in addition, consistent with an oxidative damage response, attenuation of such response after administration of proanthocyanidins, which are naturally occurring antioxidant compounds. The same authors reported changes in several markers that are consistent with a generalized endoplasmic reticulum (ER) response in the liver to environmental stressors. Likewise, Liu et al. (2013) showed Pb responsiveness of ER stress markers, and the antagonistic effect of quercetin (a natural flavonoid) on this response. Barkaoui et al. (2020) reported finding alleviation of Pb-induced oxidative effects from administration of antioxidative, phenolic compounds extracted from Plantigo albicans.

Cell death by apoptosis may be a downstream result of the molecular sequelae of Pb exposure described in the preceding paragraph. Indeed, such a result has been reported in mouse livers, both phenotypically and via molecular markers (Dumková et al., 2017; Long et al., 2016).

9.1.5 Biological Plausibility

This section describes biological pathways that potentially underlie effects of Pb on the liver and hepatic function. Figure 9-1 depicts the proposed pathways as a continuum of upstream events, connected by arrows, which may lead to downstream events observed in epidemiologic studies. This discussion of how exposure to Pb may lead to hepatic effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated above. Note that the structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the current Pb ISA are discussed in Section IS.4.2.

The hepatic effects of Pb exposure have been studied in many experimental models. The pathway proposed, outlined in Figure 9-1, involves the induction of oxidative stress and inflammation leading to downstream cellular loss and metabolic changes that could plausibly be responsible for the development of health effects in the liver. Oxidative stress control and inflammation are highly regulated processes and are tightly linked. As discussed above and in both the 2013 Pb ISA and 2006 Pb Air Quality Criteria Document (AQCD), inflammatory signaling and marker of oxidative stress have been found in the livers of animals exposed to Pb (see Section 9.1.3 and (U.S. EPA, 2013, 2006). Hepatic inflammation and oxidative stress co-occur thus it is difficult to determine if one process precedes the other, thus, they are grouped in the same grey box in Figure 9-1.

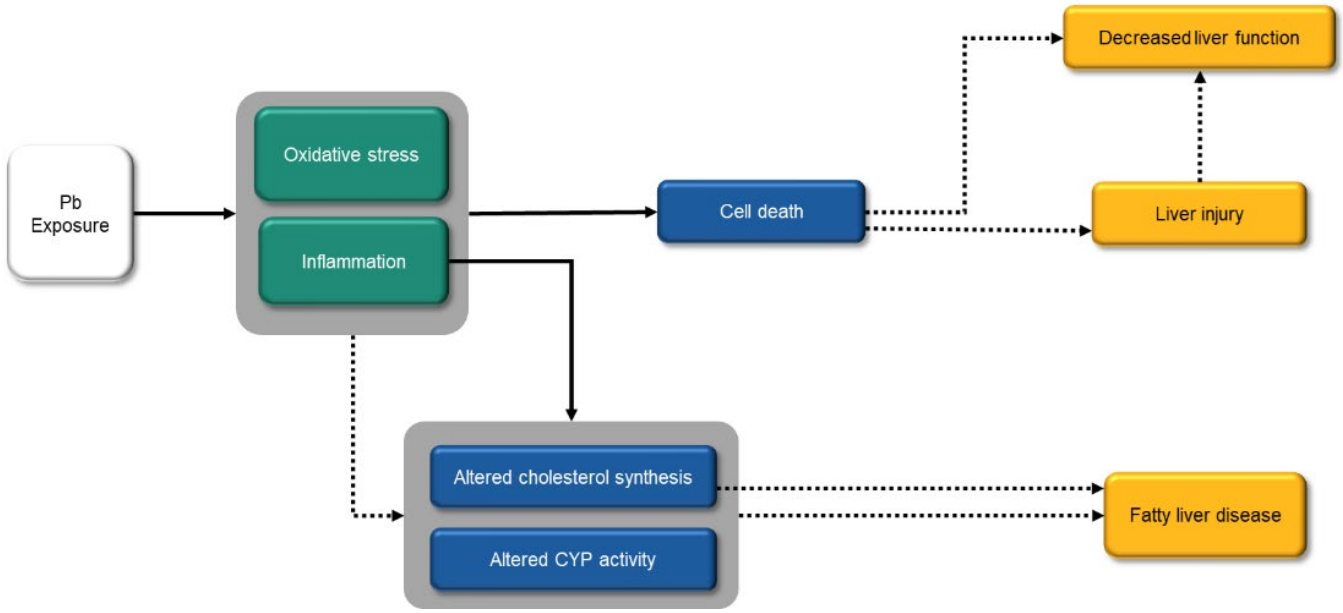
Regulation of inflammation and oxidative stress involve widespread gene expression changes that could plausibly alter the expression of metabolizing enzymes and proteins necessary for cholesterol synthesis and maintaining lipid homeostasis which could lead to fat accumulation and subsequent fatty liver disease. As discussed in the 2013 Pb ISA, Pb treatment can cause elevated cholesterol levels through changes in cholesterol synthesis pathways in the liver. Pb can also alter the expression and activity of CYP enzymes that are important in the response to xenobiotics as well as metabolism of cholesterol-derived steroid hormones. A recent study in knockout mice showed that mice deficient in the Il-1 inflammatory mediators were protected from the hypercholesterolemia in response to Pb compared to wild type mice (Kojima et al., 2012). Knockout mice also did not experience the messenger ribonucleic acid (mRNA) upregulation cholesterol synthesizing enzymes *HMGR* and *Cyp51* or the downregulation of bile acid synthesizing enzyme *Cyp7a1*. These data support the necessity of inflammation to the regulation of cholesterol metabolism and are the basis for the solid line from inflammation to the box containing CYP activity and altered cholesterol synthesis in Figure 9-1.

Excessive damage from oxidative stress and inflammatory responses could lead to cell death which, in excess, could lead to changes in hepatocyte structure and ultimately decrease liver function. As discussed above and in the 2013 Pb ISA and 2006 Pb AQCD, many animal studies have shown that Pb exposure of varying durations and developmental stages results in liver injury, which is most commonly measured as increased activity of liver enzymes (e.g., AST, ALT, ALP) in the blood serum or plasma. Increases of liver enzyme activity have been seen in the serum of humans occupationally exposed to Pb

(Mazumdar and Goswami, 2014; U.S. EPA, 2013). As mentioned above, elevated liver enzymes in the blood can serve as an indirect markers of liver damage. Previous research has shown that exposure to Pb in animal models can lead to upregulation of cell death pathways (U.S. EPA, 2013) and more recent studies provide additional support (Almasmoum et al., 2019; Abu-Khudir et al., 2017; Hasanein et al., 2016; Long et al., 2016; Mabrouk et al., 2016; Liu et al., 2013; Pal et al., 2013; Liu et al., 2012, 2011). Studies have shown that treatment with antioxidants, like vitamin E (Almasmoum et al., 2019), vitamin C (Upadhyay et al., 2009), or therapeutic compounds that have anti-inflammatory and antioxidant properties (Abu-Khudir et al., 2017; Hasanein et al., 2016; Long et al., 2016; Mabrouk et al., 2016; Liu et al., 2013; Pal et al., 2013; Liu et al., 2012) can prevent the Pb-induced upregulation of apoptotic pathways and concomitantly reduced both markers of oxidative damage and serum markers of liver injury. Interestingly, some therapeutic compounds reduce the liver Pb burden suggesting that the reduction in oxidative stress may be caused by toxicokinetic changes that reduce the liver Pb exposure concentration (Liu et al., 2013; Liu et al., 2011), however, some studies have seen that antioxidant treatment can reduce oxidative stress even while live Pb levels remain elevated suggesting that oxidative stress is directly related to downstream liver damage (Almasmoum et al., 2019; Long et al., 2016; Mabrouk et al., 2016; Reckziegel et al., 2016). Together these data provide support for the solid line from the box containing inflammation and oxidative stress to cell death.

Excessive cell loss can result in changes to liver architecture and trigger repair processes that can lead to liver scarring, both of which can lead to loss of liver function. The 2013 Pb ISA discussed studies that showed that Pb treatment led to noticeable histologic changes including signs of increased fibrotic liver changes (U.S. EPA, 2013). More recent work supports this with evidence that liver histologic changes are accompanied by increased markers of apoptosis and necrosis (Long et al., 2016; Mabrouk et al., 2016). A study also showed that 4 months of Pb exposure in rats increased wound repair signaling pathways which corresponded to increased deposition of extracellular matrix proteins in the liver (Perez Aguilar et al., 2014). Sufficient damage to the liver can reduce liver function which can be measured as a reduced level of protein in the blood. Recent studies have shown decreases in serum proteins following Pb exposure that coincide with molecular or histological signs of liver damage (Almasmoum et al., 2019; El-Tantawy, 2016; Hasanein et al., 2016). Similar evidence is seen in the 2013 Pb ISA. Together, it is plausible that widespread cell death in the liver can lead to changes in hepatocyte structure that leads to liver damage and resulting decline in liver function.

The proposed pathway leading from Pb exposure to hepatic health effects begins with the induction of inflammation and increase in oxidative stress. This results in both changes in metabolizing enzymes and cholesterol synthesis that could be responsible for fatty accumulation in the liver. Widespread oxidative damage results in cell loss which could disrupt the normal liver structure and contribute to loss of liver function. Together, the evidence supports a plausible pathway from Pb exposure to the hepatic effects seen in epidemiologic and animal tox studies.



CYP = cytochrome P450.

Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence related to Pb exposure, and the arrows indicate a proposed relationship between those effects. Solid arrows denote evidence of essentiality as provided, for example, by an inhibitor of the pathway used in an experimental study involving Pb exposure. Dotted arrows denote a possible relationship between effects. Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color coded (white, exposure; green, initial effect; blue, intermediate effect; orange, effect at the population level or a key clinical effect). Here, population-level effects generally reflect results of epidemiologic studies. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below. The structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the 2022 Pb ISA are discussed in IS.7.2.

Figure 9-1 Potential biological pathways for hepatic effects following exposure to Pb.

9.1.6 Summary and Causality Determination

The 2013 Pb ISA (U.S. EPA, 2013) concluded that the available evidence was "inadequate to determine if there is a causal relationship between Pb exposure and hepatic effects." A limited number of occupational epidemiologic studies evaluated potential associations between increased BLLs and decreases in serum protein and albumin levels and increased liver function enzymes, oxidative stress, and antioxidant status. The implications of the occupational epidemiologic evidence were limited because of the cross-sectional design of the studies, the high BLLs examined (means >29 µg/dL), and the lack of consideration for potential confounding by factors such as age, diet, BMI, smoking, or other occupational exposures. Similar changes in liver function enzymes were found in mature animals exposed to high levels of Pb during adulthood, and animals exposed during gestation and lactation. Pb exposure was also shown to impair lipid metabolism in animals, as evidenced by increased hepatic cholesterogenesis, and altered triglyceride and phospholipid levels (Sharma et al., 2010; Ademuyiwa et al., 2009; Khotimchenko and Kolenchenko, 2007). Multiple toxicological studies observed Pb-associated increases in hepatic

oxidative stress, generally indicated by an increase in lipid peroxidation along with a decrease in GSH levels and CAT, SOD, and GPx activities (Pandya et al., 2010; Sharma et al., 2010; Yu et al., 2008; Adegbesan and Adenuga, 2007; Jurczuk et al., 2007; Khotimchenko and Kolenchenko, 2007; Jurczuk et al., 2006). However, the relevance of the toxicological evidence was uncertain, as many studies administered Pb as bolus doses. Additionally, few toxicological studies reported the resulting BLLs and those studies that did provide this evidence had BLLs of limited relevance to environmentally exposed humans (>30 µg/dL). Thus, despite some evidence of Pb-induced hepatic effects, uncertainties related to the relevance of the available studies limited the causal conclusions that could be drawn in the 2013 Pb ISA.

Recent toxicological studies include more relevant routes of exposure (i.e., drinking water, oral gavage, and inhalation) and exposures resulting in lower BLLs than those available for the previous ISA (BLL range: 3.6–30.2 µg/dL). These studies provide consistent evidence of Pb-induced increases in AST, ALT, ALP, and GGT activities, which are indicative of reduced liver function (Barkaoui et al., 2020; Dumková et al., 2020b; Gao et al., 2020; Andjelkovic et al., 2019; Laamech et al., 2017; Long et al., 2016; Liu et al., 2013; Berrahal et al., 2011). Additionally, recent studies provide consistent evidence of Pb-associated increases in hepatic oxidative stress, as indicated by decreases in GSH levels and CAT, SOD, and GPx activities (Barkaoui et al., 2020; Gao et al., 2020; Andjelkovic et al., 2019; Laamech et al., 2017; Li et al., 2017; Long et al., 2016). While impaired lipid metabolism was reported in the 2013 Pb ISA, a limited number of recent studies of cholesterol have reported contrasting results, one indicating Pb-induced increases in total cholesterol (Laamech et al., 2017) and the other reporting decrements in total cholesterol (Dumková et al., 2020a).

In contrast to toxicological evidence, recent epidemiologic studies evaluating the relationship between BLLs and hepatic effects are generally inconsistent or inconclusive. Similar to studies evaluated in the 2013 Pb ISA, most recent studies implement cross-sectional designs, although they include more robust adjustment for potential confounders and populations with much lower mean BLLs. Still, these studies do not address potentially large differences in past versus current exposures. There is therefore uncertainty as to the specific timing, duration, frequency, and level of Pb exposure that contributed to any observed associations. The strongest evidence for direct liver injury comes from a large cross-sectional analysis of adults in China that reported a positive association between BLLs and NAFLD prevalence measured by ultrasound (Zhai et al., 2017). Other cross-sectional analyses used biomarkers or biomarker indices to assess NAFLD, which are less accurate than ultrasonic imaging and may introduce non-differential misclassification. Non-differential misclassification of a dichotomous outcome is likely to bias results toward the null. The available biomarker studies of NAFLD did not provide convincing evidence that BLLs are associated with NAFLD prevalence (Chung et al., 2020; Reja et al., 2020; Werder et al., 2020). Results from studies that examined serum biomarkers of general liver function (e.g., AST, ALT, ALP, GGT, and bilirubin) provided some evidence that BLLs are associated with increased biomarker levels (Chen et al., 2019; Obeng-Gyasi, 2019; Pollack et al., 2015), but the inferences that can be drawn from two of these studies is limited due to study populations that had biomarkers well within

normal ranges (Chen et al., 2019; Obeng-Gyasi, 2019). There are also a few recent studies that examined serum lipids in adults or children and the results are inconsistent. Across studies, contrasting associations were observed between BLLs and specific lipids, with no discernable pattern of associations between BLLs and triglycerides, LDL cholesterol, HDL cholesterol, or total cholesterol.

Overall, recent toxicological studies build upon evidence from the 2013 Pb ISA and provide largely consistent evidence that indicates exposure to Pb can result in altered liver function and hepatic oxidative stress. Compared to the 2013 Pb ISA, recent toxicological studies include routes of exposure and BLLs that are more relevant to humans. Results from a limited number of recent epidemiologic studies examining liver enzymes are generally coherent with the toxicological evidence, indicating Pb-associated increases in enzymes that are consistent with altered liver function. However, due to the reported liver enzyme levels in the epidemiologic studies, there is uncertainty as to whether the observed changes in enzymes are indicative of liver injury. Additionally, epidemiologic studies of direct liver injury provide inconsistent evidence of an association with BLLs. Thus, based on the strength of the toxicological evidence and some remaining inconsistencies and uncertainties in the epidemiologic evidence, **the collective evidence is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and hepatic effects.** The key evidence, as it relates to the causal framework, is summarized in Table 9-1.

Table 9-1 Evidence that is suggestive of, but not sufficient to infer, a causal relationship between Pb exposure and hepatic effects.

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent evidence from animal toxicological studies at relevant BLLs	Toxicological studies provide largely consistent evidence that indicates exposure to Pb can result in:		
	Altered liver function	Berrahal et al. (2011) Liu et al. (2013) Long et al. (2016) Andjelkovic et al. (2019) Gao et al. (2020) Dumková et al. (2020b) Laamech et al. (2017) Barkaoui et al. (2020)	Range of mean BLLs across studies: 18.0 to 29.0 µg/dL
	Increases in hepatic oxidative stress, as indicated by decreases in GSH levels and CAT, SOD, and GPx activities	Li et al. (2017) Long et al. (2016) Andjelkovic et al. (2019) Barkaoui et al. (2020) Gao et al. (2020) Laamech et al. (2017)	Range of mean BLLs across studies: 3.6 to 30.2 µg/dL
Limited or inconsistent evidence from epidemiologic studies at relevant BLLs	Inconsistent evidence of associations between BLLs and NAFLD	See Section 9.1.3.1	Range of mean BLLs across studies: 1.0 to 5.29 µg/dL
	Some evidence that BLLs are associated with increased levels of serum biomarkers of liver function, but limited inference due to study populations that had biomarkers well within normal ranges	Pollack et al. (2015) Chen et al. (2019) Obeng-Gyasi (2019)	Range of mean BLLs across studies: 1.0 to 8.7 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Biological Plausibility	The proposed pathway leading from Pb exposure to hepatic health effects begins with the induction of inflammation and increase in oxidative stress. This results in both changes in metabolizing enzymes and cholesterol synthesis that could be responsible for fatty accumulation in the liver. Widespread oxidative damage results in cell loss which could disrupt the normal liver structure and contribute to loss of liver function.	See Section 9.1.4	

BLLs = blood lead levels; CAT = catalase; GSH = glutathione; GPx = glutathione peroxidase; NAFLD = nonalcoholic fatty liver disease; Pb = lead; SOD = superoxide dismutase.

[a]Based on aspects considered in judgments of causality and weight-of-evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the Pb biomarker levels at which the evidence is substantiated.

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9.2 Metabolic Effects

9.2.1 Introduction, Summary of the 2013 ISA, and Scope of the Current Review

The 2013 Pb ISA (U.S. EPA, 2013) did not have a separate discussion of potential metabolic effects of exposure to Pb. However, evidence relevant to metabolic effects was provided by a small number of studies that examined glucose and insulin homeostasis, lipids, cholesterol, and liver health endpoints. These studies provided evidence for modes of action and were discussed across a few sections of the 2013 Pb ISA (U.S. EPA, 2013), including Section 4.4 (Cardiovascular Effects), Section 4.5 (Renal Effects), and Section 4.9.1 (Effects on the Hepatic System). There was no causality determination for metabolic effects in the 2013 Pb ISA (U.S. EPA, 2013).

The metabolic effects reviewed in this section include diabetes mellitus and insulin resistance (Section 9.2.3.1), metabolic syndrome and its components (Section 9.2.3.2), and effects on body weight measures (Section 9.2.3.3). Other metabolic indicators, such as changes in liver function, serum lipids, and neuroendocrine signaling, are discussed in other sections of this appendix (Sections 9.2 and 9.4).

9.2.2 Scope

The scope of this section is defined by PECOS statements. The PECOS statement defines the objectives of the review and establishes study inclusion criteria thereby facilitating identification of the most relevant literature to inform the Pb ISA.[1] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies included in the 2013 Pb ISA, including many that do not meet the current PECOS criteria, are discussed in this appendix to establish the state of the evidence prior to this assessment. Except for supporting evidence used to demonstrate the biological

[1] The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

plausibility of Pb-associated metabolic effects, recent studies were only included if they satisfied all of the components of the following discipline-specific PECOS statements:

Epidemiologic Studies:

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect.

Exposure: Exposure to Pb[1] as indicated by biological measurements of Pb in the body – with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure;[2] or intervention groups in randomized trials and quasi-experimental studies.

Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles).

Outcome: Metabolic effects.

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

Experimental Studies:

Population: Laboratory nonhuman mammalian animal species (e.g., mouse, rat, guinea pig, minipig, rabbit, cat, dog) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).

Exposure: Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a BLL of 30 µg/dL or below.[3,4]

Comparators: A concurrent control group exposed to vehicle-only treatment or untreated control.

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[1] Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[2] Studies that estimate Pb exposure by measuring Pb concentrations in particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm^3 (PM_{10}) and particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm^3 ($PM_{2.5}$) ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with BLLs are lacking.

[3] Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.

[4] This level represents an order of magnitude above the upper end of the distribution of U.S. young children's BLL. The 95th percentile of the 2011–2016 NHANES distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (Egan et al., 2021) and the proportion of individuals with BLL that exceed this concentration varies depending on factors including (but not limited to) housing age, geographic region, and a child's age, sex, and nutritional status.

Outcomes: Metabolic effects.
Study design: Controlled exposure studies of animals in vivo.

9.2.3 Epidemiologic Studies on Metabolic Effects

9.2.3.1 Diabetes Mellitus and Insulin Resistance

Diabetes mellitus is a chronic condition characterized by an inability to regulate glucose in the blood by producing or responding to insulin. A number of epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) examined diabetes as a potential at-risk factor that could modify the relationship between Pb exposure and other health outcomes, but none examined the direct relationship between Pb exposure and diabetes incidence or prevalence. Recent studies have examined this relationship, commonly categorizing diabetes mellitus status as meeting one or more of the following criteria: (1) elevated fasting blood glucose (FBG), (2) self-reported use of insulin or oral medications for diabetes, or (3) self-reported physician diagnosis with diabetes. There are three primary types of diabetes: type I, type II, and gestational (GDM). Some of the evaluated studies distinguished between types of diabetes mellitus, while others did not. Most studies were cross-sectional in design, meaning temporality between exposure and outcome could not be established.

Recent epidemiologic studies examining the relationship between Pb exposure and diabetes mellitus, or insulin resistance have reported mostly null findings across lifestages. In adult populations, a limited number of case-control and cross-sectional studies examining diabetes prevalence reported null or inverse associations between BLLs and diabetes mellitus or levels of insulin resistance. Results from recent studies examining insulin resistance in adolescents and gestational diabetes in pregnant women are also mostly null. Measures of central tendency for Pb biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 9-6. An overview of the recent evidence is provided below.

Studies in Adults

In a recent cross-sectional analysis of blood Pb and diabetes using data from the 2009 and 2010 cycles of the KNHANES, Moon (2013) observed a negative trend in diabetes prevalence across blood Pb quartiles. Compared to the lowest blood Pb quartile (geometric mean (GM): 1.43 μg/dL), the largest reductions in the odds of diabetes were observed in the highest exposure quartile (GM: 4.08 μg/dL; OR = 0.745 [95% CI: 0.516, 1.077]) and in the second highest quartile (GM: 2.74 μg/dL) (OR = 0.759 [95% CI: 0.531, 1.086]). Similarly, in sex-stratified analyses of subjects without diabetes, Moon (2013) reported slight reductions in the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR),

HOMA of β-cell function (HOMA-β), and fasting insulin per log unit increase in blood Pb. The observed results were comparable in men and in women.

Two recent cross-sectional case-control studies originating from the Nord-Trondelag Health Study (HUNT3) evaluated differences in blood Pb measurements between subjects with and without type II diabetes and reported results that are also consistent with a null or negative association (Hansen et al., 2017; Simić et al., 2017). Specifically, Hansen et al. (2017) identified 128 cases of previously undiagnosed, screening-detected type II diabetes and 755 age- and sex-matched controls. The authors observed a slight, but notably imprecise increase in odds of screening-detected type II diabetes for blood Pb quartile 4 compared to quartile 1 (OR = 1.12 [95% CI: 0.58, 2.16]). As indicated by the wide confidence intervals, the increase in odds is difficult to distinguish from chance. In a parallel analysis, Simić et al. (2017) identified 267 cases of self-reported type II diabetes and 609 frequency-matched controls from the same HUNT3 cohort. Consistent with results from Moon (2013), (Simić et al., 2017) observed a substantial reduction in diabetes prevalence for BLLs in the highest quartile compared to the lowest (OR = 0.24 [95% CI: 0.13, 0.47]). The observation of a negative association for Pb and type II diabetes by Simić et al. (2017) but not Hansen et al. (2017) may be related to differences in exposure contrast between identified cases and controls. Hansen et al. (2017) reported median BLLs of 1.99 µg/dL for controls and 1.94 µg/dL for cases, while Simić et al. (2017) reported median BLLs of 2.02 µg/dL for controls and 1.64 µg/dL for cases. Additionally, the differences could be due to an effect of diabetes treatment on BLLs, which highlights an uncertainty of these cross-sectional analyses.

Studies in Adolescents

A recent study assessed the relationship between exposure to Pb in utero and insulin resistance in adolescence (Liu et al., 2020). Pregnant mothers were enrolled in the ELEMENT project from 1997–1999 and 2001–2003 and their children were followed until 2015. There was a null association between first trimester maternal blood Pb ≥5 µg/dL and HOMA-IR in adolescence. In combined and sex-stratified analyses, associations were null.

Studies in Pregnant Women

A number of recent studies have investigated the relationship between Pb exposure and GDM. These studies, most of which have reported null associations between BLLs and GDM, are discussed in more detail in Section 8.4.1.1.2 of the Reproductive and Developmental Effects Appendix.

9.2.3.2 Metabolic Syndrome and its Components

Metabolic syndrome (MetS) describes a set of cardiometabolic conditions that increase a person's risk for cardiovascular diseases. Components of MetS include elevated blood pressure, low HDL

cholesterol, elevated blood tryglicerides, elevated FBG, and a high waist circumference, also referred to as abdominal obesity. A MetS diagnosis is commonly defined as meeting three or more of the following criteria: (1) elevated blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or current use of blood pressure medication); (2) low HDL cholesterol (<40 mg/dL in women or <50 mg/dL in men); (3) elevated serum triglycerides (≥150 mmHg) or current use of anti-dyslipidemia medication; (4) elevated FBG (≥100 µg/dL); (5) abdominal obesity (waist circumference ≥90 cm in men or ≥85 cm in women). None of the studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) examined the relationship between Pb exposure and MetS. Recent evidence for the effects of Pb exposure on MetS and its components is inconsistent. Measures of central tendency for Pb biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 9-3. An overview of the recent evidence is provided below.

9.2.3.3 Metabolic Syndrome

A number of recent large, population-based cross-sectional studies have analyzed the relationship between BLLs and MetS prevalence and provide inconsistent evidence of an association. Across studies, mean and/or median BLLs were below 5 µg/dL, including some below 2 µg/dL. Studies analyzing data from overlapping cycles of the KNHANES observed increased MetS prevalence in participants with higher BLLs (Moon, 2014; Rhee et al., 2013). Specifically, Rhee et al. (2013) reported that 2008 KNHANES participants with BLLS in the highest exposure quartile (3.07–19.43 µg/L) were 2.57 (95% CI: 1.46, 4.51) times more likely to have MetS than subjects in the lowest quartile (0.42–1.73 µg/L). The authors noted a consistent concentration-response trend across quartiles. In an analysis incorporating more KNHANES cycles (2007–2012), Moon (2014) observed a smaller increase in the odds of MetS for subjects in the second highest exposure quartile (GM 2.51 µg/dL) (OR = 1.21 [95% CI: 0.90, 1.62]) compared to the lowest (GM 1.23 µg/dL) but did not observe a clear dose-response trend across quartiles.

In contrast to KNHANES studies, other analyses of data from a variety of large population-based surveys noted negative associations between BLLs and MetS (Wen et al., 2020; Bulka et al., 2019; Shim et al., 2019). Bulka et al. (2019) used data from two cycles (2011–2014) of the NHANES to perform a cross-sectional analysis of blood Pb and MetS prevalence. The authors observed reduced odds of MetS with increasing blood Pb quartile, with the largest reduction observed in subjects in the highest quartile of lead exposure (1.64–15.98 µg/dL) compared to the lowest quartile (0.18–0.70 µg/dL) (OR = 0.81 [95% CI: 0.64, 1.03]). Shim et al. (2019) and Wen et al. (2020) similarly reported reduced odds of MetS associated with increased BLLs in the Korean National Environmental Health Survey II (KNHANES II) and a survey of adults in Taiwan, respectively.

Components of Metabolic Syndrome

In addition to cross-sectional studies evaluating MetS prevalence, several recent studies have assessed the potential effects of Pb on the individual components of MetS (abdominal obesity [often measured by waist circumference], low HDL cholesterol, elevated triglycerides, and elevated FBG; studies evaluating blood pressure and hypertension are discussed in Section 4.3). Similar to studies that evaluated MetS prevalence, most of these studies analyzed cross-sectional data from nationally representative health surveys. In general, results from recent studies were inconsistent across individual MetS components, with the exception of blood pressure and serum triglycerides.

Waist Circumference

Recent KNHANES analyses of BLLs and waist circumference were inconsistent (Lee and Kim, 2016, 2013; Rhee et al., 2013). In an analysis of KNHANES participants from 2005–2010, Lee and Kim (2013) observed no apparent association between BLLs and waist circumference. The same authors evaluated more recent KNHANES cycles (2007–2012) and observed slightly increased odds of waist circumference ≥85 cm in the second (>2.199–3.011 μg/d) and third (>3.011 μg/dL) blood Pb tertiles compared to the first tertile (≤2.199 μg/dL), but slightly decreased odds per twofold continuous increase in blood Pb (Lee and Kim, 2016). In contrast, in an analysis of 2008 KNHANES participants, Rhee et al. (2013) found a modest but positive association between blood Pb and abdominal circumference as a continuous variable.

Results from two recent NHANES analyses were similarly inconsistent (Bulka et al., 2019; Wang et al., 2018c). Wang et al. (2018c) used data from NHANES cycles between 2003 and 2014 and observed a 0.8% (95% CI: 0.6, 1.0%) reduction in waist circumference per 1-SD increase in $\log_{10}$-transformed blood Pb (μg/dL). While the large sample size of this analysis leads to precise 95% CIs, the relevance of a notably small decrement in waist circumference is unclear. In contrast, a study including two NHANES cycles that overlapped with the Wang et al. (2018c) study (2011–2014) reported negative associations between BLLs and probability of abdominal obesity (Bulka et al., 2019).

HDL Cholesterol and Serum Triglycerides

The previously discussed KNHANES analyses also assessed HDL cholesterol and serum triglycerides. These studies do not provide evidence that BLLs are associated with increased odds of low HDL cholesterol (Lee and Kim, 2016, 2013; Rhee et al., 2013). The same studies did provide consistent evidence of higher serum triglycerides in association with higher BLLs, although these studies were notably conducted in overlapping populations (i.e. non-independent samples). Lee and Kim (2013) and Lee and Kim (2016) observed slight increases in odds of high serum triglycerides (≥150 μg/dL) with higher BLLs (analyzed as a continuous variable and as tertiles). Similarly, Rhee et al. (2013) reported a modest positive association between serum triglycerides and log-transformed BLLs.

In addition to studies that examined HDL cholesterol and serum triglycerides in conjunction with MetS, a few other recent studies also evaluated these measures as part of a broader lipids profile. As discussed in Section 9.1.3.3, these studies were inconsistent for HDL cholesterol and triglycerides, including a prospective cohort study of older Veterans participating in the NAS that reported null associations between BLLs at baseline and HDL cholesterol and triglyceride levels after three to four years of follow-up (Peters et al., 2012).

Elevated Fasting Glucose

The majority of recent population-based cross-sectional studies of MetS components did not observe associations between BLLs and FBG. Specifically, KNHANES analyses (Lee and Kim, 2016; Rhee et al., 2013) and a recent NHANES analysis (Bulka et al., 2019) reported null associations between BLLs and FBG. In contrast, in an analysis of earlier KNHANES cycles, Lee and Kim (2013) reported blood Pb to be positively associated with elevated FBG (≥100 μg/dL), with the odds of elevated FBG increasing with each doubling of BLLs (OR = 1.118 [95% CI: 0.953, 1.311]). In addition to large cross-sectional studies, a smaller cross-sectional analysis of adults of African descent across five countries of varying social and economic development in Africa also examined the relationship between BLLs and elevated FBG (Ettinger et al., 2014). Ettinger et al. (2014) reported a large increase in the odds of elevated FBG (≥100 mg/dL) in subjects with a blood Pb exposure level above the median (1.66 μg/dL) compared to those below it (OR = 4.99 [95% CI: 1.97, 12.69]). However, the small sample size (n = 150) in this study reduces statistical power, as well as the likelihood that an observed result reflects a true effect.

9.2.3.4 Body Weight Measures in Adults

A few epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) examined obesity as a potential risk factor that could modify the relationship between Pb exposure and other health outcomes, but none examined the direct relationship between Pb exposure and body weight measures in adults. Recent studies have examined this relationship, commonly assessing body weight using body mass index (BMI), a measure of body fat that is calculated as a person's weight divided by the square of their height. For adults, overweight is defined as having a BMI of 25 kg/m^2 or greater and obesity is defined as having a BMI of 30 kg/m^2 or greater. Studies examining Pb and body weight measures in children and adolescents are discussed in the Reproductive and Developmental Effects Appendix of this ISA (Section 8.5.1.1).

A limited number of recent studies have examined the relationship between Pb exposure and body weight measures in adults. Overall, the current evidence for the effects of Pb exposure on body weight measures is inconsistent, although small sample sizes limit the interpretation of a few of the studies. Additionally, recent studies are cross-sectional, which reduces confidence in their results because temporality between exposure and outcome cannot be established. Measures of central tendency for Pb

biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 9-3. An overview of the recent evidence is provided below.

Recent studies examining Pb exposure and body weight measures in adults utilize cross-sectional study designs. In an analysis of a large population-based survey of Chinese citizens, Wang et al. (2018a) observed small but precise increases in BMI (β = 0.24 kg/m^2 [95% CI: 0.08, 0.40 kg/m^2]) and odds of being overweight or obese (OR = 1.13 [95% CI: 1.02, 1.25]) per natural log unit increase in blood Pb (µg/L). In order to account for potential reverse causality, the authors used Mendelian randomization to assess the relationship between BLLs and genetic variants associated with increased BMI. Because the genetic variants precede exposure, the variants are expected to be associated with BLLs if BMI is a potential causal factor of increased BLLs. Wang et al. (2018a) reported null associations between BLLs and an aggregate measure of single nucleotide polymorphisms constructed to represent susceptibility to high BMIs.

Other recent studies were less informative due to small sample sizes. In a cross-sectional analysis of adults of African descent across five countries of varying social and economic development in Africa, Ettinger et al. (2014) compared the prevalence of being overweight (BMI ≥25) or being obese (BMI ≥30) among subjects above versus below the median blood Pb exposure level (1.66 µg/dL). Among subjects with above median blood Pb, Ettinger et al. (2014) observed slightly reduced odds of being overweight (OR = 0.88 [95% CI: 0.31, 2.51]), but increased odds of being obese (OR = 2.70 [95% CI: 0.75, 9.75]). The observed associations, however, were notably imprecise due to the small sample size (n = 150). In contrast, another small cross-sectional study of 145 adult men living in China observed a null association between BLLs and BMI (Guo et al., 2019). As is the case in both of these studies, limited statistical power resulting from a small sample size simultaneously reduces the likelihood of detecting a true effect and the likelihood that an observed result reflects a true effect, which might explain the incongruous results.

9.2.4 Toxicological Studies on Metabolic Effects

The 2013 Pb ISA did not have a section devoted to toxicological studies related to the effect of Pb on metabolism. However, as discussed in the Section 9.1.4, a few studies evaluated in the 2013 Pb ISA demonstrated that Pb exposure can impair lipid metabolism in animals, as evidenced by increased hepatic cholesterogenesis, and altered triglyceride and phospholipid levels (Sharma et al., 2010; Ademuyiwa et al., 2009; Khotimchenko and Kolenchenko, 2007). The relevance of the toxicological evidence is uncertain, as many studies administered Pb as bolus doses and/or results were observed in animals with high BLLs. In subsequent years, there have been a few PECOS-relevant publications on Pb exposure and metabolic effects. In general, these studies cover disparate endpoints, but provide some evidence of Pb-induced changes in metabolic activity in rodents.

In a lifetime study using mice, Faulk et al. (2014) assessed perinatal Pb exposures via Pb acetate in drinking water from conception to weaning. Average maternal BLLs for exposed groups ranged from 4.1 to 32 µg/dL. The study findings included sex-specific increases in energy expenditure, food intake, body weight, total body fat, activity, and insulin response. In addition, a study in weanling rats that focused on neuropathology found that lead exposure decreased cholesterol levels in brain tissue (Zhou et al., 2018). The latter study, which also used Pb acetate in drinking water, reported BLLs ranging from 14.7 to 28.9 µg/dL. Finally, in an investigation of the effects of vitamin D metabolism in rats, Rahman et al. (2018) reported that Pb interferes with vitamin D metabolism by affecting the expression of its metabolizing enzymes.

9.2.5 Summary and Causality Determination

There was no causality determination for metabolic effects in the 2013 Pb ISA (U.S. EPA, 2013). The number of studies examining Pb exposure and metabolic effects has expanded substantially since the 2013 Pb ISA (U.S. EPA, 2013), highlighted by a number of recent epidemiologic studies, as well as a few animal toxicological studies currently available for review. The focus of this causality determination is on altered glucose resistance, diabetes mellitus, MetS, and obesity. Notably, there is significant overlap between components of metabolic health and the cardiovascular and hepatic systems. While blood pressure and serum lipids are important components of MetS, they are also discussed in detail in the cardiovascular effects appendix (Appendix 4) and hepatic effects section (Section 9.1), and contribute to the causality determinations therein. For the metabolic effects causality determination, these endpoints are considered to the extent that they contribute to a diagnosis of MetS.

There is some evidence from a limited number of animal toxicological studies that exposure to Pb resulting in BLLs relevant to humans alters cholesterol metabolism (Zhou et al., 2018) and leads to increases in body weight, body fat, and insulin response (Faulk et al., 2014). In contrast, recent epidemiologic studies are inconsistent across a range of metabolic outcomes and thus not coherent with the limited toxicological evidence. A limited number of cross-sectional studies examining diabetes prevalence and insulin resistance in adults reported null (Hansen et al., 2017; Simić et al., 2017) and negative (Moon, 2013) associations with BLLs. Further, results from analyses of MetS in large national surveys in the United States and Korea were largely inconsistent. Many of these same studies also provide generally inconsistent evidence of associations between BLLs and individual components of MetS, though there is substantial epidemiologic and toxicological evidence that exposure to Pb leads to increased blood pressure and hypertension (Section 4.3). While a limited number of KNHANES analyses demonstrate consistent associations between BLLs and serum triglycerides (Lee and Kim, 2016, 2013; Rhee et al., 2013), these studies include overlapping study populations and therefore do not provide independent evidence of associations. Additionally, a recent prospective cohort study of older adults observed null associations between BLLs at baseline and serum triglyceride levels measured three to four years later (Peters et al., 2012). Despite observed associations between BLLs and some of the individual

components of MetS, the available evidence examining the cluster of components does not consistently associate BLLs with MetS. Collectively, given the insufficient quantity of toxicological studies and inconsistency in epidemiologic results, **the evidence is *inadequate to infer the presence or absence of a causal relationship* between Pb exposure and metabolic effects.**

9.3 Effects on the Gastrointestinal System

9.3.1 Introduction, Summary of the 2013 ISA, and Scope of the Current Review

The 2013 Pb ISA concluded that "because of the insufficient quantity and quality of studies, the available evidence was inadequate to determine if there is a causal relationship between Pb exposure and gastrointestinal effects" (U.S. EPA, 2013). There were very few studies evaluated in the 2013 Pb ISA that examined Pb exposure and gastrointestinal (GI) effects in humans or animals. Epidemiologic evidence of an association between Pb exposure and GI effects was limited to a small number of occupational studies of prevalent symptoms in Pb-exposed workers. The internal validity and generalizability of these studies was limited by cross-sectional study designs, lack of consideration for potential confounders, and notably higher BLLs (≥40 μg/dL) than those experienced by the general population. In addition to the epidemiologic evidence, there were a limited number of toxicological studies that provide evidence of Pb-induced effects on mechanisms underlying GI damage and impaired function.

9.3.2 Scope

The scope of this section is defined by PECOS statements. The PECOS statement defines the objectives of the review and establishes study inclusion criteria thereby facilitating identification of the most relevant literature to inform the Pb ISA.[1] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria

[1] The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies included in the 2013 Pb ISA, including many that do not meet the current PECOS criteria, are discussed in this appendix to establish the state of the evidence prior to this assessment. Except for supporting evidence used to demonstrate the biological plausibility of Pb-associated effects on the gastrointestinal system, recent studies were only included if they satisfied all of the components of the following discipline-specific PECOS statements:

Epidemiologic Studies

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect.

Exposure: Exposure to Pb[1] as indicated by biological measurements of Pb in the body – with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure[2]; or intervention groups in randomized trials and quasi-experimental studies.

Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles).

Outcome: Effects on the gastrointestinal system.

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials, and quasi-experimental studies examining interventions to reduce exposures.

Experimental Studies

Population: Laboratory nonhuman mammalian animal species (i.e., mouse, rat, Guinea pig, minipig, rabbit, cat, dog; whole organism) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages);

[1] Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[2] Studies that estimate Pb exposure by measuring Pb concentrations in particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm^3 (PM_{10}) and particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm^3 ($PM_{2.5}$) ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with BLLs are lacking.

Exposure: Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a BLL of 30 µg/dL or below.[1,2]

Comparators: A concurrent control group exposed to vehicle-only treatment or untreated control.

Outcomes: Effects on the gastrointestinal system.

Study design: Controlled exposure studies of animals in vivo.

9.3.3 Epidemiologic Studies on the Gastrointestinal System

The epidemiologic evidence evaluated in the 2013 Pb ISA was limited to a small number of occupational cohort studies of prevalent GI symptoms in Pb-exposed workers (U.S. EPA, 2013). As noted in Section 9.3.1, these studies had a number of limitations, including cross-sectional study designs, lack of consideration for potential confounders, and notably higher BLLs (≥40 µg/dL) than those experienced by the general population. There are no recent PECOS-relevant epidemiologic studies that evaluate potential associations between exposure to Pb and effects on the gastrointestinal system. A limited number of studies reported associations between BLLs and gut microbiota diversity, as discussed in the Immune System Effects Appendix (Section 6.6). However, these studies do not inform the relationship between Pb exposure and specific GI health effects.

9.3.4 Toxicological Studies on the Gastrointestinal System

In the 2013 Pb ISA (U.S. EPA, 2013), specific attention was drawn to a pair of rat studies; one reporting frequency-dependent inhibition of electric field-stimulated relaxations to nonadrenergic noncholinergic (NANC) nerve stimulation in rat gastric fundus (possibly due to the modulated release of NO), and the other focusing on Pb-induced oxidative stress in the gastric mucosa, wherein an increase in gastric mucosal damage induced by the acidified ethanol was observed. Neither of these studies reported BLLs. Neither of the two pertinent studies since the 2013 Pb ISA directly addresses these findings [(Reddy et al., 2018; Kosik-Bogacka et al., 2011); see below].

In a chronic exposure study with rats, Kosik-Bogacka et al. (2011) confirmed an inhibitory effect of Pb on electrophysiological parameters, among other findings. These findings were strengthened by

[1] Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.
[2] This level represents an order of magnitude above the upper end of the distribution of U.S. young children's BLL. The 95th percentile of the 2011–2016 NHANES distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (Egan et al., 2021) and the proportion of individuals with BLL that exceed this concentration varies depending on factors including (but not limited to) housing age, geographic region, and a child's age, sex, and nutritional status.

results showing the ability of L-ascorbic acid to (at least partially) abrogate the effects of Pb exposure. Mean BLLs in this study were reported at 7 µg/dL.

In a 2018 microbiome study, Reddy et al. (2018) found that Pb-exposed rats had decreased δ-aminolevulenic acid dehydratase (ALAD) activity and intestinal lactobacillus levels, irrespective of the dietary iron supplementation. Withdrawal of Pb exposure increased lactobacilli, whereas re-exposure to Pb decreased lactobacilli population. BLLs were reported in the range of 19 to 48 µg/dL.

9.3.5 Summary and Causality Determination

The 2013 Pb ISA concluded that evidence was "inadequate" to determine a causal relationship between Pb exposure and GI effects (U.S. EPA, 2013). This causality determination was based on an insufficient quantity and quality of studies in the cumulative body of evidence. A limited number of occupational cohort studies indicated associations between BLLs and prevalent symptoms, such as stomach pain, gastritis, constipation, and intestinal paralysis. However, the implications of these findings are limited by the cross-sectional study designs, high BLLs associated with effects (mostly ≥40 µg/dL), and limited consideration of potential confounding by factors such as age, smoking, alcohol use, nutrition, or other occupational exposures. Toxicological evidence indicates that Pb is absorbed primarily in the duodenum by active transport and diffusion, although variability is observed by Pb compound, age of intake, and nutritional factors. There was some coherence between the evidence in Pb-exposed workers and observations in animals that Pb induces damage to the intestinal mucosal epithelium, decreases duodenum contractility and motility, reduces absorption of calcium ions (Ca^{2+}), inhibits NANC relaxations in the gastric fundus, and induces oxidative stress (lipid peroxidation, decreased SOD and CAT) in the gastric mucosa.

Recent studies are limited in number, and while some provide potential biological plausibility for Pb-induced GI effects, none directly inform the relationship between Pb exposure and GI effects. Given the insufficient quantity and quality of studies, **the evidence remains *inadequate to infer the presence or absence of a causal relationship* between Pb exposure and gastrointestinal effects.**

9.4 Effects on the Endocrine System

9.4.1 Introduction, Summary of the 2013 ISA, and Scope of the Current Review

The 2013 Pb ISA (U.S. EPA, 2013) evaluated a limited number of studies examining the relationship between exposure to Pb and effects on the endocrine system. Epidemiologic and toxicological evidence related to male and female sex hormones, which was generally inconsistent, is

discussed in more detail in Appendix 8 (Sections 8.6.1.1 and 8.7.2). In addition to studies on sex hormones, results from a small number of epidemiologic and toxicological studies on Pb-associated endocrine effects such as changes in thyroid hormones, cortisol, corticosterone, and vitamin D levels were also inconsistent. Further, epidemiologic studies were mostly cross-sectional and included limited consideration for potential confounders. As a whole, the limited quantity, quality, and consistency of the available evidence was "inadequate to determine if there is a causal relationship between Pb exposure and endocrine effects related to thyroid hormones, cortisol, and vitamin D."

9.4.2 Scope

The scope of this section is defined by PECOS statements. The PECOS statement defines the objectives of the review and establishes study inclusion criteria thereby facilitating identification of the most relevant literature to inform the Pb ISA.[1] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies included in the 2013 Pb ISA, including many that do not meet the current PECOS criteria, are discussed in this appendix to establish the state of the evidence prior to this assessment. Except for supporting evidence used to demonstrate the biological plausibility of Pb-associated effects on the gastrointestinal system, recent studies were only included if they satisfied all of the components of the following discipline-specific PECOS statements:

Epidemiologic Studies:

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect.

[1] The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

Exposure: Exposure to Pb[1] as indicated by biological measurements of Pb in the body – with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure[2]; or intervention groups in randomized trials and quasi-experimental studies.

Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles).

Outcome: Effects on the endocrine system.

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

Experimental Studies:

Population: Laboratory nonhuman mammalian animal species (e.g., mouse, rat, guinea pig, minipig, rabbit, cat, dog) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).

Exposure: Oral, inhalation, or intravenous routes administered to a whole animal (*in vivo*) that results in a BLL of 30 µg/dL or below.[3,4]

Comparators: A concurrent control group exposed to vehicle-only treatment or untreated control.

Outcomes: Effects on the endocrine system.

Study design: Controlled exposure studies of animals in vivo.

9.4.3 Epidemiologic Studies on the Endocrine System

A limited number of epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) reported associations between exposure to Pb and endocrine effects related to changes in thyroid

[1] Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[2] Studies that estimate Pb exposure by measuring Pb concentrations in particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 µm^3 (PM_{10}) and particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 µm^3 ($PM_{2.5}$) ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with BLLs are lacking.

[3] Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.

[4] This level represents an order of magnitude above the upper end of the distribution of U.S. young children's BLL. The 95th percentile of the 2011–2016 NHANES distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (Egan et al., 2021) and the proportion of individuals with BLL that exceed this concentration varies depending on factors including (but not limited to) housing age, geographic region, and a child's age, sex, and nutritional status.

hormones, cortisol, and vitamin D levels. However, most studies were cross-sectional in design, and many did not consider potential confounding factors. Further, while some studies did find associations between Pb exposure and endocrine effects, the results for specific hormones were not consistent.

A limited number of recent epidemiologic studies of Pb exposure and endocrine effects also implement cross-sectional analyses but included more robust adjustment for potential confounding factors, including use of thyroid medication. The majority of recent studies are large NHANES analyses that provide generally consistent evidence of null associations between Pb exposure and endocrine effects of thyroid hormone and cortisol levels. However, given that these studies examined overlapping study populations, the generally consistent results across these studies should not be considered independent evidence of a null association. Most recent studies evaluated potential associations between Pb exposure and thyroid hormone levels, including triiodothyronine (T3), thyroxine (T4), and thyroid stimulating hormone (TSH). There were a few studies that looked at associations between Pb exposure and cortisol levels and no recent PECOS-relevant studies that looked at Pb exposure and vitamin D levels. Measures of study-specific BLLs and endocrine effect estimates are highlighted in Table 9-9. An overview of recent evidence is provided below.

The most consistent evidence from recent studies indicates null associations between BLLs and TSH, T3, and free T4 (FT4) levels in adults. A few recent NHANES analyses, which included nationally representative study populations of adults over 20 years old, reported null associations between BLL and TSH levels in adults (Krieg, 2019; Chen et al., 2013; Mendy et al., 2013; Christensen, 2012). Recent NHANES analyses also provide generally consistent evidence of null associations between BLLs and FT4 levels (Luo and Hendryx, 2014; Chen et al., 2013; Mendy et al., 2013) as well as between blood Pb and T3 levels (Nie et al., 2017; Luo and Hendryx, 2014; Chen et al., 2013; Mendy et al., 2013; Christensen, 2012).

Recent NHANES studies evaluating a potential association between BLLs and total T4 levels were less consistent. While some recent studies reported null associations between BLLs and T4 levels in adults (Luo and Hendryx, 2014; Chen et al., 2013), others observed negative associations (Krieg, 2019; Mendy et al., 2013; Christensen, 2012). For example, Mendy et al. (2013) noted a 0.162 µg/dL (95% CI: −0.321, −0.004 µg/dL) decrease in T4 per 1 µg/dL increase in BLL. Additionally, while Luo and Hendryx (2014) noted a null association between BLLs and T4 levels in the total population, the authors observed a significant negative association between blood Pb and T4 levels among men after stratifying by sex. Krieg (2019) also found a negative association between blood Pb and T4 levels, reporting a 38.91% (95% CI: −51.25, −23.44) decrease in T4 per 1 µg/dL increase in blood lead level.

A limited number of NHANES analyses evaluated potential associations between blood Pb and free T3 (FT3) levels (Luo and Hendryx, 2014; Chen et al., 2013; Mendy et al., 2013). In an analysis of adults, Mendy et al. (2013) reported a null association between blood Pb and FT3 levels in the general adult population. This is consistent with the findings of Chen et al. (2013), who reported a null association between BLLs and FT3 levels in both adolescents (12–19 years old) and adults (≥20 years

old). Both studies performed analyses on the 2007–2008 continuous NHANES cycle. Luo and Hendryx (2014) evaluated 2007–2010 data, reporting a positive association between blood Pb and FT3 in the general adult population. The authors reported a modest 0.04 μg/dL (95% CI: 0.01, 0.08) increase in FT3 per 1 μg/dL increase in blood Pb in adults in the highest tertile of blood Pb when compared to the lowest. After stratifying by sex, males were also found to have a positive association with a 0.05 μg/dL (95% CI: 0.01, 0.09) increase in FT3 per 1 μg/dL increase of blood Pb in the highest tertile compared to the lowest.

In addition to the NHANES analyses discussed above, another recent cross-sectional study examined the relationship between BLLs and thyroid hormone levels in a small study of pregnant women (n = 291) from the Yugoslavia Prospective Study of Environmental Lead Exposure Cohort (Kahn et al., 2014). Kahn et al. (2014) reported a null association between BLL and TSH levels and a negative association between blood Pb and FT4 levels.

Two recent cross-sectional studies examined associations between BLLs and cortisol levels (Ngueta et al., 2018; Souza-Talarico et al., 2017). In a small study of older adults (n = 65) in Montreal, Canada, Ngueta et al. (2018) reported null associations between BLLs and both diurnal and stress-reactive cortisol secretion. In contrast, another small study of non-occupationally exposed Brazilian older adults (n = 126), Souza-Talarico et al. (2017) reported positive associations between BLLs and both cortisol awakening response (CAR) and overall cortisol concentration. The authors reported a 0.791 μg/dL (95% CI: 0.672, 1.073 μg/dL) increase in CAR per 1 μg/dL increase in BLL. However, it is worth noting that participants showed an elevated basal circadian level of salivary cortisol independent of Pb exposure, suggesting this population has more repeated exposure to stressful events. Furthermore, while all participants were older postmenopausal adults, sex was unevenly represented with n = 105 (83%) of the participants being women.

9.4.4 Toxicological Studies on the Endocrine System

The 2013 Pb ISA summarized a few toxicological studies that reported on effects of Pb exposure on the endocrine system. Specifically, T3 and T4 levels were found to be elevated in cows that were grazing on land near Pb/operational Zn smelters when compared with cows grazing in unpolluted areas (Swarup et al., 2007). However, when regression analyses were done to evaluate potential associations between BLLs and plasma cortisol levels in these same cows, no association was observed. Another study conducted in Wistar rats reported that 21 days of intraperitoneal (i.p.) injections with 8.0 mg/kg Pb led to increased corticosterone levels and adrenal weights [BLLs not reported; (Biswas and Ghosh, 2006)]. Some recent studies have also investigated the effects of Pb on the endocrine system (Table 9-5). The only studies that investigated adrenal gland weight were conducted in Sprague Dawley rats that were dosed from postnatal day (PND) 4 to 28 and reported no effect of Pb treatment on the weight of the adrenal glands [BLLs 3.27–12.5 μg/dL; (Amos-Kroohs et al., 2016; Graham et al., 2011)]. Findings concerning corticosterone levels in recent studies are equivocal. Some studies reported increased

corticosterone in rats exposed to Pb. Specifically, one study that dosed Long-Evans rats starting prior to conception until 304 days of age reported increases in corticosterone levels in female rats at 2 months of age but reported no changes in males at any time point [BLLs 11.3 µg/dL on PND 61 in females; (Rossi-George et al., 2011)]. Another study measured corticosterone levels in Sprague Dawley rats at different intervals following a shallow water stressor. This study reported that treatment with Pb from PND 4 to 28 increased corticosterone levels in male and female rats 0, 30, and 60 minutes following the stressor on PND 11, 0 and 30 minutes following the stressor on PND 19, and 0 and 30 minutes following the stressor on PND 29 [BLLs 3.2–12.5 µg/dL on PND 29; (Graham et al., 2011)]. A single study reported decreases in corticosterone in F3 female C57 BL/6 mice whose F1 sires were exposed to Pb from gestational day (GD) −61 to PND 21 [BLLs 0.4 µg/dL on PND 6–7; (Sobolewski et al., 2020)]. Contrasting these studies are those that did not report any effects of Pb exposure on corticosterone levels. Interestingly, these studies used similar dosing paradigms to those that reported effects with one study dosing C57 BL/6 mice starting preconceptionally through adulthood [ending on PND 365; (Cory-Slechta et al., 2013)] and the other study dosing Sprague Dawley rats from PND 4 to 28 (Amos-Kroohs et al., 2016), and neither study reported alterations of corticosterone levels in either sex.

9.4.5 Summary and Causality Determination

The 2013 Pb ISA concluded that the evidence was inadequate to determine if there is a causal relationship between Pb exposure and endocrine effects related to changes in levels of thyroid hormones, cortisol/corticosterone, and vitamin D. This causality determination was based on an insufficient quantity and quality of studies that provided inconsistent or inconclusive evidence for Pb-related endocrine effects. Epidemiologic evidence presented in the 2013 Pb ISA regarding the effects of Pb on cortisol levels consisted of a single study showing a positive association between prenatal Pb exposure and salivary cortisol levels in children following an acute stressor (Gump et al., 2008). The few epidemiologic studies investigating associations between Pb and thyroid hormone levels presented in the 2013 Pb ISA reported inconsistent associations. Toxicological evidence in the 2013 Pb ISA regarding the effects of Pb on the endocrine system in animals was sparse. Biswas and Ghosh (2006) reported that Pb exposure increased corticosterone levels and adrenal gland weights in Wistar rats. A single study evaluating thyroid hormone levels in animals summarized in the 2013 Pb ISA reported no clear associations between Pb exposure and thyroid hormone levels in cattle with environmental exposure to Pb (Swarup et al., 2007).

Recent epidemiologic and toxicological evidence evaluating the effects of Pb exposure on the endocrine system continues to be limited and inconsistent. The most recent epidemiologic studies measured associations between BLLs and thyroid hormone levels. Results from these studies were mostly null, though there was some inconsistent evidence of an inverse association between BLLs and T4 levels in three studies (Krieg, 2019; Mendy et al., 2013; Christensen, 2012), and a single study noted sex-specific associations between BLLs and T4 and FT4 levels (Luo and Hendryx, 2014). While the results are generally consistent, the analyses include overlapping study populations, so they should not be

interpreted as independent evidence of a null association. Additionally, consistent with the studies evaluated in the 2013 Pb ISA, recent studies are cross-sectional in design, which introduces uncertainty about the temporality between exposure and outcome. No recent toxicological studies investigating the effects of Pb on thyroid hormone levels were available. Only a few recent epidemiologic studies examined Pb effects on cortisol levels (Ngueta et al., 2018; Souza-Talarico et al., 2017). In terms of associations of Pb exposure and cortisol levels in humans, evidence was limited and inconsistent. Only two studies were available that measured Pb exposure with cortisol outcomes (Ngueta et al., 2018; Souza-Talarico et al., 2017), and both had small sample sizes. Multiple toxicological studies reported on the effects of Pb exposure on corticosterone levels in animals, but results are equivocal. One study reported decreases (Sobolewski et al., 2020), two studies reported increases (Graham et al., 2011; Rossi-George et al., 2011), and two studies reported no effect (Amos-Kroohs et al., 2016; Cory-Slechta et al., 2013) on corticosterone levels in Pb-intoxicated animals. In terms of the effects of Pb on adrenal gland weights in animals, only two recent studies investigated the effects of Pb on adrenal gland weight. These studies reported no effects of Pb on adrenal gland weight in Sprague Dawley rats (Amos-Kroohs et al., 2016; Graham et al., 2011), contrasting with the only study that investigated adrenal gland weights in the 2013 Pb ISA (Biswas and Ghosh, 2006) which reported increased adrenal gland weights. This contrast may be due to variability in route of exposure used in the experimental design leading to differences in BLLs between the animals in Biswas and Ghosh (2006), and the more recent studies. Specifically, Biswas and Ghosh (2006) dosed animals with 8 mg/kg/d of Pb via i.p. injection, whereas the most recent publications dosed animals with either 1 or 10 mg/kg/d of Pb b via oral gavage (Amos-Kroohs et al., 2016) or indirectly dosed animals via Pb in the milk from their dams which were dosed via oral gavage (Graham et al., 2011). No recent PECOS-relevant epidemiologic or toxicological studies were identified that measured vitamin D levels.

In conclusion, recent epidemiologic and toxicological studies continue to provide limited and inconsistent evidence for endocrine system effects associated with Pb exposure. Due to the insufficient quantity and quality of the studies available for review and the inconsistent results across those studies, **the evidence remains *inadequate to infer the presence or absence of a causal relationship* between Pb exposure and endocrine effects related to changes in thyroid hormones, cortisol/corticosterone, and vitamin D levels.**

9.5 Effects on the Musculoskeletal System

9.5.1 Introduction, Summary of the 2013 ISA, and Scope of the Current Review

The 2013 Pb ISA evaluated the effects of Pb exposure on bone and teeth (U.S. EPA, 2013). In order to be more inclusive of other health effects related to bone and teeth, this ISA expands the

considered health outcomes to include effects on the entire musculoskeletal system. The musculoskeletal system consists of the bones, teeth, muscles, joints, cartilage, and other connective tissues that support the body, allow for movement, and protect vital organs. Primary effects on the musculoskeletal system include increases in osteoporosis, increased frequencies of falls and fractures, changes in bone cell function as a result of replacement of bone calcium with Pb, and depression in early bone growth. Other effects include tooth loss and periodontitis. Mechanistic evidence from toxicological studies includes effects on cell proliferation, procollagen type I production, intracellular protein, and osteocalcin in human dental pulp cell cultures.

A small body of epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) provided consistent evidence of associations between Pb biomarker levels and various effects on bone and teeth, including an increase in osteoporosis, increased frequencies of falls and fractures, tooth loss, and periodontitis. The results from these studies, adjusting for potential confounding by age and SES-related factors, were supported by strong toxicological evidence evaluated in the 2013 Pb ISA and the 2006 Pb AQCD (U.S. EPA, 2006), which reported effects in bone and teeth in animals following Pb exposure. Exposure of animals to Pb during gestation and the immediate postnatal period was reported to significantly depress early bone growth with the effects showing concentration-dependent trends. Systemic effects of Pb exposure included disruption in bone mineralization during growth, alteration in bone cell differentiation and function due to alterations in plasma levels of growth hormones and calcitropic hormones such as 1,25-[OH]2D3 and impact on Ca2+- binding proteins and increases in Ca2+ and phosphorus concentrations in the bloodstream. Bone cell cultures exposed to Pb had altered vitamin D-stimulated production of osteocalcin accompanied by inhibited secretion of bone-related proteins such as osteonectin and collagen. In addition, Pb exposure caused suppression in bone cell proliferation most likely due to interference from factors such as growth hormone (GH), epidermal growth factor (EGF), transforming growth factor-beta 1 (TGF-β1), and parathyroid hormone-related protein (PTHrP).

As in bone, Pb exposure was found to easily substitute for Ca2+ in the teeth and was taken up and incorporated into developing teeth in experimental animals. Since teeth do not undergo remodeling like bones do during growth, most of the Pb in the teeth remains in a state of permanent storage. Pb has also been shown to decrease cell proliferation, procollagen type I production, intracellular protein, and osteocalcin in human dental pulp cell cultures. Adult rats exposed to Pb have exhibited an inhibition of the posteruptive enamel proteinases, delayed teeth eruption times, as well as a decrease in microhardness of surface enamel. Further discussion of these processes and effects, including corresponding references, can be found in sections 5.8.7 through 5.8.13 of the 2006 AQCD (U.S. EPA, 2006).

In considering the weight of the evidence, the 2013 Pb ISA (U.S. EPA, 2013) concluded that "a causal relationship is likely to exist between Pb exposure and effects on bone and teeth."

9.5.2 Scope

The scope of this section is defined by PECOS statements. The PECOS statement defines the objectives of the review and establishes study inclusion criteria, thereby facilitating identification of the most relevant literature to inform the Pb ISA.[1] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies included in the 2013 Pb ISA, including many that do not meet the current PECOS criteria, are discussed in this appendix to establish the state of the evidence prior to this assessment. Except for supporting evidence used to demonstrate the biological plausibility of Pb-associated effects on the musculoskeletal system, recent studies were only included if they satisfied all of the components of the following discipline-specific PECOS statements:

Epidemiologic Studies:

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect.

Exposure: Exposure to Pb[2] as indicated by biological measurements of Pb in the body – with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure[3]; or intervention groups in randomized trials and quasi-experimental studies.

Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles).

Outcome: Effects on the musculoskeletal system.

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[1] The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

[2] Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[3] Studies that estimate Pb exposure by measuring Pb concentrations in particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm^3 (PM_{10}) and particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm^3 ($PM_{2.5}$) ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with BLLs are lacking.

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

Experimental Studies:

Population: Laboratory nonhuman mammalian animal species (e.g., mouse, rat, guinea pig, minipig, rabbit, cat, dog) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).

Exposure: Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a BLL of 30 µg/dL or below.[1,2]

Comparators: A concurrent control group exposed to vehicle-only treatment or untreated control.

Outcomes: Effects on the musculoskeletal system.

Study design: Controlled exposure studies of animals in vivo.

9.5.3 Epidemiologic Studies on the Musculoskeletal System

A limited number of cross-sectional epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) provided consistent evidence of associations between Pb biomarker levels and osteoporosis and tooth loss after adjusting for potential confounding by age and SES-related factors. Uncertainties in the evidence base included limited consideration of potential confounding by nutritional factors, a lack of temporality between exposure and outcome, and uncertainty in the level, timing, frequency, and duration of Pb exposure that contributed to the observed associations. Recent epidemiologic studies of the musculoskeletal system generally examine one of three groups of endpoints: (1) bone mineral density (BMD); (2) joint degeneration; and (3) oral health. Results from recent studies, which adjust for a range of potential confounders, provide generally consistent evidence of an association between BLLs and osteoporosis, osteoarthritis, dental caries, and periodontal disease. Recent studies evaluating musculoskeletal effects are largely cross-sectional analyses, which are unable to establish temporality between exposure and outcome. Additionally, with BLLs, it is difficult to characterize the specific timing, duration, frequency, and level of Pb exposure that contributed to the observed associations. This uncertainty may apply particularly to assessments of BLLs, which in nonoccupationally-exposed adults, reflect both current exposures and cumulative Pb stores in bone that are mobilized during bone

[1] Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.
[2] This level represents an order of magnitude above the upper end of the distribution of U.S. young children's BLL. The 95th percentile of the 2011–2016 NHANES distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (Egan et al., 2021) and the proportion of individuals with BLL that exceed this concentration varies depending on factors including (but not limited to) housing age, geographic region, and a child's age, sex, and nutritional status.

remodeling. Measures of central tendency for Pb biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 9-11. An overview of the recent evidence is provided below.

9.5.3.1 Bone Mineral Density

A number of recent cross-sectional studies provide generally consistent evidence of an association between exposure to Pb and BMD in adults. In these studies, BMD (g/cm^2) was measured via X-ray absorptiometry or ultrasound and often converted to a standardized score (i.e., *z*- and *t*-scores)[1]. Osteoporosis and osteopenia are characterized by varying degrees of BMD decrements that can compromise bone microarchitecture. A z-score below −1 often corresponds to osteopenia, whereas a z-score below −2.0 to −2.5 is categorized as osteoporosis. There are significant sex and age differences in the incidence of osteoporosis and osteopenia, with postmenopausal women being at greatest risk for declines in BMD. Because osteoporosis and osteopenia are more common in women, many of the recent epidemiologic studies evaluating the relationship between BLLs and BMD are either conducted in study populations comprised of older women or stratified by sex. Importantly, the cross-sectional nature of the studies does not rule out the possibility that the association is driven by increased BLLs due to higher bone turnover in individuals with osteoporosis. Additionally, although most analyses include study populations with mean BLLs <3 μg/dL, study participants were born prior to the phase-out of leaded gasoline and therefore likely had much higher past Pb exposures, making it difficult to characterize the specific timing, duration, frequency, and level of Pb exposure that contributed to the observed associations.

A few recent analyses of data from large, nationally representative health surveys provide generally consistent evidence of an association between BLLs and BMD in women (Wang et al., 2019; Cho et al., 2012; Lee and Kim, 2012). In an analysis of 2008 KNHANES data, Cho et al. (2012) observed increased odds of osteoporosis associated with increasing BLL quartiles in postmenopausal women. The authors noted associations at low levels (e.g., Q2 [1.83 to <2.32 μg/dL] versus quartile 1 [<1.83 μg/dL]) that were similar in magnitude to comparisons between the higher quartiles and the first quartile, suggesting a potentially non-linear association. In a similar study, Lee and Kim (2012) analyzed data from the same KNHANES cycle but expanded the age range to include premenopausal women. The authors reported that increases in BLLs were associated with decreased BMD at several bone sites. Additionally, Pb-related BMD decrements were consistently higher in postmenopausal women compared to premenopausal women. For example, a 1 μg/dL increase in BLLs was associated with a −0.28 g/cm^2

[1]Standardized scores are used to analyze BMD data as deviations from average BMD in matched healthy populations. Underlying populations vary by study.

(95% CI: −0.45, −0.11 g/cm^2) decrease in femoral BMD in postmenopausal women compared to a −0.15 g/cm^2 (95% CI: −0.33, 0.03 g/cm^2) decrease in premenopausal women.

In contrast to KNHANES analyses, an analysis of more recent NHANES cycles (2013–2014) observed null associations between BLLs and BMD in postmenopausal women (Wang et al., 2019). Notably, the authors did not control for hormone therapy, which could impact BLLs due to changes in bone turnover rates. Wang et al. (2019) did note that a 1 µg/dL increase in BLLs was associated with small decrements in femoral (−0.06 g/cm^2 [95% CI: −0.08, −0.03 g/cm^2]) and spinal (−0.05 g/cm^2 [95% CI: −0.08, −0.02 g/cm^2]) BMD in premenopausal women, as well as increases in 10-year fracture risk scores in the total population (including adult men and women). The findings in premenopausal women are somewhat consistent with a recent cross-sectional analysis of premenopausal women in western New York that observed a 0.02 (−0.02, 0.05) g/cm^2 decrease spinal BMD associated with a 1 µg/dL increase in BLLs (Pollack et al., 2013). However, in contrast to the results from Wang et al. (2019), Pollack et al. (2013) reported null associations between BLLs and total hip and wrist BMD in premenopausal women.

In a smaller cross-sectional analysis of adults from two communities in southwestern China, including one with a history of Pb mining and smelting, Li et al. (2020b) observed some evidence of sex-specific differences in Pb-associated BMD levels. Specifically, female study participants with BLLs ≥3.4 µg/dL had increased odds of osteoporosis compared to female study participants with BLLs <3.4 µg/dL (OR = 1.33 [95% CI: 0.61, 2.88]); whereas an inverse association was reported for men (OR = 0.60 [95% CI: 0.24, 1.49]). However, given the imprecise effect estimates (i.e., wide 95% CIs), it is difficult to draw firm conclusions on these sex-specific comparisons.

Other recent studies evaluated the relationship between Pb exposure and BMD in analyses combining men and women. The inferences that can be drawn from these studies are limited due to established sex-specific differences in osteoporosis incidence. In an analysis of 2008–2011 KNHANES cycles, Lim et al. (2016) observed increased odds of osteoporosis or osteopenia across BLL quartiles, with the largest increase in odds noted in quartile 4 (≥2.93 µg/dL) compared to quartile 1 (<1.66 µg/dL; OR = 1.49 [95% CI: 1.12, 1.98]). In a much smaller study of Korean adults, Lee and Park (2018) similarly reported a decrease in BMD t-scores associated with a 1 µg/dL increase in BLLs that was greater in magnitude in participants with a history of smoking (−0.472 [95% CI−0.85, −0.094]) compared to non-smokers (−0.148 [95% CI: −0.369, 0.073]). The authors also examined over 344,396 single nucleotide polymorphisms (SNPs) mapped to gene-coding regions to assess potential interactions between BLLs and genetic variations. The observed interactions were inconsistent after adjustment for multiple testing, but many implicated genes and pathways involved in angiogenesis, bone mass, and nuclear receptor signaling, provide areas of interest for exploring possible mechanisms that may underlie the observed relationship between BLLs and osteoporosis.

9.5.3.2 Osteoarthritis

A few recent cross-sectional studies examined the association between BLLs and osteoarthritis (OA) in adults. In an analysis of multiple KNHANES cycles (2010–2012), Park and Choi (2019) reported that an increase in natural log BLLs was associated with an increase in the odds of radiographic and symptomatic knee OA (radiographic osteoarthritis [rOA] and symptomatic osteoarthritis [sxOA]) in postmenopausal women (OR = 1.77 [95% CI 1.17, 2.67] and 1.50 [95% CI: 0.90, 2.53], respectively). There is some evidence that the association is mediated by BMI, but there is evidence of a direct association as well (i.e., adjusted for BMI). The authors noted null associations between BLLs and back OA.

In a cross-sectional analysis of African American and white adults, Nelson et al. (2011b) also observed associations between BLL and rOA and sxOA in the knee. In a similar study, the same group noted associations between BLLs and some biomarkers of joint tissue metabolism, including NTX-I, which is responsible for bone turnover; CTX-II, which is associated with prevalence of rOA in the knee; COMP (cartilage oligomeric matrix protein), which is a cartilage biomarker; and CPII (carboxypropeptide of type II collagen), which is linked with collagen synthesis (Nelson et al., 2011a). Notably, the authors examined a wide range of biomarkers and stratified their models by sex, increasing the likelihood of multiple testing bias.

Although all of the studies examining OA had low median BLLs (<2.5 μg/dL), study participants were born prior to the phase-out of leaded gasoline and therefore likely had much higher past Pb exposures, making it difficult to characterize the specific timing, duration, frequency, and level of Pb exposure that contributed to the observed associations. Additionally, similar to studies of osteoporosis, the cross-sectional nature of the studies does not rule out the possibility that the association is driven by cartilage turnover resulting in increased Pb in blood.

9.5.3.3 Oral Health

Recent epidemiologic studies of Pb exposure and oral health are split into two major categories: (1) periodontal disease in adults and (2) dental caries in children.

A limited number of recent studies of periodontal disease in adults examined overlapping KNHANES cycles from 2008 to 2010 (Han et al., 2013; Kim and Lee, 2013; Won et al., 2013). These studies, all of which defined periodontal disease according to the World Health Organization's Community Periodontal Index, provided consistent evidence of an association between BLLs and the prevalence of periodontitis. All of the studies included extensive adjustment for potential confounders, including oral hygiene. Given that these studies examined largely overlapping study populations, the observed results should not be considered independent evidence of an association. Kim and Lee (2013) noted associations that were stronger in magnitude in men (OR = 1.85 [95% CI: 1.26, 2.71] per doubling

of BLL) compared to women (OR = 1.30 [95% CI: 0.88, 1.91] per doubling of BLL), and that associations were slightly attenuated, but still positive after adjustment for blood mercury (Hg) and cadmium (Cd; 1.69 [95% CI: 1.15, 2.50] and 1.24 [95% CI: 0.83, 1.85], respectively). In analyses that stratified by smoking, effect estimates were imprecise (i.e., wide 95% CIs), but comparable in magnitude for smokers and non-smokers (Han et al., 2013; Won et al., 2013).

Recent epidemiologic studies of dental caries in children included more diverse study populations. A prospective analysis of mother-child pairs that recruited from hospitals serving low- to moderate-income populations in Mexico examined the relationship between Pb biomarkers at different developmental windows and incidence of decayed, missing, and filled teeth (DMFT) in adolescence [10 to 18 years old; Wu et al. (2019)]. The authors reported a 12 to 17% increase in risk of DMFT associated with a natural log increase in prenatal and early childhood BLLs. No associations were observed with concurrent BLLs or postnatal maternal bone Pb. Prenatal (mean: 5.24 to 6.36 µg/dL) and early childhood (mean: 15.18 to 15.48 µg/dL) BLLs were notably higher than concurrent levels (mean: 3.60–3.34 µg/dL), which is consistent with age-specific patterns of Pb kinetics (Sections 2.2 and 2.4). Wu et al. (2019) additionally stratified their models by sugar sweetened beverage intake (SSBI) and observed stronger associations between prenatal and early childhood BLLs and DMFT score in children with high SSBI. In recent cross-sectional studies with lower BLLs (see Table 9-6), BLLs in young children were associated with increased prevalence of dental caries in deciduous teeth (Kim et al., 2017; Wiener et al., 2015), but not permanent teeth (Kim et al., 2017).

9.5.4 Toxicological Studies on the Musculoskeletal System

The 2013 Pb ISA (U.S. EPA, 2013) evaluated a number of toxicological studies that demonstrated changes in bone cell function as a result of replacement of bone calcium with Pb depression in early bone growth. Studies also reported Pb-induced effects on cell proliferation, procollagen type I production, intracellular protein, and osteocalcin in human dental pulp cell cultures. Earlier work, summarized in the 2006 Pb AQCD (U.S. EPA, 2006), reported concentration-dependent depression of early bone growth after gestational exposure of animals to Pb. Recent evidence is limited. In a study of lifetime Pb exposure in mice, Beier et al. (2016) reported a reduction in osteoclast activity and a subsequent disruption in bone accrual in Pb-exposed mice. In another publication, the same group reported no other musculoskeletal effects resulting from Pb exposure alone (Beier et al., 2017).

9.5.5 Biological Plausibility

This section describes biological pathways that potentially underlie musculoskeletal effects of Pb. Figure 9-2 depicts the proposed pathways as a continuum of upstream events, connected by arrows, which may lead to downstream events observed in epidemiologic studies. This discussion of how exposure to Pb

may lead to musculoskeletal effects contributes to an understanding of the biological plausibility of epidemiologic results evaluated above. Note that the structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the current Pb ISA are discussed in Section IS.4.2.

The proposed pathway, outlined in Figure 9-2, involves both direct and indirect effects of Pb that could plausibly result in the weakening of bones and increased risk of fractures as well as the dental effects that are measured in epidemiologic studies. Skeletal bone development and biomechanical strength is controlled by the balance between osteoblasts, the cells responsible for the production of bone matrix, and osteoclasts, the cells responsible for bone resorption. Dysregulation of this balance can lead to bone loss and decreased mineralization. Pb can directly replace Ca^{2+} in the bone matrix as well as exert direct effects on bone cells to alter bone development. Pb can also alter bone growth and differentiation signals that can further disrupt the balance of bone formation and resorption.

As discussed in the 2013 Pb ISA, Pb suppresses the differentiation of osteoblasts and promotes osteoclast function which could result in delayed bone development and reduced bone mechanical integrity. Recent literature supports this hypothesis as studies have continued to show that animals treated with Pb have decreased bone mineralization (Li et al., 2020a; Sheng et al., 2020; Qi et al., 2019; Olchowik et al., 2014), bone weight (Álvarez-Lloret et al., 2017; de Figueiredo et al., 2014), and reduced trabecular bone (Li et al., 2020a; Sheng et al., 2020; Álvarez-Lloret et al., 2017; Beier et al., 2017). Many of these studies show concurrent changes in osteoblastic and osteoclastic markers that support an overall shift to increased bone resorption. For example, recent in vivo studies have seen reductions markers of osteoblast differentiation (Qi et al., 2019; Zhang et al., 2019; Beier et al., 2017), reductions of proteins that suppress osteoclast activity (Li et al., 2020a; Sheng et al., 2020; Qi et al., 2019; Kupraszewicz and Brzóska, 2013), and increases of markers of osteoclast activity (Li et al., 2020a; Qi et al., 2019; Zhang et al., 2019; Kupraszewicz and Brzóska, 2013) suggesting that bone changes result from dysregulation of the balance between bone formation and bone resorptive processes. The mechanism behind the reduced osteoblastic activity is not fully understood but both direct and indirect mechanisms have been proposed.

Support for a direct action of Pb on osteoblast function comes from in vitro studies showing that Pb treatment of primary osteoblasts leads to reduction in mineral deposition (Beier et al., 2015; Abbas et al., 2013; Ma et al., 2012). Previously reviewed data also implicated changes in TGFβ, bone morphogenic protein (BMP), nuclear factor kappa B (NF-κB), and activator protein-1 signaling (U.S. EPA, 2013). Recent studies suggest that Pb-induced suppression of Wnt signaling and upregulation of the protein sclerostin may also be involved (Sun et al., 2019; Beier et al., 2017; Beier et al., 2015). Similar studies of dental pulp cultures showed that in vitro treatment with Pb resulted in decreased cell proliferation and reduced extracellular matrix deposition. This could explain the increased incidence of dental carries in epidemiology studies.

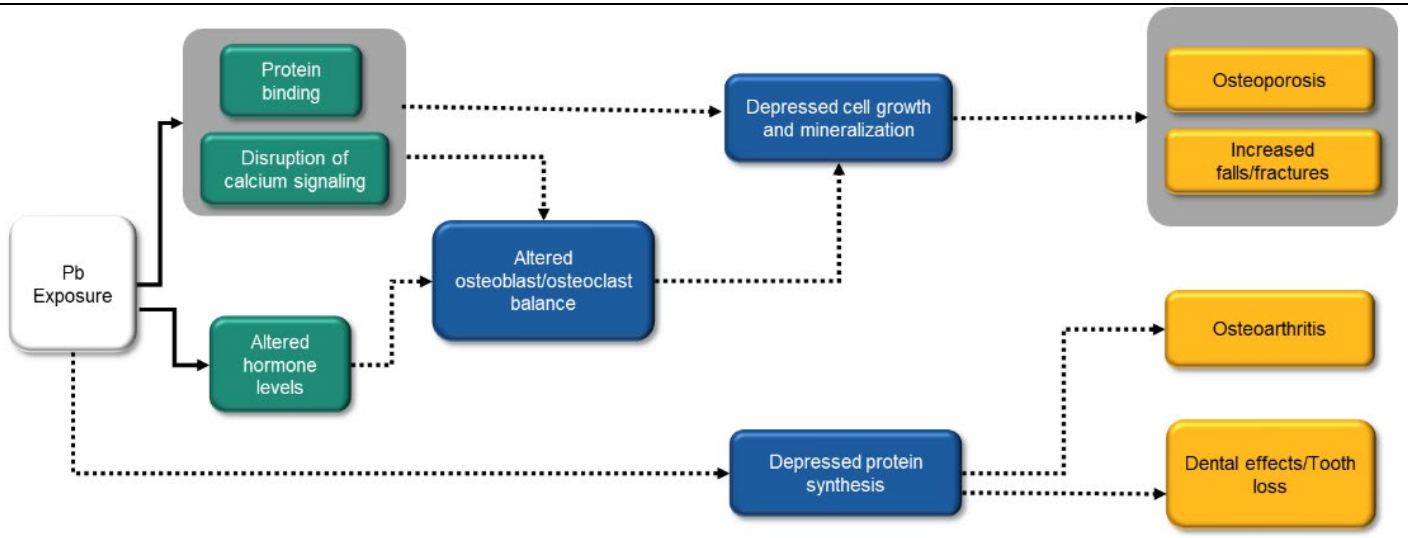
Indirect mechanisms of Pb treatment have also been discussed in the 2013 Pb ISA. The replacement of Pb for Ca^{2+} in cells can lead to Ca^{2+} release. The 2013 Pb ISA and 2006 AQCD discussed

studies that found that Pb treatment leads to increased systemic Ca^{2+} levels in the blood stream (U.S. EPA, 2013, 2006). Calcium is a cellular signaling molecule involved in mitochondrial function and cell death and thus changes in calcium signaling could have effects on cells elsewhere in the body. Bone growth can be affected by systemic signaling of hormones and vitamins that regulate osteoblast formation as well as storage and release of Ca^{2+} including parathyroid hormone (PTH), GH, BMP, and vitamin D. As discussed previously in the 2006 Pb AQCD and 2013 Pb ISA, Pb exposure can alter these pro-osteoblastic signals which are thought to be involved in the reduction of bone growth and mineralization seen following Pb exposure. Recent studies show similar alterations in calcitropic and osteoplastic signals that could be responsible for reduced bone formation (Zhang et al., 2019; Kupraszewicz and Brzóska, 2013). Together, these data provide plausible indirect pathway by which Pb exposure can regulate skeletal bone homeostasis.

The pathway for development of osteoarthritis is less well studied. Osteoarthritis results from erosion of cartilage and articular bone in the joints. Chondrocytes are responsible for matrix deposition and joint maintenance. Signaling though TGFβ is thought to be important in proper joint maintenance. A recent study showed that Pb treatment in rats induced cartilage loss which was associated with loss of extracellular matrix proteins (Holz et al., 2012). In the same study, in vitro treatment of chondrocytes from rat or chicks resulted in reduced markers of TGFβ signaling and increased markers of matrix degradation. These data suggest that Pb-induced osteoarthritis could be a result of Pb effects of chondrocytes and subsequent cartilage degradation.

Teeth do not undergo the same bone turnover processes as skeletal bone and thus Pb incorporated into the teeth is permanently sequestered. As discussed in the 2013 Pb ISA, dental effects of Pb are thought to arise from the effects of Pb on enamel producing cells in combination with the incorporation of Pb into areas of mineralization (U.S. EPA, 2013). Previously evaluated studies showed decrease cell proliferation, procollagen type I production, intracellular protein, and osteocalcin in human dental pulp cell cultures (U.S. EPA, 2013). A recent study supports the link between Pb exposure and dental effects by showing reduced molar diameter and increased dental cracks in the offspring of rats treated with Pb during either gestation or lactation (Chen et al., 2012). Together Pb-induced dental effects could result from effects on dental pulp cells resulting in reduced matrix proteins.

The toxicologic data support Pb-induced alterations in multiple aspects of bone, teeth, and joint maintenance. For skeletal bones, shift in the balance between bone building osteoblasts and bone resorbing osteoclasts could be responsible for delayed bone growth and increased bone degeneration seen in epidemiologic studies. In teeth and joints, Pb appears to suppress the synthesis of cellular matrix proteins important for joint maintenance and enamel formation which could plausibly contribute to the osteoarthritic and dental effects seen in some epidemiology studies.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence related to Pb exposure, and the arrows indicate a proposed relationship between those effects. Solid arrows denote evidence of essentiality as provided, for example, by an inhibitor of the pathway used in an experimental study involving Pb exposure. Dotted arrows denote a possible relationship between effects. Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color coded (white, exposure; green, initial effect; blue, intermediate effect; orange, effect at the population level or a key clinical effect). Here, population-level effects generally reflect results of epidemiologic studies. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below. IS.7.2 discusses the structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the 2022 Pb ISA.

Figure 9-2 Potential biological pathways for musculoskeletal effects following exposure to Pb.

9.5.6 Summary and Causality Determination

The 2013 Pb ISA concluded that evidence was "sufficient to conclude that a causal relationship is likely to exist between Pb exposure and effects on bone and teeth" (U.S. EPA, 2013). This causality determination was based on a small body of epidemiologic evidence showing associations between Pb biomarker levels and effects on bones after adjusting for potential confounding by age and SES-related factors, as well as strong toxicological evidence that reported effects on bone in animals following Pb exposure. Specifically, a few epidemiologic studies indicated an association between higher Pb biomarker levels and lower bone density in adults. A prospective study of older women provided evidence that higher BLLs (>4 μg/dL versus <3 μg/dL) were associated with greater risk of falls and osteoporosis-related fractures, as well as lower bone density measured after 2–4 years (Khalil et al., 2009). This finding was supported by cross-sectional associations between higher BLLs and lower BMD (Campbell and Auinger, 2007) and biochemical biomarkers of higher bone turnover (Nelson et al., 2011a; Machida et al., 2009) in adults. In evaluating the cross-sectional epidemiologic evidence, it is difficult to determine whether an increase in BLLs results from lower bone density or from higher bone turnover, and whether either of these effects lead to a greater release of Pb from bone into the bloodstream. Exposure of animals to Pb during gestation and the immediate postnatal period was reported to significantly depress early bone growth with the effects showing concentration-dependent trends. Systemic effects of Pb exposure included disruption in bone mineralization during growth, alteration in bone cell differentiation and function due to alterations in plasma levels of growth hormones and calcitropic hormones such as 1,25-[OH]2D3 and impact on Ca2+- binding proteins and increases in Ca2+ and phosphorus concentrations in the bloodstream. Bone cell cultures exposed to Pb had altered vitamin D-stimulated production of osteocalcin accompanied by inhibited secretion of bone-related proteins such as osteonectin and collagen. In addition, Pb exposure caused suppression in bone cell proliferation most likely due to interference from factors such as GH, EGF, transforming growth factor-beta 1 (TGF-β1), and PTHrP.

In addition to effects on bone, epidemiologic and toxicological studies evaluated in the 2013 ISA provided evidence of Pb-related effects on teeth. A limited number of epidemiologic studies reported associations between increased BLLs and increased dental caries in children (Moss et al., 1999) and periodontitis in adults (Saraiva et al., 2007). Additionally, higher patella and tibia Pb levels were associated with tooth loss in men participating in the NAS (Arora et al., 2009). This epidemiologic evidence was based on cross-sectional study design analyses, which precludes conclusions about the directionality of effects. However, these findings are supported by toxicological evidence in animals for Pb-induced increases in Pb uptake into teeth; and decreases in cell proliferation, procollagen type I production, intracellular protein, and osteocalcin in cells exposed to Pb in vitro. Despite evidence for associations between Pb exposure and effects in bone and teeth at relatively low concurrent BLLs, these outcomes were most often examined in older adults that have been exposed to higher levels of Pb earlier in life. Therefore, uncertainty still remains concerning the Pb exposure level, timing, frequency, and duration that contribute to the observed associations.

Recent cross-sectional epidemiologic studies continue to support associations between Pb exposure and effects on bone. The majority of recent studies of osteoporosis or osteopenia were conducted in female populations or included models stratified by sex to account for sex-specific difference in osteoporosis and osteopenia incidence. The evaluated studies provide generally consistent evidence of a positive association between low BLLs (mean/median ranges cross studies: 1.03 to 3.4 µg/dL) and osteoporosis or osteopenia in women (Li et al., 2020b; Wang et al., 2019; Pollack et al., 2013; Cho et al., 2012; Lee and Kim, 2012). Other studies also observed positive associations in models including men and women (Lee and Park, 2018; Lim et al., 2016), but the inferences that can be drawn from these studies are limited due to the previously noted sex differences in BMD. A few recent cross-sectional studies also reported associations between low BLLs and symptomatic and radiographic OA in the knee (Park and Choi, 2019; Nelson et al., 2011b). These findings were supported by another study demonstrating associations between BLLs and some biomarkers of joint tissue metabolism, which could either lead to OA or be indicative of prevalent OA (Nelson et al., 2011a). These studies of OA represent an emerging area of research for an endpoint that was not discussed in the 2013 Pb ISA. Recent epidemiologic evidence is prone to similar uncertainties and limitations identified in the previous ISA. Notably, the cross-sectional design of these studies does not establish temporality between the exposure and outcome. This may be particularly relevant for health outcomes that correlate with bone turnover rates that could lead to higher BLLs. Additionally, although a number of recent studies have been conducted in adult populations with low BLLs, uncertainty regarding past exposures continues to limit the characterization of the Pb exposure levels, timing, frequency, and duration that contribute to the observed associations.

The recent toxicological evidence base for effects on bones is smaller, but consistent with findings from the 2013 Pb ISA and coherent with recent epidemiologic evidence. Notably, a recent study reported a reduction in osteoclast activity and a disruption in bone accrual in Pb-exposed animals (Beier et al., 2016). This finding, along with similar evidence from previous ISAs and AQCDs, provides support for a temporal relationship between Pb exposure and effects on bone accrual and bone density that cannot be established by the available cross-sectional epidemiologic evidence.

In addition to studies of Pb exposure and effects on bone, recent epidemiologic studies have also explored the relationship between BLLs and effects on teeth. Recent studies in adults focused on the prevalence of periodontitis, whereas studies in children examined the prevalence or incidence of dental caries. A group of studies examining overlapping KNHANES cycles observed positive associations between low BLLs and periodontitis prevalence in adults (Han et al., 2013; Kim and Lee, 2013; Won et al., 2013), including some evidence of a stronger association in men, and persistent associations in models adjusting for Hg and Cd (Kim and Lee, 2013). Given the largely overlapping study populations, the observed results should not be interpreted as independent evidence of an association. Additionally, the use of BLLs in adult populations with higher past exposures limits the ability to characterize the Pb exposure levels, timing, frequency, and duration that contribute to the observed associations. In a prospective birth cohort study of low- to moderate-income mother-child pairs, increases in prenatal and early childhood

BLLs were associated with increased risk of dental caries in adolescence (Wu et al., 2019). The authors also observed a null association with concurrent BLLs, which suggests that there may be critical windows of exposure earlier in life. These findings were supported by a few cross-sectional studies that reported associations between BLLs in early childhood and increased prevalence of dental caries in deciduous teeth (Kim et al., 2017; Wiener et al., 2015). No recent toxicological studies have examined the effects of Pb exposure on teeth, but as described earlier, previous and recent mechanistic evidence provides biological plausibility for the observed epidemiologic associations.

In summary, there is an expanded epidemiologic evidence base that continues to demonstrate associations between BLLs and various musculoskeletal effects after adjusting for potential confounding. However, the recent epidemiologic evidence does not thoroughly address uncertainties identified in the previous ISA, including unclear temporality of exposure and outcome resulting from mostly cross-sectional study designs, and a lack of studies that adequately characterize the Pb exposure levels, timing, frequency, and duration that contribute to the observed associations. Although there are not many recent toxicological studies that meet PECOS relevance, the evaluated studies are consistent with a large evidence base from the previous ISA and AQCD, which provides support for the observed epidemiologic associations. **Overall, the collective evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and musculoskeletal effects.** The key evidence, as it relates to the causal framework, is summarized in Table 9-2.

Table 9-2 Summary of evidence for a likely to be causal relationship between Pb exposure and musculoskeletal effects.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent evidence from epidemiologic studies of osteoporosis and osteopenia	Evidence from cross-sectional epidemiologic studies supports associations between Pb exposure and osteoporosis or osteopenia in adult female populations.	Cho et al. (2012) Wang et al. (2019) Lee and Kim (2012) Pollack et al. (2013) Li et al. (2020b)	Mean/median ranges cross studies: 1.03 to 3.4 µg/dL
Supporting evidence from toxicological studies with relevant exposures investigating effects on bone	Toxicological evidence is coherent with epidemiologic evidence and provides support for a temporal relationship between Pb exposure and effects on bone accrual and bone density	Beier et al. (2016) (U.S. EPA, 2013) (U.S. EPA, 2006)	Mean range of 20.8 to 49.9 µg/dL
Consistent evidence from epidemiologic studies of dental caries in children	A prospective birth cohort study provides evidence that increases in prenatal and early childhood BLLs are associated with increased risk of dental caries in adolescence	Wu et al. (2019)	Mean (males, female): 15.48, 15.18 µg/dL
	Supporting cross-sectional evidence of associations between early childhood BLLs and dental caries in deciduous teeth	Kim et al. (2017) Wiener et al. (2015)	Geometric Mean: 1.53 µg/dL Mean NR (28.2% <2 µg/dL; 48.3% 2 to <5 µg/dL; 18.4% 5 to <10 µg/dL; 5.1% >10 µg/dL)

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
Biological Plausibility	Pb can directly replace Ca^{2+} in the bone matrix as well as exert direct effects on bone cells to alter bone development. Pb can also alter bone growth and differentiation signals that can further disrupt the balance of bone formation and resorption. Pb has also been shown to decrease cell proliferation, procollagen type I production, intracellular protein, and osteocalcin in human dental pulp cell cultures.	Section 9.5.4.	

BLLs = blood lead levels; Ca^{2+} = calcium ions; NR = not reported; Pb = lead.

[a]Based on aspects considered in judgments of causality and weight-of-evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the Pb biomarker levels at which the evidence is substantiated.

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9.6 Effects on Ocular Health

9.6.1 Introduction, Summary of the 2013 ISA, and Scope of the Current Review

This section of effects on ocular health focuses on impairments related to the structure of the eye, including but not limited to cataracts, glaucoma, macular degeneration, and retinal stippling. Studies examining effects on vision that are related to sensory processing in the central nervous system can be found in Appendix 3 of this ISA (Sections 3.5.6.2 and 3.6.3.2). The 2013 Pb ISA concluded that because the studies of effects on ocular health were of insufficient quantity and quality, the overall evidence was "inadequate to determine a causal relationship between Pb exposure and ocular effects" (U.S. EPA, 2013). There were very few studies evaluated in the 2013 Pb ISA that examined Pb exposure and ocular effects in humans or animals. Those studies that were reviewed examined disparate outcomes and the epidemiologic studies lacked rigorous statistical analyses.

9.6.2 Scope

The scope of this section is defined by PECOS statements. The PECOS statement defines the objectives of the review and establishes study inclusion criteria thereby facilitating identification of the most relevant literature to inform the Pb ISA.[1] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies included in the 2013 Pb ISA, including many that do not meet the current PECOS criteria, are discussed in this appendix to establish the state of the evidence prior to this assessment. Except for supporting evidence used to demonstrate the biological plausibility of Pb-associated effects on the ocular health, recent studies were only included if they satisfied all of the components of the following discipline-specific PECOS statements:

[1] The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

Epidemiologic Studies:

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect.

Exposure: Exposure to Pb[1] as indicated by biological measurements of Pb in the body – with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure;[2] or intervention groups in randomized trials and quasi-experimental studies.

Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles).

Outcome: Effects on ocular health.

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

Experimental Studies:

Population: Laboratory nonhuman mammalian animal species (e.g., mouse, rat, guinea pig, minipig, rabbit, cat, dog) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).

Exposure: Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a BLL of 30 µg/dL or below.[3,4]

Comparators: A concurrent control group exposed to vehicle-only treatment or untreated control.

Outcomes: Ocular effects.

Study design: Controlled exposure studies of animals in vivo.

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[1] Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[2] Studies that estimate Pb exposure by measuring Pb concentrations in particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm^3 (PM_{10}) and particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm^3 ($PM_{2.5}$) ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with BLLs are lacking.

[3] Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.

[4] This level represents an order of magnitude above the upper end of the distribution of U.S. young children's BLL. The 95th percentile of the 2011–2016 NHANES distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (Egan et al., 2021) and the proportion of individuals with BLL that exceed this concentration varies depending on factors including (but not limited to) housing age, geographic region, and a child's age, sex, and nutritional status.

9.6.3 Epidemiologic Studies on Ocular Health

A limited number of epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) did not provide evidence of an association between exposure to Pb and ocular health. A cross-sectional study of macular degeneration reported higher concentrations of Pb in the retinal tissue of donors with macular degeneration compared to those without (Erie et al., 2009). However, the authors did not control for confounders in this comparison of means. Another study measured BLLs in smokers and non-smokers with cataracts, but the authors did not make comparisons between exposure to Pb and severity of cataracts (Mosad et al., 2010).

Recent studies provide inconsistent evidence of an association between exposure to Pb and ocular effects. The majority of recent studies evaluating ocular health and Pb exposures are population-based cross-sectional analyses, which are unable to establish temporality between exposure and outcome. Additionally, because many of the observed ocular impairments generally occur in older adult populations who likely had higher past than current Pb exposure, there is uncertainty regarding the Pb exposure level, duration, frequency, and timing that may contribute to any observed associations. Measures of central tendency for blood and/or bone Pb levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 9-13. An overview of the recent evidence is provided below.

A limited number of recent studies have evaluated the relationship between levels of Pb in the blood or bone and glaucoma. The strongest evidence for an association comes from a longitudinal analysis of the Veterans Affairs NAS, a prospective cohort study of male Veterans (Wang et al., 2018b). Wang et al. (2018b) reported that increases in tibia and patella Pb were associated with 28% (95% CI: −1%, 65%) and 42% (95% CI: 11%, 82%) increases in risk of primary open-angle glaucoma, respectively. These results are supported by a recent KNHANES mediation analysis that evaluated intraocular pressure, which is an important risk factor for glaucoma (Park and Choi, 2016). The authors reported that a 1 μg/dL increase in blood Pb was associated with a 0.09 mmHg (95% CI: 0.06, 0.12 mmHg) increase in intraocular pressure, after accounting for indirect effects of exposure to Pb through increases in blood pressure. The estimated total effect (i.e., not controlling for mediation by blood pressure) for a 1 μg/dL increase in blood Pb was 0.11 mmHg (standard error not reported). In contrast, two recent large cross-sectional studies of the KNHANES did not observe an association between BLLs and glaucoma (Lee et al., 2016; Lin et al., 2015). However, potential associations with chronic age-related diseases, such as glaucoma, may be better evaluated using measurements of Pb in bone, which has a much longer half-life than in blood and is therefore a better indicator of cumulative exposure.

In addition to studies of glaucoma, there were also a few recent population-based cross-sectional studies that examined the association between BLLs and age-related macular degeneration (AMD) in older adults (Hwang et al., 2015; Park et al., 2015; Wu et al., 2014). AMD is a common eye-disorder in older adults that is caused by retinal damage, resulting in deteriorated central vision. Two recent studies of the KNHANES provided evidence of an association between BLLs and AMD (Hwang et al., 2015;

Park et al., 2015). Using data from the 2008–2011 cycles of KNHANES, Park et al. (2015) reported a 12% (95% CI: 2%, 23%) increase in the odds of early-stage AMD (i.e., damaged macula with no vision loss) and a 25% (95% CI: 5%, 50%) increase in the odds of late-stage AMD (i.e., damaged macula with vision loss) per 1 µg/dL increase in blood Pb. In a similar study that analyzed one additional year of KNHANES data (2008–2012), Hwang et al. (2015) similarly observed increasing odds of early-stage AMD with increasing quintiles of Pb exposure. Notably, in analyses stratified by sex, the observed associations in the total population appeared to be driven by a much stronger association in women. The authors also reported associations for late-stage AMD, but the case numbers were so low for each quintile that the reduced statistical power to detect an association made the results unreliable. In contrast to the results from the KNHANES studies, Wu et al. (2014) reported null associations between BLLs and AMD in an analysis of older adults in the 2005–2008 cycles of the U.S. NHANES.

Additional cross-sectional studies examined other ocular health effects for disparate outcomes, including an NHANES analysis of cataract surgery in older adults (Wang et al., 2016) and a KNHANES study of dry eye disease (Jung and Lee, 2019). Both of these studies reported null associations between BLLs and the ocular health outcome of interest.

9.6.4 Toxicological Studies on Ocular Health

The 2013 Pb ISA (U.S. EPA, 2013) made note of a limited number of animal studies finding Pb-induced mouse retinal progenitor cell proliferation and neurogenesis, as well as increased opacity of rat lens after Pb exposure.

Two recent toxicological studies were identified since the 2013 Pb ISA for inclusion in the present Pb ISA. Perkins et al. (2012) described remodeling of rod and cone synaptic mitochondria in mice after postnatal exposure to Pb acetate in drinking water (21 µg/dL BLL at weaning). The observed Pb-induced changes are consistent with deficits in range of vision. The effect of Pb on rod and cone mitochondria was mediation by Bcl-xL, a protein that has been implicated in Pb-induced apoptosis. Using adult rats exposed to Pb acetate in drinking water (1–20 µg/dL BLL), Shen et al. (2016) found increased blood-retinal permeability. The authors noted an association between long-term increased vascular permeability with retinal dysfunction and degeneration.

9.6.5 Summary and Causality Determination

The 2013 Pb ISA concluded that evidence was "inadequate" to determine a causal relationship between Pb exposure and ocular health effects (U.S. EPA, 2013). This causality determination was based on an insufficient quantity and quality of studies in the cumulative body of evidence. Although a cross-sectional epidemiologic study reported higher concentrations of Pb in the retinal tissue of donors with macular degeneration compared to those without (Erie et al., 2009), the study did not account for smoking

status as potential confounder. Toxicological studies were limited in number, but reported Pb-induced retinal progenitor cell proliferation, retinal electroretinograms, and lens opacity.

Since the completion of the 2013 Pb ISA, there has been an increase in the number of epidemiologic studies that examine the relationship between Pb exposure and ocular health effects. Recent epidemiologic studies provide inconsistent evidence of an association between Pb exposure and ocular health effects. The strongest evidence comes from a prospective cohort study of male Veterans that reported large, but imprecise associations between bone Pb levels and glaucoma (Wang et al., 2018b). These results are supported by a cross-sectional association between BLLs and intraocular pressure, which is an important risk factor for glaucoma (Park and Choi, 2016). However, additional population-based cross-sectional studies in the same population reported null associations between BLLs and glaucoma (Lee et al., 2016; Lin et al., 2015). No recent experimental studies examined endpoints related to glaucoma.

Findings from a limited number of population-based cross-sectional studies of Pb exposure and AMD were inconsistent across populations – with null results observed in a U.S.-based study and a positive association in a South Korean-based study. A recent toxicological study reported Pb-induced increases in blood-retinal permeability, which may lead to increased risk of macular degeneration.

Although the evidence base has expanded since the completion of the previous assessment, the limited number of studies and the inconsistent results do not provide sufficient information to draw a conclusion regarding causality. **Thus, the evidence remains *inadequate to infer the presence or absence of a causal relationship* between exposure to Pb and ocular health effects.**

9.7 Effects on the Respiratory System

9.7.1 Introduction, Summary of the 2013 ISA, and Scope of the Current Review

The 2013 Pb ISA evaluated studies of respiratory effects related to inflammatory and atopic diseases (like asthma) separately from effects on lung function, morphology, and respiratory symptoms. Similarly, in this review, studies evaluating the effect of Pb on asthma are discussed with effects on the immune system in Appendix 6. This section discusses the effects of Pb on the respiratory system in the otherwise healthy lung. The 2013 Pb ISA concluded that there was "insufficient quantity and quality of studies" related to the impacts of Pb on the non-asthmatic lung and the evidence was therefore "inadequate to determine a causal relationship" (U.S. EPA, 2013). Epidemiologic studies in non-asthmatics were lacking in number, consistency, and statistical rigor, despite observed associations between BLLs and respiratory effects in children and asthmatics (Appendix 6). The few respiratory toxicological studies described previously were in vivo and in vitro studies that administered concentrated ambient particulate matter, of which Pb was a component. The ability to evaluate the independent effect of Pb in these studies was limited due to the inability to account for confounding effects of copollutants and the lack of characterization of Pb particles in the samples. Given the limitations of these studies, the scope for this review was narrowed to remove toxicological studies that analyzed the health effects of Pb containing mixtures but lacked a Pb alone treatment group.

9.7.2 Scope

The scope of this section is defined by PECOS statements. The PECOS statement defines the objectives of the review and establishes study inclusion criteria thereby facilitating identification of the most relevant literature to inform the Pb ISA.[1] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria

[1] The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies included in the 2013 Pb ISA, including many that do not meet the current PECOS criteria, are discussed in this appendix to establish the state of the evidence prior to this assessment. Except for supporting evidence used to demonstrate the biological plausibility of Pb-associated effects on the immune system, recent studies were only included if they satisfied all of the components of the following discipline-specific PECOS statements:

Epidemiologic Studies:

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect.

Exposure: Exposure to Pb[1] as indicated by biological measurements of Pb in the body – with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure[2]; or intervention groups in randomized trials and quasi-experimental studies.

Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles).

Outcome: Effects on the respiratory system.

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

Experimental Studies:

Population: Laboratory nonhuman mammalian animal species (e.g., mouse, rat, guinea pig, minipig, rabbit, cat, dog) of any lifestage (including preconception, in utero, lactation, peripubertal, and adult stages).

[1] Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[2] Studies that estimate Pb exposure by measuring Pb concentrations in particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm^3 (PM_{10}) and particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm^3 ($PM_{2.5}$) ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with BLLs are lacking.

Exposure: Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a BLL of 30 µg/dL or below.[1,2]

Comparators: A concurrent control group exposed to vehicle-only treatment or untreated control.

Outcomes: Effects on the respiratory system.

Study design: Controlled exposure studies of animals in vivo.

9.7.3 Epidemiologic Studies on the Respiratory System

A limited number of epidemiologic studies evaluated in the 2013 Pb ISA did not provide strong evidence of an association between BLLs and airway responses in asthma-free populations. Further, these studies lacked rigorous statistical analysis and included limited consideration of potential confounders. In panel and time-series epidemiologic studies considering ambient air Pb (measured in $PM_{2.5}$ or PM_{10} air samples), associations were reported between short-term increases in air Pb and decreases in lung function and increases in respiratory symptoms and asthma hospitalizations in children but not adults. Despite this evidence for respiratory effects related to air Pb concentrations, the limitations of air Pb studies – including the limited data on the size distribution of Pb-PM, the uncertain relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with BLLs, and the lack of adjustment for other correlated particulate matter (PM) chemical components – precluded firm conclusions about ambient air Pb-associated respiratory effects. Recent studies have examined lung function and respiratory symptoms in non-asthmatic children and adults. While the majority of recent studies utilized cross-sectional designs that are unable to establish temporality between exposure and outcome, most adjust for a wide range of potential confounders and examine populations with lower BLLs. In general, recent evidence in children is inconsistent, though there is some evidence from a prospective cohort study that BLLs are associated with accelerated lung function decline in adults. Notably, because adult populations likely had higher past than current Pb exposure, there is uncertainty regarding the Pb exposure level, duration, frequency, and timing that may contribute to the observed association. Measures of central tendency for blood and/or serum Pb levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 9-15. An overview of the recent evidence, delineated by lifestage, is provided below.

[1] Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.

[2] This level represents an order of magnitude above the upper end of the distribution of U.S. young children's BLL. The 95th percentile of the 2011–2016 NHANES distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (Egan et al., 2021) and the proportion of individuals with BLL that exceed this concentration varies depending on factors including (but not limited to) housing age, geographic region, and a child's age, sex, and nutritional status.

9.7.3.1 Respiratory Effects in Children

A limited number of recent cross-sectional studies have examined the relationship between BLLs and pulmonary function or respiratory symptoms in children. Studies conducted in different locations reported inconsistent evidence of an association between BLLs and pulmonary function. In an analysis of 6- to 17-year-old children participating in the 2011–2012 NHANES survey cycle, Madrigal et al. (2018) reported modest and imprecise increases in mean forced expiratory volume (FEV1) (41.9 mL [95% CI: −46.9, 130.6 mL]) and forced vital capacity (FVC) (45.5 mL [95% CI: −49.2, 140.2 mL]) for children with BLLs in the highest quartile (>0.86 μg/dL) compared to children with BLLs in the first quartile (<0.44 μg/dL). Similar comparisons were null for FEV1:FVC and forced expiratory flow $(FEF)_{25\%–75\%}$. Notably, while the study population had a very low median BLL (0.56 μg/dL), there were small exposure contrasts between exposure quartiles, which may have limited the statistical power to detect an association. In contrast with the NHANES analysis, smaller cross-sectional studies conducted in preschool-aged children in China (Zeng et al., 2017) and 10- to 15-year-old children in Poland (Little et al., 2017) observed limited evidence of associations between BLLs and decreased FVC (Little et al., 2017; Zeng et al., 2017) or FEV1 (Zeng et al., 2017). Both studies noted small and imprecise associations and had small sample sizes. Limited statistical power resulting from a small sample size reduces the likelihood of detecting a true effect and the likelihood that an observed result reflects a true effect, which might explain the incongruous results. Additionally, the associations observed by Little et al. (2017) may have been subject to unmeasured confounding (e.g., by age, SES factors, environmental tobacco smoke), as the authors only adjusted their regression models for children's heights.

In addition to studies of pulmonary function, a single study examined respiratory symptoms in children. (Zeng et al., 2016) reported inconsistent associations between BLLs and respiratory symptoms in preschool-aged children in China, including some living in a community near an e-waste facility. The authors compared children with BLLs ≥5 μg/dL to those with BLLs <5 μg/dL and reported that those in the higher exposure group had decreased odds of parental-reported wheeze and dyspnea, a slight increase in the odds of parental-reported phlegm, and no perceptible change in parental-reported cough. Caution is warranted in interpreting results of parental-reported symptoms in locations with known environmental contamination due to potential over-reporting of symptoms.

9.7.3.2 Respiratory Effects in Adults

A limited number of recent studies have examined the relationship between blood or serum Pb levels and respiratory effects in adults. There is evidence from a prospective cohort study that BLLs are associated with accelerated lung function decline in adults, although a large, population-based cross-sectional study reports conflicting results. All of the studies evaluated in this subsection reported low levels of blood or serum Pb levels (mean and geometric mean levels <3 μg/dL).

The most compelling evidence of an association between Pb exposure and lung function in adults comes from a prospective cohort study of adults living adjacent to a large industrial complex in South Korea (Pak et al., 2012). The authors reported that BLLs were associated with accelerated lung function decline, measured as the difference in spirometric measurements taken at baseline and after two-years of follow-up. Specifically, Pak et al. (2012) noted accelerated decline in FVC (−177 mL [95% CI: −330, −24]) and FEV1 (−107 mL [95% CI: −215, 1]) per 1 µg/dL increase in BLL at baseline. Notably, because adult populations likely had higher past than current Pb exposure, there is uncertainty regarding the Pb exposure level, duration, frequency, and timing that may contribute to the observed association. In contrast to results from Pak et al. (2012), a recent cross-sectional study of 2008–2012 KNHANES participants with low BLLs observed null associations between BLLs and FVC and FEV1 in adults (Leem et al., 2015).

Leem et al. (2015) also examined obstructive lung function (FEV1/FVC <0.7) in the same population and observed a null association with BLLs. In a similar recent analysis of a large population-based health survey (NHANES), (Rokadia and Agarwal, 2013) reported a large, but imprecise increase in the odds of obstructive lung function (94% [95%: 10%, 342%] per 1 µg/dL increase in serum Pb levels) that appears to be driven by an association in participants with moderate to severe obstructive lung function (349% [95%: 70%, 715%] per 1 µg/dL increase in serum Pb levels). The observed associations were similar in analyses stratified by smoking status, although the associations in non-smokers were even less precise due to a smaller number of cases.

9.7.4 Toxicological Studies on the Respiratory System

The 2013 ISA evaluated a limited number of studies investigating the effects of ambient particulate mixtures of which Pb was a component. The effects directly attributable to Pb were not able to be distinguished from other confounding mixture components. The PECOS criteria used in this ISA to identify new respiratory toxicological studies focused on identifying studies that studied Pb exposure alone. One study reviewed in the 2013 Pb ISA showed that injection of Pb acetate resulted in histologic signs of damage and inflammation in the lung although uncertainty regarding the biological relevance of Pb injection remained A few new experimental studies were identified that investigated the effect of inhaled Pb and met our PECOS criteria (Table 9-9). The studies, all published by the same group, assessed the localization and clearance of inhaled ultrafine (>100 nm in diameter) Pb particles and the corresponding effect on lung (and secondary organ) tissue structure. These studies involved 2–11 weeks of exposures (24 hours/day, 7 days/week) to inhaled Pb nanoparticles after which the investigators analyzed lung histology and markers of lung damage. Exposure of female mice to roughly 10^6 particles/cm^3 lead oxide (PbO) particles for 6 weeks led to a mean BLL of 132 ng/g (~13.922 µg/dL) and corresponded to histological signs of lung damage including alveolar septal wall thickening, emphysema, perivascular infiltration of immune cells, and signs of thrombosis (Dumková et al., 2017). Exposure to a higher concertation of PbO (2.23×10^6 particles/cm^3) for 3 days, 2, 6, and 11 weeks led to BLLs ranging

from 10.4 µg/dL at 2 weeks up to 17.4 µg/dL after 11 weeks of exposure. The BLL at 3 days was not reported. Histological signs of cellular infiltration and alveolar septal wall thickening was observed after 6 and 11 weeks of PbO exposure along with signs of macrophage proliferation (PCNA-staining) (Dumková et al., 2020b). These effects were not reported for the two-week exposure or an acute 3-day exposure to PbO. Despite increased signs of lung inflammation, signs of fibrosis and apoptosis were not observed. Interestingly, a 5-week recovery period with no PbO exposure following 6 weeks of PbO exposure was able to reduce both the lung Pb concertation and partially recover the histopathological signs of inflammation seen at 6 weeks of PbO (Dumková et al., 2020b).

In a separate experiment, a similar procedure as Dumková et al. (2020b) was followed using more soluble $Pb(NO_3)_2$ nanoparticles in place of PbO. Mice were exposed to $Pb(NO_3)_2$ particles for either 3 days, 2 weeks, 6 weeks, or 11 weeks and a separate recovery group that was exposed to $Pb(NO_3)_2$ for 6 weeks and then filtered air for 5 weeks (Dumková et al., 2020a). Similar to the results with PbO, $Pb(NO_3)_2$ exposure showed an increase in histological signs of inflammation and lung damage. Histological effects with $Pb(NO_3)_2$ particle exposure were seen starting at 2 weeks of exposure and did not completely resolved in the recovery group. Exposure to $Pb(NO_3)_2$ reduced the number of lung macrophages (CD68 positive stained cells) in the lung tissue which corresponded to an increase in neutrophils (Myeloperoxidase positive cells) and mastocytes (Toluidine blue staining). Similar to the findings with PbO, a 5-week recovery period with no $Pb(NO_3)_2$ exposure following 6 weeks of $Pb(NO_3)_2$ exposure was able to reduce both the lung Pb concertation and partially recover the histopathological signs of inflammation. While macrophage number was partially restored after a 5-week recovery period, the level of mastocytes remained elevated. Lung mRNA for inflammatory genes like IL-1B, IL-1a, and tumor necrosis factor-α were largely unchanged however RNA levels of NF-κB and IL6 were suppressed after 3 days and 11 weeks of $Pb(NO_3)_2$ suggesting that $Pb(NO_3)_2$ dysregulates the inflammatory response in the lung. While the data presented in these studies are mostly qualitative, it provides some preliminary evidence of respiratory effects from inhalation of either $Pb(NO_3)_2$ or PbO nanoparticles.

9.7.5 Summary and Causality Determination

The effects of Pb on asthma incidence and host defense, which includes data related to host response to lung infection, are analyzed in the context of allergic disease and immune suppression (Section 6.7.1 and Section 6.7.2).

The 2013 Pb ISA determined that the evidence for respiratory effects was "inadequate to determine a causal relationship between Pb exposure and respiratory effects in populations without asthma." This determination was based on inconsistent findings among studies and the limited quantity and quality of both epidemiologic and experimental toxicologic evidence of respiratory effects. While there was some epidemiologic evidence of an association between short-term increases in ambient air Pb and decreases in lung function, these studies were not informative to the causality determination due to

notable uncertainties regarding the size distribution of ambient air Pb, the relationship between ambient air Pb and BLLs, and the confounding effects of co-occurring pollutants.

Evidence evaluated in the 2013 Pb ISA showed inconsistent relationships between BLLs and bronchial responsiveness and lung function. Results from recent epidemiologic studies of the effect of blood Pb on lung function and respiratory symptoms in children remain inconsistent (Section 9.7.3.1). In adults, a new prospective cohort study provides evidence of accelerated lung function decline in those with higher BLLs (Pak et al., 2012), however the relationship between lung function decrements and BLLs is inconsistent in a few recent cross-sectional analyses (Section 9.7.3.2). This lack of consistency in the epidemiologic literature is compounded by uncertainty related to exposure assessment and relative lack of adjustment for correlated air pollutants. Toxicological data in the 2013 ISA was mostly limited to studies of concentrated ambient PM of which Pb was a component within a mixture of pollutants, leaving uncertainty for the role of Pb in the observed effects. New toxicological studies evaluating inhalation of Pb particles are limited in number but do provide evidence of gross histologic signs of transient inflammation and lung damage; however, these data are largely qualitative and the impact of these changes on lung function are unknown. Uncertainty still remains about the relative size distribution of Pb particles in ambient air and thus how well experimental generation of Pb particles reflects ambient concentrations and particle size distribution. Given the lack of consistency across a small body of epidemiologic evidence and uncertainty in the direct relevance of a limited number of toxicological results to human lung function, the evidence is not sufficient to draw a conclusion regarding causality. **Thus, the cumulative body of evidence is *inadequate to infer the presence or absence of a causal relationship* between Pb exposure and respiratory effects in populations without asthma**.

9.8 Mortality

9.8.1 Introduction, Summary of the 2013 ISA, and Scope of the Current Review

In the 2013 Pb ISA (U.S. EPA, 2013), the strongest evidence for Pb-associated mortality was from studies examining cardiovascular mortality. The evidence did not provide strong support for Pb-associated mortality other than through cardiovascular pathways, and very few studies examined total (nonaccidental) mortality. For these reasons, the 2013 Pb ISA evaluated studies of all-cause mortality together with studies examining cardiovascular mortality, and these studies were all included within the cardiovascular disease chapter. Although this evidence contributed to the "causal relationship" between Pb exposure and coronary heart disease, there were no distinct causality determinations for total or cause-specific mortality. In this ISA, the strongest evidence for Pb-associated cause-specific mortality continues to come from studies of cardiovascular mortality. However, additional studies examining total non-accidental mortality have become available since the last ISA, and this section discusses and evaluates

those studies. Studies that examine cardiovascular-related mortality or other cause-specific mortality are discussed in detail within the appropriate outcome-specific appendices (e.g., cardiovascular disease (CVD)-related mortality is discussed in Appendix 4) and are briefly summarized in this section.

9.8.2 Scope

The scope of this section is defined by PECOS statements. The PECOS statement defines the objectives of the review and establishes study inclusion criteria thereby facilitating identification of the most relevant literature to inform the Pb ISA.[1] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies included in the 2013 Pb ISA, including many that do not meet the current PECOS criteria, are discussed in this appendix to establish the state of the evidence prior to this assessment. Except for supporting evidence used to demonstrate the biological plausibility of Pb-associated effects on mortality, recent studies were only included if they satisfied all the components of the following PECOS statements:

Population: Any human population, including specific populations or lifestages that might be at increased risk of a health effect.

Exposure: Exposure to Pb[2] as indicated by biological measurements of Pb in the body – with a specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb exposure[3]; or intervention groups in randomized trials and quasi-experimental studies.

[1] The following types of publications are generally considered to fall outside the scope and are not included in the ISA: review articles (which typically present summaries or interpretations of existing studies rather than bringing forward new information in the form of original research or new analyses), Pb poisoning studies or clinical reports (e.g., involving accidental exposures to very high amounts of Pb described in clinical reports that may be extremely unlikely to be experienced under ambient air exposure conditions), and risk or benefits analyses (e.g., that apply concentration-response functions or effect estimates to exposure estimates for differing cases).

[2] Recent studies of occupational exposure to Pb were considered insofar as they addressed a topic area of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

[3] Studies that estimate Pb exposure by measuring Pb concentrations in particulate matter with a nominal mean aerodynamic diameter less than or equal to 10 μm^3 (PM_{10}) and particulate matter with a nominal mean aerodynamic diameter less than or equal to 2.5 μm^3 ($PM_{2.5}$) ambient air samples are only considered for inclusion if they also include a relevant biomarker of exposure. Given that size distribution data for Pb-PM are fairly limited, it is difficult to assess the representativeness of these concentrations to population exposure [Section 2.5.3 (U.S. EPA, 2013)]. Moreover, data illustrating the relationships of Pb-PM_{10} and Pb-$PM_{2.5}$ with BLLs are lacking.

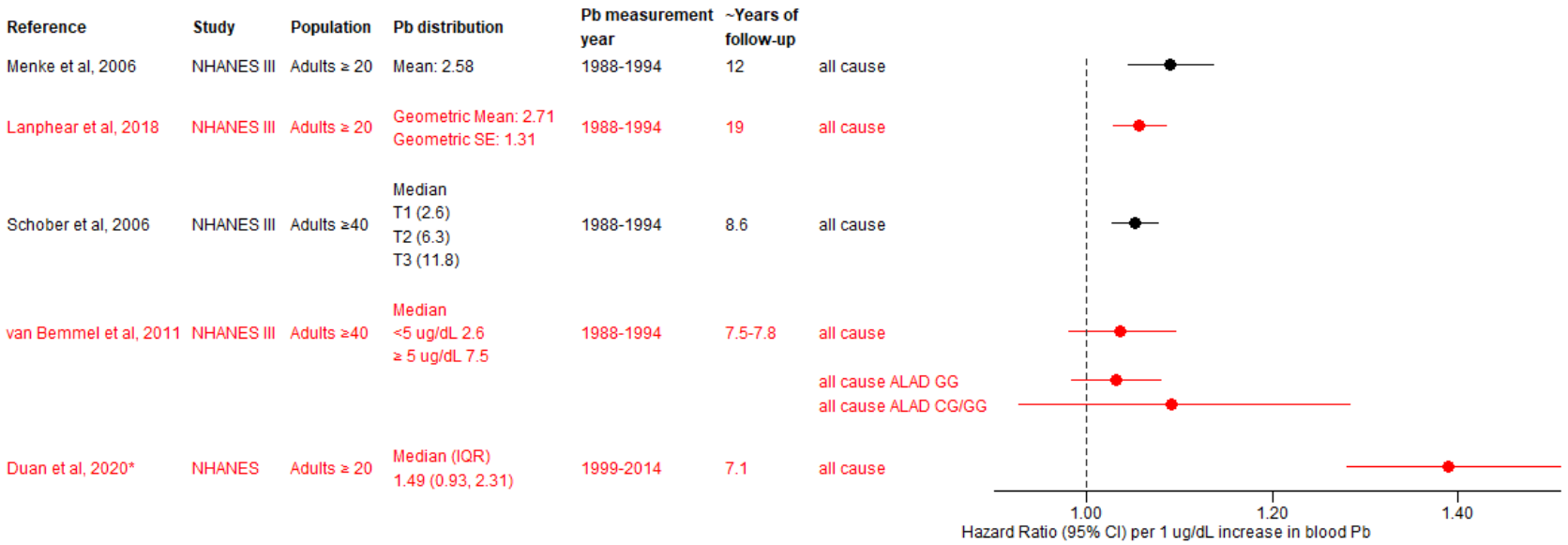
Comparison: Populations, population subgroups, or individuals with relatively higher versus lower levels of the exposure metric (e.g., per unit or log unit increase in the exposure metric, or categorical comparisons between different exposure metric quantiles).

Outcome: Mortality.

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

9.8.3 Total (non-Accidental) Mortality

The 2013 Pb ISA (U.S. EPA, 2013) evaluated a small number of studies that examined the association between biomarkers of Pb exposure and all-cause mortality. Overall, these studies reported consistently positive associations between Pb biomarkers and all-cause mortality. Specifically, Lustberg and Silbergeld (2002) indicated an increased risk of all-cause mortality when comparing the highest tertiles of BLLs (20–29 μg/dL) to the lowest (<10 μg/dL). Lustberg and Silbergeld (2002) conducted this analysis among NHANES II cohort, which had high BLLs (mean 14 μg/dL). Additionally, Schober et al. (2006) and Menke et al. (2006) both evaluated the NHANES III cohort, which had an overall lower BLL (mean: 2.6 μg/dL), and still identified a positive association between BLLs and all-cause mortality (Figure 9-1). Notably, both NHANES cohorts included adult study populations with higher past than recent Pb exposures, making it difficult to characterize the specific timing, duration, frequency, and level of Pb exposure that contributed to the observed associations. Recent evidence continues to support the association between Pb biomarkers and all-cause mortality. Study-specific details, including biomarker Pb levels, study population characteristics, confounders, and select results from these studies, are highlighted in Figure 9-3 and Table 9-17. Studies in Figure 9-3 are standardized to be interpreted as the risk of all-cause mortality associated with a 1 μg/dL increase in BLL. Study details in Table 9-10 include standardized results as well as results that could not be standardized based on the information provided in each paper. An overview of the recent evidence is provided below.



ALAD GG and ALAD CG/GG = variants of 5-aminolevulinic acid dehydratase, T1 = Tertile 1, T2 = Tertile 3, T4 = Tertile 4, NHANES = National Health and Nutrition Examination Survey.

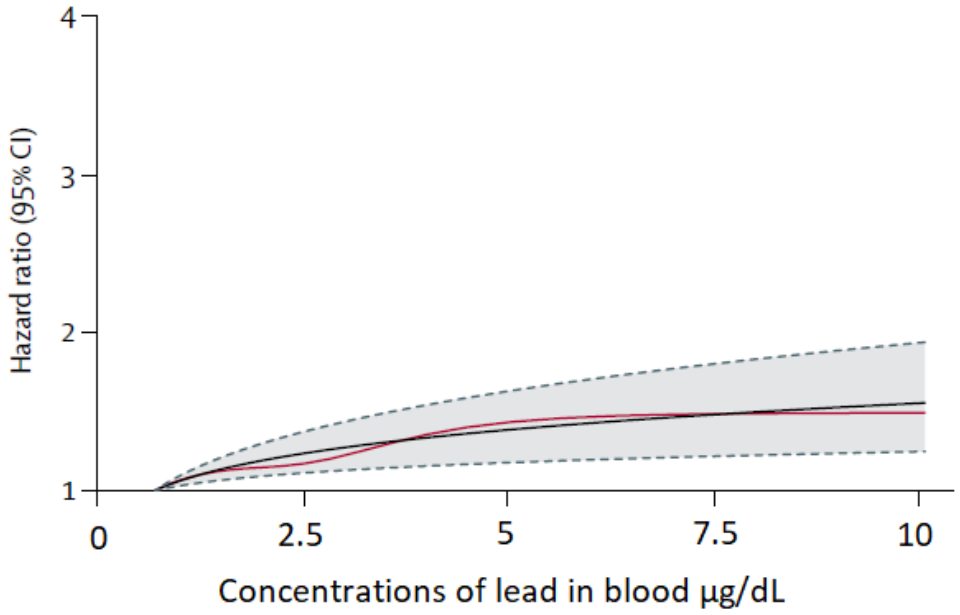
Note: Red text: Studies published since the 2013 Pb ISA; Black text: Studies included in the 2013 Pb ISA.

Effect estimates are standardized to a 1 µg/dL increase in blood Pb. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th–90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval.

*Study estimated relative risk.

Figure 9-3 Effect estimates for associations of blood Pb with all-cause mortality.

In a recent extended analysis of the NHANES III cohort, Lanphear et al. (2018) increased the average follow-up time of the Menke et al. (2006) analysis by over 7 years (from 12 to ~19 years), resulting in a substantial increase in the number of total deaths observed (4,222 versus 1,661). Lanphear et al. (2018) reported that a 1 µg/dL increase in BLL was associated with a hazard ratio (HR) of 1.06 [95% CI: 1.03, 1.09]) for all-cause mortality. The authors also calculated the population attributable fraction for both all-cause and cardiovascular mortality, to estimate the proportional reduction in mortality that would be expected if BLLs in those ≥20 were reduced to 1 µg/dL. Lanphear et al. (2018) estimated that the population attributable fraction for all-cause mortality was 18% (95% CI: 10.9–26.1), while the population attributable fraction for cardiovascular mortality was 28.7% (95% CI: 15.5, 39.5). Therefore, given the proportion of all-cause mortality attributable to cardiovascular causes (both in this study [~38%] and nationally [~33%; NHLBI, 2017, 3980932}]), while CVD mortality is likely strongly influencing a large proportion of the all-cause mortality signal, it does not account for all of it. The authors also used a five-knot restricted cubic spline analysis to assess potential non-linearities and observed a generally sigmoidal concentration-response (C-R) relationship between BLLs and all-cause mortality, with some attenuation of the C-R relationship below 2.5 µg/dL (Figure 9-4). The general shape of the C-R relationship is consistent with previous results from Menke et al. (2006).



Note: Restricted cubic spline (5 knots) (red line) and adjusted HRs (black line) with 95% CI's (hatched lines) for all-cause mortality.
Source: Adapted from Lanphear et al. (2018).

Figure 9-4 Dose-response relationship between blood Pb levels and all-cause mortality.

Other recent studies also evaluated the relationship between blood Pb and total mortality using NHANES data. Using NHANES III, van Bemmel et al. (2011) estimated an increased association between BLLs and all-cause mortality (HR: 1.04 [95% CI: 0.98, 1.10]). In addition, van Bemmel et al.

(2011) also evaluated this relationship by polymorphisms in 5-aminolevulinic acid dehydratase (ALAD). A critical mechanism of Pb toxicity is its ability to interact and inhibit key enzymes, such as ALAD, in the heme biosynthesis pathway. This study evaluated associations between BLLs, and mortality stratified by ALAD variant (ALADGG [more common genotype] or ALADCG/GG). However, there was little difference between the estimates generated when stratified (ALADGG HR: 1.03 [95% CI:0.98, 1.08], ALADCG/GG HR: 1.09 [95% CI:0.93, 1.28]), when comparing BLLs ≥5 μg/dL to levels <5 μg/dL. Using more recent NHANES cycles (1999–2014), Duan et al. (2020) also reported a positive association between blood Pb and all-cause mortality (RR: 1.39 [95% CI: 128, 1.51]). In a similar analysis using recent KNHANES cycles (2007–2015), Byun et al. (2020) evaluated the association between BLLs and total (nonaccidental) mortality using KNHANES (2007–2015) baseline data, and mortality data linked through 2018. Overall, there were positive associations between increasing tertiles of blood Pb exposure and all-cause mortality. Compared to the first tertile of BLLs (<1.91 μg/dL), the HR for all-cause mortality was 2.02 (95% CI: 1.20, 3.40) for the second tertile (1.91–2.71 μg/dL) and 1.91 (95% CI: 1.13, 3.23) for the third tertile (>2.71 μg/dL).

In addition to studies using nationally representative survey data, a recent study by Hollingsworth and Rudik (2021) implemented a quasi-experimental design to examine the effect of the phase out of leaded gasoline in automotive racing on mortality rates in older adults. Comparing time periods prior to and after the phaseout of leaded gasoline in professional racing series (i.e., the National Association for Stock Car Auto Racing [NASCAR] and the Automobile Racing Club of America [ARCA]), the authors used a difference-in-differences technique to estimate county-level changes in air Pb concentrations, elevated BLL prevalence among children, and mortality rates in race counties and counties bordering race counties relative to control counties. A detailed discussion of results for air Pb concentrations and BLLs is presented in Section 2.4.1. In short, there were substantial declines in both air Pb concentrations and the prevalence of children with elevated BLLs associated with the phaseout of leaded gasoline. The authors also reported significant declines in mortality rates over this same period. Specifically, in the period following de-leading of gasoline, there was an estimated decline in annual age-standardized all-cause mortality rates of 91 deaths per 100,000 in race counties and 38 deaths per 100,000 in border counties. Similar to the exposure results, the mortality estimates appear to demonstrate a distance gradient. Although this analysis includes county-level data, the difference-in-difference approach controls for spatially varying confounders by estimating the difference in mortality rates in adjoining years in the same county and controls for temporally varying confounders by assessing the difference of those differences between locations. The authors additionally adjust for potential confounders that may vary spatially and temporally (e.g., unemployment rate and quantity of Toxic Release Inventory [TRI] lead emissions). Hollingsworth and Rudik (2021) did not adjust for potential copollutant exposures, but provide evidence that there is no differential effect of leaded and unleaded races on other copollutant concentrations (i.e., CO, VOCs, PM_{10}, $PM_{2.5}$, NO_2, and O_3) in the weeks leading up to and following the race. However, because the mortality rates are an annual measure, there is remaining uncertainty regarding potential differential trends in the long-term average of other pollutants that could be correlated with the phaseout of leaded gasoline in NASCAR and ARCA.

Since Pb has been identified as being associated with renal insufficiency, previous studies have further assessed if Pb accumulates in patients with end-stage renal disease (ERSD). In a recent prospective cohort study in Taiwan, Lin et al. (2011) followed study subjects on maintenance hemodialysis for a period of 18 months. Overall, subjects included in the study had higher BLLs (mean: 11.5 μg/dL) than the general Taiwanese population (mean: 7.7 μg/dL). It is suspected that hemodialysis patients may experience higher BLLs since their kidneys may no longer be able to excrete Pb from the body due to a total loss of renal function (Appendix 5). Among this group, there was a strong but imprecise association between BLLs and all-cause mortality when comparing those in the second tertile of BLLs (8.51–12.64 μg/dL) to those in the first tertile of BLLs (<8.51 μg/dL) (HR: 2.69 [95% CI: 0.47, 3.44]). This effect was higher in magnitude, but even more imprecise among those in the third tertile of BLLs (>12.64 μg/dL) (HR: 4.70 [95% CI: 1.92, 11.49]), compared with the first tertile of blood Pb. The imprecise effect estimates in this analysis are likely due to a combination of the relatively small sample size and short follow-up period, leading to a small number of deaths included in the analysis. The small number of cases reduces statistical power, as well as the likelihood that an observed result reflects a true effect.

In contrast to the generally consistent evidence of an association between BLLs and all-cause mortality, a small Canadian study evaluating several trace metals observed a null association between all-cause mortality and BLLs among hemodialysis patients (≥18 years of age) (Tonelli et al., 2018). Patients in this cohort had relatively low BLLs (1st decile: 0.06 μg/dL, 10th decile 1.74 μg/dL), and there was no observed relationship between BLLs and all-cause mortality when comparing the highest to the lowest decile. The authors only presented quantitative results for statistically significant associations, so it is unclear whether there was any evidence of a non-statistically significant association. Additionally, Tonelli et al. (2018) was likely underpowered to detect a HR in the range reported in other studies of BLLs and all-cause mortality (Figure 9-4).

9.8.4 Cause-Specific Mortality

The mortality studies available for review in the 2013 Pb ISA focused primarily on cardiovascular mortality, and consistently reported positive associations with overall cardiovascular mortality and cause-specific cardiovascular mortality. Recent studies also evaluate cardiovascular mortality in addition to other cause-specific mortality outcomes.

Recent analyses further indicate a positive association between Pb exposure and cardiovascular mortality and are further described in Section 4.10. In summary, there were several studies using nationally representative data with low BLLs (mean <2 μg/dL) that consistently reported increased associations between biomarkers of Pb exposure and cardiovascular mortality. However, these populations were largely similar (mostly from NHANES III or other more recent NHANES cycles) and

still include individuals with sizeable historic exposures to Pb. For specific causes of CVD mortality (e.g., myocardial infarction (MI), ischemic heart disease (IHD), stroke), the measures of association were higher in magnitude but were less precise (i.e., wider 95% CIs), likely due to the smaller number of cause-specific cardiovascular-related deaths. Additionally, in the quasi-experimental study discussed in Section 9.8.3, deleading of racing gas led to declines in county-level cardiovascular mortality rates (Hollingsworth and Rudik, 2021). This evidence helps to strengthen the evidence base indicating an association between biomarkers of Pb exposure and increased risk of cardiovascular mortality.

Several recent studies also evaluated the relationship between Pb exposure biomarkers and cancer mortality, as described in Section 10.4. In summary, there were a limited number of studies evaluating Pb biomarkers of exposure and overall cancer mortality. Most studies relied on nationally representative data and yielded inconsistent but mostly null associations between Pb exposure and cancer mortality. However, the follow-up period in many of these analyses was short (<11 years), with a small number of cancer deaths and a lack of control of some potential influential confounders, such as comorbidities and BMI.

Additionally, some studies evaluated alternative cause-specific mortality outcomes. A cohort study analyzed data from five NHANES cycles (1999–2008) and reported a positive, but imprecise association between blood Pb and Alzheimer's disease (AD) mortality [Section 3.5.4; (Horton et al., 2019)]. The imprecise effect estimate is likely due to the small number of AD mortality cases (n = 81) that resulted from AD mortality being determined by the listing of the immediate cause of death rather than the underlying cause of death. Additionally, Lin et al. (2011) prospectively evaluated subjects on maintenance hemodialysis for a period of 18 months and evaluated infection-caused mortality. Among this group there was an imprecise increase in mortality (HR: 5.35 [95% CI: 1.38, 20.83]) in the highest tertile (>12.64 μg/dL) compared to the lowest tertile (<8.51 μg/dL). This association persisted (HR: 4.72 [95% CI: 1.27, 17.54]) even after correction for hemoglobin (dividing BLL by hemoglobin concentration). Finally, a quasi-experimental reported a decrease in county-level respiratory mortality rates in association with the phase out of leaded gasoline in automotive racing (Hollingsworth and Rudik, 2021).

9.8.5 Biological Plausibility

In evaluating the biological plausibility of reported associations between Pb exposure and total non-accidental mortality, this section considers the biological evidence supporting health outcomes likely to contribute to total mortality. As summarized above, studies consistently report positive associations between Pb exposures and cardiovascular-related mortality, with much more limited evidence for associations with other causes of mortality. Overall, cardiovascular mortality is the most common contributor to total non-accidental mortality (i.e., accounting for about 33% of total mortality) (NHLBI, 2017). As it pertains to Pb exposure, the available evidence provides strong support for Pb-associated

cardiovascular effects and supports a continuum of effects leading to cardiovascular mortality, as described further in Appendix 4. Direct evidence for cardiovascular effects following Pb exposures comes from numerous animal toxicological studies, and there is coherence between these animal studies and epidemiologic studies that report associations with some of the same cardiovascular outcomes (e.g., increased blood pressure, changes in cardiac electrophysiology). Animal studies additionally support the biological plausibility of the consistent epidemiologic associations reported between body Pb concentrations and cardiovascular outcomes such as hypertension and cardiovascular mortality. Section 4.10 characterizes the strong evidence indicating the mechanisms by which exposure to Pb could plausibly progress from initial events to endpoints relevant to the cardiovascular system, such as hypertension, exacerbation of IHD, and potential MI or stroke. In particular, exposures to Pb can result in oxidative stress and systemic inflammation, which could potentially lead to impaired vascular function, a pro-atherosclerotic environment, and increases in blood pressure. There is animal toxicological evidence demonstrating all of these effects following exposure to Pb (Section 4.8). Atherosclerosis and increased blood pressure can then set the stage for an MI or stroke that could result in mortality. Thus, the progression demonstrated in the available evidence for cardiovascular morbidity supports potential biological pathways by which Pb exposure could result in cardiovascular mortality.

The current evidence strongly supports a plausible relationship between Pb exposure and cardiovascular mortality. Additionally, Pb may act on other biological pathways leading to death. There is some limited evidence that BLLs are associated with other causes of mortality, including AD and infection. The strongest evidence for biologically supported pathways leading to neurodegenerative disease include the effect of Pb on cellular protein function and subsequent initiation of oxidative stress- and inflammation-mediated pathways (Section 3.3). AD, specifically, has been linked with increased markers of neuroinflammation. Studies with exposure of postweaning animals to Pb have shown increased inflammation associated with AD markers, as well as inhibition of AD markers following postexposure treatment with anti-inflammatory and antioxidative molecules. Regarding infection-related mortality, biological plausibility for the observed association is provided by toxicological and epidemiologic studies demonstrating (1) skewing of T cell populations, promoting Th2 cell formation and cytokine production, (2) decreased IFN-γ production, (3) decrements in macrophage function, (4) production of inflammatory mediators, and (5) disruption of the microbiome, all of which could lead to immunosuppression (Section 6.6.1).

9.8.6 Summary and Causality Determination

The 2013 Pb ISA did not make a causality determination regarding the relationship between Pb exposure and total (nonaccidental) mortality, but these studies did support the causality determinations made within the cardiovascular disease chapter. The evidence available at the time of the last review was limited but reported consistently positive associations between Pb biomarkers and all-cause mortality (Menke et al., 2006; Schober et al., 2006). These results were additionally supported by consistent

positive associations between BLLs and overall cardiovascular mortality (Section 4.10) as well as cause-specific cardiovascular mortality (e.g., MI, IHD, stroke)). Menke et al. (2006) examined the shape of the C-R relationship between BLLs and all-cause mortality using quadratic spline models, which generally appeared to support a linear, no-threshold relationship, although the HRs were somewhat attenuated at BLLs <2.5 µg/dL. Notably, the majority of mortality studies analyzed participants from NHANES cohorts, either NHANES II or NHANES III, so while the results are consistent, they do not represent a range of independent study populations. Additionally, while some of the studies evaluated in the 2013 Pb ISA examined populations with low mean BLLs (<3 µg/dL), study participants were born prior to the phase-out of leaded gasoline and therefore likely had much higher past Pb exposures, making it difficult to characterize the specific timing, duration, frequency, and level of Pb exposure that contributed to the observed associations.

Prospective cohort studies evaluated since the completion of the 2013 Pb ISA continue to provide consistent evidence of positive associations between Pb exposure and total (nonaccidental) mortality. Many recent analyses further evaluated the association between BLLs and the risk of mortality using NHANES cohorts linked to mortality databases, including an extended analysis of the NHANES III cohort with additional years of follow-up (Lanphear et al., 2018) and analyses of more recent NHANES cycles (Byun et al., 2020; Duan et al., 2020; van Bemmel et al., 2011). In addition to NHANES analyses, another analysis of participants from a nationally representative survey [KNHANES; (Byun et al., 2020)] and a smaller prospective cohort study of hemodialysis patients (Lin et al., 2011) provide evidence of an association between BLLs and total (non-accidental) mortality. These findings are supported by a quasi-experimental study that reported a decline in county-level all-cause mortality rates following the phase out of leaded gasoline in automotive racing (Hollingsworth and Rudik, 2021). Recent studies continue to include populations with low mean blood Pb concentrations, but do not address potentially large differences in past versus current exposures. Thus, there is remaining uncertainty as to the specific timing, duration, frequency, and level of Pb exposure that contributed to the observed associations. The observed associations between BLLs and total mortality are large in magnitude (Figure 9-3), though uncertainty in the levels of Pb exposure that contributed to the observed associations may also introduce uncertainty in the magnitude of the effect. One recent study examined the C-R relationship between blood Pb and total mortality (Lanphear et al., 2018). Similar to Menke et al. (2006), Lanphear et al. (2018) observed generally sigmoidal spline curves with some evidence of attenuation of the C-R relationship below 2.5 µg/dL (Figure 9-4).

The body of evidence for total mortality is supported by strong evidence of consistent positive associations with cardiovascular mortality (Section 4.10, which comprises a large portion of total mortality). In addition to a greater number of studies reporting consistent associations between BLLs and cardiovascular mortality, the evidence base includes a wider range of study populations and expanded evidence on the C-R relationship that generally supports a linear relationship with no evidence of a threshold. There is coherence of effects across the scientific disciplines (i.e., animal toxicological,

controlled human exposure, and epidemiologic studies) and biological plausibility for Pb-related cardiovascular disease (Appendix 4), which supports the Pb-mortality relationship.

Overall, recent epidemiologic studies build upon evidence from the 2013 Pb ISA and provide largely consistent evidence of an association between biomarkers of Pb exposure and total mortality. A few uncertainties remain in the evidence base, including a limited number of studies and analyses of similar or overlapping study populations. However, these studies are supported by more robust evidence of Pb-related cardiovascular mortality, which comprises nearly 33% of total mortality. In addition, evidence for cardiovascular morbidity provides biologically plausible pathways through which Pb exposure could result in mortality. There is also very limited evidence that Pb exposure is positively associated with other causes of mortality, including AD and infection. Biological plausibility for these outcomes is demonstrated by pathways leading from Pb exposure to neurodegenerative disease and immunosuppression, respectively. However, although there is toxicological evidence that developmental exposure to Pb increases the expression of proteins related to AD, the epidemiologic evidence relating Pb exposure to incident AD remains limited. The evidence for Pb-associated all-cause and cardiovascular mortality and strong supporting evidence for Pb-associated cardiovascular effects indicates **there is sufficient evidence to conclude that there is a *causal relationship* between Pb exposure and total (nonaccidental) mortality.** The key evidence, as it relates to the causal framework, is summarized in Table 9-3.

Table 9-3 Summary of evidence for a causal relationship between Pb exposure and total mortality.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent epidemiologic evidence from multiple studies at relevant BLLs	Increases in total mortality in multiple nationally represented studies. Total mortality associations are further supported by increases in cardiovascular mortality conducted within nationally represented studies.	(Hollingsworth and Rudik, 2021; Byun et al., 2020; Duan et al., 2020; Lanphear et al., 2018; van Bemmel et al., 2011; Menke et al., 2006)	Median, Mean, and Geometric Mean BLLs: 1.49–2.71 μg/dL
Epidemiologic evidence supports no evidence of a threshold between Pb biomarkers of exposure and total mortality at the concentration ranges examined	Recent studies provide direct evidence of a linear or sigmoidal, no-threshold C-R relationship at lower concentrations of BLLs.	(Menke et al., 2006) (Lanphear et al., 2018)	Mean BLL: 2.58 μg/dL Geometric Mean BLL: 2.71 μg/dL
Biological plausibility from cardiovascular morbidity evidence	Strong evidence for coherence of effects across scientific disciplines and evidence for a range of cardiovascular effects in response to increases in biomarkers of Pb exposure, especially for increases in blood pressure and hypertension. The collective body of cardiovascular morbidity evidence provides biological plausibility for a relationship between biomarkers of Pb exposure and cardiovascular mortality, which comprises ~33% of total mortality.	Appendix 4	

BLLs = blood lead levels; C-R = concentration-response; Pb = lead.

[a]Based on aspects considered in judgments of causality and weight-of-evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).

[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.

[c]Describes the Pb biomarker levels at which the evidence is substantiated.

9.9 Evidence Inventories – Data Tables to Summarize Study Details

Table 9-4 Epidemiologic studies of exposure to Pb and hepatic effects.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Direct Evaluation of Liver Injury					
†Zhai et al. (2017) Yangtze River Delta Region China 1 yr (2014) Cross-sectional	SPECT-China n = 2011 General population, ≥18 yr old with no history of excessive alcohol consumption or viral hepatitis	Blood Pb measured in venous whole blood using atomic absorption spectrometry Age at measurement: ≥18 yr old Median: Males: 5.29 µg/dL Females: 4.49 µg/dL 25th: Males: 3.61 µg/dL Females: 2.98 µg/dL 75th: Males: 7.28 µg/dL Females: 6.59 µg/dL	Nonalcoholic fatty liver disease Two doctors performed abdominal ultrasounds and categorized liver status as normal or fatty using predefined criteria Age at outcome: ≥18 yr old	Age, region, education, current smoking, current drinking, ALT, diabetes, waist circumference, BMI, LDL cholesterol, HDL cholesterol, triglycerides, total cholesterol, and blood cadmium levels	**ORs for NAFLD prevalence across blood Pb quartiles** *Males* Q1: Ref. Q2: 1.70 (0.84, 3.42) Q3: 1.84 (0.88, 3.86) Q4: 2.17 (0.99, 4.75) *Females* Q1: Ref. Q2: 1.38 (0.96, 2.00) Q3: 1.50 (1.02, 2.18) Q4: 1.61 (1.08, 2.41)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Werder et al. (2020) Gulf Region United States 2012–2013 Cross-sectional	Gulf Long-Term Follow-up Study n = 214 Non-smoking ≥30 year old male oil spill response workers and oil spill safety trainees with no history of liver disease or heavy alcohol use	Blood Pb measured in venous whole blood using solid-phase micro-extraction with gas chromatography/mass spectrometry Age at measurement: >30 Mean: 1.82 (1.76)	Liver injury Cytokeratin 18 (CK18 M65 and CK18 M30) Age at outcome: >30	Age, race, alcohol consumption, serum cotinine, BMI, diabetes dx, and education	**Change in CK18 M65 (U/L)** 2.4 (−12.69, 17.49) **Change in CK18 M30 (U/L)** 21.7 (9.94, 33.46)
†Chung et al. (2020) South Korea 2 yr (2016–2017) Cross-sectional	KNHANES n = 4420 Adults, ≥20 yr old	Blood Pb measured in venous whole blood using GFAAS Age at measurement: ≥20 yr old Mean: 1.81 µg/dL Max: 20.16 µg/dL	Hepatic steatosis and fibrosis Hepatic steatosis (HS) as indicated by an HS Index = 36 (8 × (ALT/AST ratio) + BMI (+2 if female; +2 if had diabetes mellitus)). Hepatic Fibrosis (HF) as indicated by a fibrosis-4 (FIB-4) score >2.67 ((age × AST level)/(platelet level × v(ALT level)). Age at outcome: ≥20 yr old	Age, smoking status, alcohol consumption, hypertension status, obesity status, diabetes status, hypertriglyceridemia status, blood Hg, blood Cd.	**ORs** **Hepatic Steatosis** *Men* 0.83 (0.66, 1.03) *Women* 0.98 (0.80, 1.19) **Fibrosis** *Men* 0.70 (0.44, 1.09) *Women* 0.72 (0.42, 1.26)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Reja et al. (2020) United States 5 yr (2011–2016) Cross-sectional	NHANES n = 2499 General population ≥20 yr old with nonalcoholic fatty liver disease (NAFLD)	Blood ≥20 yr old Mean: 1.01 µg/dL 75th: 1.62 µg/dL	Liver fibrosis NAFLD Fibrosis Score Age at outcome: ≥20 yr old (concurrent with exposure)	Age, gender, waist circumference, hypertension, liver function test, hemoglobin A1c, triglycerides, smoking, and PIR	**ORs (NAFLD Fibrosis Score >0.676)** Q1: Reference Q2: 2.79 (1.39, 5.63) Q3: 3.74 (2.01, 6.96) Q4: 5.93 (2.88, 12.24)
Serum Biomarkers of Liver Function					
†Pollack et al. (2015) Buffalo, NY United States 2 menstrual cycles (8 visits per cycle) (2005–2007) Cohort	BioCycle n = 259 Premenopausal women followed for 2 menstrual cycles	Blood Pb measured in venous whole blood using ICP-MS Age at measurement: 27.4 (SD: 8.2) 1.03 µg/dL	ALT, ALP, AST, Bilirubin ALT (U/L), ALP (U/L), AST (U/L), Bilirubin (mg/dL) Age at outcome: 27.4 (SD: 8.2)	Linear mixed models adjusted for age, BMI, race, average calories, alcohol intake, smoking, and cycle day	**AST (% change):** 5.02 (−1.36, 11.41) **ALT (% change):** 6.39 (3.07, 9.72) **ALP (% change):** 2.14 (−5.05, 9.33)
†Chen et al. (2019) Guangdong China 1 yr (2015) Cross-sectional	n = 267 Hospitalized patients from two regions in Guangdong (one e-waste polluted area and a matched control area). Patients with heart or kidney disease, those taking drugs with hepatic toxicity, and those with a history of alcohol consumption or smoking were excluded.	Blood Pb was measured in venous whole blood using GFAAS Age at measurement: 4 to 85 yr old Median: Exposed: 8.7 µg/dL; Control: 5.1 µg/dL 75th: Exposed: 12.2 µg/dL; Control: 8.4 µg/dL	Abnormal liver function Abnormal liver function defined as two transminases (AST, ALT, or GGT) above normal range or one at least two times higher than normal range (40 U/L) Age at outcome: 4 to 85 yr old (concurrent with exposure)	Age, gender, hepatic disease, RBC, Hb, and platelets	**OR for Prevalence of Abnormal Liver Function** 1.94 (1.00, 3.73)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Christensen et al. (2013) United States 2 yr (2003–2004) Cross-sectional	NHANES n = 1345 General population, ≥12 yr old. No chronic hepatitis or liver disease, and no high alcohol intake.	Blood Pb measured in venous whole blood using ICP-MS Age at measurement: ≥12 yr old Mean NR	Liver function Serum ALT Age at outcome: ≥12 yr old	Sex, Race/Ethnicity, Age, PIR, BMI	**Change in ALT (U/L)** Q1: Reference Q2: −0.068 (−0.14, 0.004) Q3: −0.039 (−0.113, 0.035) Q4: −0.103 (−0.185, −0.021)
†Obeng-Gyasi (2019) United States NHANES 2009–2016 Cross-sectional	NHANES n = 7,730 young adults (18–44); 5,744 middle-aged adults (45–65) General population; ages 18–65	Blood BLL measured in venous whole blood using ICP-MS Age at measurement: ≥18 yr old Mean: Young adults: 1.03 µg/dL Middle-aged adults: 1.62 µg/dL	GGT (U/L) Serum GGT (U/L) Age at outcome: ≥18 yr old	Gender, BMI, income, ethnicity, and alcohol consumption	**ORs (GGT >18 U/L)** *Young Adults* 1.94 (1.65, 2.28) *Middle-Aged Adults* 1.34 (1.14, 1.58)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Serum Lipids					
†Peters et al. (2012) United States Blood Pb measured between 1999–2008; Serum lipids measured 3 to 4 yr after blood Pb Cohort	Normative Aging Study n = 426 Older male Veterans	Blood, Bone Blood Pb measured in venous whole blood using GFAAS Mean: 4.01 ± 2.30 µg/dL	Serum lipids Triglycerides, total cholesterol, HDL-C, LDL-C Age at outcome: 3 to 4 yr after blood Pb	Age at baseline, yr between baseline and outcome, education, BMI, alcohol intake, smoking status, pack-yr of smoking, hypertension status, and statin use	**ORs** *Total C (≥200 mg/dL)* 1.08 (0.99, 1.19) *LDL-C (≥130 mg/dL):* 1.02 (0.91, 1.15) *HDL-C (<40 mg/dL):* 0.90 (0.80, 1.00) *Triglycerides (≥200 mg/dL*): 0.99 (0.87, 1.13)
†Xu et al. (2021) United States NHANES 2005–2016 Cross-sectional	NHANES n = 7457 General population; Ages 20 to 79 yr old	Blood Pb measured in venous whole blood samples using ICP-MS Age at measurement: Mean (SD): 43.68 (15.02) yr GM: 1.23 µg/dL	Dyslipidemia Total cholesterol, LDL-C, non-HDL-C, triglycerides Age at outcome: Mean (SD): 43.68 (15.02)	Age, sex, race, BMI, education status, smoking status, alcohol consumption, physical activity, PIR, systolic blood pressure, serum cotinine, and Cd	**RRs** *Total C (≥200 mg/dL)* 1.01 (1.00, 1.01) *non-HDL-C (≥160 mg/dL)* 1.00 (0.99, 1.01) *LDL-C (≥130 mg/dL)* 1.02 (1.00, 1.04) *Triglycerides (≥200 mg/dL*) 0.99 (0.98, 1.00)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Lee and Kim (2016) Korea 2005–2010 Cross-Sectional	Korean National Health and Nutrition Examination Survey (KNHANES) n = 7559 Korean adults aged 20+	Blood Pb measured in venous whole blood using GFAAS Age at measurement Mean (SD): No MetS: 42.32 (0.294) yr; MetS: 48.36 (0.574) yr Geometric Mean (SD) No MetS: 2.73 (0.024) µg/dL; MetS: 2.96 (0.049) µg/dL	Serum Lipids Low HDL cholesterol (<40 mg/dL in women or <50 mg/dL in men); Elevated serum triglycerides (=150 mmHg) Age at outcome same as age at exposure assessment	Age, BMI, residence area, education level, smoking and drinking status, exercise, serum aspartate aminotransferase, serum alanine aminotransferase	**ORs** *HDL-C ≤40 mg/dL* 0.84 (0.66, 1.08) *TG ≥150 mg/dL* 1.12 (0.90, 1.39)
†Ettinger et al. (2014) Kumasi (Ghana), Cape Town (South Africa), Victoria (Seychelles), Kingston (Jamaica), Maywood, IL (United States) Ghana, South Africa, Seychelles, Jamaica, United States 2010–2014 Cross-sectional	Modeling the Epidemiologic Transition Study (METS) n = 150 Adults of African descent from 5 countries of varying social and economic development	Blood Pb measured in venous whole blood using ICP-MS Age at measurement Mean (SD): Males: 34.7 (6.0) yr; Females: 35.2 (6.2) yr Geometric Mean: 1.55 µg/dL Median: 1.66 µg/dL 75th: 2.6 µg/dL Max: 31.82 µg/dL	HDL and LDL cholesterol, blood pressure, triglycerides. Height and weight were measured by physical examination. Fasting glucose was measured in blood. Further outcome assessment details not provided. Age at outcome is the same as age at exposure assessment	Age, sex, site location, marital status, education, paid employment, alcohol use, fish intake	**ORs (>1.66 µg/dL vs. ≤1.66 µg/dL blood Pb)** LDL-C (≥2.59 mmol/L) 0.680 (0.289, 1.597) Triglycerides (≥1.7 mmol/L) 0.09 (0.030, 0.250) HDC-C (<1.03 [males]; <1.29 [females] mmol/L) 1.93 (0.740, 5.020)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Liu et al. (2020) Mexico City Mexico Pregnant women recruited between 1997–1999 and 2001–2003, follow-up among offspring began in 2015 Cohort	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) n = 369 Mother/child pairs from a birth cohort study of pregnant women from 2 public hospitals serving low to moderate-income populations	Blood Maternal Blood Pb measured in venous whole blood using GFAAS Age at measurement: Maternal age (SD): 26.7 (5.6) yr Mean of prenatal blood: 4.3 µg/dL	Serum lipids Total cholesterol, triglycerides, HDL-C, LDL-C Age at outcome Child's age (SD): 13.7 (1.9) yr	Child age, sex, BMI, number of siblings at birth, maternal age, marital status education, smoking history	**Change in Z-score (≥5 µg/dL vs. <5 µg/dL blood Pb)** *Triglycerides* 0.58 (−0.05, 1.20) *Total cholesterol* −0.76 (−1.38, −0.13) *HDL-C* −0.64 (−1.28, 0.01) *LDL-C* −0.96 (−1.59, −0.33)
†Kupsco et al. (2019) Mexico City Mexico Maternal blood tested for metals in 2nd trimester, children assessed at age 4–6 Cohort	Research in Obesity, Growth Environment and Social Stress (PROGRESS) birth study n = 548 Mother/child pairs from a birth cohort study	Blood Maternal blood Pb measured second trimester in venous whole blood samples using ICP-MS Age at measurement Mean (SD): 28 (5.6) yr Mean (SD): 3.7 (2.7) µg/dL Max: 18 µg/dL	Serum lipids Triglycerides and non-HDL cholesterol Age at outcome: Mean: 4.8 yr; Range: 4–6 yr	Birth weight, gestational age, prepregnancy BMI, education, SES, parity, environmental tobacco smoke	**Change in Z-score** *Triglycerides* 0.018 (−0.028, 0.064) *non-HDL-C* −0.015 (−0.058, 0.028)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Xu et al. (2017) United States 1999–2012 Cross-sectional	NHANES n = 11662 General population; 12–19 yr old	Blood Pb measured in venous whole blood using ICP-MS Age at measurement: 12–19 yr Mean (SD): 1.17 (1.20) µg/dL	Serum lipids Total cholesterol, triglycerides, HDL-C, LDL-C Age at outcome: 12–19 yr	Age, gender, ethnicity, PIR, waist circumference, serum cotinine, and physical activity	**% Increase** *Total Cholesterol* 0.6% (−0.1%, 1.3%) *HDL-C* 0.3% (−0.5%, 1.1%) *LDL-C* 2.3% (0.3%, 4.2%) *Triglycerides* −1.1% (−2.4%, 0.2%)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; Cd = cadmium; CI = confidence interval; CK18 = cytokeratin 18; ELEMENT = Early Life Exposures in Mexico to Environmental Toxicants; FIB-4 = fibrosis-4; GFAAS = graphite furnace atomic absorption spectrometry; GGT = gamma-glutamyl transferase; Hb = hemoglobin; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; HF = hepatic fibrosis; HS = hepatic steatosis; ICP-MS = inductively coupled plasma mass spectrometry; KNHANES = Korean National Health and Nutrition Examination Survey; LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; MetS = metabolic syndrome; METS = Modeling the Epidemiologic Transition Study; NAFLD = nonalcoholic fatty liver disease; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OR = odds ratio; Pb = lead; PIR = poverty-income-ratio; PROGRESS = Programming Research in Obesity, Growth Environment and Social Stress; RBC = red blood cell; RR = risk ratio; SD = standard deviation; SES = socioeconomic status; SPECT = single photon emission computed tomography; Q = quartile; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.

†Studies published since the 2013 Integrated Science Assessment for Lead.

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Table 9-5 Animal toxicological studies of exposure to Pb and hepatic effects.

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL As Reported (µg/dL)	Endpoints Examined
Berrahal et al. (2011)	Rat (Wistar) 0 mg/L Pb Acetate, M, n = 12–16 50 mg/L Pb Acetate, M, n = 12–16	PND 40, 65	Oral, drinking water	1.76 ± 0.33 µg/100 mL for 0 mg/L Pb Acetate, 12.67 ± 1.68 µg/100 mL for 50 mg/mL Pb Acetate - PND 40 2.06 ± 0.35 µg/100 mL for 0 mg/L Pb Acetate, 7.49 ± 0.78 µg/100 mL for 50 mg/mL Pb Acetate - PND 65	Plasma Alanine Aminotransferase (ALT), Plasma Aspartate Aminotransferase (AST), Plasma Alkaline Phosphatase (ALP)
Li et al. (2017)	Mouse (BALBc) 0 mg/kg Pb Acetate, F, n = 8 100 mg/kg Pb Acetate, F, n = 8	Day 29 from exposure start	Oral, gavage	0.43 ± 0.05 µg/L for 0 mg/kg Pb Acetate 302.20 ± 25.32 µg/L for 100 mg/kg Pb Acetate	Malondialdehyde (MDA) Levels, Glutathione (GSH), Glutathione Peroxidase (GSH-PX), Total Superoxide Dismutase (T-SOD)
Liu et al. (2013)	Rat (Wistar) 0 ppm Pb, M, n = 10 500 ppm Pb, M, n = 10	Exposure d 75	Oral, drinking water	0.0448 µg/dL for 0 ppm 0.450 µg/dL for 500 ppm	Plasma Alanine Aminotransferase (ALT), Plasma Aspartate Aminotransferase (AST), GRP78 Protein Levels, Reactive Oxygen Species Activity, TBARS Levels, Total Antioxidant Capacity, ATF6 Protein Levels, ATF4 Protein Levels, P-IRE1 Protein Levels, T-IRE1 Protein Levels, XBP-1 Protein Levels, P-JNK Protein Levels, JNK Protein Levels, PI3K Protein Levels, P-Akt Protein Levels, T-Akt Protein Levels

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL As Reported (µg/dL)	Endpoints Examined
Long et al. (2016)	Mouse (Kunming) 0% Pb Acetate, M, n = 7 0.2% Pb Acetate, M, n = 21	Six weeks exposure	Oral, drinking water	36.42 ± 17.48 µg/L for 0% Pb Acetate, 214.64 ± 36.24 µg/L for 0.2% Pb Acetate	Plasma Alkaline Phosphatase (ALP), Plasma Alanine Aminotransferase (ALT), Plasma Aspartate Aminotransferase (AST), Malondialdehyde (MDA) Levels, Glutathione (GSH), Glutathione Peroxidase (GSH-PX), Total Superoxide Dismutase (T-SOD), Apoptosis, Bcl-2 Gene Expression, Bax Gene Expression, Bcl-2 Protein Levels, Bax Protein Levels, Nrf2 Protein Levels, HO-1 Protein Levels, Gamma-GCS Protein Levels, Nrf-2 Gene Expression, HO-1 Gene Expression, Gamma-GCS Gene Expression, GRP78 Protein Levels, Grp78 Gene Expression, Chop Gene Expression
Andjelkovic et al. (2019)	Rat (Wistar) 0 mg Pb Acetate per kg bw, M, n = 8 150 mg Pb Acetate per kg bw, M, n = 6	24 h posttreatment	Oral, gavage	25 µg/L for 0 mg Pb Acetate per kg bw, 290 µg/L for 150 mg Pb Acetate per kg bw	Plasma Aspartate Aminotransferase (AST), Plasma Alanine Aminotransferase (ALT), Plasma Alkaline Phosphatase (ALP), Lactate Dehydrogenase (LDH), Malondialdehyde (MDA) Levels, Advanced Oxidation Protein Products Level (AOPP), Total Thiol (-SH) Groups Level, Prooxidative-Antioxidative Balance (PAB), Total Superoxide Dismutase (T-SOD)

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL As Reported (µg/dL)	Endpoints Examined
Dumková et al. (2017)	Mouse (ICR) 0 particles/cm^3, F, n = 10 1.23 × 10^6 particles/cm^3, F, n = 10	Week 6 of exposure	Inhalation	1.1 µg/dL for 0 particles/cm^3, 13.2 µg/dL for 1.23 × 10^6 particles/cm^3, F, n = 10	Histopathology, Proliferating Cell Nuclear Antigen (PCNA) Immunohistochemistry, Apoptotic Cells (TUNEL-Positive), Na-K ATPase Expression
Barkaoui et al. (2020)	Rat (Wistar) 0 g/L Pb Acetate, M, n = 6 1 g/L Pb Acetate, M, n = 6	Exposure day 30	Oral, drinking water	11.1 ± 0.12 µg/dL for 0 g/L Pb Acetate 23.8 ± 0.912 µg/dL for 1 g/L Pb Acetate	GSH, CAT, T-SOD, GSH-PX, MDA Levels, Histopathology, CAT qRT-PCR, GPx qRT-PCR, SOD qRT-PCR, NF-κB qRT-PCR, IL-6 qRT-PCR, TNF-alpha qRT-PCR
Gao et al. (2020)	Rat (Sprague Dawley) 0 mg/kg bw, Pb2+, M/F, n = 10 5 mg/kg bw, Pb2+, M/F, n = 10	Four weeks postexposure	Oral, gavage	0.02 mg/kg for 0 mg/kg bw, Pb2+, 0.1 ± 0.03 mg/kg for 5 mg/kg bw, Pb2+	T-SOD, CAT, MDA Levels, GSH, Histopathology, Plasma AST, Plasma ALT, Cr, BUN
Dumková et al. (2020b)	Mouse (Not Specified) 0 µg/m^3 PbO NPs, F, n = NR, 2, 6, 11 wk 78.0 µg/m^3 PbO NPs, F, n = NR, 6 wk followed by 0 µg/m^3 PbO NPs, 5 wk 78.0 µg/m^3 PbO NPs, F, n = NR, 2, 6, 11 wk	Exposure week 2, 6, 11	Inhalation	0 µg/dL for 0 µg/m^3 PbO NPs, F, n = NR, 2, 6, 11 wk 2.7 µg/dL for 78.0 µg/m^3 PbO NPs, F, n = NR, 6 wk followed by 0 µg/m^3 PbO NPs, 5 wk 10.4 µg/dL for 78.0 µg/m^3 PbO NPs - 2 wk 14.8 µg/dL for 78.0 µg/m^3 PbO NPs - 6 wk 17.4 µg/dL for 78.0 µg/m^3 PbO NPs - 11 wk	Plasma Alkaline Phosphatase (ALP), Plasma Alanine Aminotransferase (ALT), Plasma Aspartate Aminotransferase (AST), Cr

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL As Reported (µg/dL)	Endpoints Examined
Dumková et al. (2020a)	Mouse (CD1), (ICR) 0 µg/m^3 Pb(NO3)2 NPs, F, n = 10 - 3 d, 2, 6, 11 wk 68.6 µg/m^3 Pb(NO3)2 NPs, F, n = 10 - 3 d, 2, 6, 11 wk 68.6 µg/m^3 Pb(NO3)2 NPs, F, n = 10 - 6 wk, followed by 0 µg/m^3 Pb(NO3)2 NPs - 5 wk	Exposed 3 d, 2, 6, 11 wk	Inhalation	0 µg/dL for 0 µg/m^3 - all groups 3.1 µg/dL for 68.6 µg/m^3 - 3 d 4.0 µg/dL for 68.6 µg/m^3 - 2 wk 4.7 µg/dL for 68.6 µg/m^3 - 6 wk 8.5 µg/dL for 68.6 µg/m^3 - 11 wk 1.0 µg/dL for 68.6 µg/m^3 – 6 wk followed by 0 µg/m^3 - 5 wk	Histopathology, NF-kB qRT-PCR, TNF-alpha qRT-PCR, IL-1 alpha, IL-1 beta, IL-6 qRT-PCR, TGFbeta1, Plasma Alkaline Phosphatase (ALP)
Laamech et al. (2017)	Mouse (IOPS) 0 mg/kg body weight/day Pb Acetate, M, n = 12 5 mg/kg body weight/day Pb Acetate, M, n = 12	Exposure day 40	Oral, gavage	0.010 µg/mL for 0 mg/kg body weight/day Pb Acetate, 0.18 µg/mL for 5 mg/kg body weight/day Pb Acetate	Histopathology, Plasma Alanine Aminotransferase (ALT), Plasma Aspartate Aminotransferase (AST), Total Cholesterol (TC), Total Bilirubin (TB), Malondialdehyde (MDA) Levels, Protein Carbonyl (PCO), Glutathione (GSH), Catalase, Total Superoxide Dismutase (T-SOD), Glutathione Peroxidase (GSH-PX)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AOPP = advanced oxidation protein products; AST = aspartate aminotransferase; BUN = blood urea nitrogen; BLL = blood lead levels; CAT = catalase; Cr = chromium; D = day(s); GSH = glutathione; GSH-PX = glutathione peroxidase; LDH = lactate dehydrogenase; h = hour; MDA = malondialdehyde; NF-κB = nuclear factor kappa B; NP = nanoparticle; PAB = prooxidative-antioxidative balance; Pb = lead; PCNA = proliferating cell nuclear antigen; PCO = protein carbonyl; PND = postnatal day; qRT-PCR = real-time quantitative reverse transcription-polymerase chain reaction; TB = total bilirubin; TBARS = thiobarbituric acid reactive substance; TC = total cholesterol; T-SOD = total superoxide dismutase; wk = week(s).

Table 9-6 Epidemiologic studies of exposure to Pb and metabolic effects.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Diabetes and Insulin Resistance - Adults					
†Moon (2013) Korea 2007–2012 Cross-Sectional	KNHANES n = 3,184 Adults aged ≥30 yr	Blood Pb was measured in venous whole blood using GFAAS Age at measurement Mean (SD): No diabetes: 49.4 (12.4) yr Diabetes: 58.8 (10.9) yr Geometric Mean (SD): No diabetes: 2.41 (1.52) µg/dL Diabetes: 2.47 (1.59) µg/dL	Diabetes, HOMA-IR, HOMA-ß (%), fasting insulin (mIU/L) Age at outcome is the same as age at exposure assessment	Age, sex, region, smoking, alcohol consumption, regular exercise, BMI (sex-stratified analyses only)	**OR (95% CI) for prevalent diabetes across blood Pb quartiles:** Q1 (GM 1.43 µg/dL): Reference Q2 (GM 2.13 µg/dL): 0.91 (0.64, 1.29) Q3 (GM 2.74 µg/dL): 0.76 (0.53, 1.09) Q4 (GM 4.08 µg/dL): 0.75 (0.52, 1.08); **Change in HOMA-IR, HOMA-ß, and Fasting Insulin per unit increase in log-blood Pb** *log(HOMA-IR)* Men: −0.04 (−0.10, −0.02), Women: −0.04 (−0.09, −0.01) log(HOMA-ß) Men: −0.05 (−0.11, 0.01), Women: −0.05 (−0.10, 0.01) *Fasting insulin (mIU/L)* Men: −0.53 (−1.23, 0.16) Women: −0.27 (−1.00, 0.46)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Hansen et al. (2017) Nord-Trondelag County Norway 2006–2008 Nested Case-Control	Nord-Trondelag Health Study (HUNT3) n = 883 Adults aged ≥20 yr. Cases (n = 128) were HUNT3 participants diagnosed with diabetes. Controls (n = 755) were age- and sex-matched HUNT3 participants without diabetes.	Blood Pb was measured in venous whole blood using ICP-MS Age at measurement Mean (SD): Cases: 61.4 (14.1) yr Controls: 65.2 (10.3) yr Median (10th–90th percentile): Cases: 19.9 (10.8–38.0) µg/L Controls: 19.4 (11.0–37.2) µg/L	Type 2 diabetes Individuals were screened for diabetes at a physical examination using an oral glucose tolerance test. Diagnosis with type 2 diabetes was defined as having fasting serum glucose ≥7.0 mmol/L and/or 2 h glucose ≥11.1 mmol/L as well as glutamic acid decarboxylase antibodies (GADA) <0.08 ai. Age at outcome is the same as age at exposure assessment	Age, sex, BMI, waist-to-hip ratio, education, income, smoking, family history of diabetes	**OR (95% CI) for prevalent type 2 diabetes Q4 vs Q1:** 1.12 (0.58, 2.16)
†Simić et al. (2017) Norway 2006–2008 Nested Case-Control	Nord-Trondelag Health Study (HUNT3) n = 945 Adults aged ≥20 yr. Cases (n = 270) were HUNT3 participants diagnosed with type 2 diabetes. Controls (n = 615) were age- and sex-matched participants without diabetes.	Blood Pb was measured in venous whole blood using ICP-MS Age at measurement Mean (SD): Cases: 59.2 (12.2) yr Controls: 65.4 (10.6) yr Median (10th–90th percentile): Cases: 16.4 (9.7–35.2) µg/L Controls: 20.2 (11.2–37.9) µg/L	Type 2 diabetes Type 2 diabetes was defined as self-reported diabetes excluding type I diabetes as indicated by GADA index, measured in blood at a physical examination. Age at outcome is the same as age at exposure assessment	BMI, waist-to-hip ratio, first-degree family history of diabetes, smoking habits, area, education, economic status, alcohol consumption, blood calcium	**OR (95% CI) for prevalent type 2 diabetes Q4 vs Q1:** 0.24 (0.13, 0.47)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Diabetes and Insulin Resistance - Adolescents					
†Liu et al. (2020) Mexico City Maternal enrollment: 1997–1999 and 2001–2003 Child follow-up: 2015 Prospective Birth Cohort	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) Study n = 369 Adolescents aged 10–18 yr	Blood Maternal Pb (1st trimester) was measured in venous whole blood using GFAAS Age at measurement Mean maternal age in 1st trimester of pregnancy (SD): 26.7 (5.6) yr Geometric Mean (95% CI): 4.3 (4.0, 4.6) µg/dL	Fasting serum glucose Z-score (mg/dL), HOMA-IR Z-score Serum fasting glucose (mg/dL) was measured using an enzymatic method. Serum insulin (µU/mL) was measured using immunoturbidimetric assay. HOMA-IR was calculated as insulin (µU/mL)*glucose (mg/dL)/405. Age at outcome Mean child age (SD): 13.7 (1.9) yr	Child age, sex, BMI z-score, number of siblings at birth, maternal age, marital status, education, smoking history	**Change in mean fasting glucose and HOMA-IR Z-scores for maternal blood Pb ≥5 µg/dL vs. maternal blood Pb <5 µg/dL** *Fasting glucose z-score* All: −0.05 (−0.69, 0.60) Boys: −0.05 (−0.34, 0.25) Girls: −0.06 (−0.35, 0.23) *HOMA-IR z-score* All: −0.11 (−0.63, 0.42) Boys: −0.04 (−0.28, 0.20) Girls: 0.04 (−0.19, 0.27)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Metabolic Syndrome (MetS) and Its Components					
†Moon (2014) Korea 2007–2012 Cross-Sectional	KNHANES n = 3,950 Adults aged ≥20 yr	Blood Pb measured in venous whole blood using GFAAS. Age at measurement Mean (SD): No MetS: 42.7 (14.6) yr; MetS: 54.4 (12.8) yr Mean (SD) No MetS: 2.08 (1.00) µg/dL; MetS: 2.50 (1.01) µg/dL	Metabolic syndrome MetS was defined as meeting at least 3 of the following: (1) elevated blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg or current use of blood pressure medication), (2) low HDL cholesterol (<40 mg/dL in women or <50 mg/dL in men), (3) elevated serum triglycerides (≥150 mmHg) or current use of antidyslipidemia medication, (4) elevated fasting plasma glucose levels, (5) abdominal obesity (waist circumference ≥90 cm in men or ≥85 cm in women). Age at outcome is the same as age at exposure assessment	Age, sex, region, smoking, alcohol consumption, regular exercise, BMI	**OR (95% CI) for prevalent MetS across blood Pb quartiles** Q1 (GM 1.23 µg/dL): Reference Q2 (GM 1.90 µg/dL): 0.84 (0.62, 1.13) Q3 (GM 2.51 µg/dL): 1.21 (0.90, 1.62) Q4 (GM 3.79 µg/dL): 1.07 (0.79, 1.45)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Rhee et al. (2013) Korea 2008 Cross-Sectional	KNHANES n = 1,405 Nationally representative survey of Korean adults	Blood Pb was measured in venous whole blood using GFAAS Age at measurement Mean (SD): No MetS: 40.3 (13.7) yr MetS: 47.1 (13.3) yr Median (25th–75th): 2.35 (1.74–3.06) µg/dL 75th: 3.06 µg/dL Max: 19.43 µg/dL	MetS, abdominal circumference, triglycerides, HDL cholesterol, fasting glucose MetS was defined using the Modified National Cholesterol Education Program Adult Treatment Panel III Criteria, with the exception of waist circumference measurement cut-offs of ≥90 cm for males and ≥85 cm for females based on criteria from the Korean Society for the Study of Obesity. TC, triglycerides, HDL cholesterol, and fasting plasma glucose were assessed using an automated analyzer with enzymatic assays. Abdominal circumference was measured by a professional. Age at outcome is the same as age at exposure assessment	Age, sex, smoking, education, TC, creatinine, AST, AMT, fasting serum insulin	**OR for MetS prevalence across log-transformed Pb quartiles** Q1 (≤1.73 µg/dL): Reference Q2 (1.74–2.35 µg/dL): 1.56 (0.90, 2.71) Q3 (2.35–3.06 µg/dL): 1.63 (0.94, 2.83) Q4 (≥3.07 µg/dL): 2.57 (1.46, 4.51) **Change in outcomes per unit increase in log-transformed Pb** Abdominal circumference 0.051 (−0.001, 0.107) cm Triglycerides 0.080 (0.023, 0.137) mg/dL HDL Cholesterol 0.033 (−0.020, 0.086) mg/dL Fasting Glucose 0.019 (−0.029, 0.067) mg/dL

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Bulka et al. (2019) United States 2011–2014 Cross-Sectional	NHANES n = 1,088 Nationally representative survey of U.S. adults	Blood Pb was measured in venous whole blood using ICP-MS Age at measurement: 20–60 yr Mean (SD) NHANES 2011–2012: 1.17 (0.04) µg/dL; NHANES 2013–2014: 1.00 (0.03) µg/dL	MetS, triglycerides, HDL cholesterol, blood glucose, abdominal obesity MetS was defined as meeting at least 3 of the following: (1) elevated blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg or current use of blood pressure medication), (2) low HDL cholesterol (<40 mg/dL in women or <50 mg/dL in men), (3) elevated serum triglycerides (≥150 mmHg) or current use of antidyslipidemia medication, (4) elevated fasting plasma glucose levels, (5) abdominal obesity (waist circumference ≥90 cm in men or ≥85 cm in women). Waist circumference (cm) was measured at the physical examination by a trained professional. Serum HDL (µg/dL), triglycerides (mg/dL), and blood glucose (mg/dL) were measured in blood samples obtained in the morning following an overnight fast. Age at outcome: 20–60 yr	Age, race/ethnicity, family income-poverty ratio, total caloric intake, educational attainment, smoking status, average number of drinks per day past year, physical activity status, survey cycle, BMI (excluding abdominal obesity analysis), serum cotinine	**PRs for outcomes across Pb quartiles** *MetS* Q1 (0.18−0.70 µg/dL): Reference Q2 (0.71–1.05 µg/dL): 0.90 (0.73, 1.11) Q3 (1.06–1.63 µg/dL): 0.84 (0.69, 1.05) Q4 (1.64–15.98 µg/dL): 0.81 (0.64, 1.03) *High Triglycerides* Q1: Reference Q2: 0.85 (0.72, 0.99) Q3: 0.76 (0.64, 0.92) Q4: 0.82 (0.67, 1.01) *Low HDL* Q1: Reference Q2: 0.90 (0.76, 1.07) Q3: 0.79 (0.65, 0.97) Q4: 0.73 (0.59, 0.89) *High Glucose* Q1: Reference Q2: 1.03 (0.86, 1.23) Q3: 0.86 (0.68, 1.08) Q4: 0.95 (0.77, 1.17) *Abdominal Obesity* Q1: Reference Q2: 0.93 (0.82, 1.07) Q3: 0.91 (0.80, 1.04) Q4: 0.66 (0.56, 0.78)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Shim et al. (2019) Korea 2012–2014 Cross-Sectional	Korean National Environmental Health Survey II (KNEHS) n = 5,251 Nationally representative survey of adults in Korea	Blood Pb was measured in venous whole blood using GFAAS Age at measurement Mean (SE): No MetS: 49.87 (0.22) yr MetS: 61.59 (0.50) yr Geometric Mean (SE) No MetS: 0.71 (0.48) µg/dL MetS: 0.76 (0.49) µg/dL	MetS MetS was defined as meeting at least 3 of the following: (1) elevated blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg or current use of blood pressure medication), (2) low HDL cholesterol (<40 mg/dL in women or <50 mg/dL in men), (3) elevated serum triglycerides (≥150 mmHg) or current use of antidyslipidemia medication, (4) elevated fasting plasma glucose levels, (5) abdominal obesity (waist circumference ≥90 cm in men or ≥85 cm in women). Age at outcome is the same as age at exposure assessment	Age, sex, education, income, marital status, aspartate aminotransferase, alanine aminotransferase	**ORs for MetS prevalence across blood Pb quartiles** Q1: Reference Q2: 0.94 (0.72, 1.24) Q3: 1.00 (0.76, 1.31) Q4: 0.86 (0.65, 1.14) Quartile levels NR
†Wen et al. (2020) Taiwan June 2016-September 2018 Cross-Sectional	N = 2444 General population	Blood Pb was measured in venous whole blood using ICP-MS Age at measurement: Mean (SD): 55.1 (13.2) yr Mean: 1.6 µg/dL	MetS	Age, sex, TC, LDL cholesterol, hemoglobin, eGFR, uric acid	**OR MetS prevalence per log unit increase in blood Pb:** 0.86 (0.61, 1.20)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
			MetS was defined as meeting at least 3 of the following: (1) elevated blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg or current use of blood pressure medication), (2) low HDL cholesterol (<40 mg/dL in women or <50 mg/dL in men), (3) elevated serum triglycerides (≥150 mmHg) or current use of antidyslipidemia medication, (4) elevated fasting plasma glucose levels, (5) abdominal obesity (waist circumference ≥90 cm in men or ≥85 cm in women). Age at outcome: Mean (SD): 55.1 (13.2) yr		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Lee and Kim (2016) Korea 2007–2012 Cross-Sectional	KNHANES n = 9,880 Korean adults aged ≥20 yr	Blood Pb measured in venous whole blood using GFAAS Age at measurement Mean (SD): *Males* No MetS: 43.5 (0.23) yr MetS: 48.7 (0.48) yr *Females* No MetS: 43.5 (0.25) yr MetS: 51.4 (0.60) yr Geometric Mean (SD): *Males* No MetS: 2.57 (0.02) µg/dL MetS: 2.64 (0.04) µg/dL *Females* No MetS: 1.86 (0.01) MetS: 1.92 (0.04) µg/dL	MetS, waist circumference (cm), serum HDL (mg/dL), serum triglycerides (mg/dL), blood glucose (mg/dL) MetS was defined as meeting at least 3 of the following: (1) elevated blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg or current use of blood pressure medication), (2) low HDL cholesterol (<40 mg/dL in women or <50 mg/dL in men), (3) elevated serum triglycerides (≥150 mmHg) or current use of antidyslipidemia medication, (4) elevated fasting plasma glucose levels, (5) abdominal obesity (waist circumference ≥90 cm in men or ≥85 cm in women). Waist circumference (cm) was measured at the physical examination by a trained professional. Serum HDL (µg/dL), triglycerides (mg/dL), and blood glucose (mg/dL) were measured in blood samples obtained in the morning following an overnight fast. Age at outcome is the same as age at exposure assessment	Age, BMI, residence area, education level, smoking and drinking status, exercise, AST, ALT	**OR (95% CI) for outcomes across blood Pb tertiles** *MetS prevalence* T1 (≤2.20 µg/dL): Reference T2 (2.20–3.01 µg/dL): 1.032 (0.788, 1.352) T3 (>3.01 µg/dL): 0.817 (0.626, 1.065) *Waist circumference (≥85 cm)* T1: Reference T2: 1.11 (0.83, 1.50) T3: 1.11 (0.81, 1.51) *Serum HDL (≤40 mg/dL)* T1: Reference T2: 1.00 (0.80, 1.24) T3: 0.76 (0.59, 0.97) *Serum triglycerides (≥150 mg/dL)* T1: Reference T2: 1.13 (0.93, 1.39) T3: 1.08 (0.87, 1.33) *Blood glucose (≥100 mg/dL)* T1: Reference T2: 0.83 (0.68, 1.02) T3: 1.04 (0.85, 1.28)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Lee and Kim (2013) Korea 2005–2010 Cross-Sectional	KNHANES n = 7,559 Korean adults aged ≥20 yr	Blood Pb measured in venous whole blood using GFAAS Age at measurement Mean (SD): No MetS: 42.3 (0.29) yr MetS: 48.4 (0.57) yr Geometric Mean (SD): No MetS: 2.734 (0.024) µg/dL MetS: 2.957 (0.049) µg/dL	MetS, waist circumference, serum HDL, serum trigylcerides, blood glucose MetS was defined as meeting at least 3 of the following: (1) elevated blood pressure (SBP ≥130 mmHg or DBP ≥85 mmHg or current use of blood pressure medication), (2) low HDL cholesterol (<40 mg/dL in women or <50 mg/dL in men), (3) elevated serum triglycerides (≥150 mmHg) or current use of antidyslipidemia medication, (4) elevated fasting plasma glucose levels, (5) abdominal obesity (waist circumference ≥90 cm in men or ≥85 cm in women). Waist circumference (cm) was measured at the physical examination by a trained professional. Serum HDL (µg/dL), triglycerides (mg/dL), and blood glucose (mg/dL) were measured in blood samples obtained in the morning following an overnight fast. Age at outcome is the same as age at exposure assessment	Age, BMI, residence area, education level, smoking and drinking status, exercise, serum aspartate aminotransferase, serm alanine aminotransferase	**OR (95% CI) for outcomes across blood Pb tertiles** *MetS Prevalence* T1 (≤2.362 µg/dL): Reference T2 (>2.362–3.282 µg/dL): 1.267 (0.950, 1.690) T3 (>3.282 µg/dL: 0.984 (0.735, 1.317) *Waist circumference (≥85 cm)* T1: Reference T2: 1.04 (0.75, 1.45) T3: 0.89 (0.64, 1.24) *Serum HDL (≤40 mg/dL)* T1: Reference T2: 0.98 (0.79, 1.23) T3: 0.96 (0.77, 1.20) *Serum triglycerides (≥150 mg/dL)* T1: Reference T2: 1.01 (0.82, 1.24) T3: 1.07 (0.87, 1.32) *Blood glucose (≥100 mg/dL)* T1: Reference T2: 1.00 (0.81, 1.24) T3: 1.14 (0.91, 1.44)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Wang et al. (2018c) United States 2003–2014 Cross-Sectional	NHANES n = 9537 NHANES participants aged 20+, 2003–2014	Blood Pb was measured in venous whole blood using ICP-DRC-MS Age at measurement Mean (SD): 49.2 (18.0) yr Geometric mean (SD): 1.32 (2.00) µg/dL	Waist circumference (cm) Waist circumference (cm) was measured during minimal respiration to the nearest 0.1 cm at the level of the iliac crest at the time of NHANES physical examination. Age at outcome: Mean (SD): 49.2 (18.0) yr	Age, sex, race/ethnicity, education, smoking status, physical activity, NHANES cycle, and urinary creatinine	**Change in waist circumference (cm) per 1-SD increase in log(10)-transformed Pb (SD NR):** 0.008 (−0.010, −0.006)
†Peters et al. (2012) United States Blood Pb measured between 1999–2008; Serum lipids measured 3 to 4 yr after blood Pb Cohort	Normative Aging Study n = 426 Older male Veterans	Blood, Bone Blood Pb measured in venous whole blood using GFAAS Mean: 4.01 ± 2.30 µg/dL	Serum lipids Triglycerides, HDL-C Age at outcome: 3 to 4 yr after blood Pb	Age at baseline, yr between baseline and outcome, education, BMI, alcohol intake, smoking status, pack-yr of smoking, hypertension status, and statin use	**ORs** **Low HDL-C (<40 mg/dL):** 0.899 (0.804, 1.004) **High Triglycerides (≥200 mg/dL):** 0.993 (0.874, 1.129)
†Ettinger et al. (2014) Kumasi, Ghana; Cape Town, South Africa; Victoria, Seychelles; Kingston, Jamaica; Maywood, Illinois (United States) 2010–2014 Prospective Cohort	Modeling the Epidemiologic Transition Study (METS) n = 150 Adults of African descent from 5 countries of varying social and economic development	Blood Pb was measured in venous whole blood using DRC-ICP-MS Age at measurement Mean (SD): Males: 34.7 (6.0) yr Females: 35.2 (6.2) yr Geometric Mean (95% CI): 1.55 (1.30, 1.85) µg/dL Median (95% CI): 1.66 (1.34, 1.93) µg/dL	Waist Circumference ≥94 cm (males) or ≥80 cm (females), Fasting Glucose ≥100 mg/dL Fasting glucose was measured in blood. Further outcome assessment details not provided. Age at outcome is the same as age at exposure assessment	Age, sex, site location, marital status, education, paid employment, alcohol use, fish intake, percent body fat	**ORs for blood Pb above the median (1.66 µg/dL) vs below the median** Waist Circumference [≥94 cm (m) or ≥80 cm (f)] 4.53 (1.06, 19.48) Fasting Glucose (≥100 mg/dL) 4.99 (1.97, 12.69)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
		75th: 2.6 µg/dL Max: 31.82 µg/dL			
			Body Weight		
†Wang et al. (2018a) China 2014 Cross-Sectional	SPECT-China n = 3922 Chinese citizens aged ≥18 yr who had lived in their current area for 6+ mo	Blood Pb was measured in venous whole blood using GFAAS Age at measurement: Mean (SD): Normal weight subjects: 50.9 (13.9) yr Overweight subjects: 54.0 (12.3) yr Obese subjects: 56.2 (11.2) yr Median (25th–75th percentiles) Normal weight: 3.9 (2.6, 5.6) µg/dL Overweight subjects: 4.3 (2.9, 6.1) µg/dL Obese subjects: 4.4 (2.7, 6.2) µg/dL	BMI (kg/m^2) BMI was calculated as weight (kg) divided by squared height (m^2). Overweight (including obese) was defined as BMI ≥25 kg/m^2. Age at outcome is the same as age at exposure assessment	Age, sex, economic status, rural/urban residence, current smoking, diabetes, hypertension, dyslipidemia	**OR (95% CI) for overweight or obese (BMI ≥25 kg/m^2) across blood Pb quartiles** Q1 (≤2.69 µg/dL): Reference Q2 (2.69–4.01 µg/dL): 1.09 (0.89, 1.33) Q3 (4.01–5.60 µg/dL): 1.15 (0.94, 1.40) Q4 (≥5.60 µg/dL): 1.40 (1.14, 1.71)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Ettinger et al. (2014) Kumasi, Ghana; Cape Town, South Africa; Victoria, Seychelles; Kingston, Jamaica; Maywood, Illinois (United States) 2010–2014 Prospective Cohort	Modeling the Epidemiologic Transition Study (METS) n = 150 Adults of African descent from 5 countries of varying social and economic development	Blood Pb was measured in venous whole blood using DRC-ICP-MS Age at measurement Mean (SD): Males: 34.7 (6.0) yr Females: 35.2 (6.2) yr Geometric Mean (95% CI): 1.55 (1.30, 1.85) µg/dL Median (95% CI): 1.66 (1.34, 1.93) µg/dL 75th: 2.6 µg/dL Max: 31.82 µg/dL	Overweight (BMI ≥25), Obese (BMI ≥30) Height and weight were measured by physical examination. Age at outcome is the same as age at exposure assessment	Age, sex, site location, marital status, education, paid employment, alcohol use, fish intake, percent body fat	**ORs for blood Pb above the median (1.66 µg/dL) vs below the median** Overweight (BMI ≥25) 0.88 (0.31, 2.51) Obese (BMI ≥30) 2.70 (0.75, 9.75)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Guo et al. (2019) China 2015 Cross-Sectional	N = 145 Adult men recruited through a physical examination center	Blood Pb was measured using ICP-MS Age at measurement Mean (SD): 39 (12) yr Mean (SD): 8.5 (3.8) µg/dL; Median: 7.9 µg/dL 75th: 10.8 µg/dL Max: 28.2 µg/dL	BMI (kg/m2) Age at outcome Mean (SD): 39 (12) yr	Age	**Change in BMI (kg/m2) per log increase in blood Pb:** 0.05 (−3.64, 3.74)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; DRC-ICP-MS = dynamic reaction cell for inductively coupled plasma mass spectrometry; eGFR = estimated glomerular filtration rate; ELEMENT = Early Life Exposures in Mexico to Environmental Toxicants; GADA = glutamic acid decarboxylase antibodies; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; HDL = high-density lipoprotein; HDL-C = high-density lipoprotein cholesterol; HOMA-IR = Homeostatic Model Assessment for Insulin Resistance; HOMA- β = HOMA of β-cell function; ICP-MS = inductively coupled plasma mass spectrometry; KNHANES = Korean National Health and Nutrition Examination Survey; MetS = metabolic syndrome; METS = Modeling the Epidemiologic Transition Study; NR = not reported; OR = odds ratio; Pb = lead; SBP = systolic blood pressure; SD = standard deviation; SPECT = single photon emission computed tomography; TC = total cholesterol; Q = quartile.

[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.

†Studies published since the 2013 Integrated Science Assessment for Lead.

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Table 9-7 Animal toxicological studies of exposure to Pb and metabolic effects.

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL As Reported (µg/dL)	Endpoints Examined
Faulk et al. (2014)	Mouse (Agouti), 0.0 ppm Pb, M/F, n = 30 2.1 ppm Pb, M/F, n = 28 16 ppm Pb, M/F, n = 33 32 ppm Pb, M/F, n = 29 (Longitudinal phenotypic measures were taken from a total of 120 a/a mice, on average 2.7 mice per litter)	Mo 3, 6, 9	Oral, drinking water	Mean maternal BLL, tested at weaning, were below the LOD for the control group, and 4.1 (61.3) µg/dL, 25.1 (67.3) µg/dL, and 32.1 (611.4) µg/dL in the three exposure groups, 2.1 ppm, 16 ppm, and 32 ppm, respectively	Oxygen Consumption, CO_2 Production, Food Intake, Body Weight, Body Fat
Rahman et al. (2018)	Rat (Wistar) 0% Pb Acetate, M/F, n = 37 0.2% Pb Acetate, M/F, n = 38	PND 21, 30	Oral, drinking water	2.2 ± 0.07 µg/dL for 0% Pb Acetate, 12.4 ± 3.3 µg/dL for 0.2% Pb Acetate - PND 21 3.3 ± 1.7 µg/dL for 0% Pb Acetate, 22.7 ± 6.0 µg/dL for 0.2% Pb Acetate - PND 30	Serum 25(OH)D, Serum 1,25(OH)2D, Hepatic 25-Hydroxylase Protein Levels, Hepatic 25-Hydroxylase Immunohistochemistry

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL As Reported (µg/dL)	Endpoints Examined
Zhou et al. (2018)	Rat (Sprague Dawley), 0% Pb Acetate, M, n = 20 0.5% Pb Acetate, M, n = 20 1% Pb Acetate, M, n = 20 2% Pb Acetate, M, n = 20	PND 52	Oral, drinking water	11.4 µg/L for 0% 147 µg/L for 0.5% 226 µg/L for 1% 289 µg/L for 2%	Cholesterol Content, mRNA level of SREBP2 in the cortex, mRNA level of SREBP2 in the hippocampus, mRNA level of LDL-R in the cortex, mRNA level of HMG-CR in the hippocampus, mRNA level of HMG-CR in the cortex, protein level of SREBP2 in the cortex, mRNA level of LDL-R in the hippocampus, protein level of HMG-CR in the cortex, protein level of LDL-R in the cortex, protein level of SREBP2 in the hippocampus, protein level of HMG-CR in the hippocampus, protein level of LDL-R in the hippocampus, immunohistochemistry of SREBP2 in the cortex, immunohistochemistry of HMG-CR in the cortex, immunohistochemistry of LDL-R in the cortex, immunohistochemistry of SREBP2 in the hippocampus, immunohistochemistry of HMG-CR LDL-R in the hippocampus, immunohistochemistry of LDL-R in the hippocampus, mRNA level of LXR-α in the cortex, mRNA level of ABCA1 in the cortex, mRNA level of LXR-α in the hippocampus, mRNA level of ABCA1 in the hippocampus, protein level of LXR-α in the cortex, protein level of ABCA1 in the cortex, protein level of LXR-α in the hippocampus, protein level of ABCA1 in the hippocampus

ABCA1 = ATP-binding cassette transporter ABCA1 (member 1 of human transporter sub-family ABCA); BLL = blood lead level; CO_2 = carbon dioxide; F = female; HMG-CR = 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase; LDL-R = low-density lipoprotein receptor; LOD = limit of detection; LXR-α = liver X receptor alpha; M = male; mRNA = messenger ribonucleic acid; Pb = lead; PND = postnatal day; SREBP2 = Sterol Regulatory Element Binding Transcription Factor 2.

Table 9-8 Animal toxicological studies of exposure to Pb and gastrointestinal effects.

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL As Reported (µg/dL)	Endpoints Examined
Kosik-Bogacka et al. (2011)	Rat (Wistar), Control (distilled water), M, n = 9 0.1% Pb, M, n = 9	Day 270	Oral, drinking water	0.34±0.23 µg/dL for 0.0%, 7.21 ± 1.27 µg/dL for 0.1%	transepithelial electrical potential difference (PD), changes in the transepithelial electrical potential difference during mechanical stimulation (dPD), transepithelial electrical resistance (R)
Reddy et al. (2018)	Rat (Sprague Dawley), Control Diet (CD), M, n = 10 Control Diet, F, n = 10 Iron Deficient (ID), M, n = 10 Iron Deficient, F, n = 10 Control Diet + Pb, M, n = 10 Control Diet + Pb, F, n = 10 Iron Deficient + Pb, M, n = 10 Iron Deficient, F, n = 10	Microbiome Counts at Week 0, 4, 8, 10, 12 BLL at End of Week 8	Oral, gavage	2.3 ± 1.16 µg/dL - CD, M 19.3±6.23 µg/dL – CD + Pb, M 2.5 ± 0.89 µg/dL - ID, M 47.5 ± 3.78 µg/dL – ID + Pb, M 1.9 ± 0.81 µg/dL - CD, F 13.5 ± 3.52 µg/dL – CD + Pb, F 1.5 ± 0.31 µg/dL - ID, F 29.80 ± 8.30 µg/dL – ID + Pb, F	Fecal Lactobacilli (Counts), Fecal E. Coli (Counts), Fecal Yeast (Counts)

BLL = blood lead level; dPD = transepithelial electrical potential difference during mechanical stimulation; F = female; M = male; PD = transepithelial electrical potential difference; R = resistance

Table 9-9 Epidemiologic studies of exposure to Pb and endocrine effects.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Chen et al. (2013) United States 2007–2008 Cross-sectional	NHANES n = 5,418 Adolescents and adults in the general U.S. population who had no reported thyroid diseases, thyroid medications, pregnancy, and sex steroid medications.	Blood Pb Blood Pb was measured in venous whole blood using GFAAS Age at measurement: ≥12 yr old Mean: 0.93 µg/dL Max: 9.20 µg/dL	TSH, thyroglobulin (Tg), and thyroid hormones (T3, FT3, T4, FT4) TSH and thyroid hormones measured in serum using the Beckman Immunoassay System. Age at outcome: ≥12 yr old	Age, sex, race/ethnicity, creatinine-adjusted urinary iodine, BMI Z-score, and serum cotinine level	**Change in T4 (µg/dL)[b]** *Adolescents (12–19 yr old)* (−0.02, 0.04) *Adults (≥19 yr old)* −0.01 (−0.02, 0.01) **Change in FT4 (ng/dL)[b]** *Adolescents (12–19 yr old)* (−0.01, 0.04) *Adults (≥19 yr old)* 0.01 (−0.01, 0.02) **Change in T3 (ng/dL)[b]** *Adolescents (12–19 yr old)* (−0.01, 0.04) *Adults (≥19 yr old)* −0.0004 (−0.02, 0.02) **Change in FT3 (pg/mL)[b]** *Adolescents (12–19 yr old)* (−0.002, 0.04) *Adults (≥19 yr old)* 0.01 (−0.001, 0.02) **Change in TSH (µIU/mL)[b]** *Adolescents (12–19 yr old)* −0.05 (−0.18, 0.07) *Adults (≥19 yr old)* −0.01 (−0.06, 0.04)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Change in Tg (ng/mL)[b] *Adolescents (12–19 yr old)* 0.05 (−0.13, 0.24) *Adults (≥19 yr old)* 0.01 (−0.03, 0.06)
†Krieg (2019) United States 1988–1994 Cross-sectional	NHANES III n = 16,573 General population, ≥20 yr old	Blood Pb Blood Pb was measured in venous whole blood using AAS Age at measurement: ≥20 yr old Mean: 3.55 µg/dL (SE = 0.10)	TSH and T4 TSH and thyroid hormones measured in serum using the Beckman Immunoassay System. Age at outcome: ≥20 yr old	Linear regression model adjusted for race-ethnicity, sex, age, session, BMI, pregnant, menopause, hormone pill use, vaginal cream use, hormone patch use, urinary creatinine	**Change in TSH (%)** −1.2 (−5.6, 3.3) **Change in T4 (%)** −38.9 (−51.3, −23.4) **Change in Log_{10}-TSH (µU/mL)[b]** *Male* 0.01 (−0.04, 0.05) *Female (Not pregnant)* −0.04 (−0.08, 0.01) *Female (Pregnant)* −0.03 (−0.26, 0.20) **Change in Log_{10}-T4 (µg/dL)[b]** *Male* −0.15 (−0.48, 0.18) *Female (Not pregnant)* −0.52 (−0.83, −0.21) *Female (Pregnant)* −2.01 (−3.09, −0.93)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Mendy et al. (2013) United States 2007–2008 Cross-sectional	NHANES n = 4,652 General population ≥20 yr old, excluding pregnant women, individuals with a history of thyroid disease, or under treatment for thyroid dysfunction	Blood Pb Blood Pb was measured in venous whole blood using GFAAS Age at measurement: ≥20 yr old Mean (SD): 1.52 ± 1.20 µg/dL Max: 33.12 µg/dL	TSH and thyroid hormones (T3, FT3, T4, FT4) TSH and thyroid hormones measured in serum using the Beckman Immunoassay System Age at outcome: ≥20 yr old	Age, gender, race/ethnicity, smoking, alcohol consumption, BMI, physical activity, iodine intake, medications, and bone mineral density	**Change in T3 (ng/dL)** −0.774 (−2.269, 0.722) **Change in FT3 (pg/mL)** 0.015 (−0.007, 0.037) **Change in T4 (µg/dL)** −0.162 (−0.321, −0.004) **Change in FT4 (ng/mL)** (−0.011, 0.011) **Change in TSH (mIU/mL)** 0.015 (−0.088, 0.118)
†Christensen (2012) United States 2007–2008 Cross-sectional	NHANES n = 1,587 General population, ≥20 yr old, excluding individuals with thyroid disease or cancer, or were taking thyroid medications	Blood Pb Blood Pb was measured in venous whole blood using GFAAS Age at measurement: ≥20 yr old Median: 1.3 µg/dL 75th: 2.1 µg/dL	TSH and thyroid hormones (T3, T4) TSH and thyroid hormones measured in serum using the Beckman Immunoassay System. Age at outcome: ≥20 yr old	Age, sex, race, BMI, serum lipids, serum cotinine, pregnancy and menopausal status, and use of selected medications	**Change in ln(T3) (ng/dL)** 0.004 (−0.016, 0.023) **Change in ln(FT3) (pg/mL)** 0.008 (−0.002, 0.017) **Change in ln(T4) (µg/dL)** −0.018 (−0.036, 0) **Change in ln(FT4) (pg/mL)** −0.001 (−0.018, 0.015) **Change in ln(TSH) (mIU/L)** 0.027 (−0.031, 0.085)

†Luo and Hendryx (2014) United States 2007–2010 Cross-sectional	NHANES n = 6,231 General population ≥20 yr old, excluding pregnant women, individuals with history of thyroid disease, or missing data.	Blood Pb Blood Pb was measured in venous whole blood using GFAAS Age at measurement: ≥20 yr old Mean: 1.82 µg/dL Max: 33.10 µg/dL	TSH, thyroglobulin (Tg), and thyroid hormones (T3, FT3, T4, FT4) TSH and thyroid hormones measured in serum using the Beckman Immunoassay System. Age at outcome: ≥20 yr old	Adjusted for age, sex, race and ethnicity, serum cotinine, BMI, and creatinine-adjusted urinary iodine	**Change in T3 across tertiles (ng/dL)[b]** T1: Reference T2: 1.02 (−0.90, 2.94) T3: 0.69 (−2.37, 3.76) ***Women Only*** T1: Reference T2: −0.36 (−3.72, 3.00) T3: 0.61 (−5.02, 6.23) ***Men Only*** T1: Reference T2: 1.96 (−0.98, 4.91) T3: 0.69 (−2.59, 3.97) **Change in FT3 across tertiles (pg/mL)[b]:** T1: Reference T2: 0.03 (0.001, 0.07) T3: 0.04 (0.01, 0.08) ***Women Only*** T1: Reference T2: 0.02 (−0.04, 0.08) T3: 0.03 (−0.04, 0.11) ***Men Only*** T1: Reference T2: 0.03 (−0.01, 0.07) T3: 0.05 (0.01, 0.09) **Change in T4 across tertiles (µg/dL)[b]:** T1: Reference T2: 0.01 (−0.16, 0.14) T3: −0.09 (−0.28, 0.11 ***Women Only***

T1: Reference
T2: 0.12 (−0.10, 0.35)
T3: 0.02 (−0.29, 0.33)
Men Only
T1: Reference
T2: −0.14 (−0.35, 0.08)
T3: −0.20 (−0.40, 0.01)

Change in FT4 across tertiles (ng/dL)[b]:
T1: Reference
T2: 0.007 (−0.01, 0.02)
T3: 0.002 (−0.01, 0.01)
Women Only
T1: Reference
T2: 0.02 (0.01, 0.04)
T3: 0.02 (−0.003, 0.04)
Men Only
T1: Reference
T2: −0.02 (−0.03, 0.005)
T3: −0.01 (−0.04, 0.008)

Change in Log-Tg across tertiles (ng/mL)[b]:
T1: Reference
T2: 0.04 (−0.04, 0.13)
T3: 0.02 (−0.07, 0.12)
Women Only
T1: Reference
T2: 0.08 (−0.03, 0.19)
T3: −0.06 (−0.19, 0.08)
Men Only
T1: Reference
T2: −0.001 (−0.13, 0.17)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					T3: 0.05 (−0.08, 0.17) **Change in Log-TSH across tertiles (uIU/mL)[b]:** T1: Reference T2: 0.01 (−0.05, 0.07) T3: 0.02 (−0.06, 0.09) ***Women Only*** T1: Reference T2: 0.05 (−0.06, 0.16) T3: 0.02 (−0.09, 0.14) ***Men Only*** T1: Reference T2: −0.04 (−0.13, 0.06) T3: −0.02 (−0.11, 0.07)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Nie et al. (2017) Shanghai and 7 provinces China 2014 Cross-sectional	SPECT-China study n = 5,628 Residents of these regions are 99.5% Han Chinese. Exclusion criteria included age under 18 yr old, less than 6 mo spent at current residence, and severe communication problems or acute illness (thyroid resection or iodine-131 therapy, malignant tumor, subacute thyroiditis, liver cirrhosis)	Blood Pb Whole blood measured using AAS Age at measurement: 18–93 yr old Median: Men: 44.00 µg/L Women: 37.87 µg/L Mean: Men: 29.00±62.18 µg/L Women: 25.03±54.61 µg/L	TSH, thyroid hormones (T3, T4), thyroid peroxidade antibody (TPOAb) and thyroglobulin antibodies (TGAb) Thyroid dysfunction and subclinical thyroid dysfunction were measured by immunochemiluminometric assays Age at outcome: 18–93 yr old	Linear and logistic regression model adjusted for age, BMI, smoking status (men only) and drinking status	**Change in TPOAb (%)** *Men* 0.50 (-0.80, 1.82) *Women* 1.41 (0.00, 2.84) **Change in TGAb (%)** *Men* -0.60 (-1.88, 0.70) *Women* 0.20 (-1.09, 1.51) **Change in TSH (%)** *Men* -0.40 (-1.29, 0.40) *Women* 1.11 (0.30, 1.82)
†Kahn et al. (2014) Pristina and Mitrovica Yugoslavia 1985–1986 Cross-sectional	Yugoslavia Prospective Study of Environmental Lead Exposure n = 291 Pregnant women in second trimester, major central nervous system defects, multiple births, and residence >10 km from clinic	Blood Pb Whole blood samples taken in Yugoslavia and transported on wet ice to Columbia University. Blood Pb measured using GFAAS. Age at measurement: 16–41 yr old Mean µg/dL (SD): Pristina: 5.57 (2.01) Mitrovica: 20.00 (6.99)	TSH, thyroid hormones (FT4), and thyroid peroxidase antibodies (TPOAb) FT4 and TPOAb were measured by a radioimmunoassay procedure. TSH was measured using an immunoradiometric assay Age at outcome: 16–41 yr old	Logistic regression model adjusted for: FT4: height, ethnicity, BMI, fetal gestational age, maternal education, adults per room; TSH: hemoglobin, ethnicity, BMI, fetal gestational age, maternal age; TPOAb: ethnicity, fetal gestational age, maternal age, adults per room.	**Change in FT4 (ng/dL)[b]** −0.074 (−0.10, −0.046) **Change in Log-TSH (µIU/mL)[b]** 0.026 (−0.065, 0.12) **Change in Log-TPOAb (IU/mL)[b]** 0.31 (0.17, 0.46) **OR[b]** *TPOAb ≥vs. <10 IU/mL* 2.41 (1.53, 3.82)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Souza-Talarico et al. (2017) São Paulo Brazil Cross-sectional	N = 126 105 women and 21 men ages 50–82 yr old with a mean of 9.8 (±4.5) yr of education	Blood Pb Fasting blood Pb was measured using ICP-MS Age at measurement: 50–82 yr old Median: 2.1 µg/dL (SD: ±0.9) Max: 6.1 µg/dL	Cortisol concentration and allostatic load Six neuroendocrine, metabolic, and anthropometric biomarkers were analyzed, and values were transformed into an AL index using clinical reference cut-offs. Salivary samples were collected at home over 2 d at awakening, 30-min after waking, afternoon, and evening periods to determine cortisol levels. Age at outcome: 50–82 yr old	Age, gender, time of awakening, socioeconomic status (SES), GDS, and PSS scores	**Change in CAR (µg/dL min)[b]** 0.791 (0.672, 1.073) **Change in total AUC (µg/dL hr)[b]** 0.889 (0.829, 0.953)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Ngueta et al. (2018) Montreal Canada 2004–2006 Cross-sectional	Study of Genetics, Stress and Cognitive Development n = 65 75% of participants were women, 95% were Caucasian, 90% were current smokers	Blood Pb Blood Pb levels were determined using inductively coupled plasma mass spectroscopy Age at measurement: 50–67 yr old Median: 2.48 µg/dL Mean: 2.41 µg/dL (SD = 0.15)	Diurnal basal cortisol levels and acute cortisol responsivity Basal Cortisol: Participants were instructed to collect saliva five times per day during three consecutive weekdays: upon awakening, 30 min after awakening, at 2:00 p.m., at 4:00 p.m., and at bedtime Stress reactivity: A total of nine saliva samples were collected for measurement of salivary cortisol: two baseline samples, one postanticipatory, and six post-TSST tasks: one after 15 min and then five sampled every 10 min Age at outcome: 50–67 yr old	Linear model adjusted for age, gender, waist-hip ratio, smoking status and income levels.	**Change in basal cortisol levels (µg/dL)** -0.01 (-0.05, 0.02) **Change in reactive cortisol levels (µg/dL)** -0.01 (-0.03 0.01)

AAS = atomic absorption spectrometry; BMI = body mass index; CAR = cortisol awakening response; CI = confidence interval; d = day(s); GFAAS = graphite furnace atomic absorption spectrometry; FT3 = free triiodothyronine; FT4 = free thyroxine; ICP-MS = inductively coupled plasma mass spectrometry; NHANES = National Health and Nutrition Examination Survey; Pb = lead; SD = standard deviation; SE = standard error; SES = socioeconomic status; SPECT = single photon emission computed tomography; Tg = thyroglobulin; T = tertile; TGAb = thyroglobulin antibodies; TPOAb = thyroid peroxidade antibody; TSH = thyroid stimulating hormone; yr = year(s)

[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.

[b]Effect estimate unable to be standardized due to insufficient distribution information.

†Studies published since the 2013 Integrated Science Assessment for Lead.

Table 9-10 Animal toxicological studies of exposure to Pb and endocrine effects.

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL As Reported (µg/dL)[b]	Corticosterone Levels
Rossi-George et al. (2011)	Rat (Long-Evans) Control (untreated), M/F, n = 10 dams 50 ppm, M/F, n = 9 dams 150 ppm, M/F, n = 11 dams	GD−61 to PND 304	Dams were dosed starting 2 mo prior to mating through lactation. Pups were weaned on PND 21 and continued on the regimen of their dam until euthanasia post-testing at approximately 10 mo of age.	0.979 µg/dL for 0 ppm, 19.091 µg/dL for 50 ppm, 35.245 µg/dL for 150 ppm – PND 21 Females 1.469 µg/dL for 0 ppm, 11.259 µg/dL for 50 ppm, 25.699 µg/dL for 150 ppm – PND 61 Females 1.713 µg/dL for 0 ppm, 11.993 µg/dL for 50 ppm, 29.615 µg/dL for 150 ppm – PND 304 Females 1.935 µg/dL for 0 ppm, 19.597 µg/dL for 50 ppm, 31.935 µg/dL for 150 ppm – PND 21 Males 2.177 µg/dL for 0 ppm, 12.581 µg/dL for 50 ppm, 26.855 µg/dL for 150 ppm – PND 61 Males 1.694 µg/dL for 0 ppm, 15.968 µg/dL for 50 ppm, 29.274 µg/dL for 150 ppm – PND 304 Males	Adrenal Weight, Corticosterone Levels
Graham et al. (2011)	Rat (Sprague Dawley) Control (vehicle), M/F, n = 12–18 (6–8/6–8)	PND 4 to PND 28	Rats were gavaged every other day from P4 until P28.	0.267 µg/dL for 0 mg/kg, 3.27 µg/dL for 1 mg/kg 12.5 µg/dL for 10 mg/kg – PND 29	Adrenal Weight, Corticosterone Levels

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL As Reported (µg/dL)[b]	Corticosterone Levels
	1 mg/kg Pb, M/F, n = 12–18 (6–8/6–8) 10 mg/kg Pb, M/F, n = 12–18 (6–8/6–8)				
Cory-Slechta et al. (2013)	Mouse (C57BL.6) Control (untreated), M, n = 8–17 Control (untreated), F, n = 8–13 100 ppm Pb, M, n = 8–17 100 ppm Pb, F, n = 8–13	GD −61 to PND 365	Dams were exposed starting 2 mo prior to mating. Offspring were continued on the same exposure as their dams until the end of the experiment at 12 mo of age.	0.34 µg/dL for 0 ppm FI males 0.11 µg/dL for 0 ppm FS males 0.34 µg/dL for 0 ppm FI females 0.16 µg/dL for 0 ppm FS females 6.94 µg/dL for 100 ppm FI males 6.16 µg/dL for 100 ppm FS males 9.38 µg/dL for 100 ppm FI females 7.07 µg/dL for 100 ppm FS females	Adrenal Weight, Corticosterone Levels
Amos-Kroohs et al. (2016)	Rat (Sprague Dawley) Control (vehicle, see notes), M/F, n = 16 (8/8) 1 mg/kg Pb, M/F, n = 16 (8/8) 10 mg/kg Pb, M/F, n = 16 (8/8)	P4 until P10, 18, or 28.	Rats were gavaged every other day from PND4 until PND10, 18, or 28.	1.24 µg/dL for 0 mg/kg Pb 2.79 µg/dL for 1 mg/kg Pb 9.07 µg/dL for 10 mg/kg Pb	Corticosterone Levels
Sobolewski et al. (2020)	Mouse (C57BL.6) F0 Control (assume untreated), F, n = 10 100 ppm Pb, F, n = 10 20 females were in control and 20 received Pb but these groups were further divided, and some received prenatal stress and others did not.	GD –61 to PND 21	Exposure started 2 mo prior to mating and continued through PND 21 (weaning) of the F1. F3 was technically not directly exposed.	F1 0.0 µg/dL for Control 12.5 µg/dL for 100 ppm – PND 6–7 F3 0.0 µg/dL for Control	Corticosterone Levels

F# = filial generation; F = female; GD = gestational day; M = male; mo = month(s); Pb = lead; PND = postnatal day.

Table 9-11 Epidemiologic studies of exposure to Pb and musculoskeletal effects.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Osteoporosis and Bone Mineral Density					
†Cho et al. (2012) South Korea 2008 Cross-Sectional	KNHANES n = 481 Postmenopausal women	Blood Blood Pb measured in venous whole blood using GFAAS Age at measurement: Mean (SD): Q1: 64.03 (8.52) yr Q2 and Q3: NR Q4: 61.78 (8.62) yr Median: 2.32 µg/dL 25th: 1.83 µg/dL 75th: 2.88 µg/dL	Osteoporosis BMD measured in hip, neck, and spine using X-ray absorptiometry. Osteoporosis defined as T-score <2.5 at any of the measurement sites Age at outcome is the same as the age at exposure assessment	Age, BMI, alcohol intake, cigarette smoking, exercise, use of oral contraceptive pill, hormone therapy, caloric intake, calcium intake, fish consumption, and vitamin D level	**OR Osteoporosis Prevalence** Q1: Ref. Q2: 1.41 (0.75, 2.67) Q3: 1.34 (0.70, 2.56) Q4: 1.50 (0.79, 2.86)
†Wang et al. (2019) United States 2013–2014 Cross-sectional	NHANES n = 1859 General population; ≥40 yr old	Blood, Urine Blood Pb measured in whole blood using ICP-MS Age at measurement: ≥40 yr Mean: 1.24 µg/dL 75th: 1.81 µg/dL	BMD and fracture risk BMD measured via DXA scan; Fracture risk measured via Fracture Risk Assessment score – a composite index of fracture risk factors Age at outcome: ≥40 yr	Age, race/ethnicity, BMI, serum 25(OH)D level, smoking, drinking, treatment for osteoporosis, and use of prednisone	**Change in BMD (g/cm^2)** *Femur* *Males* −0.01 (−0.03, 0.01) *Premenopausal Women* −0.06 (−0.08, −0.03) *Menopausal Women* 0.01 (−0.01, 0.03) *Spine*

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Males 0.01 (-0.01, 0.03) *Premenopausal Women* −0.05 (−0.08, −0.02) *Menopausal Women* 0.02 (−0.01, 0.04) **Change in 10-yr Fracture Risk Score** *Hip* 0.45 (0.28, 0.62) *Major* 1.22 (0.68, 1.77)
†Lee and Kim (2012) South Korea 2008–2009 Cross-Sectional	KNHANES n = 832 Women ages ≥40 yr	Blood Blood Pb measured in venous whole blood using GFAAS Age at measurement: Mean (SD): 56.1 (10.4) yr GM: 2.182 µg/dL	BMD BMD in the femoral neck, trochanter, intertrochanter, Ward triangle, total femur, and lumbar 1–4. Measured using DXA Age at outcome: Mean (SD): 56.1 (10.4) yr	Residence area, obesity, educational level, smoking status, drinking status, number of pregnancies, hormone treatment, contraceptive oral pill and daily calcium intake for pre- and postmenopausal, and time since menopause for postmenopausal	Change in BMD (g/cm2) Premenopausal Women Total Femur −0.15 (−0.33, 0.03) Trochanter −0.18 (−0.41, 0.05) Intertrochanter −0.11 (−0.25, 0.03) Femoral Neck −0.11 (−0.28, 0.07)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Ward's Triangle −0.11 (−0.26, 0.03) Lumbar 1–4 −0.09 (−0.24, 0.06) Menopausal Women Total Femur −0.28 (−0.45, −0.11) Trochanter −0.30 (−0.55, −0.06) Intertrochanter −0.22 (−0.35, −0.08) Femoral Neck −0.21 (−0.39, −0.02) Ward's Triangle −0.13 (−0.29, 0.03) Lumbar 1–4 −0.17 (−0.31, −0.04)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Pollack et al. (2013) Western New York United States 2005–2007 Cross-Sectional	BioCycle Study n = 248 Premenopausal women ages 18–44 yr	Blood Blood Pb measured in venous whole blood using ICP-MS Age at measurement: Mean (SD): 27.4 (8.2) yr Mean: 1.03 µg/dL	Bone mineral density BMD in the hip, spine, wrist, and whole body (g/cm2) measured via DXA Age at outcome: Mean (SD): 27.4 (8.2) yr	Age, BMI, race, parity, caloric intake, and age at menarche	**Change in BMD (g/cm2)** Whole Body −0.004 (−0.03, 0.021) Total Hip −0.002 (−0.035, 0.031) Lumbar Spine −0.016 (−0.048, 0.016) Wrist 0.001 (−0.012, 0.014)
†Li et al. (2020b) Sichuan Province China Cross-sectional	n = 799 Study area included two rural towns, one with a history of heavy metal contamination. Generally healthy adults ages 40–75 yr old who lived in study area for ≥15 yr and subsisted on rice and vegetables grown in study area.	Blood, Urine Blood Pb measured in venous whole blood using ICP-MS Age at measurement: 40–75 yr Median 3.4 µg/dL 75th: 4.7 µg/dL	BMD Osteoporosis (BMD T-score <2.0); BMD measured via X-ray absorptiometry Age at outcome: 40–75 yr	Age, BMI, and smoking status	**OR Osteoporosis Prevalence (≥3.4 µg/dL vs. <3.4 µg/dL blood Pb)** Males 0.6 (0.24, 1.49) Females 1.33 (0.61, 2.88) Non-Smoking Females 0.94 (0.4, 2.21)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Lim et al. (2016) South Korea 2008–2011 Cross-Sectional	KNHANES n = 2429 General population; ≥18 yr old	Blood Blood Pb measured in venous whole blood using GFAAS Age at measurement: ≥18 yr Median: 2.22 µg/dL 25th: 1.66 µg/dL 75th: 2.93 µg/dL	BMD (osteoporosis and osteopenia) Ostopenia (BMD T-score <−1.0) and Osteoporosis (BMD T-score <−2.5) Age at outcome: ≥18 yr	Age, sex, smoking status, alcohol consumption, geographic region, education level, occupation, and family income	**ORs for Osteoporosis or Osteopenia prevalence across blood Pb quartiles** Q1: Ref. Q2: 1.08 (0.85, 1.37) Q3: 1.18 (0.91, 1.53) Q4: 1.49 (1.12, 1.98)
†Lee and Park (2018) Ansung and Ansan South Korea 2001–2002 Cross-Sectional	Korean Association Resource (KARE) Cohort n = 443 Adults aged 40–65 yr from two South Korean communities, on rural (Ansung) and one urban (Ansan)	Blood Blood Pb measured in venous whole blood using GFAAS Age at measurement: 40–65 yr GM: 4.44 µg/dL	BMD BMD (T-score) measured via ultrasound Age at outcome: 40–65 yr	Age, sex, geographic region, income, and physical activity	**Change in BMD T-score** *All* −0−0.26 (−0.45, −0.07) *Ever Smokers* −0.47 (−0.85, −0.09) *Current Smokers* −0.60 (−1.02, −0.17) *Never Smokers* −0.15 (−0.37, 0.07)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
			Osteoarthritis		
†Park and Choi (2019) South Korea 4 Years (2010–2012) Cross-sectional	KNHANES n = 884 Women, ≥55 yr old	Blood BLL measured in venous whole blood using GFAAS Age at measurement: Mean: 62.9 yr Median: 2.22 µg/dL Max: 7.84 µg/dL	Osteoarthritis Radiographic and symptomatic osteoarthritis. Radiographic OA (rOA) assessed in the hip, knee, and spine using the Kellgren-Lawrence grading system. Symptomatic OA (sxOA) assessed using a combination of radiographic evidence and self-reported symptoms Age at outcome: Mean: 62.9 yr	Age, smoking status, alcohol use, physical activity, education, occupation, income, diabetes, hypertension, and BMI	**ORs for Osteoarthritis prevalence per ln-unit increase in blood Pb (µg/dL)** rOA Knee 1.77 (1.17, 2.67) sxOA Knee 1.50 (0.90, 2.53) rOA Back 1.05 (0.70, 1.59) sxOA Back 0.68 (0.39, 1.18)
†Nelson et al. (2011a) Johnston County, N.C. United States 2003–2004 and 2006–2008 Cross-Sectional	Johnston County Osteoarthritis Project n = 668 African American and White adults ages ≥45 yr old	Blood Blood Pb measured in venous whole blood using ICP-MS Age at measurement Mean (SD): Females: 62.4 (9.4) yr Males: 64.5 (10.8) yr Median: Females: 1.9 µg/dL Males: 2.2 µg/dL Max: Females: 25.4 µg/dL	Osteoarthritis Urine and serum biomarkers of joint tissue metabolism Age at outcome: Mean (SD): Females: 62.4 (9.4) yr Males: 64.5 (10.8) yr	Age, race, BMI, and smoking status	**% Change in urine and serum biomarkers of joint tissue metabolism** *Males* *uNTX-I* 1.2% (−1.0, 3.4%) *UCTX-II* 1.4% (−0.6, 3.4%) *COMP* 1.6% (−0.1, 3.2%)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Males: 25.1 µg/dL			*C2C* 0.0% (−1.0, 1.0%) *CPII* −0.2% (−1.4, 1.0%) *C2C:CPII* 0.0% (−1.4, 1.4%) *HA* 0.2% (−2.5, 3.0%) *Females* *uNTX-I* 7.7% (3.9, 11.7%) *UCTX-II* 5.1% (0.8, 9.5%) *COMP* −0.8% (−2.8, 1.2%) *C2C* 0.0% (−1.6, 1.6%) *CPII* 1.7% (−0.6, 4.1%) *C2C:CPII* −1.2% (−3.5, 1.1%)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					HA −0.8% (−6.6, 5.3%)
†Nelson et al. (2011b) Johnston County, N.C. United States 2003–2004 and 2006–2008 Cross-Sectional	Johnston County Osteoarthritis Project n = 1635 African American and White adults ages ≥45 yr old	Blood Blood Pb measured in venous whole blood using ICP-MS Age at measurement: Mean (SD): 65.3 (11.0) yr Mean: 2.4 µg/dL	Osteoarthritis Radiographic and symptomatic osteoarthritis. Radiographic OA (rOA) assessed in the knee using the Kellgren-Lawrence grading system. Symptomatic OA (sxOA) assessed using a combination of radiographic evidence and self-reported symptoms Age at outcome: Mean (SD): 65.3 (11.0) yr	Age, sex, race, ethnicity, BMI, current smoking, and current drinking	**ORs for Prevalent Osteoarthritis of the Knee** rOA 1.10 (1.00, 1.20) sxOA 1.08 (0.96, 1.20)
Oral Health – Adults					
†Won et al. (2013) South Korea 2009 Cross-Sectional	KNHANES n = 1966 General population; ≥19 yr old	Blood Blood Pb measured in venous whole blood using GFAAS Age at measurement: ≥19 yr Mean NR T1: <1.73 µg/dL T2: 1.73–3.04 µg/dL T3: >3.04 µg/dL	Periodontal disease Community Periodontal Index (code ≥3, corresponding to pockets >3.5 mm) Age at outcome: ≥19 yr	Age, sex, family income, education level, use of floss, use of interproximal toothbrush, alcohol consumption, smoking status, ETS in workplace, diabetes, hypertension, and oral health status	**ORs for Prevalent Periodontal Disease across blood Pb tertiles** T1: Ref. T2: 1.37 (0.97, 1.93) T3: 1.31 (0.88, 1.96)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Han et al. (2013) South Korea 2008–2010 Cross-Sectional	KNHANES n = 4716 General population; ≥19 yr old	Blood Blood Pb measured in venous whole blood using GFAAS Age at measurement: ≥19 yr GM: Periodontitis: 2.60 µg/dL No periodontitis: 2.12 µg/dL	Periodontal disease Community Periodontal Index (code ≥3, corresponding to pockets >3.5 mm) Age at outcome: ≥19 yr	Age, gender, income, education, frequency of daily toothbrushing, regular dental check-up, smoking, alcohol consumption, physical activity, fasting plasma glucose, BMI, white blood cell count and urine cotinine concentration.	**ORs for Prevalent Periodontal Disease across blood Pb quintiles** Q1 (≤1.59 µg/dL) Ref. Q2 (1.59–2.05 µg/dL) 1.36 (1.00, 1.85) Q3 (2.05–2.52 µg/dL) 1.3 (0.96, 1.76) Q4 (2.52–3.57 µg/dL) 1.55 (1.13, 2.13) Q5 (≥3.17 µg/dL) 1.6 (1.15, 2.22)
†Kim and Lee (2013) South Korea 2008–2009 Cross-Sectional	KNHANES n = 3996 General population; ≥20 yr old	Blood Blood Pb measured in venous whole blood using GFAAS Age at measurement: ≥20 yr GM: 2.31 µg/dL	Periodontal Disease Community Periodontal Index (code ≥3, corresponding to pockets >3.5 mm) Age at outcome: ≥20 yr	Age, body mass index (BMI), residence area, education level, household income, smoking and drinking status, hemoglobin, glucose, use of floss or interproximal toothbrush, decayed, missing, or filled permanent teeth (DMFT), and active caries	**ORs for Prevalent Periodontal Disease across blood Pb quintiles** Males 1.854 (1.265, 2.717) Males (adjusted for Hg, Cd) 1.699 (1.154, 2.502) Females 1.301 (0.883, 1.917) Females (w/ Hg and Cd)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					1.242 (0.833, 1.851)
Oral Health – Children and Adolescents					
†Wu et al. (2019) Mexico City Mexico Initial Recruitment: 1997–2005; Follow-up: 2008–2013 Cohort	Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) n = 173 to 386 (depending on exposure metric) Mother/child pairs recruited from 2 public hospitals serving low- to moderate-income populations	Blood Maternal and child blood Pb measured in venous whole blood using GFAAS. Maternal bone Pb measured using K-XRF Age at measurement: Maternal BLL: 1st, 2nd, and 3rd trimester Child BLL: 1, 2, 3, and 4 yr, and in adolescence (10 to 18 yr) Maternal bone: Postnatally Mean (males, females): 1st trimester: 6.06, 6.36 µg/dL 2nd trimester: 5.24, 5.25 µg/dL 3rd trimester: 5.67, 5.73 µg/dL Childhood: 15.48, 15.18 µg/dL Adolescence: 3.60, 3.34 µg/dL Maternal tibia: 8.64, 9.68 µg/g Maternal patella: 7.18, 8.64 µg/g	Dental caries Teeth evaluated by trained examiners who assigned decayed, missing, filled tooth (DMFT) scores Age at outcome: Adolescence (10 to 18 yr)	Sex, cohort, mother's education, sugar sweetened beverages intake	**Rate Ratio of Decayed, Missing, and Filled Teeth per ln-unit increase in blood or bone Pb** 1st Trimester BLL 1.07 (0.90, 1.27) 2nd Trimester BLL 1.12 (0.94, 1.32) 3rd Trimester BLL 1.17 (0.99, 1.37) Childhood BLL 1.14 (0.94, 1.38) Adolescent BLL 0.97 (0.81, 1.16) Maternal Patella Pb 0.95 (0.88, 1.03) Maternal Tibia Pb 0.98 (0.88, 1.08)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Kim et al. (2017) Seoul, Daegu, Cheonan, and Busan South Korea 2005–2010 Cross-sectional	The Children's Health and Environment Research (CHEER) group n = 1,565 (children w/ permanent teeth) and 1,241 (children w/ deciduous teeth) School-aged children from urban, rural, and industrialized areas with BLLs <5 µg/dL	Blood Blood Pb measured in venous whole blood using GFAAS Age at measurement: "School-aged" GM: 1.53 µg/dL	Dental caries DMFS sum by trained dental hygienists Age at outcome: "School-aged"	Sex, age (categorical), household income (categorical), and urinary cotinine level (categorical)	**PR for Decayed and Filled Surfaces** *Deciduous Teeth* *Decayed Surfaces* 1.16 (0.91, 1.49) *Filled Surfaces* 1.11 (0.98, 1.25) *DMFS* 1.14 (1.02, 1.27) *Permanent Teeth* *Decayed Surfaces* 0.69 (0.45, 1.07) *Filled Surfaces* 0.87 (0.73, 1.04) *DMFS* 0.83 (0.69, 0.99)
†Wiener et al. (2015) United States 1988–1994 Cross-Sectional	NHANES III n = 3127 General population; 2 to 6 yr old	Blood Blood Pb measured in venous whole blood using GFAAS Age at measurement: 2 to 6 yr Mean NR 28.2% <2 µg/dL; 48.3% 2 to <5 µg/dL; 18.4% 5 to <10 µg/dL;	Dental caries Number of teeth with at least one decayed or filled surface as detected by trained examiners Age at outcome: 2 to 6 yr	Sex, race/ethnicity, age, urban status, census region, poverty index, family education, ETS exposure, birth weight, breastfed, dental visit, and parental perception of oral health	**PR for Decayed and Filled Surfaces** <2 µg/dL: Ref. 2–5 µg/dL: 1.84 (1.36, 2.50) 5–10 µg/dL:

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		5.1% >10 µg/dL			2.14 (1.36, 3.36) >10 µg/dL: 1.91 (1.17, 3.11)

BLL = blood lead level; BMD = bone mineral density; BMI = body mass index; CHEER = Children's Health and Environment Research; CI = confidence interval; C2C = serum cleavage neoepitope of type II collagen; COMP = cartilage oligomeric matrix protein; CPII = carboxypropeptide of type II collagen; DMFS =; DMFT = decayed, missing, and filled teeth; DXA = Dual-energy X-ray absorptiometry; ELEMENT = Early Life Exposures in Mexico to Environmental Toxicants; ETS = environmental tobaccos smoke; GFAAS = Graphite furnace atomic absorption spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; KARE = Korean Association Resource; KNHANES = Korean National Health and Nutrition Examination Survey; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OA = osteoarthritis; Pb = lead; PR = prevalence ratio; rOA = radiographic osteoarthritis; sxOA = symptomatic osteoarthritis; SD = standard deviation; Q = quartile; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.

†Studies published since the 2013 Integrated Science Assessment for Lead.

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Table 9-12 Animal toxicological studies of exposure to Pb and musculoskeletal effects.

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL As Reported (µg/dL)	Endpoints Examined
Beier et al. (2017)	Mouse (C57BL.6), 0 ppm Pb, M/F, n = NR 100 ppm Pb, M/F, n = NR	PND 240	Oral, drinking water	0.17 ± 0.19 ng/dL for 0 ppm, 58.67 ± 4.61 ng/dL for 100 ppm - PND 240	Serum Protein Levels of Dickkopf-1, Serum Protein Levels of Sclerostin (scl), Serum Protein Levels of C-terminal telopeptide (CTx-1), Serum Protein Levels of type 1 procollagen (P1NP), Energy to Femur Failure (Males, 8 moo), Femur Yield Load / Maximum Load (Males, 8 moo), Maximum Femur Stiffness (Males, 8 moo), Osteoclast Surface/Bone Surface (Oc.S/BS) by Micro-Computed Tomography (microCT), Osteoclast Number/Trabecular Area (N.Oc/Tb.Ar) by Micro-Computed Tomography (microCT), Osteoblast Number/Trabecular Area (N.Ob/Tb.Ar) by Micro-Computed Tomography (microCT), Adipocyte size (Ad Size) by Micro-Computed Tomography (microCT), Adipocyte Volume/Total Volume (AV/TV) by Micro-Computed Tomography (microCT), Bone Volume to Total Volume (BV/TV) by Micro-Computed Tomography (microCT)

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL As Reported (µg/dL)	Endpoints Examined
Beier et al. (2016)	Mouse (C57BL.6), 0 ppm Pb, F, 200 ppm Pb, F, 500 ppm Pb,/F	PND 30, 90, 180, 360	Oral, drinking water	0 ng/mL for 0 ppm, 50 ng/mL for 100 ppm, 100 ng/mL for 300 ppm - PND 28	Femur Length, Areal Bone Mineral Density (aBMD), Bone Mass, Bone Weight, Body Fat, Femur Diameter, P1NP (ng/mL), TRAP5b (U/L), CTx (ng/mL), Calcitonin (pg/mL), 17 beta-estradiol (ng/mL), Dkk-1 (ng/mL), Femoral BV/TV, Tb.N, Tb.Sp, Conn.D, SMI, Cort Th, Cort BA, Tb Extension, Bone Strength, Beta-Catenin Protein Levels, TNF-Alpha Protein Levels, NF-κB Protein Levels, b-catenin RT-PCR, Peroxisome Proliferator-Activated Receptor-c RT-PCR, CD47 RT-PCR, Nuclear Factor Of Activated T Cells RT-PCR, CTSK RT-PCR

aBMD = areal bone mineral density; AV/TV = adipocyte volume/total volume; BV/TV = bone volume to total volume; CTx-1 = C-terminal telopeptide; mo = month(s); microCT = Micro-Computed Tomography; NF-κB = nuclear factor kappa B; N.Oc/Tb.Ar = Osteoclast Number/Trabecular Area; Oc.S/BS = Osteoclast Surface/Bone Surface; P1NP = type 1 procollagen; PND = postnatal day; RT-PCR = reverse transcription-polymerase chain reaction; scl = sclerostin; TNF = tumor necrosis factor.

Table 9-13 Epidemiologic studies of exposure to Pb and ocular effects.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Glaucoma					
†Wang et al. (2018b) United States 1991–1999 (Follow-up through 2014) Cohort	Veterans Affairs NAS n = 702 Healthy male Veterans at time of enrollment in the NAS (1963) and without glaucoma at baseline (time of bone lead measurement)	Bone Tibia and patella lead measured using K-XRF Age at measurement: Mean age: 66.8 Mean – Tibia: 21.7 µg/g Patella: 31.0 µg/g	Glaucoma Incident cases of primary open-angle glaucoma identified using validated criteria to assess medical records	Age, BMI, education, job type, pack-yr, diabetes mellitus, systemic hypertension, and ocular hypertension.	**HRs for Glaucoma Incidence** *Tibia Pb* 1.28 (0.99, 1.65) *Patella Pb* 1.42 (1.11, 1.82)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Park and Choi (2016) South Korea 2008–2012 Cross-sectional	KNHANES n = 8371 General population, ≥20 yr old with no history of glaucoma	Blood Blood Pb was measured in venous whole blood using GFAAS Age at measurement: ≥20 yr old GM: 2.19 µg/dL	Intraocular pressure Intraocular pressure measured using a Goldmann applanation tonometer Age at outcome: ≥20 yr old	Age, sex, smoking status, alcohol consumption, job status, education, residence, hypertension medication use, and family history of glaucoma	**Change in intraocular pressure (mmHg):** 0.088 (0.06, 0.117)
†Lin et al. (2015) South Korea 2008–2009 Cross-sectional	KNHANES n = 2680 General population, ≥19 yr old with no history of retinal disease or stroke	Blood Blood Pb was measured in venous whole blood using GFAAS Age at measurement: ≥19 yr old Mean – w/ glaucoma: 2.70 µg/dL w/o glaucoma: 2.52 µg/dL	Glaucoma Presence of glaucoma was assessed by testing of visual function using frequency-doubling technology. Age at outcome: 19 yr old	Age, sex, exercise, and ferretin and aspartate aminotransferase levels	**OR for Glaucoma Prevalence[b]:** 1.04 (0.84, 1.29)
†Lee et al. (2016) South Korea 2008–2012 Cross-sectional	KNHANES n = 5198 General population, ≥19 yr old without a history of glaucoma or age-related macular degeneration	Blood Blood Pb was measured in venous whole blood using GFAAS Age at measurement: ≥19 yr old GM – No Glaucoma: 2.32 µg/dL; Glaucoma: 2.28 µg/dL	Glaucoma Presence of glaucoma was assessed by testing of visual function using frequency-doubling technology. Age at outcome: ≥19 yr old	Age group, region of residence, occupation, education level, smoking status, hypertension, family history of glaucoma, and IOP	**ORs for Glaucoma Prevalence[b]** *Normal IOP* 0.93 (0.65, 1.34) *Low-Teen IOP* 1.16 (0.74, 1.83) *High-Teen IOP* 0.65 (0.36, 1.18)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Age-Related Macular Degeneration					
†Park et al. (2015) South Korea 2008–2011 Cross-sectional	KNHANES n = 3865 General population, ≥40 yr old	Blood Blood Pb was measured in venous whole blood using GFAAS Age at measurement: ≥40 yr old Mean: 2.69 µg/dL	Age-related macular degeneration Macular degeneration was assessed using retinal photographs. Photographs were graded at least twice using a standardized protocol. Age at outcome: ≥40 yr old	Age, sex, smoking status, occupation, residence, household income, anemia, BMI	**Early-Stage AMD (OR):** 1.12 (1.02, 1.23) **Late-Stage AMD (OR):** 1.25 (1.05, 1.50)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Hwang et al. (2015) South Korea 2008–2012 Cross-sectional	KNHANES n = 4933 General population, ≥40 yr old	Blood Blood Pb was measured in venous whole blood using GFAAS Age at measurement: ≥40 yr old Mean: 3.15 µg/dL Quintile 1: <1.75 µg/dL Quintile 2: 1.75–2.25 µg/dL Quintile 3: 2.25–2.73 µg/dL Quintile 4: 2.73–3.38 Quintile 5: >3.38 µg/dL	Age-related macular degeneration Macular degeneration was assessed using retinal photographs. Photographs were graded twice using a standardized protocol. Age at outcome: ≥40 yr old	NA	**ORs (Early-Stage AMD; Quintiles)** Q1: Reference Q2: 1.04 (0.62, 1.73) Q3: 1.14 (0.70, 1.84) Q4: 1.26 (0.78, 2.06) Q5: 1.55 (0.94, 2.53) *Men Only:* Q1: Reference Q2: 0.66 (0.31, 1.40) Q3: 1.32 (0.68, 2.56) Q4: 0.80 (0.40, 1.60) Q5: 1.32 (0.68, 2.54) *Women Only:* Q1: Reference Q2: 1.72 (0.86, 3.46) Q3: 1.83 (0.90, 3.73) Q4: 1.41 (0.72, 2.77) Q5: 1.92 (1.06, 3.48)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Wu et al. (2014) United States 2005–2008 Cross-sectional	NHANES n = 5390 General population, ≥40 yr old	Blood Blood Pb was measured in venous whole blood using ICP-MS Age at measurement: ≥40 yr old GM: 1.61 µg/dL; Median: 1.77 µg/dL 75th: 2.61 µg/dL Max: 26.8 µg/dL Quartile 1: 0.18–1.2 µg/dL Quartile 2: 1.21–1.77 µg/dL Quartile 3: 1.78–2.61 µg/dL Quartile 4: 2.62–26.8 µg/dL	Age-related macular degeneration Macular degeneration was assessed using retinal photographs. Photographs were graded twice using a standardized protocol. Age at outcome: ≥40 yr old	Age, aged-squared, gender, race, education, BMI, pack-yr	**ORs for AMD Prevalence (Quartiles)** Q1: Reference Q2: 0.86 (0.60, 1.22) Q3: 1.00 (0.68, 1.48) Q4: 0.86 (0.59, 1.26)
Other Ocular Effects					
†Wang et al. (2016) United States 1999–2008 Cross-sectional	NHANES n = 9763 General population, ≥50 yr old	Blood Blood Pb was measured in venous whole blood using AAS (1999–2002) and GFAAS (2003–2008) Age at measurement: 50+ yr old GM: 1.97 µg/dL	Cataract surgery Self-reported cataract surgery Age at outcome: ≥50 yr old	Age, race, gender, education, diabetes mellitus, BMI, serum cotinine, and pack-yr	**OR for Cataract Surgery per doubling of BLL:** 0.97 (0.88, 1.06)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Jung and Lee (2019) South Korea 2010–2012 Cross-sectional	KNHANES n = 23376 General population, ≥40 yr old	Blood Blood Pb was measured in venous whole blood using GFAAS Age at measurement: ≥40 yr old GM – Male: 2.82 µg/dL; Female: 2.05 µg/dL Tertile 1: <2.03 µg/dL Tertile 2: 2.03–2.82 µg/dL Tertile 3: >2.82 µg/dL	Dry eye disease Self-reported symptoms of dry eye disease Age at outcome: ≥40 yr old	Age, sex, smoking status, alcohol consumption, region, education, occupation, family income, family history of ophthalmologic disease, and history of ophthalmologic surgery	**ORs for Dry Eye Disease Prevalence (Tertiles)** **T1:** Reference **T2:** 1.12 (0.85, 1.48) **T3:** 0.79 (0.56, 1.1)

AAS = atomic absorption spectrometry; AMD = age-related macular degeneration; BMI = body mass index; GFAAS = Graphite furnace atomic absorption spectrometry; GM = geometric mean; HR = hazard ratio; ICP-MS = inductively coupled plasma mass spectrometry; IOP = intraocular pressure; KNHANES = Korean National Health and Nutrition Examination Survey; K-XRF = K-Shell X-Ray Fluorescence; NA = not available; NAS = Normative Aging Study; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; T = tertile; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.

[b]Per natural log unit increase in µg/dL of blood Pb.

†Studies published since the 2013 Integrated Science Assessment for Lead.

Table 9-14 Animal toxicological studies of Pb exposure and ocular effects.

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL As Reported (µg/dL)	Endpoints Examined
Shen et al. (2016)	Rat (Sprague Dawley), 0 ppm Pb, M, n = 12 (BLL), n = 6 (other endpoints) 55 ppm Pb (0.01%), M, n = 12 (BLL), n = 6 (other endpoints) 109 ppm Pb (0.02%), M, n = 12 (BLL), n = 6 (other endpoints)	BLL weeks 1, 2, 3, 4, 5, 6; Other Endpoints week 6	Oral, drinking water	1.11 ± 0.08 µg/dL for 0.00% 12.58 ± 2.42 µg/dL for 0.01% 19.00 ± 2.59 µg/dL for 0.02%	Retinal Thickness, Blood-Retina-Barrier Permeability, Occludin Protein Levels, Claudin 5 Protein Levels, Immunofluorescence Protein Levels of Occludin, Immunofluorescence Protein Levels of Claudin 5, Western Blot Protein Levels of Occludin, Western Blot Protein Levels of Claudin-5, Western Blot Protein Levels of pAkt (Ser473), Western Blot Protein Levels of pAkt (Thr308)
Perkins et al. (2012)	Mouse (C57BL.6), Bcl-xL Transgenic ((C57BL.6), Background)Wild Type 0.0% Pb Acetate, M/F, n = 3 to 7, varying between groups and between assays Wild Type 0.015% Pb Acetate, M/F, n = 3 to 7, varying between groups and between assays Transgenic 0.0% Pb Acetate, M/F, n = 3 to 7, varying between groups and between assays Transgenic 0.015% Pb Acetate, M/F, n = 3 to 7, varying between groups and between assays	BLL PND 21, PND 60 Other Endpoints PND 60 to 70	Oral, drinking water	1.9 ± 1.0 µg/dl for 0.0%, 20.6 ± 4.7 µg/l for 0.015% Pb -– PND 21 3.6 ± 1.8 µg/dl for 0.0%, 5.6 ± 2.7 µg/l for 0.015% Pb –– PND 60	Conventional Transmission Electron Microscopy (TEM) of Cell and Organelle Structure, Three-Dimensional Electron Microscope Tomography of Cell and Organelle Structure, Mitochondrial Cristae Measurements in Rod Spherules, Mitochondrial Cristae Measurements in Cone Pedicles, Mitochondrial Crista Junction Diameter and Density in Rod Spherules, Mitochondrial Crista Junction Diameter and Density in Cone Pedicles, Photoreceptor and Synaptic Terminal Oxygen Consumption (Light-Adapted)

BLL = blood lead level; CI = confidence interval; F = female; M = male; pAkt = phosphorylated Akt; Pb = lead.

Table 9-15 Epidemiologic studies of Pb exposure and respiratory effects.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Children and Adolescents					
†Madrigal et al. (2018) United States 2011–2012 Cross-sectional	NHANES n:1234 Children and adolescents aged 6–17 yr	Blood Pb measured in venous whole blood using ICP-MS. Age at measurement: 6–17 yr old Median: 0.56 µg/dL 25th percentile: 0.44 µg/dL 75th percentile: 0.85 µg/dL	Pulmonary function: FEV_1, FVC, FEV_1: FVC, and $FEF_{25–75\%}$ Spirometry was performed in the standing position using a standardized protocol according to the recommendations of the American Thoracic Society for FEV1 and FVC. Age at outcome: 6–17 yr old	Age, sex, race, height, family income to poverty ratio, serum cotinine, use of anti-asthmatic, bronchodilator, or inhaler medications	**Change in lung function parameters across blood Pb quartiles** *FEV_1* Q1: Ref. Q2: 4.8 (−98.3, 107.8) Q3: 22.3 (−49.3, 93.9) Q4: 41.9 (−46.9, 130.6) *FVC* Q1: Ref. Q2: 1.6 (−88.5, 91.7) Q3: 23.8 (−46.4, 94.0) Q4: 45.5 (−49.2, 140.2) *FEV_1:FVC* Q1: Ref. Q2: 0.0003 (−0.01, 0.01) Q3: −0.001 (−0.01, 0.01) Q4: 0.002 (−0.01, 0.02) *$FEF_{25–75\%}$* Q1: Ref. Q2: −8.1 (−229.8, 213.7) Q3: −28.9 (−160.5, 102.7) Q4: 0.71 (−193.1, 192.5)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Zeng et al. (2017) Guiyu, Xiashan, and Haojiang Guangdong Province, China November - December 2013 Cross-sectional	Preschool children aged 5–7 yr n = 206 (n = 100 from Guiyu, n = 54 from Xiashan, n = 52 from Haojiang)	Blood Pb measured in venous whole blood using GFAAS Age at measurement: 5–7 yr old Median Exposed (Guiyu): 5.53 µg/dL Unexposed (Xiashan and Haojiang): 3.57 µg/dL 75th Percentile: Exposed: 7.04 µg/dL Unexposed: 4.86 µg/dL	Lung function parameters: FVC and FEV1 Spirometry was conducted with a portable spirometer; results of three readings were recorded and the highest FVC and FEV1 was used in the analysis Age at outcome: 5–7 yr old	Age, gender, height, family member daily smoking, family income level, parental education level, daily outdoor play time, and living area	**Change in lung function parameters per ln-unit increase in blood Pb (µg/dL)** *FEV_1 (mL)* −15 (−93, 63) *FVC (mL)* −29 (−100, 43)
†Little et al. (2017) Legnica-Głogów District Poland 1995 and 2007 Cross-sectional	Polish schoolchildren aged 10–15 yr n = 184 male n = 189 female	Blood Pb measured in venous whole blood using GFAAS Age at measurement: 10–15 yr	FVC A Spiro ProVR unit was used to measure pulmonary function. FVC was computed by the instrument as a percentage of gender-, age- and height-specific normative data. Age at outcome: 10–15 yr	Adjusted for height	**Change in FVC (mL) per log_{10}-unit increase in blood Pb (µg/dL)** *Boys* −5.1 (−13.9, 3.7) *Girls* −12.9 (−23.2, −2.6)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Zeng et al. (2016) Guiyu and Haojiang China December 2012 to January 2013 Cross-sectional	Children age 3–8 n = 470 children n = 170 from Haojiang and n = 300 from Guiyu)	Blood Pb measured in venous whole blood using GFAAS. Age at measurement: 3–8 yr old Medians Guiyu: 6.24 µg/dL Haojiang: 4.75 µg/dL 75th: BLL: Guiyu: 8 µg/dL Haojiang: 5.76 µg/dL	Respiratory symptoms: wheeze, cough, dyspnea, and phlegm The respiratory symptoms such as wheeze, cough, phlegm, and dyspnea were defined by the standard questionnaire from the European Community Respiratory Health Survey (ECRHS) Age at outcome: 3–8 yr old	Age, gender, passive smoking, living in Guiyu, whether use home as workshop, whether home close to e-waste recycling site, and whether child contact e-waste	**OR (≥5 µg/dL vs. <5 µg/dL blood Pb)** *Wheeze* 0.64 (0.32, 1.27) *Dyspnea* 0.64 (0.23, 1.79) *Cough* 0.95 (0.6, 1.52) *Phlegm* 1.2 (0.72, 2.01)
Adults					
†Pak et al. (2012) Shiwha and Banwol Korea 2005 and 2007 (Shiwha) and 2006 and 2008 (Banwol) Cohort	Shiwha and Banwol Environmental Health Cohort (SBEHC) Men and women over the age of 30 residing in Shiwha or Banwoi and completed both pulmonary function tests during cycle 1 (2005–2006) and cycle 2 (2007–2008) n = 263 (n = 112 males)	Blood Pb measured in venous whole blood using GFAAS GM (GSD): Cycle 1: 1.55 (1.76) µg/dL Cycle 2: 1.96 (1.66) µg/dL	FEV_1 and FVC Pulmonary function was measure via spirometry Age at outcome: 30+	Age, sex, baseline height, baseline FVC, methacholine, cotinine level	**Accelerated FVC Decline** 177.0 (24.1, 329.9) **Accelerated FEV_1 Decline** 107.0 (−0.8, 214.8)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Leem et al. (2015) Korea 2008–2012 Cross-sectional	KNHANES n = 5972 Adults ≥20 yr who completed spirometry and had blood measurements	Blood Pb measured in venous whole blood using GFAAS Age at measurement: 20+ Mean BLL non-OLF: 2.36 µg/dL OLF: 2.77 µg/dL	Obstructive lung function (OLF) Spirometry was used for lung function. OLF was defined as FEV1/FVC <0.7 Age at outcome: 20+	Age, sex, BMI, and smoking status	**Change in lung function parameters per ln-unit increase in blood Pb (µg/dL)** *FEV_1 (mL)* 0 (−116, 116) *FVC (mL)* 9 (−3, 21) *FEV_1/FVC (%)* −0.002 (−0.004, 0)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Rokadia and Agarwal (2013) United States 2007–2010 Cross-sectional	NHANES n = 9575 (1164 OLD and 8411 non-OLD) General population; ≥18 yr old	Serum Pb measured from venous whole blood samples using ICP-MS Age at measurement: 18–79 yr Geom. mean (SE) non-OLD: 1.18 (1.0) µg/dL OLD: 1.73 (1.02) µg/dL	Obstructive lung disease (OLD) Spirometric data were collected from NHANES participants; Participants with OLD were defined as FEV 1 /FVC <0.7; Mild OLD: FEV1 = 80% predicted; Moderate–severe OLD: FEV1 <80% predicted Age at outcome: 18–79 yr	Age, sex, race, BMI, chronic kidney disease, diabetes, hyperlipidemia, hypertension, stroke, coronary artery disease, smoking, serum C-reactive protein concentration, and serum cotinine concentration	**ORs for OLD Prevalence** *All OLD* 1.94 (1.10, 3.42) *Mild OLD* 1.21 (0.55, 2.66) *Moderate–Severe OLD* 3.49 (1.70, 7.16)

BLL = blood lead level; BMI = body mass index; CI = confidence interval; ECRHS = European Community Respiratory Health Survey; FEF = forced expiratory flow; FEV1 = forced expiratory volume; FVC = forced vital capacity; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; GSD = gestational sac diameter; ICP-MS = inductively coupled plasma mass spectrometry; KNHANES = Korean National Health and Nutrition Examination Survey; NHANES = National Health and Nutrition Examination Survey; OLD = obstructive lung disease; OLF = obstructive lung function; OR = odds ratio; Pb = lead; SBEHC = Shiwha and Banwol Environmental Health Cohort; Q = quartile; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.

†Studies published since the 2013 Integrated Science Assessment for Lead.

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Table 9-16 Animal toxicological studies of exposure to Pb and respiratory effects.

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL As Reported (µg/dL) b	Endpoints Examined
Dumková et al. (2017)	Mouse (ICR) experiment 1 Control (clean air), F, n = 5 1.23 × 10^6 PbO particles/cm^3, F, n = 5 experiment 2 Control (clean air), F, n = 5 0.956 × 10^6 PbO particles/cm^3, F, n = 5	NR	Mice were exposed to PbO NPs 24 hr/d for 6 wk.	<11 ng/g for control (<1.166 µg/dL) 132 ng/g for Pb-exposed (13.992 µg/dL)	IHC, Histology
Dumková et al. (2020b)	Mouse (CD1) (ICR) Control (clean air), F, n = 10 (2 wk, 6 wk, 11 wk) PbO, F, n = 10 (2 wk, 6 wk, 11 wk) PbO recovery, F, n = 10 (6 wk PbO, 5 wk clean air)	NR	Mice were exposed to clean air or PbO np 24 hr/d 7 d/wk for 2 wk, 6 wk, or 11 wk. a recovery group was exposed to PbO for 6 wk and then clean air for 5 wk (11 wk total)	<3 ng/g in control (2 wk, 6 wk, 11 wk) (<0.3 µg/dL) 104 ng/g PbO 2 wk (10.4 µg/dL) 148 ng/g PbO 6 wk (14.8 µg/dL) 174 ng/g PbO 11 wk (17.4 µg/dL) 27 ng/g PbO recovery (6 wk/clean air 5 wk) (2.7 µg/dL)	Western blot, Histology, IHC, PCR

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL As Reported (µg/dL) b	Endpoints Examined
Dumková et al. (2020a)	Mouse (ICR) Control (clean air), F, n = 10 (d 3, 2 wk, 6 wk, 11 wk) $Pb(NO3)_2$ (68.6 µg/m^3), F, n = 10 (d 3, 2 wk, 6 wk, 11 wk) Recovery ($Pb(NO3)_2$ 68.6 µg/m^3), F, n = 10 (6 wk Pb/5 wk recovery)	6 wk - 8 wk at start	Mice were exposed to $Pb(NO3)_2$ np or clean air 24 hr/d, 7 d/wk for 3 d, 2 wk, 6 wk, or 11 wk. To assess recovery, a separate group of mice were exposed to $Pb(NO3)_2$ for 6 wk and then clean air for 5 wk.	<3 ng/g for control at all timepoints (d 3, 2 wk, 6 wk, 11 wk) (<0.3 µg/dL) 31 ng/g for Pb(NO3)2 d 3 (3.1 µg/dL) 40 ng/g for Pb(NO3)2 2 wk (4.0 µg/dL) 47 ng/g for Pb(NO3)2 6 wk (4.7 µg/dL) 85 ng/g for Pb(NO3)2 11 wk (8.5 µg/dL) 10 ng/g for Pb(NO3)2 exposure 6 wk and clean air for 5 wk (1.0 µg/dL)	PCR, Histology, IHC

BLL = blood lead level; BMI = body mass index; d = day(s); hr = hour(s); IHC = immunohistochemistry; NP = nanoparticle; Pb = lead; Pb(NO3)2 = lead nitrate; PbO = lead monoxide; PCR = polymerase chain reaction; wk = week(s).

Table 9-17 Epidemiologic studies of Pb exposure and total mortality.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Menke et al. (2006) NHANES III 1988–1994, mortality follow-up in 2001 ~12 yr of follow-up Cohort	NHANES III n = 13,946, ≥20 yr Average individual born ~1946	Blood (GFAAS with Zeeman correction) (µg/dL) Mean: 2.58 Tertiles T1 <1.93 T2 1.94–3.62 T3 ≥3.63 Age of measurement Mean 44.4	All-cause mortality	Cox proportional hazard regression analysis adjusted age, race/ethnicity, sex, urban residence, cigarette smoking, alcohol consumption, education, physical activity, household income, menopausal status, BMI, CRP, TC, diabetes mellitus, hypertension, GFR category	**HR** All-cause 1.09 (1.05, 1.14)
Schober et al. (2006) NHANES III 1988–1994, mortality follow-up in 2006 ~8.55 yr of follow-up Cohort	NHANES III n = 9,686, ≥40 yr Average individual born in or before ~1951	Blood (GFAAS with Zeeman correction) (µg/dL) T1 <5 (median 2.6) T2 5–9 (median 6.3) T3 ≥10 (median 11.8) Age of measurement ≥40 yr	All-cause mortality	Cox proportional hazard regression analysis adjusted for sex, age, race/ethnicity, smoking, education level. Did not evaluate BMI or cormorbidities	**HR** All-cause 1.05 (1.03, 1.08)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Lustberg and Silbergeld (2002) NHANES II 1976–1980, mortality follow-up in 1992 Cohort	NHANES II n = 4,190, aged 30–74 Average individual born ~1924	Blood (GFAAS with Zeeman correction)[b] (µg/dL) Mean (SD) 14.0 (5.1) Median: 13 T1: <10 T2: 10–19 T3: 20–29 Age of measurement Mean (SD) 54.1 (13.2)	All-cause and circulatory mortality	Cox proportional hazard regression analysis adjusted for age, sex, location, education, race, income, smoking, BMI, exercise	**HR (T1: Referent)[c]** *All-cause* T2: 1.40 (1.16–1.69) T3: 2.02 (1.62–2.52)
Khalil et al. (2009) Baltimore, MD and Monongahela Valley, PA Blood Pb measured 1990–1991, mortality follow-up for ~12 yr	Study of Osteoporotic Fractures n = 533 women, ages 65–87 yr	Blood (GFAAS with Zeeman correction) (µg/dL) Mean (SD) 5.3 (2.3) Range 1–21 Age of measurement Mean 70	All-cause mortality	Cox proportional hazards regression analysis adjusted for age, clinic, BMI, education, smoking, alcohol intake, estrogen use, hypertension, total hip BMD, walking for exercise, and diabetes	**HR (≥8 µg/dL vs. <8 µg/dL blood Pb)[c]** All-cause: 1.59 (1.02, 2.49)
†Lanphear et al. (2018) United States 1988–1994 mortality follow-up in 2011 ~19 yr of follow-up (IQR 17.6–21.0 yr) Cohort	NHANES III n = 14,289 ≥ 20 yr Average individual born ~1947	Blood (GFAAS with Zeeman correction) (µg/dL) Geometric Mean 2.71 Geometric SE 1.31 10th percentile 1.0 90th percentile 6.7 Age of measurement Mean 44.1	All-cause, CVD, and IHD mortality	Cox proportional hazards regression analysis adjusting for age, sex, household income, ethnic origin, BMI, smoking status, alcohol consumption, physical activity, concentration of cadmium in urine, blood pressure, healthy eating index tertiles, HbA1C, and serum cholesterol	**HR** All-cause: 1.06 (1.03, 1.09) CVD: 1.10 (1.05, 1.15) IHD: 1.14 (1.08, 1.20)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†van Bemmel et al. (2011) United States 1988–1994, follow-up through 2007 ~7.8 yr of follow-up for those with low blood Pb ~7.5 yr of follow-up for those with high blood Pb Cohort	NHANES III n = 3,349 Adult age ≥40 yr Average individual born ~1932	Blood (GFAAS with Zeeman correction) (µg/dL) Median <5 µg/dL 2.6 ≥5 µg/dL 7.5 Age of measurement <5 µg/dL 57 ≥5 µg/dL 61	All-cause and CVD mortality	Cox proportional hazards adjusting for age, education, sex, smoking status, and race/ethnicity	**HR** *All-cause* All: 1.04 (0.98, 1.10) $ALAD^{GG}$ 1.03 (0.98, 1.08) $ALAD^{CG/GG}$ 1.09 (0.93, 1.28)
†Duan et al. (2020) United States 1999–2014, follow-up through end of 2015 ~ 7.1 yr of follow-up Cohort	NHANES n = 18,602 Age ≥20 yr Average individual born ~1960	Blood (ICP-MS) (µg/dL)[d] Median (IQR) 1.49 (0.93, 2.31) Age of measurement Mean (SD) 45.9 (0.3)	All-cause mortality	Poisson regression analyses adjusted for: sex, age, ethnicity, education, poverty-income-ratio (PIR), cotinine category, BMI, physical activity, hypertension, and diabetes	**RR** All-cause: 1.39 (1.28, 1.51)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Byun et al. (2020) Korea 2007–2015, mortality follow-up in 2018 (between 3–11 yr of follow-up) Cohort	KNHANES n = 7,308 Individuals with a BLL less than 10 µg/dL, who were aged 30 yr and over at the baseline examination, and who were not diagnosed with cancer or IHD Average individual born in or before ~1981	Blood (GFAAS with Zeeman background correction) (µg/dL) Geometric mean: 2.26 Blood Pb tertiles: T1: <1.91 T2: 1.91–2.71 T3: >2.71 Age at measurement: ≥30 yr	All-cause mortality	Cox proportional hazard models adjusted for age and sex, household income, education, occupation, smoking status, drinking frequency, BMI, and physical activity, high-lead-containing food intake (grains, vegetables, and seafood)	**HR[c]** T1: Reference T2: 2.02 (1.20, 3.40) T3: 1.91 (1.13, 3.23)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Lin et al. (2011) Taiwan Years not reported Cohort (18 mo of follow-up)	n = 927 Taiwanese adult patients with end-stage renal disease (ERSD) on hemodialysis for >6 mo, age >18	Baseline blood Pb (ETAAS) (µg/dL) Mean: 11.5 Median: 10.4 T1: <8.51 T2: 8.51–12.64 T3: <12.64 Age of measurement Mean (SD) 55.2 (13.5)	All-cause, and Infection-cause mortality	Multivariate Cox model adjusting for age, previous cardiovascular diseases (stroke, MI, PID, congestive heart failure (CHF)), education level, hemodialysis vintage, using fistula, normalized protein catabolic rate, hemoglobin, serum albumin, creatinine, cardiothoracic ratio, and logarithmic transformation of high-sensitivity C-reactive protein (CRP)	**HR (T1: Referent)[c]** *All-cause* T2 2.69 (0.47, 3.44) T3 4.70 (1.92, 11.49) *Infection-cause* T2 4.33 (0.35, 6.54) T3 5.35 (1.38, 20.83) *Hemoglobin-corrected:* *All-cause:* T2: 3.52 (0.41, 5.01) T3: 4.98 (1.86, 13.33) *Infection-cause:* T2: 3.02 (0.23, 2.07) T3: 4.72 (1.27, 17.54)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Tonelli et al. (2018) Canada Cohort (2 yr of follow-up)	n = 1,278 Patients on incident hemodialysis ≥18 yr	Plasma Pb (ICP-MS) (µg/dL) Deciles 1 0.06 2 0.19 3 0.28 4 0.35 5 0.44 6 0.55 7 0.68 8 0.83 9 1.08 10 1.74	All-cause mortality	Logistic regression adjusting for age, sex, race/ethnicity, unemployment prior to dialysis, yr dialysis initiated, dialysis duration, predialysis care, arteriovenous access, comorbidities (atrial fibrillation, MI, BMI, cancer, cerebrovascular disease, CHF, lung disease, diabetes, dementia, hypertension, liver disease, peripheral vascular disease, psychiatric disease, substance misuse), albumin, and creatinine. *All variables were considered candidate variables and were included based on stepwise regression results	Authors indicate a null relationship between blood Pb deciles and all-cause mortality; quantitative results not reported

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Hollingsworth and Rudik (2021) United States Quasi-experimental design	Elderly population (≥65 yr) Assessed the change in deaths (National Vital Statistics System) occuring among this age group before and after the phaseout of leaded gasoline in professional racing (NASCAR, ARCA). Compared mortality rates in race-counties to bordering counties Average individual born in or before ~1942	County-level blood Pb measurements in children	All-cause mortality	Difference-in-difference approach controlling for SES at the county level (median income, unemployment rates, percent minority population), TRI Pb emissions data	Decline in age-standardized mortality rate per 100,000 population Race counties: 91 Border counties: 38

ARCA = Automobile Racing Club of America; BLL = blood lead level; BMD = bone mineral density; BMI = body mass index; CHF = congestive heart failure; CI = confidence interval; CHF = congestive heart failure; CRP = C-reactive protein; CVD = cardiovascular disease; ERSD = end-stage renal disease; ETAAS = electrothermal atomic absorption spectrometry; GFAAS = graphite furnace atomic absorption spectrometry; GFR = glomerular filtration rate; HR = hazard ratio; ICP-MS = inductively coupled plasma mass spectrometry; IHD = ischemic heart disease; IQR = interquartile range; KNHANES = Korean National Health and Nutrition Examination Survey; MI = myocardial infarction; mo = month(s); NASCAR = National Association for Stock Car Auto Racing; NHANES = National Health and Nutrition Examination Survey; Pb = lead; PIR = poverty-income-ratio; RR = risk ratio; SD = standard deviation; SES = socioeconomic status, T = tertile; TC = total cholesterol; wk = week(s); yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.

[b] Blood Pb analysis method unclear, assumed based on data source.

[c] Unable to be standardized.

[d] Units assumed to be µg/dL (written as µg/L in the paper).

†Studies published since the 2013 Integrated Science Assessment for Lead.

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