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United States Environmental Protection Agency

Integrated Science Assessment for Lead

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Office of Research and Development
Center for Public Health & Environmental Assessment

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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://assessments.epa.gov/isa/document/&deid=359536.

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ACRONYMS AND ABBREVIATIONS

AD	Alzheimer's disease
ADHD	attention-deficit/hyperactivity disorder
AL	allostatic load
ALAD	δ-aminolevulinic acid dehydratase
APOE	apolipoprotein E
AQCD	Air Quality Criteria Document
AQS	Air Quality System
As	arsenic
AWQC	ambient water quality criteria
BAEP	brainstem auditory evoked potential
BLL	blood lead level
BLM	biotic ligand model
BMD	benchmark dose
BMI	body mass index
BMS	Baltimore Memory Study
BP	blood pressure
Ca^{2+}	calcium ion(s)
CAD	coronary artery disease
CASAC	Clean Air Scientific Advisory Committee
Cd	cadmium
CEC	cation exchange capacity
CHD	coronary heart disease
CI	confidence interval
C-R	concentration-response
CVD	cardiovascular disease
d	day(s)
DOC	dissolved organic carbon
DTH	delayed-type hypersensitivity
EC_{10}	effect concentration at 10% inhibition
EC_{50}	half maximal effect concentration
Fe	iron
FRM	Federal Reference Method
FSIQ	full-scale intelligence quotient
GABA	gamma-aminobutyric acid
GRIN	glutamate ionotropic receptor N-methyl D aspartate-type subunit
GST	glutathione S-transferase
HAZ	height-for-age Z-score
Hb	hemoglobin
HERO	Health and Environmental Research Online
HFE	hemochromatosis gene
Hg	mercury
HISA	Highly Influential Scientific Assessment
HMOX1	heme oxygenase-1
hr	hour(s)
HRV	heart rate variability
IEUBK	Integrated Exposure Uptake Biokinetic
IFN-γ	interferon-gamma
Ig	immunoglobulin
IHD	ischemic heart disease
IL-4	interleukin-4
IQ	intelligence quotient
IRP	Integrated Review Plan
IS	Integrated Synthesis
ISA	Integrated Science Assessment
KNHANES	Korea National Health and Nutrition Examination Survey
LC	lethal concentration
LECES	Level of Biological Organization, Exposure, Comparison, Endpoint, and Study Design
LOEC	lowest observed effect concentration
MDI	Mental Development Index
Mg^{2+}	magnesium ion
MI	myocardial infarction
mo	month(s)
Mn	manganese
mtDNA	mitochondrial DNA
NAAQS	National Ambient Air Quality Standards
NAS	Normative Aging Study
NASCAR	National Association for Stock Car Auto Racing
NASGLP	North American Soil Geochemical Landscapes Project
NEI	National Emissions Inventory
NHANES	National Health and Nutrition Examination Survey
NOAA	National Oceanic and Atmospheric Administration
NOEC	no-observed-effect concentration
OM	organic matter
OMB	Office of Management and Budget
Pb	lead
PDI	Psychomotor Developmental Index
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
PHQ	Patient Health Questionnaire
PM	particulate matter
PP	pulse pressure

PQAPP	Program-level QA Project Plan	Th	T helper
QA	quality assurance	TSP	total suspended particulate
RBC	red blood cell	TT	tetanus toxoid
SE	standard error	U.S. EPA	United States Environmental Protection Agency
SES	socioeconomic status		
SHEDS	Stochastic Human Exposure and Dose Simulation	VDR	vitamin D receptor
		wk	week(s)
SNP	single nucleotide polymorphism	yr	year(s)

EXECUTIVE SUMMARY

ES.1 Purpose and Scope of the Integrated Science Assessment for Lead

The Federal Clean Air Act requires the United States Environmental Protection Agency (U.S. EPA) to set National Ambient Air Quality Standards (NAAQS) for criteria air pollutants that are considered harmful to public health and the environment, including lead (Pb), and to periodically review the science upon which the NAAQS are based. Pb emitted into air can be inhaled or ingested or can deposit and accumulate in other environmental media (e.g., soil, water, sediment, biota), contributing to a wide range of effects in humans and wildlife. This Integrated Science Assessment (ISA), prepared by the U.S. EPA, is a synthesis and evaluation of the most policy-relevant science that forms the scientific foundation for the review of the primary (health-based) and secondary (welfare-based) NAAQS for Pb. The Pb primary NAAQS is established to protect public health, including at-risk populations, with an adequate margin of safety. The Pb secondary NAAQS is intended to protect the public welfare from known or anticipated adverse effects of Pb in the ambient air and, in this regard, this ISA focuses specifically on ecological effects.

This Executive Summary (ES) provides an overview of the important conclusions drawn in the ISA across scientific disciplines, beginning with information on sources of Pb emissions in ambient air, the fate and transport of Pb in the environment, concentration trends of Pb in air and non-air media, and pathways of exposure, followed by the health and welfare effects of Pb. Health effects evidence evaluated in the Pb ISA includes experimental animal studies and observational epidemiologic studies. Welfare effects evidence evaluated in the Pb ISA includes experimental and observational studies examining the effects of Pb on terrestrial, freshwater, and saltwater ecosystems and biota. A more extensive summary of the evidence and conclusions of the Pb ISA is presented in the Integrated Synthesis (IS), and detailed study-level information and an in-depth characterization of the weight-of-evidence conclusions are included in individual appendices for each topic area. Studies considered in the development of the ISAs are documented in the U.S. EPA Health and Environmental Research Online (HERO) database. The publicly accessible HERO project page for this ISA contains the references that were considered for inclusion and provides bibliographic information and abstracts.

The previous ISA for Pb was published in 2013 (U.S. EPA, 2013) and included peer-reviewed literature published through September 2011. Prior Pb assessments include the 2006 Air Quality Criteria Document (AQCD) for Pb (U.S. EPA, 2006), the 1986 Pb AQCD (U.S. EPA, 1986a) and its associated addendum (U.S. EPA, 1986b), the 1990 Supplement to the 1986 addendum (U.S. EPA, 1990), and the 1977 Pb AQCD (U.S. EPA, 1977). The most recent review of the primary and secondary Pb NAAQS was completed in 2016, at which time the existing standards from 2008 were retained without revision (81 FR 71906). In the 2008 review, the interpretation of the science in the 2006 Pb AQCD led to the decision to

lower the levels of the primary and secondary NAAQS for Pb by ten-fold, from the 1978 levels of 1.5 μg/m^3 to a level of 0.15 μg/m^3. The averaging time was revised to a rolling three-month period with a maximum (not-to-be-exceeded) form, evaluated over a three-year period. U.S. EPA's decision to revise the primary standard in 2008 was based on the substantially expanded body of health effects evidence available at that time, including evidence for cognitive effects of Pb exposure in children. The revised 2008 standard was established to increase protection against air Pb related human health effects, including neurocognitive effects, for children and other at-risk populations. In 2016, the U.S. EPA Administrator concluded that the existing primary standard provides health protection from air emissions for Pb for at-risk groups, especially children, and the existing secondary standard provides protection against adverse effects to public welfare from air emissions for Pb, including harm to aquatic and terrestrial ecosystems (81 FR 71906).

This ISA focuses on synthesizing and integrating the evidence that has become available since the 2013 Pb ISA with the information and conclusions from previous assessments. Key policy-relevant conclusions are intended to inform the U.S. EPA's review of the Pb NAAQS, including conclusions on the populations at increased risk of Pb-related effects, the Pb exposure concentrations at which such effects occur, and the overall strength of the evidence supporting relationships between Pb exposures and health or welfare effects. Conclusions on the overall strength of evidence are described using a five-level hierarchy that classifies the weight of evidence for causation into one of the following categories:

- Causal relationship
- Likely to be a causal relationship
- Suggestive of, but not sufficient to infer, a causal relationship
- Inadequate to infer a causal relationship
- Not likely to be a causal relationship

These causality determinations are made for broad health and welfare effect categories and are informed by evaluating evidence across scientific disciplines for consistency, coherence, and biological plausibility, as well as for uncertainties. The ISA's approach to evaluating the weight of evidence and reaching causality determinations is described in more detail in the Preamble to the Integrated Science Assessments (U.S. EPA, 2015).

ES.2 Pb in Ambient Air

Exposure to Pb can occur from contaminated air, water, soil, and dust. When it is released from industrial processes into the air, Pb is mainly emitted into the air in particulate form (IS.2.3). In general, fine particulate Pb is mostly soluble and removed from the atmosphere by wet deposition, and coarse particulate Pb is mostly insoluble and removed from the atmosphere by dry deposition. Total Pb emissions have steadily decreased for decades largely due to the elimination of leaded gasoline used in

automobiles before 1996, and, in later years, to reductions in emissions from metals processing sources (U.S. EPA, 2022b, 2013, 2006). From 1990 to 2020, there was a steep decline in total U.S. Pb emissions, from about 5 kton/year to less than 1 kton/year. Over this time period, industrial sources have been replaced by non-road mobile sources as the dominant category of Pb emissions, with emissions from aircraft that operate on leaded aviation fuel as the largest emissions source in this category (U.S. EPA, 2021). Total estimated national air emissions from the 2020 National Emissions Inventory (NEI) were 621 tons, with 69% from emissions associated with use of leaded aviation gasoline, 18% from industrial sources, including smelting and metals processing, 9% from fuel combustion, and 3% from wildland fires. All other sources of Pb air emissions combined were estimated to account for about 2% of total U.S. Pb emissions in the NEI. Pb emissions from residential wood combustion are not included in the 2020 NEI but can also be a source in areas affected by wood smoke in the winter. In addition to contemporary Pb emissions into the atmosphere, soil-bound Pb near historical sources can potentially become airborne under some wind or traffic conditions. This resuspended legacy Pb is also not included in the NEI.

Several recent studies indicated substantial spatial variability in urban ambient air Pb concentrations influenced by proximity to local sources or industrial activities. Across urban and neighborhood scales, these variations in ambient air Pb concentrations may not be captured by national monitoring networks. Seasonal trends were reported in numerous recent studies, but results were mixed, and no consistent national pattern of seasonality was apparent. Shifts in Pb size distributions since the 1980s from a mass median diameter usually smaller than 2.5 μm to a mass median diameter between 2.5–10 μm have been documented in ambient air near roads, near industrial sources, in rural locations, and in urban locations within the United States and the European Union. No recent studies specifically investigated background Pb concentrations, but a plausible range of 0.2 to 1 ng/m^3 was proposed based on earlier studies in the 2013 Pb ISA (U.S. EPA, 2013).

ES.3 Fate and Transport

Pb emitted into the atmosphere can be distributed into soil, water, and other media (IS.2.4). The fate and transport of Pb emitted into the air depends on particle size, which in turn depends largely on the source emissions. Particle-bound Pb associated with fine particulate matter is transported long distances and can be found in remote areas, while Pb associated with coarse particulate matter is more likely to deposit closer to its source. After deposition, resuspension of soil-bound Pb can contribute to airborne concentrations near major Pb sources. Once deposited in soil, Pb is strongly retained in soil organic material, and subsequent Pb fate and transport through the soil column is influenced by several physicochemical factors, such as storage in leaf litter, amount and decomposition rates of organic matter, composition of organic and inorganic soil constituents, microbial activity, and soil pH. These physicochemical properties are based on soil forming factors (i.e., climate, organisms, parent material, relief (shape of the landscape), time, and anthropogenic input). Soils that differ in these factors will subsequently have different physicochemical properties and different trends in Pb transport. In water,

runoff from urban or historically industrial areas contains higher Pb concentrations than non-urban areas. Recent studies have improved our understanding of soil fate and transport in many areas. These include the relationships between street characteristics, population density, and land cover with runoff. Recent research has also expanded on the influence of seasonality and precipitation events on runoff. In addition, there have been advances in research on transport and sedimentation. While Pb deposition has decreased in the last half century with the phase-out of leaded gasoline and stricter regulation of some Pb sources, accumulated Pb-contaminated sediments in areas with a history of industry and urbanization are vulnerable to resuspension and both down and upstream movement following a disturbance event. For example, dam removal or other disturbances to water bodies can lead to resuspension and dissolution of Pb-contaminated sediment that was previously deposited. With the predicted increase in drought alongside less frequent but more severe precipitation patterns across most of the United States, there may be a potential for remobilization of legacy Pb.

Additional media besides air, water, and soil play a role in understanding how Pb moves and changes over time in the urban environment (IS.2.2). Urban soil, resuspended dust, road dust, and house dust serve as urban compartments between which Pb can be transported or cycled. High Pb concentrations are characteristic of urban soil in comparison to other soils and are often related to legacy sources. Studies in several U.S. cities have explored the high spatial variability of urban soil Pb concentrations, with hot spots related to income and racial disparities. In recent studies, associations between airborne Pb and elemental indicators of airborne soil have been observed, suggesting the potential for contaminated soil to be a source of airborne Pb locally in urban and industrial areas under some circumstances. Resuspension of urban soil can also be a source of Pb in house dust.

ES.4 Trends

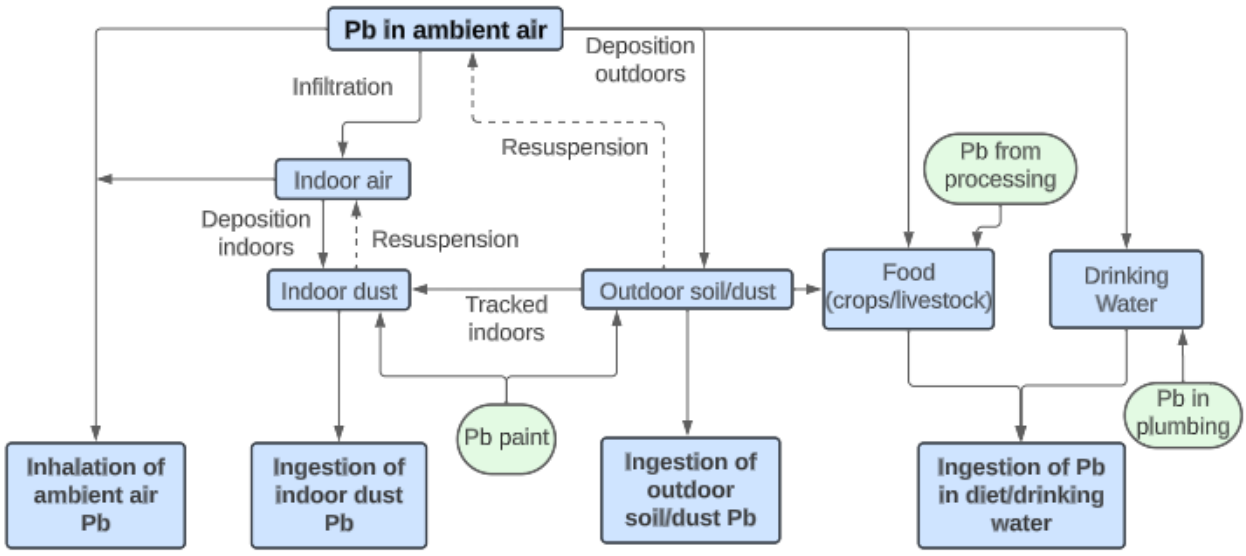
Pb concentrations in ambient air in the United States have decreased since the 1970s, mainly due to the phase-out of Pb in gasoline (IS.3). For some monitors, there has also been a more recent period of continued decline in ambient concentrations corresponding to reductions in Pb emissions from local and regional industrial sources. Based on Pb monitoring network data, the national median of maximum 3-month average Pb concentrations across monitoring sites declined by 89% from 1990 to 2010 for a mix of 74 source-oriented and non-source-oriented monitors that operated continuously through this period (IS.3). For a smaller population of 37 monitors with a higher proportion of source-oriented monitors that operated continuously from 2010 to 2021, the national median of maximum 3-month average Pb concentrations across monitoring sites decreased by 88% over that period (IS.3). This recent decrease was driven by the 2008 Pb NAAQS revision and the steepest declines were observed over the period from 2012 to 2015 at mostly source-oriented monitors when emissions from nearby sources were being reduced to meet the new 2008 Pb NAAQS requirements (IS.3). The declining trend since 2010 is therefore more representative of a small number of communities near major sources than an urban or national median. A national trend is more difficult to assess because the number of non-source-oriented

monitors is small, and their observed concentrations are close to method detection limits on most days (IS.3).

Changes in the patterns of Pb emissions over time and between regions of the United States are also detectable in non-air environmental media and biota (IS.3). Pb may be retained in soils, sediments, the shells of long-lived bivalves, or trees, where it provides a historical record of Pb deposition over periods of decreasing Pb emissions, such as the phase-out of Pb from on-road gasoline and reductions in industrial releases. Overall, evidence from national and regional surveys of Pb in environmental media and biota reflects a decline in anthropogenic emissions of Pb. However, Pb persists in environmental media and is still observed in measurable concentrations within biota, particularly near historic and current sources of Pb pollution. Long-term monitoring of Pb concentration trends in biota (e.g., the National Oceanic and Atmospheric Administration Mussel Watch program) and soil surveys covering large spatial extents (e.g., the U.S. Geological Survey North American Soil Geochemical Landscapes Project) provide essential records of Pb concentrations in the environment observed across decades and regions. Information on atmospheric Pb concentration trends can be difficult to interpret due to the influence of other anthropogenic inputs of Pb and heterogeneity associated with natural environments. Despite reductions in Pb pollution in recent decades, anthropogenic Pb persists in the environment.

ES.5 Exposure

Exposures are considered air-related if they pass through the air compartment at any point prior to plant, animal, or human contact. For example, air-related Pb exposure may occur through direct inhalation of air that contains Pb or ingestion of food, water, dust and soil, or other materials that have been contaminated by Pb originally in ambient air. Non-ambient air-related exposures include those from an occupation, hand-to-mouth contact with Pb-containing consumer goods, hand-to-mouth contact with dust or chips of peeling Pb-containing paint, or ingestion of Pb in drinking water conveyed through Pb pipes. Pb body burden is an aggregation of all of these different exposures. Figure ES-1 depicts the various pathways that ambient air Pb can take through environmental media to reach human beings (IS.4).



This figure displays air-related exposure pathways of Pb through the environment. Dashed lines represent resuspension of Pb into the air. Green ovals represent sources of Pb that are not associated with the air compartment but may contribute to Pb along the exposure pathway. Pb from processing includes Pb that may end up in diet as a result of intentional or inadvertent addition of Pb to food or food additives such as spices. Other recognized sources of Pb exposure such as occupational or some consumer products are not ambient air-related and as such are not included in this figure.

Figure ES-1 Conceptual model of air-related Pb exposure through inhalation and ingestion.

The majority of Pb in the body is stored in bone (roughly 90% in adults, 70% in children; IS.5). Much of the remaining Pb is found in soft tissues; only about 1% of Pb is found in the blood. Pb in blood is primarily (~99%) bound to red blood cells. The small fraction of Pb in blood plasma (<1% of Pb in blood) may be the more toxicologically active fraction of the circulating Pb. The relationship between Pb in blood and plasma is approximately linear at relatively low daily Pb intakes and at blood Pb concentrations below ~20–30 µg/dL. Both Pb uptake to and elimination from soft tissues are much faster than they are in bone. Pb accumulates in bone regions undergoing the most active calcification at the time of exposure. Pb in bone becomes distributed in trabecular (e.g., patella) and the denser cortical bones (e.g., tibia).

Blood Pb is the most common biomarker of Pb exposure in epidemiologic studies of Pb health effects. Overall, blood Pb levels (BLLs) have been decreasing among U.S. children and adults for the past 45 years. For children aged 1–5 years, the 1976–1980 National Health and Nutrition Examination Survey (NHANES) showed a geometric mean BLL of 15.2 (95% CI: 14.3, 16.1) µg/dL with nearly all children (99.8%) exceeding 5 µg/dL. By 2011–2016, geometric mean levels declined to 0.8 (95% CI: 0.8, 0.9) µg/dL with only 1.3% exceeding 5 µg/dL (IS.6). Other common Pb exposure metrics used in epidemiologic studies are Pb in bone, which generally reflects cumulative exposure over long periods (months to years), and Pb in cord blood, which is an indicator of prenatal and neonatal blood Pb concentration.

Blood Pb is dependent on the recent exposure history of the individual, as well as the long-term exposure history that determines total body burden and the amount of Pb stored in the bone. The contribution of bone Pb to blood Pb changes throughout an individual's lifetime and depends on the duration and intensity of the exposure, age, and various other physiological stressors (e.g., nutritional status, pregnancy, menopause, extended bed rest, hyperparathyroidism) that may affect bone remodeling, which continuously occurs under normal conditions. In children, blood Pb is both an index of recent exposure and, potentially, body burden, largely due to faster exchange of Pb to and from bone of children relative to adults. Generally, bone Pb is an index of cumulative exposure and body burden. As described previously, Pb is sequestered in two types of bone compartments: Pb in cortical bone, which is denser and has a slower turnover rate, is a better marker of cumulative exposure than Pb in the more highly perfused trabecular bone, which is more likely to be correlated with blood Pb concentration. During pregnancy, Pb is transferred from the mother to the fetus. Transplacental transfer of Pb may be facilitated by an increase in the plasma/blood Pb concentration ratio during pregnancy. Maternal-to-fetal transfer of Pb appears to be related partly to the mobilization of Pb from the maternal skeleton.

ES.6 Health and Welfare Effects of Pb Exposure

The subsequent sections summarize the current evidence and causality determinations for health and welfare effects in this ISA. These causality determinations appear in Figure ES-2 and Figure ES-3, and are more fully discussed in the Integrated Synthesis and the respective health (Appendices 3–10) and welfare effects (Appendix 11) appendices: https://assessments.epa.gov/isa/document/&deid=359536.

ES.6.1 Health Effects of Pb Exposure

Pb exposure can disrupt important physiological pathways, triggering responses such as increased oxidative stress and inflammation, and lead to a diverse array of health effects. In this ISA, the body of evidence from toxicological and epidemiologic studies is evaluated for health effects that vary in severity from minor subclinical effects to more serious effects that can lead to death. The integration of evidence from these health studies, supported by the evidence from atmospheric chemistry, exposure assessment, toxicokinetics, and exposure biomarker studies, contributes to the causality determinations made for the various health outcomes. Building off the conclusions from the 2013 Pb ISA, a total of thirty causality determinations were made for health outcomes in this ISA. These determinations are summarized in Figure ES-2.

Causality Determinations for Health Effects of Pb	
Health Outcomes	**2024 Pb ISA**
Nervous System Effects Ascertained During Childhood, Adolescent, and Young Adult Lifestages	
Cognitive Effects	
Externalizing Behaviors: Attention, Impulsivity, and Hyperactivity	
Externalizing Behaviors: Conduct Disorders, Aggression, and Criminal Behavior	
Internalizing Behaviors: Anxiety and Depression	
Motor Function	
Sensory Function	↓
Social Cognition and Behavior	+
Nervous System Effects Ascertained During Adult Lifestages	
Cognitive Effects	↑
Psychopathological Effects	
Sensory Function	
Neurodegenerative Disease	↑
Cardiovascular Effects	
Cardiovascular Effects and Cardiovascular-Related Mortality	
Renal Effects	
Renal Effects	↑
Immune System Effects	
Immunosuppression	
Sensitization and Allergic Response	↓
Autoimmunity and Autoimmune Disease	
Hematological Effects	
Hematological Effects	
Reproductive and Developmental Effects	
Pregnancy and Birth Outcomes	↑
Development	
Female Reproductive Function	↑
Male Reproductive Function	
Effects on Other Organ Systems	
Hepatic Effects	↑
Metabolic Effects	+
Gastrointestinal Effects	
Endocrine System Effects	
Musculoskeletal Effects	
Effects on Ocular Health	
Respiratory Effects	
Total (Nonaccidental) Mortality	
Total (Nonaccidental) Mortality	+
Cancer	
Cancer	

Causal (9) Likely Causal (9) Suggestive (6) Inadequate (6)

+ New Causality Determination (3) ↑ or ↓ Change in Causality Determination since 2013 ISA (8)

Notes: (1) The 2013 Pb ISA made four causality determinations with respect to cardiovascular disease (CVD), including BP and hypertension (causal), subclinical atherosclerosis (suggestive), coronary heart disease (CHD; causal), and cerebrovascular disease (inadequate). This ISA follows the precedent set by the 2019 Particulate Matter and 2020 Ozone ISAs (U.S. EPA, 2020, 2019) by making a single causality determination for cardiovascular effects. (2) The 2013 Pb ISA evaluated studies of all-cause mortality together with studies examining cardiovascular mortality and did not issue a separate causality determination for total mortality.

Figure ES-2 Summary of causality determinations by health outcome.

Recent evidence continues to support causal relationships between exposure to Pb and cognitive function decrements in children, externalizing behaviors (i.e., attention, impulsivity, and hyperactivity) in children, cardiovascular effects and cardiovascular-related mortality, effects on development, and effects on male reproductive function. Expanded evidence also supports causal relationships between Pb exposure and renal effects, cognitive function decrements in adults, and total (nonaccidental) mortality. The evidence summarized in the 2013 Pb ISA was "suggestive of a causal relationship" between Pb exposure and renal effects and supported a "likely to be causal relationship" between Pb exposure and cognitive effects in adults. There was no causality determination for the relationship between Pb exposure and mortality in the 2013 Pb ISA. Evidence supporting causal relationships does not indicate a threshold for the observed effects across the range of BLLs examined (outcome specific mean BLL ranges are provided in Section IS.7.3 and throughout the health effects appendices). Recent evidence also indicates that Pb exposure is likely to cause conduct disorders, internalizing behaviors, and motor function decrements in children; depression and anxiety in adults; as well as effects on female reproductive function, effects on pregnancy and birth outcomes, immunosuppression, musculoskeletal effects, and cancer. Additional evidence is suggestive of a causal relationship between Pb exposure and sensory function decrements and effects on social cognition and behavior in children; sensory function decrements in adults; neurodegenerative disease; sensitization and allergic response; and hepatic effects; though there are more uncertainties associated with the interpretation of the evidence for these effects.

ES.6.1.1 Effects of Pb Exposure on Health Outcomes Ascertained in Children, Adolescents, and Young Adults

While Pb affects nearly every organ system, the nervous system appears to be one of the most sensitive targets. Epidemiologic studies conducted in diverse populations continue to demonstrate the harmful effects of Pb exposure on neurodevelopment in children. Given their limited exposure histories, neurodevelopmental effects observed in young children are among the effects best substantiated as occurring at the lowest BLLs. Specifically, blood Pb-associated effects on cognitive function are supported by studies in populations of children (ages 4–10) with mean or group BLLs – measured concurrently or earlier – in the range of 2–8 μg/dL (ES.7.1.3). Notably, evidence suggests that some Pb-related cognitive effects and neurodevelopmental effects may persist into adulthood (U.S. EPA, 2013). In addition to cognitive effects, epidemiologic studies also demonstrate that Pb exposure is associated with decreased attention, and increased impulsivity and hyperactivity in children (i.e., externalizing behaviors). A small number of recent studies also serve to extend the lower bound of the mean BLLs that were observed to be associated with inattention, impulsivity, and hyperactivity in the 2013 Pb ISA. These prospective studies with mean maternal and cord blood Pb levels ≤5 μg/dL report associations with some measures of inattention and impulsivity. The neurodevelopmental epidemiologic evidence is supported by findings in animal studies demonstrating both analogous effects and biological plausibility at relevant exposure levels.

Pb exposure can also exert harmful effects on blood cells and blood producing organs (potentially leading to anemia in children) and is likely to cause an increased risk of symptoms of depression and anxiety and withdrawn behavior (i.e., internalizing behaviors), decreases in motor function, delayed pubertal onset, as well as conduct disorders in children and young adults. There is continued uncertainty about the timing, frequency, and duration of Pb exposures contributing to the BLLs and effects observed in epidemiologic studies, though these uncertainties are greater in studies of older children and adults than in studies of young children (ES.7.1.4). Despite these uncertainties, there is clear and consistent evidence that Pb exposure leads to negative health effects in children; further, recently available evidence does not provide evidence of a threshold for the observed neurodevelopmental effects across the range of BLLs examined (ES.7.1.3).

ES.6.1.2 Effects of Pb Exposure on Health Outcomes Ascertained in Adults

Recent experimental animal and epidemiologic studies expand an already large body of evidence that demonstrates the effect of Pb exposure on the cardiovascular and renal systems. The evidence most strongly contributing to a causal relationship between Pb exposure and cardiovascular effects includes studies reporting Pb-related increases in blood pressure, hypertension, and cardiovascular mortality. The extent to which the effects of Pb on the cardiovascular system are reversible is not well-characterized. Recent evidence also addresses uncertainties related to reverse causality in studies examining the renal effects of Pb exposure and provides strong support for Pb-induced kidney dysfunction that is independent of baseline renal function. The cardiovascular and renal effects evidence, which includes coherence of results from epidemiologic and animal toxicological studies, is also supported by animal toxicological evidence providing biological plausibility for the observed health effects. In particular, Pb effects on the renin-angiotensin system provide a biologically plausible pathway through which Pb is capable of eliciting health effects in both organ systems.

Consistent with the evidence demonstrating blood and bone Pb-associated cardiovascular mortality, recent studies also report that Pb exposure is associated with total (nonaccidental) mortality. The strongest supporting evidence for Pb effects on mortality comes from studies of cardiovascular effects, which provide extensive epidemiologic and experimental animal evidence indicating pathways by which exposure to Pb could plausibly progress from initial events to events that could lead to cardiovascular mortality, including exacerbation of ischemic heart disease and potential myocardial infarction. There is also very limited evidence that Pb exposure may contribute to other causes of mortality, including Alzheimer's disease and infection, although this evidence is less established and has greater uncertainties.

Pb exposure can also lead to cognitive function decrements, symptoms of depression and anxiety, and immune effects in adults. Notably, the frequency, timing, level, and duration of Pb exposure causing the effects observed in adults remains an uncertainty in the evidence, and higher past exposures may

contribute to the development of health effects measured later in life. Despite these uncertainties, there is clear and consistent evidence that Pb exposure can result in harm to an array of organ systems that is evident in adulthood, with the strongest evidence for effects on the cardiovascular and renal systems, as well as cognitive function in adults.

ES.6.2 Welfare Effects of Pb Exposure

Several effects are associated with Pb exposure in terrestrial and aquatic organisms. Although Pb is present in the natural environment, it has no known biological function in plants or animals. The atmosphere and terrestrial and aquatic ecosystems are interconnected, with transfer of Pb taking place between each of these systems (IS.2). Uptake of Pb from soils, water, sediment, and biota (via diet), subsequent bioaccumulation, and toxicity vary greatly between biological species and across taxa, as characterized in the 1977 AQCD (U.S. EPA, 1977), the 1986 Pb AQCD (U.S. EPA, 1986a), the 2006 Pb AQCD (U.S. EPA, 2006), the 2013 Pb ISA (U.S. EPA, 2013), and further supported in this ISA. As reported in the 2013 Pb ISA and preceding Pb AQCDs, effects of Pb are observed across endpoints common to terrestrial, freshwater, and saltwater organisms. Those endpoints include reproduction, growth, survival, neurobehavioral and hematological effects, and physiological stress, and occur at multiple scales of biological organization, from the cellular to the ecosystem. For ecological endpoints in this ISA, biochemical (e.g., enzymes and stress markers) responses at the suborganism level of biological organization are grouped under the broad endpoint of "physiological stress." The effects of Pb at the subcellular and cellular level may lead to effects on organism reproduction, growth, and survival. Effects on these endpoints, in turn, have the potential to alter population, community, and ecosystem levels of biological organization.

In the 2013 Pb ISA, a series of causality determinations were made for effects of Pb on plants, invertebrates, and vertebrates in terrestrial, freshwater, and saltwater ecosystems using biological scale as an organizing principle (U.S. EPA, 2013). Evidence published since that time supports or slightly expands the evidence for causality in endpoints that were already established as causal in the 2013 Pb ISA (Figure ES-3). A few studies report effects at lower concentration of Pb than in the 2013 Pb ISA. New evidence for terrestrial (IS.8.1) and freshwater (IS.8.2) biota continues to support the existing causality determinations from the 2013 Pb ISA and there are no changes to those causality determinations. At the time of the 2013 Pb ISA, there were fewer studies on effects of Pb in saltwater biota than on terrestrial and freshwater organisms, and evidence was inadequate to infer causality relationships for many endpoints. Specifically, chronic toxicity data were lacking, and relatively few laboratory studies measured Pb concentration in the exposure water or sediment. Since the 2013 Pb ISA, several newly available studies verify Pb concentrations analytically and report effects on endpoints at lower concentrations than previously observed for saltwater biota; some of these studies are chronic exposure bioassays (IS.8.3). This additional information supports a change in causality determinations for three endpoints for saltwater organisms (IS.8.4). Specifically, the evidence is sufficient to conclude there is a likely to be causal

relationship between Pb exposure and reproductive and developmental effects in saltwater invertebrates. Additionally, the evidence is suggestive of, but not sufficient to infer, a causal relationship between Pb exposure and saltwater vertebrate survival, and, the evidence is suggestive of, but not sufficient to infer, a causal relationship between Pb exposure and saltwater community and ecosystem effects (Figure ES-3).

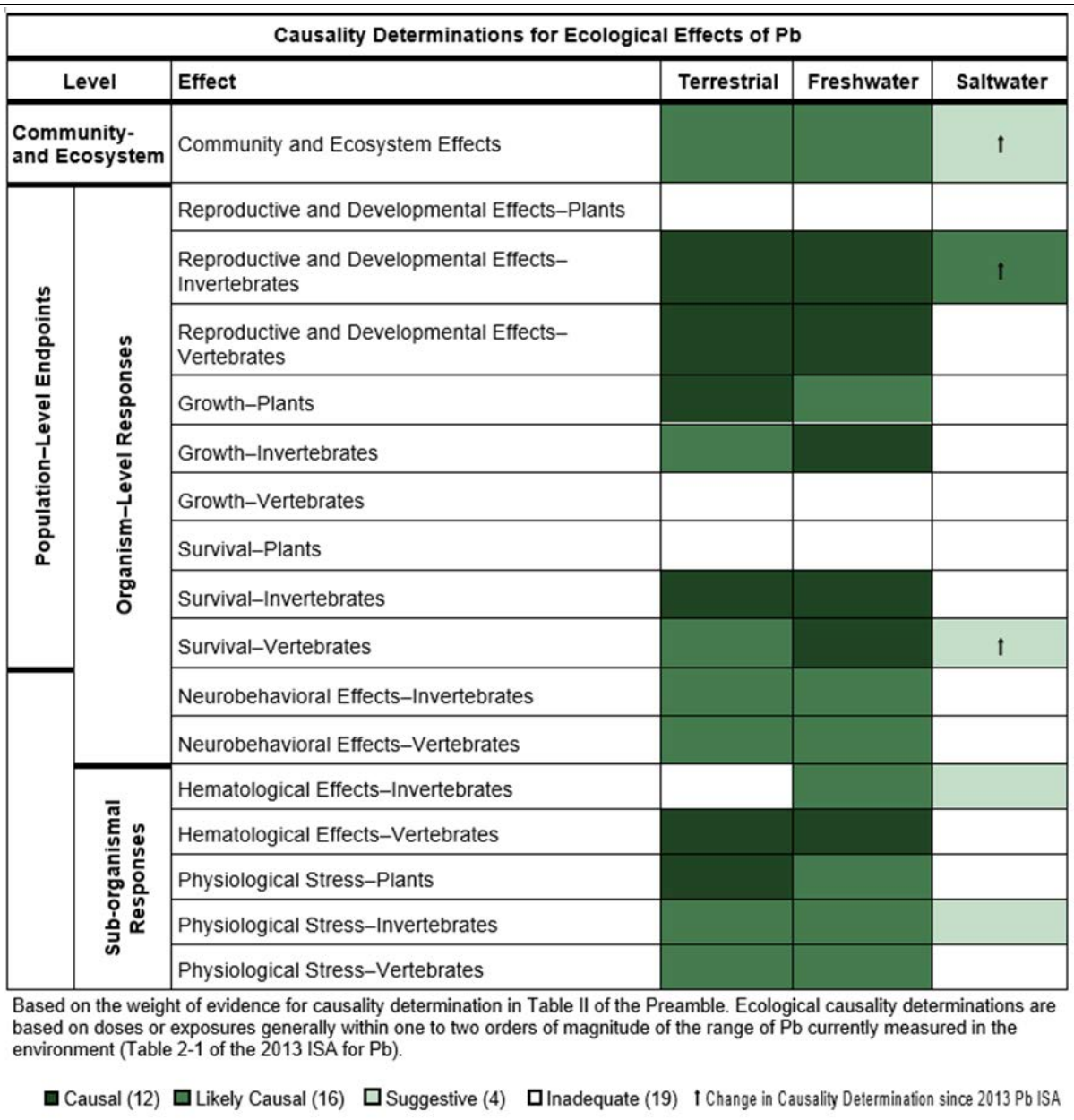


Figure ES-3 Summary of causality determinations for ecological effects of Pb.

ES.6.2.1 Effects on Development and Reproduction

Evidence from invertebrate and vertebrate studies in the Pb AQCDs, the 2013 Pb ISA, and this ISA indicates that Pb affects reproductive performance in multiple species (IS.8.4.6). Various endpoints measured in multiple taxa of terrestrial and aquatic organisms show impaired reproduction or development following Pb exposure. Decreased reproduction at the organism level of biological organization can result in a decline in how widespread a species is, the disappearance of populations of a species, a decline in the variety of different species present, and changes in the mixture of species seen in an ecological community. For freshwater invertebrates, recent evidence further supports previous observations of Pb effects on reproductive endpoints at low concentrations in some sensitive species of snails as well as zooplankton, such as cladocerans (group of small aquatic invertebrates belonging to the subphylum Crustacea) and rotifers (small aquatic invertebrates that constitute the phylum Rotifera), especially under chronic exposure scenarios (IS.8.4.6 and see Appendix 11, Table 11-5). Since the 2013 Pb ISA, the evidence base for Pb effects on reproductive and developmental endpoints in saltwater invertebrates has expanded, primarily due to multiple new embryo-larval developmental assays in mollusks and sea urchins (IS.8.4.6 and see Appendix 11, Table 11-7). This new evidence augments the previous causality determination from the 2013 Pb ISA of suggestive of, but not sufficient to infer, a causal relationship. This ISA concludes there is a likely to be causal relationship between Pb exposure and reproductive and developmental effects in saltwater invertebrates.

ES.6.2.2 Effects on Growth

As reported in this ISA, the 2013 Pb ISA, and the Pb AQCDs, exposure to Pb has been shown to have detrimental effects on growth in plants and in some species of invertebrates and vertebrates (IS.8.4.5). Evidence for effects of Pb on growth is strongest in terrestrial plants. Evidence accumulated over several decades of research shows that Pb inhibits photosynthesis and respiration in terrestrial plants, both of which in turn reduce growth (U.S. EPA, 2013, 2006, 1977). Effects reported in plants largely occur at concentrations that greatly exceed Pb concentrations typically found in U.S. soils and surface waters, but with studies that include multiple concentrations of Pb showing increased response with increasing Pb in water, sediment, or soil. Evidence for detrimental effects of Pb on growth in invertebrates has been gathered most extensively in freshwater species, with growth inhibition in a few sensitive species occurring in the range of Pb concentration values available for U.S. surface waters. In general, juvenile organisms are more sensitive than adults. Data on growth effects of Pb in vertebrates is limited. Causality determinations for growth in terrestrial, freshwater, and saltwater organisms remain unchanged from the 2013 Pb ISA (Figure ES-3).

ES.6.2.3 Effects on Survival

Survival (IS.8.4.4) may have a direct impact on population size and can lead to effects at the community and ecosystem levels of biological organization. Pb has generally not been found to affect survival of aquatic or terrestrial plants at concentrations found in the environment away from stationary sources. Freshwater invertebrates are generally more sensitive to Pb exposure than other types of organisms, with survival reduced in laboratory studies of a few species at concentrations occasionally encountered in the environment. Studies of some freshwater invertebrates reported in the 2006 Pb AQCD and 2013 Pb ISA indicate decreased survival at <20 µg Pb/L under some water quality conditions. Several studies since the 2013 Pb ISA provide further characterization for known effects on survival in a few sensitive species of freshwater invertebrates, notably snails and amphipods (shrimp-like crustaceans), at analytically verified chronic exposure ≤15 µg Pb/L (IS.8.4.4). Limited studies with vertebrates showed adverse effects of Pb on survival at concentrations higher than typical Pb levels in the environment, although juvenile organisms are usually more sensitive than adults. The 2013 Pb ISA causality determination for survival in saltwater vertebrates was inadequate. Additional evidence in this ISA (IS.8.4.4) from laboratory-based bioassays in a few saltwater fish species in which Pb exposure concentration was analytically verified demonstrates effects on survival in chronic exposures to Pb (Appendix 11, Table 11-7). Based on these new chronic studies in saltwater fish, the evidence is suggestive of, but not sufficient to infer, a causal relationship between Pb exposure and saltwater vertebrate survival.

ES.6.2.4 Neurobehavioral Effects

Pb is a known to cause impairments in the nervous system of invertebrates and vertebrates. Historical and recent evidence of Pb effects on terrestrial and freshwater animals indicates that Pb adversely affects behaviors, such as food consumption, locomotion, behavioral regulation of body temperature, and prey capture. Additional evidence since the 2013 Pb ISA includes studies quantifying alterations in foraging and feeding behavior in bees and changes in locomotion in freshwater amphipods, bivalves, and zebrafish (IS.8.4.3). The causality determinations for neurobehavioral effects of Pb in terrestrial, freshwater, and saltwater organisms remain unchanged from the 2013 Pb ISA (Figure ES-3).

ES.6.2.5 Hematological Effects

As reported in the Pb AQCDs and 2013 Pb ISA, hematological effects of Pb exposure in wildlife include inhibition of δ-aminolevulinic acid dehydratase (ALAD; an important rate-limiting enzyme needed for heme production) and altered blood cell counts and serum profiles. Decreased ALAD activity is commonly recognized as an indicator of Pb exposure across a wide range of animals as shown in both field and laboratory studies. Previous studies have indicated considerable species differences in ALAD

activity in response to Pb. Since the 2013 Pb ISA, new studies in terrestrial birds, amphibians, and mammals have continued to support the connection between Pb exposure and hematological effects (IS.8.4.2). In contrast, fewer studies were identified that quantified ALAD response in terrestrial or freshwater invertebrates, freshwater vertebrates, or in saltwater organisms. The causality determinations for hematological effects of Pb in biota remain unchanged from the 2013 Pb ISA (Figure ES-3).

ES.6.2.6 Effects on Physiological Stress

Increased levels of antioxidant enzymes (in response to oxidative stress or altered cell signaling) and increased lipid peroxidation (the process by which free radicals induce the oxidation of fatty acids, leading to cell membrane damage) are reliable biomarkers of various stresses. Oxidative damage and antioxidant activity have been observed in field studies in a wide range of species in terrestrial and aquatic environments when Pb is present (often along with other chemical stressors), and also following laboratory exposures to Pb without other stressors in plants, invertebrates and vertebrates (IS.8.4.1). Changes in markers of physiological stress may indicate increased susceptibility to other stressors, as well as diminished fitness of individual organisms. Causality determinations for physiological stress in terrestrial, freshwater, and saltwater organisms remain unchanged from the 2013 Pb ISA (Figure ES-3).

ES.6.2.7 Community and Ecosystem Effects

Uptake of Pb by terrestrial and aquatic organisms and subsequent adverse effects on survival, growth, development, and reproduction at the organism level can sometimes lead to effects at higher levels of biological organization including populations, communities, and ecosystems. In terrestrial habitats, soil microbial, plant, and animal communities may be affected in locations where soil Pb concentration is elevated, such as in the proximity to historic metal extracting and processing point sources. In freshwater ecosystems, shifts in sediment-associated microbial and invertebrate communities and aquatic plant communities are linked to the presence of Pb as well as other stressors. For terrestrial and freshwater systems, the likely to be causal determinations remain unchanged from the 2013 Pb ISA. For saltwater ecosystems, new experimental and observational studies have examined the relationship between Pb in sediment, and microbial abundance and/or diversity and saltwater foraminifera (single-celled marine organisms, usually with shells) communities (IS.8.4.7). These studies show that diversity and distribution of these organisms varies with Pb concentration and co-stressors in the environment and at different locations. This new evidence is suggestive of a causal relationship between Pb exposure and saltwater community and ecosystem effects which is a change from the 2013 Pb ISA. Although the presence of Pb is associated with shifts in biological communities, this metal rarely occurs as a sole contaminant in natural systems, making the contribution of Pb to the observed effects difficult to isolate in many locations. Furthermore, the variability of conditions in the environment affects Pb bioavailability and organism response making it difficult to characterize effects of Pb at the ecosystem scale.

ES.7 Key Aspects of Health and Welfare Effects Evidence

In addition to causality determinations, this ISA also reaches conclusions on other policy-relevant topics. These conclusions are drawn from a careful evaluation of the available evidence and the extent to which recent studies have addressed or reduced uncertainties from previous assessments. Conclusions on key policy-relevant topics are summarized below.

ES.7.1 Health Effects Evidence: Key Findings

In addition to the causality determinations for health effects (ES.6.1), the evidence evaluated in this ISA addresses some of the key policy-relevant issues of this NAAQS review, as outlined in Volume 2 of the Pb IRP (U.S. EPA, 2022a). A summary of this health evidence and Pb ISA conclusions is provided below and discussed in more detail in the Integrated Synthesis and supporting appendices.

ES.7.1.1 At-Risk Populations

The NAAQS are intended to protect public health with an adequate margin of safety, including protection for those potentially at increased risk for health effects in response to exposure to a criteria air pollutant [e.g., Pb; see Preamble (U.S. EPA, 2015)]. In addition to consideration of Pb-related health effects observed among populations with diverse characteristics, this ISA also considers those studies that examine specific populations or lifestages that may be at increased risk of Pb-related health effects, using a pragmatic approach to characterize the strength of the evidence (U.S. EPA, 2015). The risk of health effects from exposure to Pb may be modified by intrinsic (e.g., pre-existing disease, genetic factors) or extrinsic (e.g., sociodemographic or behavioral factors) factors, differences in internal dose, or differences in exposure to Pb in the environment. While a combination of factors (e.g., residential location and SES) may increase the risk of Pb-related health effects in portions of the population, information on the interaction among factors remains limited. Thus, this ISA characterizes the individual factors that potentially result in increased risk for Pb-related health effects [see Preamble (U.S. EPA, 2015)]. There is adequate evidence to classify children, minority populations, individuals in close proximity to Pb sources, individuals living in residences with factors contributing to increased house dust Pb levels, individuals with certain genetic variants, individuals with high stress levels, and those with certain nutritional excesses or deficiencies as populations at increased risk to the health effects of Pb exposure (IS.7.4). These conclusions are based on the consistency in findings across studies, as well as on coherence of results from different scientific disciplines. There is suggestive evidence for several other factors contributing to potentially increased risk of Pb-related health effects: older age, sex, pre-existing diabetes, low socioeconomic status, and high levels of exposure to other metals.

ES.7.1.2 Air-Pb–to–Blood-Pb Relationships

The relationship between air Pb and blood Pb is commonly characterized as a "slope factor," which describes the incremental change in blood Pb levels relative to a change in air Pb concentrations (IS.9.1). A larger slope indicates a larger estimated incremental contribution of air Pb to the blood Pb level in exposed populations. Epidemiologic studies evaluating air–to–blood slope factors include various study locations, populations, and analytic methodologies (e.g., model form and other considerations, such as soil Pb, that are accounted for in the model), all of which contribute to variation in the estimated slopes. Results described in the 2013 Pb ISA (U.S. EPA, 2013) provide a range of air-to-blood slope estimates from 4 to 9 μg/dL per μg/m^3 in studies of children. Newer studies after the phaseout of leaded gasoline and not focused on communities near significant air Pb sources show increasing slope factors with decreasing air Pb concentrations.

ES.7.1.3 Concentration-Response Relationships for Human Health Effects

In assessing the relationship between Pb exposure and human health effects, evidence from each previous assessment (U.S. EPA, 2013, 2006) demonstrates that progressively lower BLLs or Pb exposures are associated with cognitive deficits in children. The evidence assessed in the 2013 Pb ISA found that cognitive effects in children were substantiated to occur in populations with mean BLLs between 2 and 8 μg/dL. Recent studies generally include somewhat older children or employ modelling strategies designed to answer relatively narrow research questions and consequently do not have the attributes of the studies on which the conclusion of the 2013 Pb ISA was based (i.e., early childhood BLLs, consideration of peak BLLs, or concurrent BLLs in young children). Therefore, the recently available studies were not designed and may not have the sensitivity to detect the effect or hazard at these very low BLLs, nor do they provide evidence of a threshold for the effect across the range of BLLs examined.

Compelling evidence in the 2013 Pb ISA also supported a larger incremental negative effect of Pb on children's IQ at lower BLLs compared to higher BLLs (for BLLs ranging from 2.5 to 33.2 μg/dL; Section IS.9.2). Only a few recent studies evaluate the shape of the concentration-response (C-R) function for the relationship between Pb exposure and cognitive effects in children, but recent evidence continues to support the conclusions from the 2013 Pb ISA. Possible explanations specific to nonlinear relationships observed in studies of Pb exposure in children include a smaller incremental effect at higher Pb concentrations due to covarying risk factors, though the evidence does not reveal a consistent set of covarying risk factors that explain the differences in the blood Pb–IQ C-R relationship observed in epidemiologic studies. Additionally, although evidence indicates a larger incremental effect of Pb exposure on IQ at lower BLLs, consistent findings of higher mean IQ at lower BLLs indicate that the absolute magnitude of the effect of Pb exposure on cognitive function declines with decreasing BLL.

ES.7.1.4 Lifestages and Timing of Pb Exposure Contributing to Observed Nervous System Effects

As discussed in Section ES.5, blood Pb may reflect recent as well as past exposures because Pb is both taken up by and released from the bone. The resulting uncertainty regarding the relative proportion of blood Pb from recent versus past exposure is greater in adults and older children than in young children who have shorter exposure histories. As a result, there is inherent uncertainty in the level, timing, frequency, and duration of Pb exposures contributing to associations between adult and older children's BLLs and health outcomes observed in epidemiologic studies. In epidemiologic studies of nervous system effects with BLLs measured in younger children, recent evidence is consistent with findings from the 2013 Pb ISA, which consistently showed that BLLs measured during various lifestages and time periods (i.e., prenatal, early childhood, childhood average, and concurrent with the outcome) were associated with nervous system effects in children. A notable uncertainty in the interpretation of this evidence is the typically high correlation between blood Pb measurements at different ages in childhood, making it difficult to discern the relative importance of the various exposure metrics (i.e., BLLs at different ages) used in epidemiologic studies. Nonetheless, the epidemiologic evidence is supported by experimental evidence in monkeys that indicates that Pb exposures during multiple lifestages and time periods, including prenatal only, prenatal plus lactational, postnatal only, or lifetime starting during the juvenile period, induce impairments in cognitive function when assessed between ages 6 and 10 years. Additionally, recent prospective epidemiologic studies observed associations between childhood BLLs and decrements in IQ during late adolescence (18–19 years) and mid-adulthood (38–45 years). These findings provide insight into the persistence of Pb-associated cognitive function decrements and are consistent with the understanding that the nervous system continues to develop throughout childhood and into adolescence.

ES.7.2 Welfare Effects Evidence: Key Findings

Effects of Pb in ecosystems are primarily associated with Pb from deposition and other sources, subsequent transport, and exposure through environmental media (soil, water, sediment, biota). Pb bioaccumulates in plants and animals in terrestrial, freshwater, and saltwater environments; however, the relative contribution of Pb from different sources is usually not known. The share of Pb effects attributed to atmospheric sources is difficult to quantitatively assess due to limited information on Pb deposition to soils, water, and sediments, a lack of Pb-apportionment studies in biota, and kinetics of Pb distribution within organisms in long-term exposure scenarios.

Exposure of organisms to Pb can be via one or more pathways (e.g., uptake from soil or water, ingestion). For Pb to interact with a biological membrane and be taken up into an organism it must be bioavailable (IS.8). Generally, the greater amount of Pb available as the free Pb ion, the greater bioavailability. Conditions in the environment, such as soil composition and soil and water chemistry,

modify Pb bioavailability and subsequent toxicity to organisms. Once Pb uptake occurs, a variety of effects may occur in organisms, including impaired reproduction, decreased growth, and reduced survival, as documented in this ISA, the 2013 Pb ISA and the Pb AQCDs. These effects on individual organisms may lead to effects at the population, community, and ecosystem level of biological organization. In both terrestrial and aquatic organisms, gradients in response are observed with increasing concentration of Pb in laboratory and field studies. However, the level at which Pb elicits a specific effect in a natural system is difficult to establish due to the influence of other environmental variables (e.g., pH and organic matter) on both Pb bioavailability and toxicity, and also because of substantial species differences in Pb sensitivity. Some laboratory studies report effects within the range of Pb detected in environmental media over the past several decades. Specifically, effects on reproduction, growth, and survival in sensitive freshwater invertebrates are well-characterized from controlled studies at concentrations at or near Pb concentrations occasionally encountered in U.S. fresh surface waters. There are considerable uncertainties associated with generalizing effects observed in controlled studies on a single species to effects at higher levels of biological organization. Furthermore, available studies on community and ecosystem-level effects are usually from heavily contaminated areas where Pb concentrations are much higher than typically encountered in the general environment. Measurements of the contribution of atmospheric Pb to specific sites that are not directly contaminated by a known point source are generally unavailable, and the connection between air concentration of Pb and ecosystem exposure continues to be poorly characterized, as was reported in the 2013 Pb ISA.

ES.8 References

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INTEGRATED SYNTHESIS FOR LEAD

Overall Conclusions of the Lead (Pb) Integrated Science Assessment (ISA)

Human Health Effects

- Recent studies support and expand upon the strong body of evidence spanning scientific disciplines, reaffirming *causal relationships* between Pb exposure and several nervous system effects in children, including cognitive function decrements and externalizing behaviors (i.e., attention, impulsivity, and hyperactivity).
- Recent evidence also continues to support *causal relationships* between Pb exposure and a number of other health effects, including cardiovascular effects and cardiovascular-related mortality, hematological effects, developmental effects, and effects on male reproductive function.
- Expanded evidence supports *causal relationships* between Pb exposure and (1) renal effects (previously *suggestive of a causal relationship)* and (2) cognitive function in adults (previously *likely to be causal*).
- Drawing largely on evidence for Pb-related cardiovascular mortality, a new causality determination affirms a *causal relationship* between Pb exposure and total (nonaccidental) mortality.
- Recent experimental and epidemiologic evidence supports *likely to be causal relationships* between Pb exposure and conduct disorders in children and young adults, internalizing behaviors in children and adolescents, motor function decrements in children, psychopathological effects in adults, immunosuppression, musculoskeletal effects, effects on female reproductive function, effects on pregnancy and birth outcomes, and cancer.
- For all other health effect categories, uncertainties and limitations in the scientific evidence contribute to causality determinations that the evidence is *suggestive of, but not sufficient to infer, a causal relationship* or *inadequate to infer the presence or absence of a causal relationship*.
- Many population subgroups and different lifestages have been shown to be at increased risk of Pb-related health effects resulting from variation in exposure or biological responses to exposure. Among populations and lifestages evaluated in this ISA, current scientific evidence is adequate to conclude that children, people living in proximity to Pb sources, people with specific genetic variants, people with increased stress, and populations with certain nutritional or residential factors may be at disproportionate risk for Pb-related health effects. There is suggestive evidence that older age, sex, pre-existing disease, socioeconomic status (SES), and exposure to other metals may increase risk for health effects of Pb exposure.

Welfare Effects

- Effects of Pb in ecosystems are primarily associated with Pb from deposition and other sources, subsequent transport, and exposure through environmental media (soil, water, sediment, biota). Pb bioaccumulates in plants and animals in terrestrial, freshwater, and saltwater environments; however, the relative contribution of Pb from different sources is usually not known.
- Effects of Pb are observed in terrestrial, freshwater, and saltwater organisms across several levels of biological organization (i.e., from the cellular level of organization through individual organisms to the level of communities and ecosystems). Most evidence is from toxicity bioassays on individual organisms, rather than field-based studies.
- In most cases, new research affirms the conclusions in the 2013 Pb ISA for the endpoints of physiological stress, hematological effects, neurobehavior, survival, growth, reproduction and development, and community and ecosystem effects in terrestrial and freshwater biota. A few studies report effects at lower concentrations than in the 2013 Pb ISA.
- Additional studies in saltwater organisms address some of the uncertainties identified in the 2013 Pb ISA. There is sufficient new evidence to support a *likely to be causal relationship* between Pb exposure and reproductive and developmental effects in saltwater invertebrates. For two other endpoints, survival in saltwater vertebrates (based on fish studies) and effects on saltwater communities and ecosystems, new evidence is *suggestive of, but not sufficient to infer, a causal relationship.*

IS.1 Introduction

IS.1.1 Purpose and Overview

The Integrated Science Assessments (ISAs), prepared by the U.S. Environmental Protection Agency (U.S. EPA), serve as the scientific foundation of the National Ambient Air Quality Standards (NAAQS) review process.[1] The ISA is a comprehensive evaluation and synthesis of the policy-relevant science "useful in indicating the kind and extent of all identifiable effects on public health or welfare,[2] which may be expected from the presence of [a] pollutant in the ambient air," as described in Section 108 of the Clean Air Act (42 U.S. Code [U.S.C.] 7408).[3] For this ISA, "policy-relevant" science is described in Volume 2 of the Integrated Review Plan (IRP) for Lead (Pb) (U.S. EPA, 2022a) as referring to "scientific information and analyses intended to address key questions related to the adequacy of the standards." Those "key questions" are also laid out in Volume 2 of the IRP. As stated in the Preamble to the ISAs (U.S. EPA, 2015), hereafter "Preamble," "[t]he key policy-relevant questions included in the IRP serve to clarify and focus the NAAQS review on the critical scientific and policy issues, including addressing uncertainties discussed during the previous review and newly emerging literature." This ISA reviews and synthesizes the air quality criteria for the health and welfare effects of Pb. It draws on the existing body of evidence to evaluate and describe the current state of scientific knowledge on the most relevant issues pertinent to the current review of the Pb NAAQS, to identify changes in the scientific evidence since the previous review, and to describe remaining or newly identified uncertainties and limitations in the evidence.

This Integrated Synthesis (IS) is the main body of the Pb ISA. The following sections provide a concise synopsis of the ISA conclusions and synthesize the key findings considered in characterizing Pb exposure and relationships with health and welfare effects. The IS includes summaries of key information for each topic area covered in 12 appendices to the Pb ISA, including atmospheric science, sources, and environmental distribution; exposure, biomarkers, and toxicokinetics; the nature of health and welfare effects associated with Pb exposure, including causality determinations for relationships between exposure to Pb and specific types of health and welfare effects; and the human lifestages and populations at increased risk of the effects of Pb. This IS also discusses the evidence related to other policy-relevant issues, such as the exposure durations, metrics, and concentrations eliciting health and welfare effects; the

[1]Section 109(d)(1) of the Clean Air Act requires periodic review and, if appropriate, revision of existing air quality criteria to reflect advances in scientific knowledge on the effects of the pollutant on public health and welfare. Under the same provision, EPA is also to periodically review and, if appropriate, revise the NAAQS based on the revised air quality criteria.

[2]Under section 302(h) of the Clean Air Act, effects on welfare include, but are not limited to, "effects on soils, water, crops, vegetation, manmade materials, animals, wildlife, weather, visibility, and climate, damage to and deterioration of property, and hazards to transportation, as well as effects on economic values and on personal comfort and well-being."

[3]The general process for developing an ISA, including the framework for evaluating weight of evidence and drawing scientific conclusions and causal judgments, is described in a companion document, the Preamble to the ISAs.

concentration-response (C-R) relationships for specific effects, including the overall shape and discernibility of thresholds in these relationships; and the public health and welfare impact of effects associated with exposure to Pb.

The 2024 Pb ISA will inform U.S. EPA decisions on the primary and secondary NAAQS for Pb. The primary Pb NAAQS are established to protect public health with an adequate margin of safety, including the health of at-risk populations such as children. The secondary Pb NAAQS are intended to protect the public welfare from known or anticipated adverse effects associated with the presence of the pollutant in ambient air. The current primary and secondary Pb NAAQS were established in 2008. In that review, the levels of the primary and secondary standards were lowered tenfold, from the 1978 levels of 1.5 $\mu g/m^3$ to 0.15 $\mu g/m^3$. The averaging time was revised from a calendar quarter average to a rolling three-month period with a maximum (not-to-be-exceeded) form, evaluated over a three-year period. The revised primary standard was established to protect against air Pb-related human health effects, including intelligence quotient (IQ) loss, in the most highly exposed children. The secondary standard was set equal to the primary standard for requisite protection of organisms and ecosystems. The most recent review of the Pb NAAQS was completed in 2016, at which time the standards set in 2008 were retained without revision.

IS.1.2 Pb Integrated Science Assessment Process and Development

Each NAAQS review begins with a "Call for Information" published in the Federal Register that announces the start of the review and invites the public to assist in this process by identifying relevant research studies in the subject areas of concern. For this review of the Pb NAAQS, the Call for Information was published in the Federal Register on July 7, 2020 (85 FR 40641). Following the Call for Information, the planning phase of the review includes development of an IRP, which is made available for public comment and provided to the Clean Air Scientific Advisory Committee (CASAC) for review or consultation. Volume 2 of the IRP for Pb addresses the general approach for the review and planning for the ISA (U.S. EPA, 2022a).

The process for developing this ISA is described in detail in Appendix 12 of this ISA, *Process for Developing the Pb Integrated Science Assessment*. Through iterative NAAQS reviews, ISAs build on evidence and conclusions from previous assessments. The previous ISA for Pb was published in 2013 (U.S. EPA, 2013a) and included peer-reviewed literature published through September 2011. Prior Pb assessments include the 2006 Air Quality Criteria Document (AQCD) for Pb (U.S. EPA, 2006), the 1986 Pb AQCD (U.S. EPA, 1986b) and its associated addendum (U.S. EPA, 1986d), the 1990 Supplement to the 1986 addendum (U.S. EPA, 1990), and the 1977 AQCD for Pb (U.S. EPA, 1977). This ISA focuses on synthesizing and integrating the evidence that has become available since the 2013 Pb ISA with the information and conclusions from previous assessments. Important older studies from the 2013 Pb ISA or from the Pb AQCDs may be drawn on to reinforce key concepts and conclusions. Older studies also may

be the primary focus in some subject areas or scientific disciplines where research efforts have subsided, and/or where these older studies remain the definitive works available in the literature. The general steps for ISA development include literature search and study selection; evaluating study quality; developing initial draft materials for peer-input consultation; evaluating, synthesizing, and integrating evidence; and developing scientific conclusions and causality determinations (U.S. EPA, 2015).

These steps are described in greater detail in the Preamble (U.S. EPA, 2015), which provides a general framework for developing ISAs, and in the Process Appendix (Appendix 12), which supplements the Preamble with additional details specific to this ISA including methods for documentation, literature review, study quality evaluation, public engagement, and quality assurance (QA). As described in the Preamble, the U.S. EPA uses a structured and transparent process to evaluate scientific information and to determine the causal nature of relationships between air pollution and health and welfare effects [see Preamble (U.S. EPA, 2015)]. Development of the ISA includes approaches for literature searches, application of criteria for selecting and evaluating relevant studies, and application of a framework for evaluating the weight of evidence and forming causality determinations. As part of the external review process, one or more drafts of the ISA are made available to the public and undergo formal review by the CASAC, an independent scientific committee appointed by the U.S. EPA Administrator.

Studies considered in the development of the Pb ISA are documented in the U.S. EPA HERO database. The publicly accessible HERO project page for this ISA contains the references that were considered for inclusion and provides bibliographic information and abstracts. Within HERO, each reference has a unique HERO ID number. References can be viewed individually or filtered by appendix, discipline, or the draft in which they are referenced.

IS.1.2.1 Scope of the Pb ISA

Pb is a multimedia and persistent pollutant that contributes complexities to the review of the Pb NAAQS. Pb emitted into ambient air may subsequently be found in multiple environmental media (i.e., soil, water, sediment, biota), contributing to multiple pathways of exposure for humans and ecological receptors. This multimedia distribution of, and multipathway exposure to, air-related Pb has a key role in the Agency's consideration of the Pb NAAQS. The Pb ISA includes research relevant to assessing the health and welfare effects of Pb exposure. Health effects evidence evaluated in the ISA includes experimental animal toxicological studies and observational epidemiologic studies. Welfare evidence included in the Pb ISA focuses specifically on ecological effects. In addition to the human health and welfare effects of Pb, the ISA also evaluates other scientific information on sources of Pb to ambient air, measurement, and concentrations of Pb in ambient air, fate, and transport of Pb in the environment, pathways of human and ecological exposure, toxicokinetic characteristics of Pb in the human body, and characterization of population exposures to Pb.

The scope of the health portions of the ISA are explicitly defined by scoping statements that generally characterize the parameters for study inclusion to aid in identifying the most relevant evidence. The use of scoping statements to define study relevance is consistent with recommendations by the National Academies of Sciences, Engineering, and Medicine for improving the design of risk assessment through planning, scoping, and problem formulation to better meet the needs of decision makers (NASEM, 2018). The statement used to define the scope of the health effects portion of this ISA comprises Population, Exposure, Comparison, Outcome, and Study Design (PECOS) components. There are discipline-specific PECOS criteria for experimental and epidemiologic studies. For experimental studies, the scope of the evidence used for this ISA encompassed studies of nonhuman mammalian animal species with exposures that are relevant to the range of human exposures, with mean blood Pb levels (BLLs) up to 30 μg/dL, which is about one order of magnitude above the 95th percentile of the 2011–2016 National Health and Nutrition Examination Survey (NHANES) distribution of BLLs in children (Egan et al., 2021). The evaluation of epidemiologic studies focused on the association between exposure to Pb (as indicated by Pb levels in blood, bone, and teeth; validated environmental indicators of Pb exposure; or intervention groups in randomized trials and quasi-experimental studies) and an ensemble of health effects, including effects on the nervous system, cardiovascular effects, and reproductive and developmental outcomes. Emphasis was placed on studies conducted in non-occupationally exposed populations, but recent longitudinal studies of occupational exposure to Pb published since the literature cutoff date for the 2013 Pb ISA were considered insofar as they addressed a topic that was of particular relevance to the NAAQS review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure). Additionally, the following types of health studies 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 benefit analyses (e.g., that apply existing C-R functions or effect estimates to exposure estimates for differing cases). For the health appendices, the PECOS statement defines the scope of the studies considered in the assessment of health evidence and establishes study inclusion criteria thereby facilitating identification of the most relevant literature to inform the ISA for each health discipline.

The statement used to define the scope of the ecological effects portion of this ISA comprises Level of Biological Organization, Exposure, Comparison, Endpoint, and Study Design (LECES). The LECES statement developed by the U.S. EPA specifically for the purpose of scoping literature for the ISAs, was based on the PECOS with some concepts substituted to provide a better fit with ecological science. In the LECES, "population" (**P**ECOS) is replaced with "level of biological organization" (**L**ECES) and "outcome" (PEC**O**S) is replaced with "endpoint" (LEC**E**S). The LECES statement aids in identifying the relevant evidence in the literature for ecological effects of Pb. Other topics within scope, in addition to Pb effects on biota described in the LECES criteria above, include effects of Pb biogeochemistry on bioavailability in terrestrial, freshwater, and saltwater environments; subsequent

vulnerability of particular organisms, populations, communities, or ecosystems, as well as key uncertainties and limitations in the evidence identified in the previous review. Concentrations relevant to the welfare effects of Pb consider the range of Pb concentrations in the environment and the available evidence for concentrations at which effects are observed in plants, invertebrates, and vertebrates. Effects observed at or near Pb concentrations measured in ambient soil, sediment, and water for which local contamination is not thought to be a primary contributor are emphasized. Concentration cutoff values were applied when evaluating the ecological literature published since the 2013 Pb ISA (Appendix 12). For soil, the cutoff value for screening of terrestrial studies of Pb exposure and effects was set at a concentration of approximately 230 mg Pb/kg of soil. For aqueous exposures, the cutoff value for study screening was approximately 10 μg Pb/L and, for sediments, the literature cutoff value for study screening was approximately 300 mg Pb/kg dry weight (Appendix 12, Table 12-4). Studies at higher concentrations were included only to the extent that they informed mechanisms of action, exposure-response, or the wide range of sensitivity to Pb across taxa. Areas outside of the scope for ecological effects in the Pb ISA included site-specific studies in non-U.S. locations that did not contribute novel insights on Pb biogeochemistry or effects. Studies on mine tailings, biochar, industrial effluent, sewage, ship breaking, bioremediation of highly contaminated sites, and ingestion of Pb shot, fishing tackle or pellets were not within the scope of the ISA due to high concentration of Pb and lack of a connection to an air-related source or process.

IS.1.2.2 Organization of the ISA

The ISA consists of the Front Matter (list of authors, contributors, and reviewers), Executive Summary (ES), IS and 12 appendices: https://assessments.epa.gov/isa/document/&deid=359536. This IS consolidates the key findings from the appendices considered in characterizing Pb exposure and relationships with human and welfare effects. Subsequent appendices are organized by subject area and include a detailed assessment and description of atmospheric science (Appendix 1), exposure (Appendix 2), health evidence (Appendix 3−Appendix 10), welfare evidence (Appendix 11), and the ISA development process (Appendix 12). Appendices for each broad health effect category (e.g., nervous system effects) discuss potential biological pathways and conclude with a causality determination describing the strength of the evidence between exposure to Pb and the outcome(s) under consideration. Likewise, the appendix devoted to welfare evidence (Appendix 11) includes causality determinations for multiple effects on ecosystems.

Organization of the 2024 Pb ISA:

- Front Matter
- Executive Summary
- Integrated Synthesis
- Appendix 1. Lead Source to Concentration
- Appendix 2. Exposure, Toxicokinetics, and Biomarkers
- Appendix 3. Nervous System Effects
- Appendix 4. Cardiovascular Effects
- Appendix 5. Renal Effects
- Appendix 6. Immune System Effects
- Appendix 7. Hematological Effects
- Appendix 8. Reproductive and Developmental Effects
- Appendix 9. Effects on Other Organ Systems and Mortality
- Appendix 10. Cancer
- Appendix 11. Effects of Lead in Terrestrial and Aquatic Ecosystems
- Appendix 12. Process for Developing the Pb Integrated Science Assessment

IS.1.2.3 Quality Assurance Summary

The use of QA and peer review helps ensure that the U.S. EPA conducts high-quality science assessments that can be used to help policymakers, industry, and the public make informed decisions. QA activities performed by the U.S. EPA ensure that environmental data are of sufficient quality to support the Agency's intended use. The U.S. EPA has developed a detailed Program-level QA Project Plan (PQAPP) for the ISA Program to describe the technical approach and associated QA/quality control procedures associated with the ISA Program. All QA objectives and measurement criteria detailed in the PQAPP have been employed in developing this ISA. Furthermore, the Pb ISA is classified as a Highly Influential Scientific Assessment (HISA), which is defined by the Office of Management and Budget (OMB) as a scientific assessment that is novel, controversial, or precedent-setting, or has significant interagency interest (Bolton, 2004). OMB requires a HISA to be peer reviewed before dissemination. To meet this requirement, the U.S. EPA engages CASAC as an independent federal advisory committee to conduct peer reviews. Both peer-review comments provided by the CASAC panel and public comments submitted to the panel during its deliberations about the external review draft were considered in the development of the final ISA. For a more detailed discussion of peer review and QA, see Appendix 12.

IS.1.2.4 Evaluation of the Evidence

This ISA draws conclusions about the causal nature of relationships between exposure to Pb and categories of related health and welfare effects, the concentrations at which effects are observed, and the populations and organisms most affected by Pb, by integrating recent evidence across scientific disciplines and building on the evidence from previous assessments. Determinations are made about causation, not just association, and are based on judgments of nine aspects of the evidence, including consistency, coherence, and biological plausibility of observed effects, and on related uncertainties (U.S. EPA, 2015). In evaluating the evidence, emphasis is placed on the consideration of the strengths, limitations, and possible roles of chance, confounding, and other biases that may affect the interpretation and/or the strength of inference from the results of individual studies. The ISA uses a formal causal framework to classify the weight of evidence using a five-level hierarchy (i.e., "causal relationship"; "likely to be causal relationship"; "suggestive of, but not sufficient to infer, a causal relationship"; "inadequate to infer the presence or absence of a causal relationship"; or "not likely to be a causal relationship" as described in Table II of the Preamble (U.S. EPA, 2015).

This framework for making causality determinations was recently reviewed by an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine. The committee broadly endorsed the framework, concluding that it "allows EPA to draw conclusions that integrate scientific findings across multiple study designs and disciplines, as required by the [Clean Air Act]" (NASEM, 2022). The committee further provided recommendations on approaches to increase transparency in how evidence is integrated and on other aspects of the ISA causality framework. EPA is currently evaluating the committee's recommendations and anticipates incorporating appropriate changes to the framework in future ISAs and documenting these changes in a future revision of the Preamble.

IS.2 Pb Source to Concentration

This section characterizes the current state of atmospheric and environmental science relevant to understanding Pb exposure and Pb-related health and ecological effects described in subsequent sections. It builds on previous research reviewed in the 2013 Pb ISA (U.S. EPA, 2013a) and previous Pb AQCDs (U.S. EPA, 2006, 1986c, 1977), and it emphasizes relevant advances in sources and emissions, fate and transport, sampling and analysis methods, and concentration observations discussed in greater detail in Appendix 1 (*Lead Source to Concentration*). The scope is not limited to airborne Pb from contemporary emission sources because non-atmospheric processes as well as legacy sources are also relevant for understanding the effects of air-related Pb. For example, transport and transformation processes in soil and water after deposition are also relevant. Therefore, current research in other media is also included to promote understanding of air-related Pb in the context of non-atmospheric sources and media.

In previous ISAs, an up-to-date review of air emissions, monitoring, and concentration trends has been accomplished through a combination of analysis of U.S. EPA monitoring network data and a

synthesis of observations reported in the peer-reviewed literature. Reference data such as estimates of total emissions, coverage of network monitors, average concentrations, and concentration trends can become out of date before the document is published because these data are so frequently updated. To facilitate provision of the most current emissions and concentration data from the Pb monitoring network, a set of relevant maps and graphics that have been routinely included in previous ISAs are now contained in a separate document titled "Overview of Lead (Pb) Air Quality in the United States" (U.S. EPA, 2022b). Appendix 1 of the Pb ISA provides a literature-based synthesis of recent research on Pb sources, fate and transport, measurement, and ambient air concentrations.

Section IS.2.1 provides an overview of sources and emissions of Pb in ambient air and other environmental media. Section IS.2.2 gives descriptions of the fate and transport of Pb in air, soil, and aqueous media. Section IS.2.3 describes advances in Pb measurement methods, and Section IS.2.4 describes ambient air Pb concentrations, including spatial and temporal variability and the size distributions of Pb-bearing particulate matter (PM).

IS.2.1 Sources and Emissions

Total estimated national Pb emissions to ambient air from the 2020 National Emissions Inventory (NEI) were 621 tons, with 69% from emissions associated with use of leaded aviation gasoline, 18% from industrial sources, 9% from fuel combustion, and 3% from wildland fires. All other sources combined were estimated to account for about 2% of total U.S. Pb emissions estimated by the NEI. Pb emissions from residential wood combustion are not included in the 2020 NEI but can also be a source in areas affected by wood smoke in the winter (Appendix 1.2.3). In addition to contemporary Pb emissions into the atmosphere, historical sources of Pb that are not included in the NEI can potentially contribute to airborne Pb under some circumstances through the processes of suspension and resuspension (Appendix 1.3.4). Details of recent research and results of individual studies of Pb emissions from aviation, industrial sources, stationary fuel combustion, wildfires, automobile traffic and roads, volcanoes, and legacy sources in the United States are presented in Appendix 1.2.

IS.2.2 Fate and Transport

Pb emitted into the atmosphere can be distributed into soil, water, and other media. Pb is mainly emitted into the air in particulate form. The fate and transport of Pb emitted into the air depends on particle size, which in turn depends largely on the source. For example, Pb emitted by aircraft using leaded aviation gas is mainly associated with ultrafine particles smaller than 0.1 μm diameter, while a large fraction of airborne Pb produced by resuspension of contaminated soil near current or historic sources can be associated with coarse particles, including particles larger than 10 μm. Pb-containing particles are subject to the same atmospheric processes that transport and remove other forms of PM.

Particle-bound Pb associated with fine PM is transported long distances and found in remote areas, while Pb associated with coarse PM is more likely to deposit closer to its source. As discussed in Appendix 1.3.1, the dry deposition rate of particles increases with increasing particle size, effectively reducing transport distance and atmospheric lifetime. However, depending on the chemical counter-ion, Pb compounds vary in water solubility, determining the degree to which Pb is removed by wet deposition. After deposition, resuspension of soil-bound Pb can contribute to airborne concentrations near major Pb sources (Appendix 1.3.4). There has been little recent research on transport of airborne Pb, beyond a few individual studies outside the United States that showed agreement of Pb biomonitoring data with dispersion modeling estimates and chemical transformations of Pb to a more soluble form in polluted air under specific circumstances (Appendix 1.3.1.2).

In general, fine particulate Pb is mostly soluble and removed from the atmosphere by wet deposition, and coarse particulate Pb is mostly insoluble and removed from the atmosphere by dry deposition. Other factors also influence Pb deposition, however. The pH of precipitation can play a role because Pb solubility increases with decreasing pH. Precipitation can also scavenge insoluble particulate Pb as an aqueous suspension. Several U.S. studies, some of which have been published since the 2013 Pb ISA, have reported substantially greater deposition rates in areas near industrial sources than in nonindustrial areas. Recent studies have also filled in some details about the Pb deposition process, including studies that indicated Pb deposition increased with elevation and that Pb is enriched in atmospheric ice nuclei (Appendix 1.3.1.3).

Once deposited in soil, Pb is strongly retained in soil organic material with subsequent Pb fate and transport through the soil column influenced by several physicochemical factors, including storage in leaf litter, the amount and decomposition rates of organic matter (OM), composition of organic and inorganic soil constituents, mobile colloid abundance and composition, microbial activity, and soil pH. These physicochemical properties are based on soil forming factors: climate, organisms, parent material, relief (shape of the landscape), time, and anthropogenic input. Soils that differ in these factors will subsequently have different physicochemical properties and different trends in Pb transport. In general, leaf litter, low rates of OM decomposition, neutral pH, and soil constituents rich in charged surfaces such as OM, Fe and Mn oxides, and clay minerals will lead to increased Pb retention and sorption. Conversely, thin organic layers, increased OM decomposition, acidic pH, increases in anthropogenic Pb, and less reactive soil constituents such as quartz increase Pb leaching from soils.

In water, runoff from urban or historically industrial areas contains higher Pb concentrations than runoff from nonurban areas. Recent studies have improved our understanding of relationships between Pb runoff and street length and density, population density, and land cover, and expanded on the influence of seasonality and precipitation events on runoff as well as transport and sedimentation. While Pb deposition has decreased in the last half-century with the phaseout of leaded gasoline and stricter regulation, accumulated Pb-contaminated sediments in areas with a history of industry and urbanization are vulnerable to resuspension in water and both down and upstream movement following a disturbance

event. Dam removal or other disturbances to water bodies can lead to resuspension in water and dissolution of Pb-contaminated sediment that was previously deposited. With the predicted increase in future frequency of drought alongside less frequent but more severe precipitation patterns across most of the United States, the potential for remobilization of such legacy Pb in waterbodies is an area for consideration.

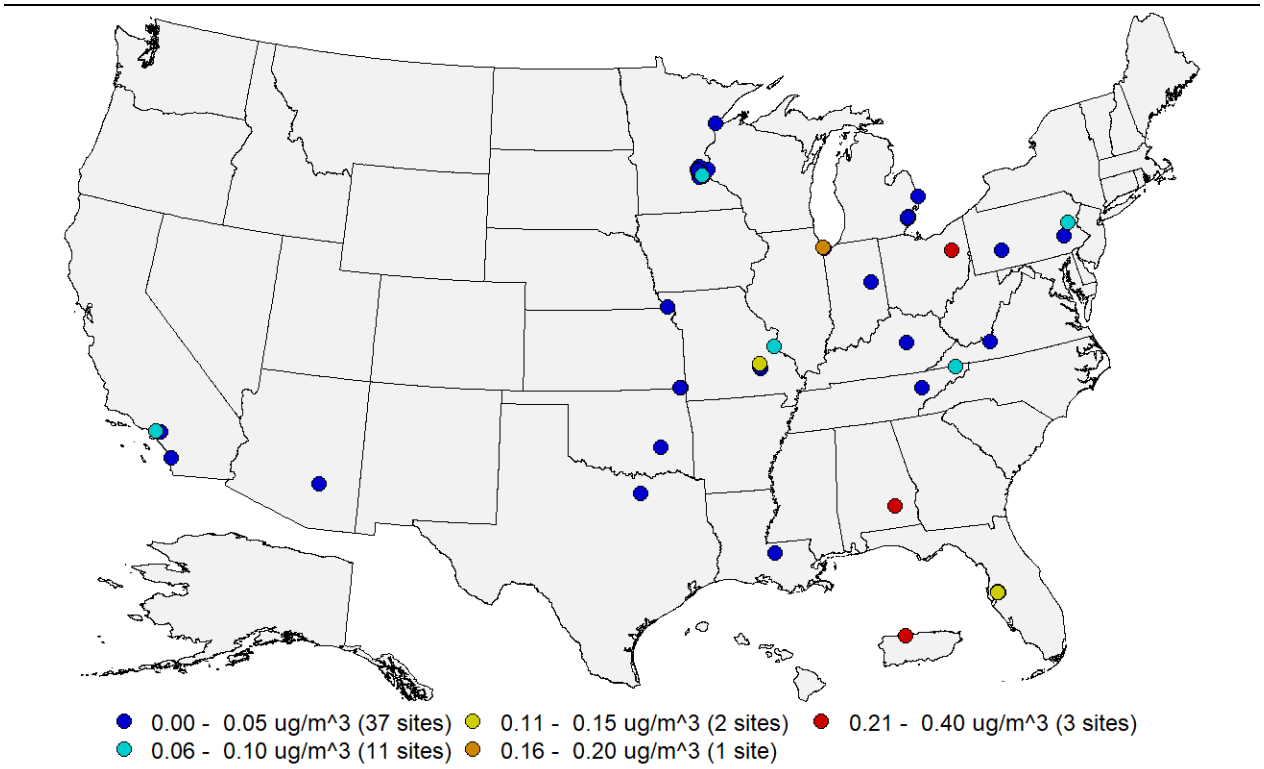
Additional media besides air, water, and soil are useful for understanding how Pb moves and changes over time in the urban environment. It is potentially useful to consider urban soil, resuspended dust, road dust, and house dust as urban compartments between which Pb can be transported or cycled. High Pb concentrations are characteristic of urban soil in comparison with other soils and are often related to legacy sources. Studies in several U.S. cities have explored the high spatial variability of urban soil Pb concentrations, with hot spots related to income and racial disparities. In recent studies, associations between airborne Pb and elemental indicators of airborne soil have been observed, suggesting the potential for contaminated soil to be a source of airborne Pb locally in urban and industrial areas under some circumstances. Suspension of urban soil into the air can also be a source of Pb in house dust (Appendix 1.3.4).

IS.2.3 Sampling and Analysis

There are two Federal Reference Methods (FRMs) for sample collection of airborne Pb. The FRM for Pb in total suspended particulate (Pb-TSP) requires a high-volume sampler and is required for all source-oriented NAAQS surveillance monitors. The FRM for Pb associated with PM_{10} (Pb-PM_{10}) is acceptable for Pb NAAQS surveillance monitoring at locations where the expected Pb concentration does not approach the NAAQS and in the absence of nearby sources of Pb associated with particles greater than 10 μm diameter. Variability in high-volume TSP sampler collection efficiency associated with effects of wind speed and sampler orientation for particles larger than 10 μm has been a serious concern since the sampler was first implemented for TSP and Pb-TSP sampling. Recent research confirmed that sampling effectiveness decreased with particle size for coarse particles and varied with wind speed and sampler orientation. A number of alternative manufacturer-designated low-volume TSP samplers have been developed, but recent studies showed that their sampling effectiveness also decreases with particle size for coarse particles. The Pb-PM_{10} FRM is not as vulnerable to sampling errors associated with the Pb-TSP FRM because it is based on a strictly defined performance standard, but Pb associated with particles larger than 10 μm in diameter can be an important contributor to airborne Pb exposure. Other recent advances in ambient air Pb sampling and analysis included the development of a new Pb analysis FRM based on inductively coupled plasma mass spectrometry, development of more relevant reference materials for ambient air Pb sampling and analysis, and development of higher time resolution sampling and analytical methods.

IS.2.4 Ambient Air Pb Concentrations

Figure IS-1 is a national map of maximum rolling 3-month average Pb concentrations in counties with Pb-TSP monitors during the period 2020−2022 (Appendix 1.5.1). Concentrations exceeded 0.15 μg/m^3 in Stark County OH (0.40 μg/m^3), Arecibo PR (0.35 μg/m^3), Pike County AL (0.22 μg/m^3), and Lake County IN (0.16 μg/m^3). Several recent studies indicated substantial spatial variability in urban ambient air Pb concentrations influenced by proximity to local sources or industrial activities. Across urban and neighborhood scales, these variations in ambient air Pb concentrations may not be captured by national monitoring networks. Seasonal trends were reported in numerous recent studies, but results were mixed, and no consistent national pattern was apparent. Size distribution data from samples collected near roads, near industrial sources, in rural locations, and in urban locations within the United States and the European Union suggest that Pb size distributions in ambient air have shifted in the 1980s from size distributions with a mass median diameter usually smaller than 2.5 μm to those with a primary mode between 2.5–10 μm. No recent studies specifically investigated background Pb concentrations, but a plausible range of 0.2 to 1 ng/m^3 was proposed based on earlier studies in the 2013 Pb ISA (U.S. EPA, 2013a).



Source: (U.S. EPA, 2023).

Figure IS-1 Pb maximum rolling 3-month average in μg/m^3 for the 2020–2022 period.

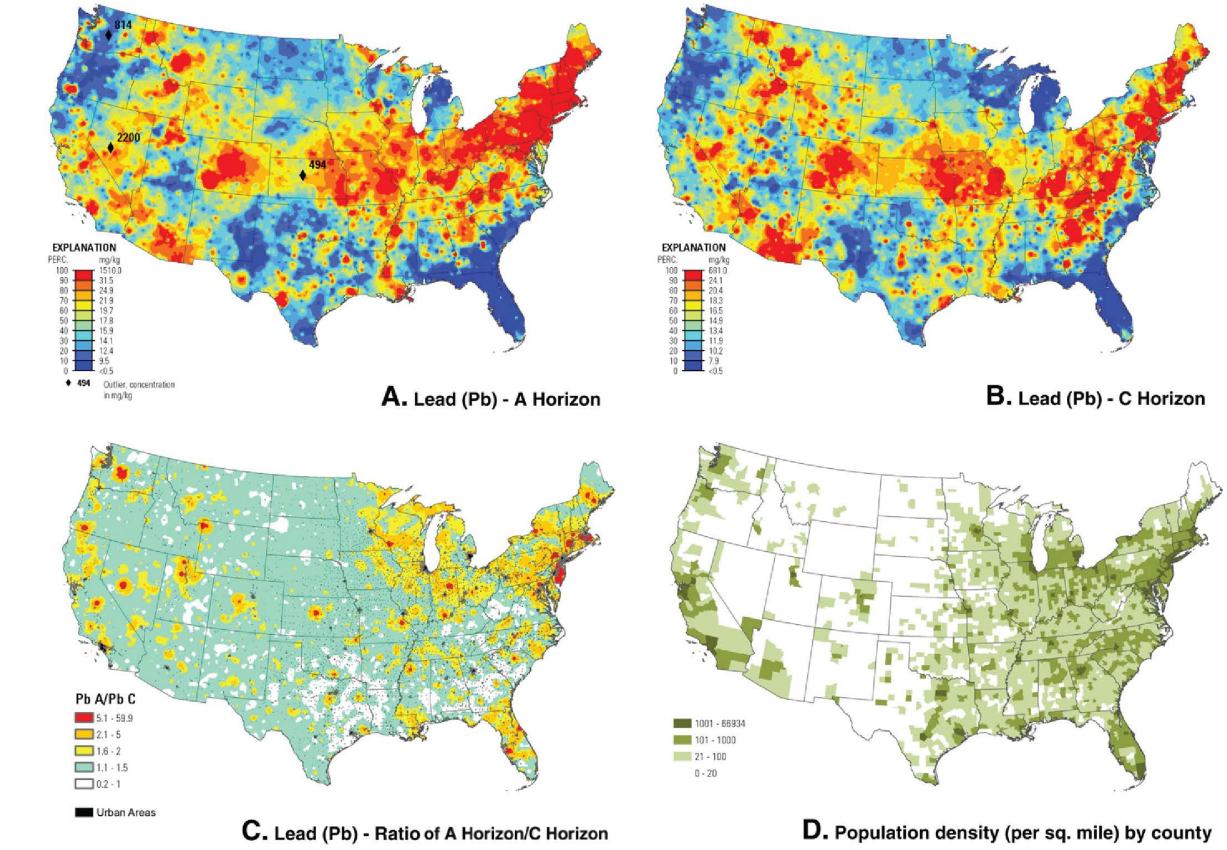
IS.3 Trends

Total Pb emissions have steadily decreased for decades, largely due to the elimination of leaded gasoline use in automobiles before 1996, and in later years because of reductions in emissions from metals processing sources (U.S. EPA, 2022b, 2013a, 2006). From 1990 to 2020, there has been a steep decline in total U.S. Pb emissions from about 5 kton/year to less than 1 kton/year (U.S. EPA, 2021). In some cases, there have been more recent periods of continued decline corresponding to reductions in Pb emissions from local and regional industrial sources. A quantitative description of the trend in ambient air concentrations based on monitoring network data is problematic for two reasons. First, air Pb concentration reporting requirements changed in 2010 from measured Pb concentration at standard temperature and pressure to Pb concentration measured under local conditions. As a result, daily concentration, and design value data from before 2010 are not directly comparable to data from after 2010. Second, as numerous monitors have been discontinued because of declining Pb concentrations, the proportion of monitors located near sources has increased. Pb monitoring network data show that the national median of maximum 3-month average Pb concentrations across monitoring sites declined by 89% from 1990 to 2010 for a mix of 74 source-oriented and non-source-oriented monitors that operated continuously through this period (Appendix 1.5.1). For a smaller population of 37 monitors with a higher proportion of source-oriented monitors that operated continuously from 2010 to 2021, the national median of maximum 3-month average Pb concentrations across monitoring sites decreased by 88% over that period (Appendix 1.5.1). This recent decrease was driven by the 2008 NAAQS revision and the steepest declines were observed over the period from 2012 to 2015 when emissions from sources near these monitors were being reduced to meet the new 2008 Pb NAAQS requirements (Appendix 1.5.1). The declining trend since 2010 is therefore more representative of a small number of communities near major sources than an urban or national median. A national trend is more difficult to assess because the number of non-source-oriented monitors is small, and their observed concentrations are close to method detection limits on most days (Appendix 1.5.1). Detailed maps and graphics of changing ambient air Pb concentrations over time are available in U.S. EPA (2022b).

Changes in the patterns of Pb emissions over time and between regions of the United States are also detectable in non-air environmental media and biota. Pb may be retained in soils, sediments, the shells of long-lived bivalves, or trees, where it provides a historical record of deposition such as phaseout of Pb from on-road gasoline and reductions in industrial releases. However, information on Pb atmospheric trends can be difficult to interpret due to the influence of other anthropogenic inputs of Pb and heterogeneity associated with natural environments. The number of studies that examine trends in Pb concentration in non-air media at national and regional scales is limited.

Concentrations of Pb in soils (Appendix 11.2.2.1) vary across the United States due to a variety of natural and anthropogenic factors, including historical Pb deposition. The United States Geological Survey North American Soil Geochemical Landscapes Project (NASGLP) provides the most comprehensive and rigorous information on the distribution of Pb across the conterminous United States

(Smith et al., 2013). In the NASGLP survey, soil samples were collected from multiple depths at 4,857 sites. In areas with historic depositional input of Pb, the concentration of Pb observed in upper-horizon soils was often higher than that observed in the bedrock. Figure IS-2C shows the ratio of A-horizon (the uppermost mineral soil) to C-horizon (a deeper soil sample generally of partially weathered parent material) Pb concentrations mapped in Woodruff et al. (2015), using inverse-distance weighting methods derived from the NASGLP survey (Smith et al., 2013). This map displays areas with increased concentrations of Pb in A-horizon soils relative to lower horizons, hinting at the lasting effect of depositional Pb pollution, where historical Pb deposition may have a relatively higher effect on people and ecosystems. Patterns of elevated A- to C-horizon soil Pb concentrations in Figure IS-2C are conspicuous in areas with historical anthropogenic sources of Pb. This pattern is observed in the northeastern United States, with a historically high population density and intensity of industrial development. Likewise, mapping highlights former Pb smelting and mining sites, for instance in areas near smelters in Everett and Tacoma, Washington or the Doe Run smelter in Herculaneum, Missouri (the last Pb smelter in the United States, which closed in 2013). Areas near mining sites, including near Leadville, Colorado, Cooke City, Montana, and northern Utah, also have a high ratio of A- to C-horizon Pb. Woodruff et al. (2015) emphasized that no known natural geological process would otherwise explain elevated A-horizon soils relative to the underlying layers.



Source: Woodruff et al. (2015).

Figure IS-2 Maps of Pb sampled from (A) A-horizon and (B) C-horizon soils, (C) the ratio of Pb observed in A-horizon to C-horizon soils, and (D) population density.

In a regional survey of forest floor soils limited to the northeastern United States featuring sequential sampling in 1980, 1990, 2002, and 2011, mean soil Pb concentrations decreased from 151 ± 29 (standard error [SE]) mg Pb/kg in 1980 to 68 ± 13 (SE) mg Pb/kg in 2011 and were estimated to decline 2.0 ± 0.3 % per year (Richardson et al., 2015; Richardson et al., 2014). A 2019 survey of peri-urban soil Pb in several southern California counties is illustrative of the regional variability in U.S. soil Pb concentrations. Soil Pb in the study (mean of 23.9 ± 13.8 mg Pb/kg) was elevated relative to the southwestern U.S. region, but lower than concentrations found at contaminated sites near point sources of Pb (Mackowiak et al., 2021). These recent national and regional surveys of soil Pb document the spatial and temporal patterns of residual pollution resulting from decades of Pb emissions. In general, areas with higher population density and intensity of industrial activity have higher soil Pb concentrations relative to rural areas. Recent results from more local studies of individual cities and neighborhoods are consistent with these results (Appendix 1.3.4).

Quantification of Pb in tree rings can be used to reconstruct historical trends of Pb in air pollution (U.S. EPA, 2006, 1986b, 1977); however, radial transport of Pb, which may vary among species, can

occur within the tree, contributing uncertainty and reducing precision of such reconstructions. Additionally, there may be a 10- to 15-year delay in tree ring Pb compared with air concentrations as Pb deposition leaches through the soil and is absorbed by the tree (U.S. EPA, 2013a). Although trends varied across tree species and regions in several North American studies published since the 2013 Pb ISA (Appendix 11.2.2.2), studies identified a temporal pattern of Pb that increased after 1850–1900 and, in some cases, peaked in 1970–1985, then decreased afterward. Tree ring studies with temporal patterns that deviate from this pattern were conducted near active industrial point sources of Pb pollution.

Temporal trends of Pb deposition in sediment show distinct peaks associated with leaded gasoline usage in the United States. These peaks are found globally, corresponding to the specific phaseout periods for the contributing countries (Appendix 1.3.3.4). Patterns of increasing Pb concentration occurring from the mid-19th century through the mid-20th century due to early industry as well as agriculture, weathering, and mining operations are identifiable in North American lake and reservoir sediments. Following the peak deposition period in the 1960s due to leaded gasoline in North America, widespread decreases in Pb concentration in sediments are seen over the following half-century, but concentration values are still higher than pre-19th century levels showing continued deposition, nonpoint contamination, and/or legacy Pb runoff contributions.

In freshwater environments, no recent studies were identified that examined spatial or temporal trends in Pb concentration in fish or invertebrates from locations across the United States. Appendix 11.3.2 summarizes several historical studies reviewed in earlier AQCDs or the 2013 Pb ISA. Limited evidence from regional studies of temporal trends in freshwater aquatic ecosystems published since the 2013 Pb ISA, including one of dissolved Pb in Appalachian streams and another of peat cores in northern Alberta, Canada, suggests that modern atmospheric deposition of Pb is not a major contributor to Pb concentrations in streams in remote locations (Appendix 11.3.2).

In long-term biomonitoring studies of saltwater biota (Appendix 11.4.2), there is some evidence of declining Pb concentrations, particularly in studies that began sampling before the 1990s. However, other studies provide mixed results, with some observations of insignificant change or even increases in Pb concentrations, likely due to non-air anthropogenic sources. The National Oceanic and Atmospheric Administration (NOAA) Mussel Watch program has monitored pollutant trends since 1986 via periodic sampling of bivalve tissue (Mytilus spp. and *Crassostrea virginica* oysters) and sediment along the U.S. coastline (Kimbrough et al., 2008). In general, the highest concentrations of Pb are in bivalves in the vicinity of urban and industrial areas. Metals concentrations in *Mytilus californianus* were sampled at long-term biomonitoring sites off the coast of California from 1977 to 2010 (specific years vary by site) (Melwani et al., 2014). Decreasing trends were observed at some sites while others showed no significant trend. In addition to tissues, quantification of chemical variation of elements taken up and deposited in shells of marine organisms (sclerochronology) provides a temporal record of Pb deposition inputs to coastal environments. Several studies in bivalves collected off the coast of the eastern United States, where Pb sources include atmospheric transport by easterly winds, show elevated Pb in shell

corresponding to the peak of Pb gasoline use in the United States and then declines after that time (Krause-Nehring et al., 2012; Gillikin et al., 2005). In a synthesis of data from 15 studies from different geographic locations that quantified Pb in marine bivalves, shell concentrations tended to be higher in areas near sources of Pb pollution (Cariou et al., 2017). In addition to bivalves, heavy metals quantified in horseshoe crab (*Limulus polyphemus*) eggs collected along Delaware Bay in 2012 showed a decline in Pb over time in a comparison with compiled data from earlier surveys conducted between 1993 and 2000 (Burger and Tsipoura, 2014). In contrast, a decade-long biomonitoring study of metals in the muscle tissue of dolphinfish (*Coryphaena hippurus*) in the southern Gulf of California from 2006–2015 found no temporal trend in Pb concentrations (Gil-Manrique et al., 2022).

Overall, evidence from surveys of Pb in environmental media and biota reflects a decline in anthropogenic emissions of Pb. However, Pb pollution persists in environmental media and is still observed in measurable concentrations within biota, particularly near sources of Pb pollution both historical and current. Long-term monitoring of Pb concentration trends in biota (e.g., the NOAA Mussel Watch program) and soil surveys covering large spatial extents (e.g., NASGLP) provide essential records of Pb concentrations in the environment observed across decades and regions.

IS.4 Human Exposure to Ambient Pb

Human exposure to Pb derives from the multiple sources of Pb in the environment and the various media through which it passes (Appendix 2.1). Air-related pathways of Pb exposure are the focus of this assessment. However, exposure studies containing Pb concentrations in other media (soil, dietary sources, consumer products, occupational sources, and ammunition) were included because cumulative body burden can occur as a result of contributions from multiple exposure pathways (i.e., ingestion of Pb-containing soil by children) and most Pb biomarker studies do not indicate species or isotopic signature, making it a challenge to link Pb exposures to specific sources. Air-related Pb exposure pathways include inhalation of Pb in ambient air along with inhalation and ingestion of Pb in indoor dust and/or outdoor soil that originated from recent or historic ambient air (e.g., air Pb that has penetrated into the residence either via the air or tracking of soil), ingestion of Pb in drinking water drawn from surface water contaminated from atmospheric deposition or contaminated from surface runoff of deposited Pb, and ingestion of Pb in dietary sources after uptake by plants or livestock of Pb that originated from the atmosphere. Soil can act as a reservoir for deposited Pb emissions. Exposure to soil contaminated with deposited Pb can occur through inhalation of resuspended soil as well as ingestion via hand-to-mouth contact. The primary contribution of ambient air Pb to young children's blood Pb concentrations is generally due to ingestion of Pb following its deposition to soils and dusts (Appendix 2.1.3.2). Nonambient air-related exposures include hand-to-mouth contact with dust or chips of peeling Pb-containing paint or ingestion of Pb in drinking water leached by corroding pipes. Several studies indicate that Pb-containing paint in the home (or home age used as a surrogate for the presence of Pb paint) are important residential factors that increase risk of elevated blood Pb (Appendix 2.1.3.2).

The size distribution of soil or dust particles containing Pb differs from the size distribution of inhalable ambient Pb-bearing PM (Appendix 2.1.3.1). Airborne particles containing Pb tend to be small (much of the distribution <10 μm) compared with soil or dust particles containing Pb (~50 μm to several hundred μm). The size of particles containing Pb that someone may be exposed to can vary due to source type and proximity to those sources. Ingestion through hand-to-mouth contact is the predominant exposure pathway for the larger particles in soil and dust containing Pb.

A number of monitoring and modeling techniques have been employed for estimating Pb exposures and associated BLLs. Environmental Pb concentration data can be collected from ambient air Pb monitors, soil Pb samples, dust Pb samples, and dietary Pb samples to estimate human exposure. Exposure estimation error depends, in part, on the collection efficiency of these methods. Models, such as the Integrated Exposure Uptake Biokinetic (IEUBK) model, coupling of the Stochastic Human Exposure and Dose Simulation (SHEDS) and IEUBK models (SHEDS-IEUBK), and the All-Ages Lead Model, simulate human exposure to Pb from multiple sources and through intake routes of inhalation and ingestion. Children's exposure to Pb is modeled using inputs including soil Pb concentration, air Pb concentration, dietary Pb intake including drinking water and Pb-dust ingestion, human activity, and biokinetic factors. The relative contribution from specific exposure pathways (e.g., water, diet, soil, ambient air) to blood Pb concentrations is situation specific. Measurements and/or assumptions can be utilized when formulating the model inputs; errors in measurements and assumptions have the potential to propagate through exposure models. Biomarkers, such as blood Pb, can also be used to provide information about exposure (Appendix 2.3).

IS.5 Toxicokinetics

The majority of Pb in the body is found in bone (roughly 90% in adults, 70% in children); only about 1% of Pb is found in the blood. Pb in blood is primarily (~99%) bound to red blood cells (RBCs). It has been suggested that the small fraction of Pb in plasma (<1%) may be the more biologically labile and toxicologically active fraction of the circulating Pb. The relationship between Pb in blood and plasma is approximately linear at relatively low daily Pb intakes (i.e., <10 μg/kg per day) and at blood Pb concentrations <25 μg/dL and becomes curvilinear at higher blood Pb concentrations due to saturable binding to RBC proteins. As BLL increases and the higher affinity binding sites for Pb in RBCs become saturated, a larger fraction of the blood Pb is available in plasma to distribute to brain and other tissues. See Appendix 2.2.2 for additional details.

The half-life of Pb in blood is approximately 20–30 days in adults and a half-life of approximately 6 days has been estimated based on data for children under the age of 3 years. An abrupt change in Pb uptake gives rise to a relatively rapid change in blood Pb, with a new quasi steady-state achieved in approximately 75–100 days (i.e., 3–4 times the blood elimination half-life). A slower phase of Pb clearance from the blood may become evident with longer observation periods following a decrease in

exposure due to the gradual redistribution of Pb among bone and other compartments. See Appendix 2.3.5 for additional details. Absorbed Pb is excreted primarily in urine and feces, with sweat, saliva, hair, nails, and breast milk being minor routes of excretion. Approximately 30% of intravenously injected Pb in humans (40%–50% in beagles and baboons) is excreted via urine and feces during the first 20 days following administration (Leggett, 1993). The kinetics of urinary excretion following a single dose of Pb is similar to that of blood (Chamberlain et al., 1978), likely because Pb in urine derives largely from Pb in plasma. See Appendix 2.2.3 for additional details.

The burden of Pb in the body may be viewed as divided between a dominant slow compartment (bone) and smaller fast compartment(s) (soft tissues). Pb uptake to and elimination from soft tissues is much faster than in bone. Pb accumulates in bone regions undergoing the most active calcification at the time of exposure. Pb accumulation is thought to occur predominantly in cortical bone during childhood and in both cortical and trabecular bone in adulthood. However, several considerations complicate the dichotomy between Pb accumulation in trabecular versus cortical bone. For example, the tibia is generally considered a cortical bone with less than 1% trabecular bone at its midshaft but is 55%–75% trabecular bone toward the ends of the bone. A high bone formation rate in early childhood results in the rapid uptake of circulating Pb into mineralizing bone; however, in early childhood, bone Pb is also recycled to other tissue compartments or excreted in accordance with a high bone resorption rate. Thus, much of the Pb acquired early in life is not permanently fixed in the bone due to rapid bone formation and reabsorption. See Appendix 2.2.2.2 for additional details.

The exchange of Pb from plasma to the bone surface is a relatively rapid process. Pb in bone becomes distributed in trabecular bone and the denser cortical bone. The proportion of cortical to trabecular bone in the human body varies by age, but on average is about 80% cortical to 20% trabecular. Of the bone types, trabecular bone is more reflective of recent exposures than is cortical bone because of the slower turnover rate and lower blood perfusion of cortical bone. Some Pb diffuses to kinetically deeper bone regions where it is relatively inert, particularly in adults. These bone compartments are much more labile in infants and children than in adults as reflected by half-times for movement of Pb from bone into the plasma (e.g., cortical half-time = 0.23 years at birth, 3.7 years at 15 years of age, and 23 years in adults; trabecular half-time = 0.23 years at birth, 2.0 years at 15 years of age, and 3.8 years in adults) (Leggett, 1993). See Appendix 2.3.5 for additional details.

Evidence for maternal-to-fetal transfer of Pb in humans is derived from umbilical cord blood to maternal blood Pb ratios (i.e., cord blood Pb concentration divided by mother's blood Pb concentration). Group mean ratios range from about 0.7 to 1.0 at the time of delivery for mean maternal BLLs ranging from 1.7 to 8.6 µg/dL. Transplacental transfer of Pb may be facilitated by an increase in the plasma/blood Pb concentration ratio during pregnancy. Maternal-to-fetal transfer of Pb appears to be related partly to the mobilization of Pb from the maternal skeleton. See Appendix 2.2.2.4 for additional details.

IS.6 Pb Biomarkers

Overall, BLLs have been decreasing among U.S. children and adults over the past 45 years. The geometric mean BLL for the entire U.S. population was 0.753 μg/dL (95% CI: 0.723, 0.784), based on the 2017–2018 NHANES data (CDC, 2021). Among children aged 1–5 years, the geometric mean was slightly lower, at 0.670 μg/dL (95% CI: 0.600, 0.748). By comparison, the 1976–1980 NHANES showed a geometric mean blood Pb of 15.2 μg/dL (95% CI: 14.3, 16.1) in children aged 1–5 years. In addition, the gap in BLLs between non-Hispanic Black children and children of different racial/ethnic groups, aged 1–5 and 6–10 years, has decreased over time, as shown by 1999–2000 to 2015–2016 NHANES data. See Appendix 2.4.1 for additional details.

Blood Pb is dependent on both the recent exposure history of the individual and the long-term exposure history, which determines body burden and Pb in bone. The contribution of bone Pb to blood Pb varies depending on the duration and intensity of the exposure, age, and various other physiological stressors (e.g., nutritional status, pregnancy, menopause, extended bed rest, hyperparathyroidism) that may affect bone remodeling, which occurs continuously under normal circumstances. In children, blood Pb is both an index of recent exposure and potentially an index of body burden, largely due to faster exchange of Pb to and from bone than in adults. In adults and children whose exposure to Pb has effectively ceased or greatly decreased, there is a rapid decline in blood Pb over the first few months followed by a more gradual, slow decline in blood Pb concentrations over the period of years due to the gradual release of Pb from bone. Bone Pb is an index of cumulative exposure and body burden. Bone compartments should be recognized as reflective of differing exposure periods, with Pb in trabecular bone exchanging with the blood more rapidly than Pb in cortical bone. Consequently, Pb in cortical bone is a better marker of cumulative exposure, while Pb in trabecular bone is more likely to be correlated with blood Pb, even in adults. See Appendix 2.2.2 and 2.3.5 for additional details.

It is important to recognize that from a single measurement of blood Pb, it cannot be determined the extent to which blood Pb reflects recent exposure, movement of Pb from bone into blood from historical exposures, or both recent and historical exposures. Additionally, a single measurement of blood Pb cannot inform whether an individual is at a steady-state blood Pb concentration or whether blood Pb is changing because of a change in Pb exposure. In contrast, multiple blood Pb concentrations over time can provide more insight into cumulative exposures and average Pb body burdens over time. The degree to which repeated sampling will reflect the actual long-term time-weighted average blood Pb concentration depends on the sampling frequency in relation to variability in exposure. High variability in Pb exposures can produce episodic (or periodic) oscillations in blood Pb concentration that may not be captured with infrequent samples. Furthermore, similar blood Pb concentrations in two individuals (or populations), regardless of their age, do not necessarily translate to similar body burdens or similar exposure histories. The blood Pb measurement method (capillary or venous) may also influence measured blood Pb concentrations because of a positive bias in capillary sample measurement and contamination of fingertips where samples were collected. See Appendix 2.3.2 for additional details.

The concentration of Pb in urine follows blood Pb concentration. There is added complexity with Pb in urine because concentration is also dependent upon urine flow rate (see Appendix 2.2.3), which requires timed urine samples that is often not feasible in epidemiologic studies. Other biomarkers have been utilized to a lesser extent (e.g., Pb in teeth, hair, and saliva) because of complications with environmental contamination or inconsistent associations with blood Pb. See Appendix 2.3 for additional details.

IS.7 Evaluation of the Health Effects of Pb

IS.7.1 Connections Among Health Effects

Broad health effect categories organized by organ system are evaluated separately in the appendices of this ISA, though the mechanisms underlying disease progression may overlap and are not necessarily restricted to a single organ system. This section provides a brief overview of how the relationship between Pb exposure and a variety of health outcomes may be related or affect one another.

Pb-induced injuries can take place via complex pathways within the body. The health effects of Pb can be triggered by both direct and indirect actions within an organ but can also cause systemic changes that can affect other areas of the body. Pb can directly bind to cellular proteins and in some instances can displace biologically relevant enzymes leading both to ion imbalance and initiation of inflammation and oxidative stress. Because the circulatory system is connected to all body systems, effects of damage in one organ system may contribute to health effects in another. Pb-induced systemic inflammation and oxidative stress can trigger systemic responses in multiple organs.

There is crosstalk between organ systems in the body. For example, the nervous system regulates the development and function of many organs and thus, modulation of the nervous system by Pb exposure (see Appendix 3) can have widespread effects. Pb has been shown to disrupt the network of signaling between the hypothalamus, pituitary, and adrenal and gonadotropic axes, which have important implications in the regulation of development, reproduction, cardiovascular function, and respiratory function. This is of particular concern with Pb exposure early in life as proper organ development requires proper hormonal and cell signaling cues. Disruption of these processes early in life can lead to lasting changes in organ structure and function. In a similar manner, the function of the liver, kidneys, and cardiovascular system are also linked. The liver plays a major role in the generation, trafficking, and metabolism of fatty acids and cholesterol, which are trafficked throughout the body for use in other organs. Alterations in cholesterol and fatty acid homeostasis by Pb can affect the organ systems that use these resources. The renin-angiotensin system provides another means of crosstalk between the kidney, liver, and cardiovascular systems. Renin, produced in the kidney, processes angiotensin, produced by the liver, which can promote vascular contraction. Pb-induced increases in angiotensin processing can lead to various effects including increased vascular constriction and increased blood pressure (BP). Chronic

increases in BP can lead to kidney damage. Although these examples are not exhaustive, they highlight means by which Pb-induced effects in one organ could lead to systemic effects capable of eliciting multiple health effects.

While all systems of the body are connected intrinsically, most of the available research examining the health effects of Pb exposures focuses on specific health endpoints. Thus, this ISA includes separate supporting appendices for Nervous System Effects (Appendix 3), Cardiovascular Effects (Appendix 4), Renal Effects (Appendix 5), Immune System Effects (Appendix 6), Hematological Effects (Appendix 7), Reproductive and Developmental Effects (Appendix 8), Effects on Other Organ Systems and Mortality (Appendix 9), and Cancer (Appendix 10).

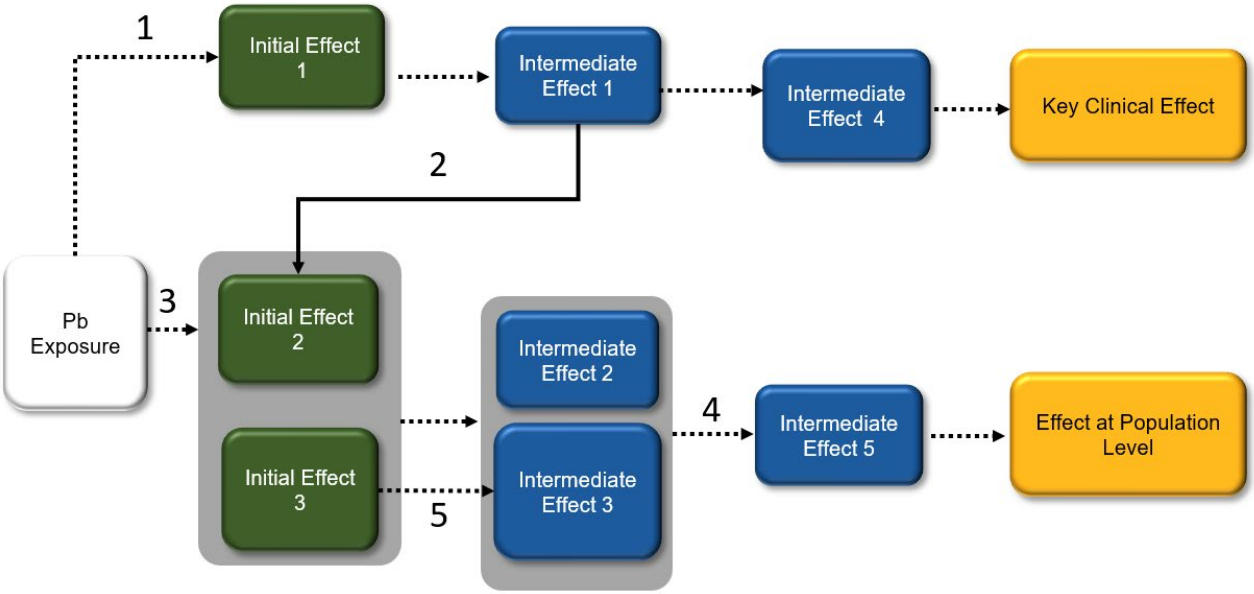
IS.7.2 Biological Plausibility

Biological plausibility can strengthen the basis for causal inference (U.S. EPA, 2015). In this ISA, biological plausibility is part of the weight-of-evidence analysis that considers the totality of the health effects evidence, including consistency and coherence of effects described in experimental and observational studies. Each of the human health appendices (Appendix 3−Appendix 10) includes a biological plausibility section that summarizes the evidence for potential pathways by which Pb exposures could result in adverse health outcomes at the population level. Although there is some overlap in the potential pathways between the appendices, each biological plausibility section is tailored to the specific health outcome category for which causality determinations are made.

Each of the biological plausibility sections includes a figure illustrating possible pathways that connect Pb exposures with health outcomes. Pathways are based on evidence evaluated in previous assessments, both AQCDs and ISAs, as well as evidence from more recent studies. The accompanying text characterizes the evidence upon which the figures are based, including results of studies demonstrating specific effects related to Pb exposure and considerations of physiology and pathophysiology. Together, the figure and text portray the available evidence that supports the biological plausibility of Pb exposure leading to specific health outcomes. Gaps in the evidence base (e.g., health endpoints for which studies have not been conducted) are represented by corresponding gaps in the figures and are identified in the accompanying text.

In the model figure below (Figure IS-3), which serves as an illustrative overview of the biological plausibility figures in the health appendices, each box represents evidence demonstrated in a study or group of studies for a particular effect related to Pb exposure. While most of the studies used to develop the figures are experimental studies (i.e., animal toxicological and in vitro studies), some observational epidemiologic studies also contribute to the pathways. These epidemiologic studies generally comprise effects observed at the population level. The boxes are arranged horizontally, with boxes on the left side representing initial effects that reflect early biological responses and boxes to the right representing

intermediate (i.e., subclinical or clinical) effects and effects at the population level. The boxes are color coded according to their position in the exposure to outcome continuum.



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 these effects. Solid arrows, in contrast to dotted arrows, denote evidence of essentiality as provided, for example, by an inhibitor of the pathway or a genetic knockout model used in an experimental study involving Pb exposure. 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 base, there are complementary gaps in the figure and the accompanying text below.

Figure IS-3 Illustrative figure for potential biological pathways for health effects following Pb exposure.

The arrows that connect the boxes indicate a progression of effects resulting from exposure to Pb. In most cases, arrows are dotted (arrow 1), denoting a possible relationship between the effects. While most arrows point from left to right, some arrows point from right to left, reflecting progression of effects in the opposite direction or a feedback loop (arrow 2). In a few cases, the arrows are solid (arrow 2), indicating that progression from ilthe upstream to downstream effect has been shown to occur as a direct result of Pb exposure. This relationship between the boxes, where the upstream effect is necessary for progression to the downstream effect, is termed *essentiality* (OECD, 2018). Evidence supporting essentiality is generally provided by experimental studies using pharmacologic agents (i.e., inhibitors) or animal models that are genetic knockouts. The use of solid lines, as opposed to dotted lines, reflects the availability of specific experimental evidence that Pb exposure results in an upstream effect which is necessary for progression to a downstream effect.

In the figures, upstream effects are sometimes linked to multiple downstream effects. To illustrate this proposed relationship using a minimum number of arrows, downstream effects are grouped together within a larger shaded box and a single arrow (arrow 3) connecting the upstream effect represented by a single box to the outside of the downstream shaded box containing the multiple effects. Multiple upstream effects may similarly be linked to a single downstream effect using an arrow (arrow 4) that originates from the outside of a shaded box, which contains multiple effects, to an individual downstream box. In addition, arrows sometimes connect one individual upstream effect to an individual downstream effect that is contained within a larger shaded box (arrow 2) or two individual effects both contained within separate larger shaded boxes (arrow 5). Thus, arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes depending on the proposed relationships between effects represented by the boxes.

IS.7.3 Summary of Health Effects Evidence

Results from health studies, supported by the evidence from atmospheric chemistry and exposure assessment studies, contribute to the causality determinations made for the health outcomes evaluated in this ISA. Recent evidence is considered in combination with the evidence presented in the 2013 Pb ISA. This ISA evaluates the available health effects evidence and presents causality determinations for 30 health effect categories. In addition to updated causality determinations for the various health outcomes that were evaluated in the 2013 Pb ISA, this ISA includes three new causality determinations for social cognition and behavior in children, metabolic effects, and total (nonaccidental) mortality. The causality determinations from this ISA and their relation to the conclusions from the 2013 Pb ISA are summarized in Table IS-1.

Table IS-1 Summary of causality determinations by health outcome

Outcome Group	Health Outcome	Causality Determination
Nervous System Effects Ascertained During Childhood, Adolescent, and Young Adult Lifestages	Cognitive effects	Causal
	Externalizing behaviors: attention, impulsivity, and hyperactivity	Causal
	Externalizing behaviors: conduct disorders, aggression, and criminal behavior	Likely to be causal
	Internalizing behaviors: anxiety and depression	Likely to be causal
	Motor function	Likely to be causal
	Sensory function	↓Suggestive
	Social cognition and behavior	+Suggestive
Nervous System Effects Ascertained During Adult Lifestages	Cognitive effects	↑Causal
	Psychopathological effects	Likely to be causal
	Sensory function	Suggestive
	Neurodegenerative disease	↑Suggestive
Cardiovascular Effects[a]	Cardiovascular effects and cardiovascular-related mortality	Causal
Renal Effects	Renal effects	↑Causal
Immune System Effects[b]	Immunosuppression	Likely to be causal
	Sensitization and allergic response	↓Suggestive
	Autoimmunity and autoimmune disease	Inadequate
Hematological Effects	Hematological effects, including altered heme synthesis and decreased RBC survival and function	Causal
Reproductive and Developmental Effects	Pregnancy and birth outcomes	↑Likely to be causal
	Development	Causal
	Female reproductive function	↑Likely to be causal
	Male reproductive function	Causal
Effects on Other Organ Systems and Mortality	Hepatic effects	↑Suggestive
	Metabolic effects	+Inadequate
	Gastrointestinal effects	Inadequate
	Endocrine system effects	Inadequate
	Musculoskeletal effects	Likely to be causal
	Ocular health effects	Inadequate
	Respiratory effects	Inadequate

Outcome Group	Health Outcome	Causality Determination
Total (nonaccidental) mortality	Total (nonaccidental) mortality	+Causal[c]
Cancer	Cancer	Likely to be causal

RBC = red blood cell.
+Denotes new causality determination.
↑ or ↓ Denotes change in causality determination from 2013 Pb ISA.
[a]The 2013 Pb ISA made four causality determinations with respect to cardiovascular disease (CVD), including BP and hypertension (*causal*), subclinical atherosclerosis (*suggestive*), coronary heart disease (CHD; *causal*), and cerebrovascular disease (*inadequate*). This ISA follows the precedent set by the 2019 Particulate Matter and 2020 Ozone ISAs (U.S. EPA, 2020, 2019) by making a single causality determination for cardiovascular effects.
[b]The evidence for immune system effects in this ISA is organized based on the World Health Organization's Guidance for Immunotoxicity Risk Assessment for Chemicals (IPCS, 2012). For comparison with the causality determinations issued in the 2013 Pb ISA, the evidence considered for "sensitization and allergic response" maps closely with "atopic and inflammatory disease," the "immunosuppression" section largely overlaps with "decreased host resistance," and the evaluation of "autoimmunity and autoimmune disease" includes consideration of the same endpoints as "autoimmunity."
[c]The 2013 Pb ISA evaluated studies of all-cause mortality together with studies examining cardiovascular mortality and did not issue a separate causality determination for total mortality.

There is substantial evidence across scientific disciplines (i.e., animal toxicology and epidemiology) demonstrating that Pb exposure can result in a range of health effects, including nervous system effects in children and adults, cardiovascular effects, and reproductive and developmental effects. The evidence that supports these causality determinations includes studies examining the potential biological pathways that provide evidence of biological plausibility; studies examining the broader health effects evidence spanning scientific disciplines; and studies examining issues related to exposure assessment, toxicokinetics, and biomarkers of Pb exposure. The subsequent sections focus on health outcome categories for which the health effects evidence indicates a "causal relationship" or a "likely to be causal relationship" and outcome categories for which a previous "causal relationship" or a "likely to be causal relationship" has been changed (i.e., "likely to be causal" changed to "suggestive of, but not sufficient to infer a causal relationship"). The evidence for Pb exposure and health effects that is "suggestive of, but not sufficient to infer, a causal relationship" or "inadequate to infer the presence or absence of a causal relationship" is noted in Table IS-1 and discussed more fully in the respective health effects appendices (Appendix 3–Appendix 10).

IS.7.3.1 Nervous System Effects Ascertained During Childhood, Adolescent, and Young Adult Lifestages

While Pb affects nearly every organ system, the nervous system appears to be one of the most sensitive targets. The collective body of recent epidemiologic and toxicological evidence, along with evidence detailed in the 2013 Pb ISA (U.S. EPA, 2013a), demonstrates effects of Pb exposure on a range of nervous system effects ascertained during childhood, adolescent, and young adult lifestages. These effects include cognitive function (Appendix 3.5.1), externalizing behaviors (Appendix 3.5.2 and Appendix 3.5.3), internalizing behaviors (Appendix 3.5.4), and motor function (Appendix 3.5.5). Tables at the end of each of the ensuing subsections provide a summary of the evidence from epidemiologic and animal toxicological studies, highlighting the state of the science in the 2013 Pb ISA and summarizing the recent evidence (Table IS-2A through Table IS-2F).

IS.7.3.1.1 Cognitive Function in Children

The epidemiologic and toxicological evidence evaluated in the 2013 Pb ISA was sufficient to conclude that there is a "causal relationship" between Pb exposure and decrements in cognitive function in children. The strongest evidence supporting this determination came from multiple prospective studies conducted in diverse populations that consistently reported associations between higher blood and tooth Pb levels and lower full-scale IQ (FSIQ), executive function, and academic performance and achievement. Most studies examined representative populations and had moderate to high follow-up participation without indication of selective participation among children with higher BLLs and lower cognitive function (i.e., no evidence of selection bias). Associations between BLL and cognitive function decrements were found with adjustment for several potential confounding factors, most commonly socioeconomic status (SES), parental IQ, parental education, and parental caregiving quality. In children ages 4–11 years, associations were found with prenatal, early childhood, childhood average, and concurrent BLLs in populations with mean or group BLLs in the range of 2–8 μg/dL. At the time of the previous review, neither epidemiologic nor experimental animal evidence had identified an individual critical lifestage or duration of Pb exposure within childhood associated with cognitive function decrements. Several epidemiologic studies observed a supralinear C-R relationship (i.e., larger decrement in cognitive function per unit increase in blood Pb level in children in the lower range of the study population blood Pb distribution). Additionally, a threshold for cognitive function decrements was not discernible from the available evidence (i.e., examination of early childhood blood Pb or concurrent blood Pb in the range of <1 to 10 μg/dL). Epidemiologic evidence in children was coherent with animal toxicological studies that observed consistent evidence of Pb-induced impairments in learning, memory, and executive function in juvenile animals. Several studies in animals indicated learning impairments with prenatal, lactational, postlactational and lifetime (with or without prenatal) Pb exposures that resulted in BLLs of 10–25 μg/dL. The biological plausibility for Pb-associated cognitive function decrements was supported by observations of Pb-induced impairments in neurogenesis, synaptogenesis, synaptic pruning, long-term potentiation, and neurotransmitter function in the hippocampus, prefrontal cortex, and nucleus accumbens.

Recent studies support the conclusion from the 2013 Pb ISA that Pb-associated cognitive effects in children occur in populations with mean BLLs between 2 and 8 μg/dL (Appendix 3.5.1.6.1). This conclusion continues to be based on studies that examined early childhood BLLs (i.e., age <3 years), considered peak BLLs in their analysis (i.e., peak <10 μg/dL), or examined concurrent BLLs in young children aged 4 years. Some recent studies reported associations of Pb exposure with cognitive effects among children with mean BLLs <2 μg/dL; however, those studies do not have the aforementioned attributes and there is heterogeneity in both the magnitude and direction of the associations at the lowest blood Pb concentrations. The observed heterogeneity may be explained in part by the distribution of at-risk factors among the populations studied, including sex, maternal stress, and co-exposures to other metals and neurotoxic chemicals. Additionally, the available studies do not generally have the sensitivity (Cooper et al., 2016) to detect the effect or hazard at these very low BLLs. Therefore, the heterogeneity

observed in studies with low mean BLLs (i.e., < 2 μg/dL) does not weaken the larger body of evidence supporting the association of Pb exposure with cognitive effects in children at BLLs ≤5 μg/dL. The collective body of epidemiologic studies provides no evidence of a threshold for cognitive effects in children across the range of BLLs examined. Epidemiologic and toxicological studies also continue to strongly support the finding that Pb exposure during multiple lifestages (prenatal through adolescence/early adulthood) is associated with cognitive function decrements in children and young adults. Recent toxicological studies extend the evidence indicating that early-life exposures are associated with cognitive effects that persisted later into adolescence and adulthood. Biological plausibility is provided by studies that describe pathways involving the interaction of Pb with cellular proteins, in some cases competing with and displacing other biologically relevant cations, leading to increased oxidative stress and the presence of inflammation, which can have widespread impacts on brain structure and function, as well as disruptions of calcium ion (Ca^{2+}) signaling that can result in alteration in brain signaling and contribute to the development of neurological impairments.

Given consistency of the results from epidemiologic studies of FSIQ, Bayley Mental Development Index (MDI), and academic performance and achievement, as well as the coherence of evidence across epidemiologic and animal toxicological studies of learning and memory, **the overall evidence remains sufficient to conclude that there is a *causal relationship* between Pb exposure and cognitive effects in children.**

Table IS-2A Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and nervous system effects ascertained during childhood, adolescent, and young adult lifestages

Cognitive Effects in Children: Causal Relationship (IS.7.3.1.1 and Appendix 3.5.1)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Clear evidence of cognitive function decrements (as measured by FSIQ, academic performance, and executive function) was reported in young children (4 to 11 yr old) with mean or group BLLs measured at various lifestages and time periods between 2 and 8 μg/dL. Clear support from animal toxicological studies that demonstrate decrements in learning, memory, and executive function with dietary exposures.	Recent longitudinal epidemiologic studies with group or population means ≤5 μg/dL add to the evidence, generally supporting conclusions from the 2013 Pb ISA. Heterogeneity in the magnitude and direction of the associations with FSIQ, which was potentially explained by modeling choices or modification of the association by exposure to other metals, sex, or maternal stress, does not weaken inference from the large body of supporting evidence. Recent experimental animal studies provide consistent evidence that Pb exposure results in learning and memory impairments, with developmental periods potentially representing a more sensitive window for exposure.

BLL = blood lead level; FSIQ = full-scale intelligence quotient; ISA = Integrated Science Assessment; Pb = lead; yr = year(s).

IS.7.3.1.2 Externalizing Behaviors: Attention, Impulsivity, and Hyperactivity in Children

The evidence presented in the 2013 Pb ISA was sufficient to conclude that there is "a causal relationship" between Pb exposure and effects on attention, impulsivity, and hyperactivity in children. Several prospective studies demonstrated associations between blood or tooth Pb levels measured years before outcomes with attention decrements and hyperactivity in children 7–20 years old, as assessed using objective neuropsychological tests and/or parent and teacher ratings, which are generally reliable and valid instruments that predict functionally important outcomes. Most of these prospective studies examined representative populations without indication of selection bias. The results from prospective studies were adjusted for potential confounding by SES as well as parental education and caregiving quality, with some studies also considering parental cognitive function, birth outcomes, substance abuse, and nutritional factors. BLLs were associated with attention decrements and hyperactivity in populations with prenatal (maternal or cord), age 3–60-month average, age 6 year, or lifetime average (to age 11–13 years) mean BLLs of 7 to 14 μg/dL, and groups with age 30-month BLLs >10 μg/dL. Most well-conducted cross-sectional studies that adjusted for potential confounding factors supported these findings, noting associations of attention decrements, impulsivity, and hyperactivity in children ages 5–7.5 years with concurrent BLLs with means of 5–5.4 μg/dL. There were a small number of studies of diagnosed attention-deficit/hyperactivity disorder (ADHD), which were limited by cross-sectional or case-control study designs, inconsistent adjustment for SES and parental education, and lack of consideration for potential confounding by parental caregiving quality. Animal toxicological studies reported increases in impulsivity or impaired response inhibition in animals with postweaning and lifetime Pb exposures that resulted in BLLs of 11 to 30 μg/dL. There was biological plausibility for Pb-associated attention decrements, impulsivity, and hyperactivity provided by observations of Pb-induced alterations in neurogenesis, synaptic pruning, and dopamine transmission in the prefrontal cerebral cortex, cerebellum, and hippocampus.

The largest uncertainty addressed by the recent evidence base is the previous lack of prospective studies examining ADHD (Appendix 3.5.2.4–3.5.2.5). The bulk of the recent evidence comprises prospective studies that establish the temporality of the association between Pb exposure and parent or teacher ratings of ADHD symptoms and clinical ADHD. Across studies, associations were observed with tooth Pb concentrations, childhood BLLs (<6 μg/dL), and with maternal or cord BLLs (2–5 μg/dL). Studies of caregiver-reported ADHD symptoms generally report associations of BLLs with composite indices, but there is some support to indicate that the associations with impulsivity and hyperactivity symptoms are stronger than the associations with inattention symptoms. Some studies addressed the validity of caregiver-assessed outcomes by evaluating internal consistency, and one study addressed reliability/validity concerns by using structural equation modeling to create latent factors for inattention and hyperactivity-impulsivity for each informant. Rating scales used in these studies are generally reliable and valid instruments that predict functionally important outcomes. Confounder adjustment has also become more consistent across recent studies of ADHD. Another recent prospective epidemiologic study examined clinical ADHD diagnoses after adjusting for parental education and SES, although not quality

of parental caregiving. In this study, children with BLLs between 5 and 10 μg/dL (measured ≤4 years old) had increased odds of clinically diagnosed ADHD at approximately 6 years of age compared with children with BLLs <2 μg/dL. Additionally, a small number of recent studies also serve to extend the lower bound of the mean BLLs that were observed to be associated with attention, impulsivity, and hyperactivity in the 2013 Pb ISA. These prospective studies with mean maternal and cord BLLs ≤5 μg/dL report associations with some measures of inattention and impulsivity (Appendix 3.5.2.1–3.5.2.3). Across studies, there is uncertainty regarding the patterns of exposure that are associated with maternal and cord BLLs and BLLs in older children, because they may be influenced by higher past exposures.

In summary, the coherence of evidence across epidemiologic and toxicological studies of externalizing behaviors, as well as biological plausibility provided by studies that outline pathways by which Pb may interfere with the normal development of externalizing behaviors **is sufficient to conclude that there is a *causal relationship* between Pb exposure and attention, impulsivity, and hyperactivity.**

Table IS-2B Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and nervous system effects ascertained during childhood, adolescent, and young adult lifestages

Externalizing Behaviors: Attention, Impulsivity, and Hyperactivity in Children: Causal Relationship (IS.7.3.1.2 and Appendix 3.5.2)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Clear evidence of attention decrements, impulsivity, and hyperactivity (assessed using objective neuropsychological tests and parent and teacher ratings) was observed in children 7–20 yr. The strongest evidence for blood Pb-associated increases in these behaviors was found in prospective studies examining prenatal (maternal or cord), age 3–60 mo, age 6 yr, or lifetime average (to age 11–13 yr) mean BLLs of 7 to 14 μg/dL and groups with early childhood (age 30 mo) BLLs >10 μg/dL. Biological plausibility was provided by animal toxicological studies demonstrating impulsivity or impaired response inhibition with relevant prenatal, lactational, postlactational, and lifetime Pb exposures.	A small number of recent studies of children with population or group mean BLLs ≤5 μg/dL contribute to the body of evidence, supporting and extending conclusions from the 2013 Pb ISA. The majority of recent studies rely on parent and teacher ratings of ADHD symptoms; notably, confounder adjustment remained inconsistent across these studies. However, prospective studies of ADHD, including a study of clinical ADHD that controlled for parental education and SES, although not quality of parental caregiving reported positive associations. Findings from studies of rodents and nonhuman primates indicate that Pb exposure changes behavior in ways consistent with increased impulsivity while experimental animal studies of hyperactivity remain inconsistent, potentially due to differential exposure and testing windows (hyperactivity was consistently observed with lactational exposure).

ADHD = attention-deficit/hyperactivity disorder; BLL = blood lead level; ISA = Integrated Science Assessment; mo = month(s); Pb = lead; SES = socioeconomic status; yr = year(s).

IS.7.3.1.3 Externalizing Behaviors: Conduct Disorders, Aggression, and Criminal Behavior in Children, Adolescents, and Young Adults

The 2013 Pb ISA concluded that "a causal relationship is likely to exist" between Pb exposure and conduct disorders in children and young adults. This determination was based on several prospective cohort studies that consistently indicated that higher earlier childhood (e.g., age 30 months, 6 years) or

lifetime average (to age 11–13 years) BLLs or tooth (from ages 6–8 years, generally reflecting prenatal and early childhood Pb exposure) Pb levels are associated with criminal offenses in children and young adults ages 19–24 years and with higher parent and teacher ratings of behaviors related to conduct disorders in children ages 7–17 years. Positive associations between Pb exposure and conduct disorders were found in populations with mean BLLs of 7–14 μg/dL. These associations were found without indication of strong selection bias and with adjustment for SES, parental education and IQ, parental caregiving quality, family functioning, smoking, and substance abuse. Associations in populations with lower BLLs that are not influenced by higher earlier Pb exposures were not well characterized. Toxicological evidence for Pb-induced aggression in animals is inconsistent, with increases in aggression found in some studies of adult animals with gestational and lifetime Pb exposure, but not juvenile animals.

Recent epidemiologic studies support and extend the findings from the 2013 Pb ISA (Appendix 3.5.3.1). The strongest evidence comes from recent prospective cohort studies of 1) self-reported conduct and aggression-related outcomes, and 2) external measures of delinquency (e.g., criminal arrests, school suspensions). These studies evaluated outcomes among individuals ages 7–33 years in relation to earlier (or cumulative) blood and bone Pb levels. Mean and/or median BLLs ranged from 2.3 to 8.7 μg/dL (measured 6.5 to 13 years) in studies reporting positive associations with self-reported conduct and aggression-related outcomes, though were higher in studies reporting positive associations with external measures of delinquency (mean: 14.4 μg/dL; measured prenatal to 6 years). There are no recent animal toxicological studies at BLLs relevant to humans; thus, the central uncertainty present in the 2013 Pb ISA database remains: there is limited and inconsistent supporting evidence from animal toxicological studies. Despite the lack of recent studies examining aggression in animals exposed to Pb, Pb-induced changes on many neurochemical endpoints that contribute to aggressive behaviors have been reported in experimental animal studies (Appendix 3.3), which provides biological plausibility for Pb-related conduct disorders and aggression.

Given the consistent positive associations observed across various populations and based on multiple outcome assessment approaches at relevant Pb exposure levels, **there is sufficient evidence to conclude that there is *likely to be a causal relationship* between Pb exposure and conduct disorders, aggression, and criminal behavior**.

Table IS-2C Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and nervous system effects ascertained during childhood, adolescent, and young adult lifestages

Externalizing Behaviors: Conduct Disorders, Aggression, and Criminal Behavior: Likely to Be Causal (IS.7.3.1.3 and Appendix 3.5.3)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Prospective epidemiologic studies demonstrated that early childhood (age 30 mo, 6 yr) or lifetime average (to age 11–13 yr) BLLs or tooth Pb levels (from ages 6–8 yr, generally reflecting prenatal and early childhood Pb exposure) are associated with criminal offenses in young adults ages 19–24 yr and with higher parent and teacher ratings of behaviors related to conduct disorders in children ages 8–17 yr. Pb-associated increases in conduct disorders were found in populations with mean BLLs 7 to 14 μg/dL; associations with lower BLLs as observed in cross-sectional studies were likely to be influenced by higher earlier Pb exposures. There is coherence in epidemiologic findings among related measures of conduct disorders. Evidence of Pb-induced aggression in animals was mixed, with increases in aggression found in some studies of adult animals with gestational plus lifetime Pb exposure, but not juvenile animals. The lack of clear biological plausibility produces some uncertainty.	Several prospective studies add to the evidence, particularly in providing evidence of positive associations between Pb exposure and direct aggressive measures, such as physical violence. A limited number of recent studies examine crime or delinquency and generally observed positive associations. Studies evaluated the associations among individuals ages 7–33 yr in relation to earlier (or cumulative) Pb levels. In the studies of self-reported conduct and aggression-related outcomes, mean BLLs were 2.3 to 8.7 μg/dL (ages 6.5 to 13 yr), while in studies of external measures of delinquency, they were higher (e.g., mean 14.4 μg/dL; prenatal to 6 yr). Studies generally controlled for most relevant confounders. There were no recent experimental animal studies of aggression; thus, toxicological evidence remains limited and inconsistent.

BLL = blood lead level; ISA = Integrated Science Assessment; Pb = lead; yr = year(s).

IS.7.3.1.4 Internalizing Behaviors: Anxiety and Depression

The evidence evaluated in the 2013 Pb ISA was sufficient to conclude that "a causal relationship is likely to exist" between Pb exposure and internalizing behaviors in children. Prospective studies in a few populations demonstrated associations between increases in early lifetime average blood (mean: ~14 μg/dL) or childhood tooth (from ages 6–8 years, generally reflecting prenatal and early childhood Pb exposure) Pb levels with higher parent and teacher ratings of internalizing behaviors, such as withdrawn behavior and symptoms of depression and anxiety in children ages 8–13 years. The available evidence of study participation by BLL and parental and teacher ratings do not suggest a high likelihood of selection bias in these studies. The results from a few cross-sectional studies in populations with mean concurrent BLLs of 5 μg/dL were inconsistent. Pb was positively associated with internalizing behaviors in models that adjusted for maternal education and SES-related variables, though consideration of potential confounding by parental caregiving quality was inconsistent. Despite some uncertainty in the epidemiologic evidence regarding potential confounding and inconsistency in the supporting cross-sectional studies, biological plausibility for the effects of Pb on internalizing behaviors was provided by a few studies in animals with dietary lactational Pb exposure, with some evidence at BLLs relevant to humans. Biological plausibility findings included Pb-induced changes in the hypothalamic-pituitary-adrenal axis and dopaminergic and gamma-aminobutyric-acid (GABA)-ergic systems.

Several recent longitudinal epidemiologic studies with high to moderate participation rates used an expanded array of instruments to assess internalizing behaviors and continue to provide support for associations with BLLs (childhood average, prenatal, and postnatal BLLs <7 µg/dL; Appendix 3.5.4.1). The majority of analyses controlled for important potential confounders including the quality of parental caregiving, which was less frequently considered by studies included in the 2013 Pb ISA. A limited number of studies aimed to distinguish between the types of internalizing behaviors associated with Pb exposure and demonstrated stronger support for Pb-associated anxiety compared with depression. Recent animal toxicological studies are coherent with the epidemiologic evidence and largely support and expand evidence of increases in anxiety-like behavior in Pb-exposed rodents with peak BLLs ranging from three to greater than 30 µg/dL, the lower end of which is lower than evidence from the 2013 Pb ISA.

Overall, given consistent evidence from both recent and previously reviewed prospective epidemiologic studies, with some remaining uncertainties regarding potential confounding by quality of parental caregiving, **the evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and internalizing behaviors in children.**

Table IS-2D Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and nervous system effects ascertained during childhood, adolescent, and young adult lifestages

Internalizing Behaviors: Anxiety and Depression: Likely to Be Causal (IS.7.3.1.4 and Appendix 3.5.4)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Prospective epidemiologic studies reported associations of higher lifetime average blood (mean: ~14 µg/dL) or childhood tooth (from ages 6–8 yr, generally reflecting prenatal and early childhood Pb exposure) Pb levels with higher parent and teacher ratings of internalizing behaviors such as symptoms of depression or anxiety and withdrawn behavior in children ages 8–13 yr. Consideration of potential confounding by parental caregiving was not consistent and findings from cross-sectional studies in populations ages 5 and 7 yr with mean BLLs of 5 µg/dL were mixed. Animal toxicological studies demonstrate depression-like behaviors and increases in emotionality with relevant lactational exposures.	Recent longitudinal studies report consistent associations between BLLs and internalizing in multiple countries with mean blood Pb concentrations typically <7 µg/dL (prenatal, early childhood, lifetime average). Recent studies used parent or teacher ratings to assess internalizing behaviors, i.e., the Child Behavior Checklist, Strengths and Difficulties Questionnaire, Behavioral Assessment System for Children, and Caregiver-Teacher Report Form. Increased anxiety-like behaviors in rodents were demonstrated at lower exposure levels (3–30 µg/dL) following developmental Pb exposure.

BLL = blood lead level; ISA = Integrated Science Assessment; mo = month(s); Pb = lead; yr = year(s).

IS.7.3.1.5 Motor Function

The evidence presented in the 2013 Pb ISA was sufficient to conclude that "a causal relationship is likely to exist" between Pb exposure and decrements in motor function in children. This determination was based on strong evidence from prospective studies that reported that higher maternal, neonatal, concurrent, and lifetime average BLLs were associated with lower scores on fine and gross motor function tests among children ages 4.5–6 years and that higher earlier childhood (ages 0–5-year average;

age 78 months) BLLs were associated with lower scores on fine and gross motor function tests among children ages 15–17 years. The means for these blood Pb metrics ranged from 4.8 to 12 μg/dL. These studies included adjustment for several potential confounding factors, including SES, parental caregiving quality, and child health, and did not have indications of substantial selection bias. Evidence from cross-sectional studies was less consistent. The biological plausibility for associations observed in children is provided by a study that found poorer balance in male mice with relevant gestational to early postnatal (postnatal day 10) Pb exposures.

Several recent birth cohort studies observed consistently lower scores on the Bayley Psychomotor Developmental Index (PDI) in association with higher maternal Pb exposure (no clear pattern by trimester of pregnancy; means or geometric means: 1.4 to 6.5 μg/dL), cord BLL (means: 1.2 to 5.6 μg/dL), and postnatal concurrent BLL (2.85–4.87 μg/dL). Pb-associated decrements in motor function were also observed in neonates and in some, but not all studies of toddlers that assessed motor function using the Gesell scale or children's abilities to perform certain tasks indicative of gross motor function. Evidence from recent toxicological studies is coherent with the epidemiologic evidence, indicating that developmental Pb exposure in rodents induces deficits in motor function at mean BLLs ≤30 μg/dL. These new studies illustrate effects of Pb exposure across a range of gross and fine motor development in novel paradigms. In addition to the effect on rotarod performance described in the 2013 Pb ISA, recent studies observed Pb-induced decrements in righting reflex, negative geotaxis reflex, ascending wire mesh, and forelimb hang tests. The available studies demonstrate consistent effects on motor function, but given the disparate effects examined do not provide evidence of consistent results for any specific test. **Overall, the evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and motor function in children.**

Table IS-2E Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and nervous system effects ascertained during childhood, adolescent, and young adult lifestages

Motor Function: Likely to Be Causal (IS.7.3.1.5 and Appendix 3.5.5)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Prospective epidemiologic studies provided evidence of associations of fine and gross motor function decrements in children ages 4–17 yr with lifetime average BLLs and with BLLs measured at various time periods with means generally ranging from 4.8 to 12 μg/dL. Results were inconsistent in cross-sectional studies with concurrent BLL means 2–5 μg/dL. Limited evidence in animal toxicological studies with relevant Pb exposures.	Several recent birth cohort studies report lower scores on the Bayley PDI at ages 12 to 36 mo in association with higher maternal Pb exposure, cord BLL, and postnatal concurrent BLL. Limited biological plausibility is provided by a small number of recent toxicological studies showing various effects on motor function in rodent models with developmental Pb exposure resulting in BLLs ≤30 μg/dL.

BLL = blood lead level; ISA = Integrated Science Assessment; mo = month(s); Pb = lead; PDI = Psychomotor Developmental Index; yr = year(s).

IS.7.3.1.6 Sensory Organ Function

The 2013 Pb ISA presented two causality determinations relating to sensory function in children: auditory function and visual function. The evidence was sufficient to conclude that "a causal relationship is likely to exist" between Pb exposure and auditory function decrements in children, while the evidence was "inadequate to determine that a causal relationship exists" between Pb exposure and visual function in children. In this ISA, recent studies inform a single causality determination for sensory organ function. A prospective epidemiologic study, as well as a few cross-sectional studies, reported associations between BLLs and hearing loss and auditory processing deficits with BLLs measured at various time periods, including prenatal maternal, neonatal (10 day, mean 4.8 μg/dL), lifetime average (to age 5 years), and concurrent (ages 4–19 years; median 8 μg/dL). Evidence for Pb-associated increases in hearing thresholds or latencies of auditory evoked potentials was found in adult monkeys with lifetime dietary Pb exposure. However, these effects in adult animals were found with higher peak or concurrent BLLs (i.e., 33–150 μg/dL); thus, the biological plausibility for epidemiologic observations is unclear. Studies examining visual effects were of limited quantity and relevance.

Recent cross-sectional and case-control studies have continued to demonstrate associations between BLLs and hearing loss in young children (aged 3–7, BLLs ~3 to 6 μg/dL) and adolescents (aged 12–19, BLLs ~1 to 8 μg/dL), particularly at higher frequencies. This is coherent with previously noted evidence in adult monkeys. Recent experimental animal studies have not further evaluated hearing thresholds in nonhuman primates at more relevant BLLs, but a recent study reported an 8–12 dB upward shift in brainstem auditory evoked potentials (BAEPs) between 4 and 32 kHz in young adult mice exposed during adolescence (peak BLLs 29 μg/dL). Similar studies did not detect differences in BAEP in rodents with lower peak BLLs (3 to 8 μg/dL); however, decrements in auditory processing (e.g., sound discrimination and localization) were demonstrated at these lower BLLs (8 μg/dL). A few recent epidemiologic studies also evaluated BAEP with inconsistent results. Evidence of visual function remains limited and inconsistent.

In conclusion, recent evidence is generally consistent with the evidence presented in the 2013 Pb ISA. Cross-sectional and case-control epidemiologic studies provide some support for positive associations between Pb exposure and impaired hearing/auditory processing. Toxicological evidence for Pb-induced auditory functioning, particularly in studies with BLLs relevant to humans, remains limited. **Taken together, the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and sensory function in children.**[4]

[4]The Preamble to the ISA, which was published after the release of the 2013 Pb ISA, included some minor changes to the weight-of-evidence descriptors for the five-level causality hierarchy . These changes resulted in the evidence for Pb exposure and effects on sensory organ function being more consistent with examples of evidence that is *"suggestive of, but not sufficient to infer, a causal relationship."* Therefore, the change from "*likely to be causal" to "suggestive of, but not sufficient to infer, a causal relationship"* reflects minor changes to the causal framework, rather than a weakening of the evidence base. See Appendix 3.5.6.4 of the Nervous System Effects Appendix for further discussion.

Table IS-2F Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and nervous system effects ascertained during childhood, adolescent, and young adult lifestages

Sensory Function: Suggestive of, but Not Sufficient to Infer, a Causal Relationship (IS.7.3.1.6 and Appendix 3.5.6)

Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
A prospective epidemiologic study and large cross-sectional studies indicated associations between BLLs and increased hearing thresholds at ages 4–19 yr. Across studies, associations were found with BLLs measured at various time periods, including prenatal maternal, neonatal (10 d, mean 4.8 µg/dL), lifetime average, and concurrent (ages 4–19 yr) BLLs (median 8 µg/dL). The lack of biological plausibility in animals with relevant exposures produces some uncertainty. The available epidemiologic and toxicological evidence for visual function is of insufficient quantity, quality, and consistency.	Recent cross-sectional and case-control studies have continued to demonstrate positive associations between BLLs and hearing loss in young children (aged 3–7, BLLs ~3 to 6 µg/dL) and adolescents (aged 12–19, BLLs ~1 to 8 µg/dL). Experimental animal studies evaluating young adult rodents found increases in BAEP thresholds at mean BLLs of 29 µg/dL but not at lower mean BLLs (3 to 8 µg/dL); however, mice with mean peak BLLs of 8 µg/dL had deficits in auditory processing, The epidemiologic and toxicological evidence for visual function was not extended.

BAEP = brainstem auditory evoked potentials; BLL = blood lead level; d = day(s); ISA = Integrated Science Assessment; Pb = lead; yr = year(s).

IS.7.3.2 Nervous System Effects Ascertained During Adult Lifestages

This ISA presents causality determinations for four nervous systems outcomes ascertained during adult lifestages, including cognitive function, psychopathological effects, sensory organ function, and neurodegenerative diseases. The available evidence is "suggestive of, but not sufficient to infer, a causal relationship" between Pb exposure and: (1) sensory organ function (Appendix 3.6.3) and (2) neurodegenerative disease (Appendix 3.6.4). Evidence related to these outcomes is discussed in the Nervous System Effects Appendix. Cognitive effects (IS.7.3.2.1) and psychopathological effects (IS.7.3.2.2), for which evidence supports a *causal relationship* and a *likely to be causal relationship* with Pb exposure, respectively, are discussed in more detail in the ensuing sections. Table IS-3A and Table IS-3B provides a summary of the evidence from epidemiologic and animal toxicological studies related to these outcomes, highlighting the recent evidence in comparison with the evidence available in the 2013 Pb ISA.

IS.7.3.2.1 Cognitive Function in Adults

The 2013 Pb ISA concluded that "a causal relationship is likely to exist between" long-term cumulative exposure to Pb and cognitive function decrements in adults. This causality determination was supported by prospective studies in the Normative Aging Study (NAS) and Baltimore Memory Study (BMS) cohorts that reported that higher cumulative exposure metrics, including baseline tibia (means 19, 20 µg/g) or patella (mean 25 µg/g) Pb levels, were associated with declines in cognitive function in adults (age >50 years) over 2- to 4-year periods. These associations were noted in models adjusted for a range of

potential confounding factors, including age, education, SES, current alcohol use, and current smoking. Supporting evidence was provided by cross-sectional analyses of the NAS, BMS, and the Nurses' Health Study, which observed inverse associations between cognitive function and Pb exposure that were stronger (i.e., greater in magnitude) for bone Pb levels compared with concurrent BLLs. Cross-sectional studies also considered more potential confounding factors, including dietary factors, physical activity, medication use, and comorbid conditions. The range of exposures and health outcomes examined in many of these studies reduced the likelihood of participation bias, specifically by adults with higher Pb exposure and lower cognitive function. The specific timing, frequency, duration, and magnitude of Pb exposures contributing to the associations observed with bone Pb levels was not discernible from the evidence. The effects of recent Pb exposures on cognitive function decrements in adults were indicated in studies of Pb-exposed workers, although these studies did not consider potential confounding by other workplace exposures. Biological plausibility for the observed associations was provided by animal toxicological studies demonstrating that relevant lifetime Pb exposures from gestation, birth, or after weaning induced learning impairments in adult animals, as well as evidence the Pb exposure altered neurotransmitter function in hippocampus, prefrontal cortex, and nucleus accumbens.

Recent prospective cohort studies with longer follow-up periods, multiple and repeatedly measured cognitive outcomes, and adjustment for multiple risk factors and confounders reduce uncertainties and strengthen the overall evidence related to the association of Pb exposure with cognitive function in adulthood. Specifically, recent cohort studies indicate that higher adult bone Pb levels (tibia mean range: 10.5 to 21.6 μg/g, patella mean range: 12.6 to 30.6 μg/g) were associated with poor cognitive function/performance during young-, mid- or older-adulthood periods (Appendix 3.6.1). A few recent prospective studies also observed associations between childhood BLLs (mean range: 3.4 μg/dL to 10.99 μg/dL at 7–12 years of age) and decrements in IQ and cognitive domains during late adolescence (18–19 years) and mid-adulthood (38–45 years) after adjustment for demographic and socioeconomic factors, maternal IQ, and childhood IQ scores. These findings provide new insight into the persistence of Pb-associated cognitive function decrements. There was some variability in the associations across the various domains of cognitive function tested within studies; however, higher Pb levels were associated with decrements in full-scale IQ (verbal comprehension, perceptual reasoning, working memory, and processing speed IQs), global cognitive function, executive function, visuospatial skills, attention, learning, and memory. Discordant Pb associations across domains of cognitive function likely reflect inherent biologic variability or differences in the outcome pathophysiology as opposed to inconsistency in the evidence. In addition to potential confounders considered in studies evaluated in the 2013 Pb ISA, recent studies control for additional behavioral, clinical, and neighborhood level factors. Results from recent toxicological studies are coherent with the epidemiologic evidence and provide evidence that exposure to Pb during adulthood impairs learning and memory function in rodents with exposure resulting in mean BLLs ≤30 μg/dL (means BLLs: 8–8.8 μg/dL; peak BLLs: 11–28 μg/dL). Additionally, a few recent studies in juvenile rodents provide some support for the association between Pb exposure during adolescence and cognitive impairment, but the evidence is less consistent.

In summary, recent prospective epidemiologic studies address uncertainties from the 2013 Pb ISA and expand and strengthen the previous body of evidence. Results from recent epidemiologic studies of childhood Pb exposure and cognitive effects in adults are coherent with previous studies in nonhuman primates demonstrating cognitive impairment following early-life exposure to Pb and are further supported by experimental animal studies providing biological plausibility for the observed associations. **Overall, the collective evidence is sufficient to conclude that there is *a causal relationship* between Pb exposure and cognitive effects in adults.**

Table IS-3A Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and nervous system effects ascertained during adult lifestages

Cognitive Effects in Adults: Likely to Be Causal (IS.7.3.2.1 and Appendix 3.6.1)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Prospective studies in the NAS and BMS cohorts indicated associations of higher baseline tibia (means 19, 20 μg/g) or patella (mean 25 μg/g) Pb levels with declines in cognitive function in adults (age >50 yr) over 2- to 4-yr periods. While the specific covariates differed between studies, these bone Pb-associated cognitive function decrements were found with adjustment for potential confounding factors such as age, education, SES, current alcohol use, and current smoking. Supporting evidence is provided by cross-sectional analyses of the NAS, BMS, and the Nurses' Health Study, which found stronger associations with bone Pb level than concurrent BLL. Cross-sectional studies also considered more potential confounding factors, including dietary factors, physical activity, medication use, and comorbid conditions. Biological plausibility for the effects of Pb exposure on cognitive function decrements in adults is provided by findings that relevant lifetime Pb exposures from gestation, birth, or after weaning induce learning impairments in adult animals and by evidence for the effects of Pb altering neurotransmitter function in hippocampus, prefrontal cortex, and nucleus accumbens.	Recent longitudinal epidemiologic studies with longer follow-up periods, multiple and repeatedly measured cognitive outcomes, and consideration of multiple risk factors/confounders provide additional evidence of associations between cumulative and early childhood exposure to Pb and cognitive decrements in adults. These studies reduce uncertainties and strengthen the overall evidence related to the association of Pb exposure with cognitive function in adulthood. Some uncertainties related to the frequency, duration, and magnitude of Pb exposures associated with cognitive decrements remain. Several recent studies of rodents with exposure resulting in mean BLLs ≤30 μg/dL add to the evidence informing the association of Pb exposure with measures of learning and memory in rodents exposed throughout adulthood.

BMS = Baltimore Memory Study; ISA = Integrated Science Assessment; NAS = Normative Aging Study; Pb = lead; SES = socioeconomic status.

IS.7.3.2.2 Psychopathological Effects in Adults

The evidence presented in the 2013 Pb ISA was sufficient to conclude that "a causal relationship is likely to exist" between Pb exposures and psychopathological effects in adults. This causality determination was based on a small body of epidemiologic evidence that demonstrated consistent positive associations between concurrent blood or bone Pb levels and self-reported symptoms of depression, anxiety, and panic disorder in large studies of adults (i.e., NHANES, NAS). Epidemiologic associations were observed in study populations of young (20–39 years old) and older (44–98 years old) adults. Because of the cross-sectional design of the epidemiologic studies, there was uncertainty regarding the temporal sequence between Pb exposure and psychopathological symptoms in adults. This uncertainty is somewhat reduced with results for tibia Pb because it is an indicator of cumulative Pb exposure. Still, because these studies included adults with likely higher past Pb exposures, uncertainty exists as to the Pb exposure level, timing, frequency, and duration contributing to the associations observed with blood or bone Pb levels. The epidemiologic evidence was supported by coherence in animal toxicological studies that demonstrated depression-like behavior and emotionality in rodents exposed to dietary lactational Pb with or without additional postlactational exposure. An uncertainty in the toxicological evidence base was the limited number of studies that administered exposures resulting in BLLs that are relevant to humans.

Recent evidence from prospective epidemiologic studies provides further support for positive associations between Pb exposures and pathological effects, including increased internalizing symptoms. A strength of the recent evidence is that two of the prospective studies reported a greater likelihood of internalizing symptoms in association with higher childhood BLLs, providing more information on the timing of Pb exposure associated with psychopathological effects. Notably, supporting evidence from recent cross-sectional epidemiologic studies conducted in diverse populations is largely inconsistent. The epidemiologic evidence is supported by coherence with results from an expanded number of toxicological studies conducted at BLLs relevant to humans. In addition to recent toxicological studies that continue to provide strong support for Pb-induced anxiety-like behaviors, and persistence of these behaviors, following developmental and cumulative exposures, there is some novel evidence for an increase in anxiety-like behavior following adult exposures. **Overall, the collective evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and psychopathological effects in adults.**

Table IS-3B Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and nervous system effects ascertained during adult lifestages

Psychopathological Effects in Adults: Likely to Be Causal (IS.7.3.2.2 and Appendix 3.6.2)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Cross-sectional studies in a few populations demonstrate associations of higher concurrent blood or tibia Pb levels with self-reported symptoms of depression and anxiety in adults. Pb-associated depression and anxiety symptoms among adults were found with adjustment for age, SES, and in the NAS, daily alcohol intake. The biological plausibility for epidemiologic evidence is provided by observations of depression-like behavior in animals with dietary lactational Pb exposure.	Recent prospective analyses provide additional support for a positive association between bone and BLLs and psychopathological effects in older adults, although results from cross-sectional studies are inconsistent. Recent toxicological studies in rodents with developmental exposure continue to provide evidence of anxiety-like behaviors. Multiple studies demonstrate the persistence of these effects into adulthood. Additionally, a few recent studies in rodents demonstrated effects of adult-only Pb exposures on anxiety-like behavior after 42–126 d of exposure (BLLs: 7.1 to 28.4 µg/dL), but not following a 30-d exposure (BLLs: 6.8 to 8.8 µg/dL).

BLL = blood lead level; d = day(s); NAS = Normative Aging Study; Pb = lead; SES = socioeconomic status.

IS.7.3.3 Cardiovascular Effects and Cardiovascular-Related Mortality

The 2013 Pb ISA made four causality determinations with respect to cardiovascular disease (CVD), using the U.S. Surgeon General's Report on Smoking as a guideline to group evidence into health outcome categories (CDC, 2004). The outcome categories evaluated included BP and hypertension, subclinical atherosclerosis, coronary heart disease (CHD), and cerebrovascular disease. This ISA follows the precedent set by the 2019 Particulate Matter and 2020 Ozone ISAs (U.S. EPA, 2020, 2019) by making a single causality determination for cardiovascular effects and cardiovascular-related mortality. This

approach allows for a more holistic evaluation of interrelated health endpoints (e.g., atherosclerosis, endothelial dysfunction, and increased BP).

The strongest evidence for cardiovascular effects of Pb exposure in the 2013 Pb ISA came from studies of BP and hypertension, which supported a *causal relationship*. Several epidemiologic studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013a) and previous AQCD documents (U.S. EPA, 2006, 1990) indicated positive associations between biomarkers of Pb exposure in adults and increases in BP and hypertension risk (Table IS-4). Previous studies do not identify an apparent threshold below which blood Pb was not significantly associated with changes in BP, for mean adult BLLs ranging from <2 μg/dL to 34 μg/dL. Meta-analyses evaluated in the 2013 Pb ISA underscore the consistency and reproducibility of the Pb-associated increases in BP and hypertension. However, the studies available at the time represented populations historically exposed to higher levels of Pb, raising uncertainty regarding the level, timing, frequency, and duration of Pb exposure contributing to the observed associations. In addition to epidemiologic evidence, the 2013 Pb ISA described a large body of animal toxicological studies that provided evidence that long-term Pb exposure (>4 weeks) in experimental animals, resulting in BLLs less than 10 μg/dL, could result in the onset of hypertension (after a latency period) in experimental animals that persists long after the cessation of Pb exposure.

The 2013 Pb ISA also presented a large body of evidence indicating a relationship between Pb exposure and cardiovascular mortality, which helped support a *causal relationship* in the 2013 Pb ISA for CHD. Specifically, prospective epidemiologic studies conducted in a number of locations reported that biomarkers of Pb exposure were associated with risk of mortality from myocardial infarction (MI), ischemic heart disease (IHD), and CHD. In addition, epidemiologic studies reviewed in the 2013 Pb ISA included some evidence of a positive association between exposure to Pb and changes in cardio electrophysiology (e.g., changes in heart rate variability [HRV] and QT interval) and atherosclerotic plaque formation. These studies, along with animal toxicological studies demonstrating the production of oxidative stress species that could inactivate the vasodilator nitric oxide, contribute to the biological plausibility of Pb-induced cardiovascular morbidity and mortality.

Recent studies greatly expand the evidence base from the 2013 Pb ISA and strengthen support for the relationship between exposure to Pb and cardiovascular effects in adults. Numerous epidemiologic studies published since the literature cutoff date for the 2013 Pb ISA reported positive associations between Pb biomarkers and increases in BP and hypertension risk (Appendix 4.3). Specifically, nationally representative cross-sectional studies in the United States, Canada, and South Korea observed positive associations between BLLs and systolic BP and/or diastolic BP in adult populations with mean BLLs ranging from ~1.5 to 3 μg/dL. Notably, in these studies of adult populations, uncertainty remains regarding the influence of higher past exposures on the level, timing, frequency, and duration of Pb exposure contributing to the observed associations. The majority of recent analyses consider a wide range of confounders including demographics, comorbid conditions, antihypertensive medication use, and other co-exposures to metals such as cadmium (Cd). In addition, there was also an extensive amount of

literature that considered effect measure modifiers including, sex, age, and race, among others (Section IS.7.4). Recent animal toxicological studies are coherent with the epidemiologic evidence of associations. In several recent studies with exposures resulting in BLLs ≤30 μg/dL, animals exposed to Pb had consistent increases in BP when compared with control treated animals. Combined with results from the 2013 Pb ISA and AQCDs, there is clear and substantial evidence that exposure to Pb results in increases in measures of BP.

A number of recent prospective cohort studies, including extended analyses of previous NHANES cohorts, reported consistent positive associations between BLLs and CVD-related mortality that are of similar magnitude to results from studies evaluated in the 2013 Pb ISA (Section 4.10). These more recent studies also reported that associations persisted after accounting for risk factors such as physical activity, serum cholesterol, and Cd levels in blood or urine. Once again, there were consistent positive associations between BLLs and mortality in populations with low mean BLLs, but the specific level, timing, frequency, and duration of Pb exposure contributing to CVD mortality in adult populations with higher past than recent exposure is not discernible from this evidence. Epidemiologic studies of mortality are consistent not only with the large amount of evidence for changes in BP and hypertension described above, but also with evidence of associations between blood or bone Pb levels and other cardiovascular outcomes. Past and recent analyses of the NAS cohort of older adult men indicate positive associations between bone Pb levels and incident IHD and prolonged QT interval. Additionally, a series of recent Korea National Health and Nutrition Examination Survey (KNHANES) studies observed increased 10-year CVD risk with increasing BLLs. These results are coherent with a toxicological study evaluated in the 2013 Pb ISA demonstrating increased incidence of arrhythmia, atrioventricular block, and a prolonged ST segment interval in Pb-exposed animals. In general, animal and in vitro toxicological evidence provides plausible pathways by which exposure to Pb could lead to serious CVD-related outcomes such as IHD and MI (Appendix 4.11). A notable pathway includes Pb resulting in oxidative stress and systemic inflammation that could potentially lead to impaired vascular function, a pro-atherosclerotic environment, and increases in BP. These effects, in particular atherosclerosis and increases in BP, can lead to MI or stroke that could result in mortality.

Taken together, the recent evidence supports and extends the evidence base reported in the 2013 Pb ISA. A large number of prospective cohort studies reported consistent associations between body Pb concentrations and cardiovascular outcomes such as increased BP, hypertension, and cardiovascular mortality. In particular, studies measuring bone Pb levels provided consistent evidence for associations between cumulative exposures and chronic health outcomes, such as hypertension, and premature mortality. This evidence is generally supported by cross-sectional epidemiologic studies and is coherent with evidence from animal toxicological studies, and further supported by experimental animal and in vitro studies demonstrating biologically plausible pathways through which exposure to Pb could lead to these outcomes. **Thus, there is sufficient evidence to conclude that there is a *causal relationship* between Pb exposure and cardiovascular effects and cardiovascular-related mortality**.

Table IS-4 Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and cardiovascular effects and cardiovascular-related mortality

Cardiovascular Effects and Cardiovascular-Related Mortality: Causal (IS.7.3.3 and Appendix 4)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Hypertension: Prospective epidemiologic studies consistently reported associations of blood and bone Pb levels with hypertension incidence and increased BP. These findings were consistent across multiple high-quality studies comprising large and diverse populations. Further support was provided by multiple cross-sectional analyses. While the adjustment for specific factors varied by study, the collective body of epidemiologic evidence included adjustment for multiple potential key confounding factors. Although epidemiologic studies in adults observed associations in populations with relatively low mean concurrent BLLs, the majority of individuals in these adult populations were likely to have had higher levels of Pb exposure earlier in life. Thus, there is uncertainty concerning the specific Pb exposure level, timing, frequency, and duration contributing to the associations observed in the epidemiologic studies. A causal relationship of Pb exposure with hypertension is supported by evidence from experimental animal studies that demonstrate effects on BP after long-term Pb exposure resulting in mean BLLs of 10 µg/dL or greater. *CHD*: Prospective epidemiologic studies of cohorts of adults during the period 1976–1994 consistently reported positive associations between BLLs and risk of CVD mortality, including MI and IHD. Several other studies reported associations between Pb biomarkers and incidence of CHD-related outcomes, including a prospective analysis reporting increased incidence of IHD (physician confirmed MI, angina pectoris) in association with increasing blood and bone Pb levels.	Recent studies strengthen support for the relationship between exposure to Pb and cardiovascular effects in adults. In particular, the strongest evidence continues to come from studies demonstrating the effect of Pb on increases in BP. The majority of recent analyses examining BP consider a wide range of potential confounders, including demographics, comorbid conditions, antihypertensive medication use, and other co-exposures to metals such as Cd. There is also an extensive amount of literature that considered effect measure modifiers, including sex, age, and race, among others. Recent animal toxicological studies provide additional evidence that exposure to Pb resulting in BLLs ≤30 µg/dL lead to increases in measures of BP. In addition to recent evidence on BP and hypertension, there is substantially more evidence for cardiovascular-related mortality, as well as some epidemiologic and toxicological evidence for effects such as changes in cardiac electrophysiology (e.g., electrocardiography measures of cardiac depolarization, repolarization, and HRV), arrythmia, and markers of atherosclerosis. There continues to be uncertainty regarding the specific Pb exposure level, timing, frequency, and duration contributing to the associations observed in the epidemiologic studies.

BLL = blood lead level; BP = blood pressure; Cd = cadmium; CHD = coronary heart disease; CVD = cardiovascular disease; HRV = heart rate variability; IHD = ischemic heart disease; MI = myocardial infarction; Pb = lead.

IS.7.3.4 Renal Effects

The 2013 Pb ISA concluded that evidence was "suggestive of a causal relationship" between Pb exposure and renal effects. Recent epidemiologic and toxicological studies extend the body of evidence presented in the 2013 Pb ISA indicating that Pb exposure is associated with reduced kidney function and kidney damage (Table IS-5). The causality determination in the 2013 Pb ISA was primarily limited by uncertainty due to the potential for reverse causality, as kidney damage could lead to increased BLLs through reduced excretion, rather than increased Pb exposure (e.g., elevated BLLs) being a causative factor of kidney impairment. A number of recent epidemiologic studies address this uncertainty with prospective study designs that control for baseline kidney function (Appendix 5.6). These studies demonstrate associations between biomarkers of Pb exposure and incident markers in kidney function in adults that are independent of baseline kidney function. Additionally, recent animal toxicological studies

provide further evidence for Pb-induced kidney damage and dysfunction (e.g., morphological changes in kidney structure, increased glomerular filtration rate, increased serum and urine creatinine, and increased blood urea nitrogen), supporting the directionality of effects. Combined, the toxicological and epidemiologic evidence indicates that reverse causality is highly unlikely to explain the epidemiologic associations between higher BLLs and decreased kidney function in adults. Toxicological studies also indicate plausible biological pathways connecting Pb exposure to renal effects, including Pb-induced oxidative stress and increases in BP (Appendix 5.9). Recent prospective epidemiologic evidence of associations between BLLs and reduced kidney function in adults are observed at BLLs <5 µg/dL, and a number of recent toxicological studies extend the evidence base to include effects in rodents with BLLs <20 µg/dL. Despite the evidence for associations at relatively low BLLs in adults, these renal outcomes were most often examined in adults who have been exposed to higher levels of Pb earlier in life, and uncertainty remains concerning the Pb exposure level, timing, frequency, and duration contributing to the observed associations.

Collectively, given the consistent evidence provided by prospective epidemiologic studies that control for baseline renal function and coherent experimental animal evidence for Pb-induced kidney damage, **there is sufficient evidence to conclude that there is a *causal relationship* between Pb exposure and renal effects.**

Table IS-5 Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and renal effects

Renal Effects: Causal (IS.7.3.4 and Appendix 5)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Longitudinal studies reported Pb-associated decrements in renal function in populations with mean BLLs of 7 and 9 µg/dL. However, the contributions of higher past Pb exposures could not be excluded. Additionally, there was uncertainty due to potential reverse causality in epidemiologic studies. Animal toxicological studies provided clear biological plausibility with evidence for Pb-induced kidney dysfunction at BLLs greater than 30 µg/dL; however, evidence in animals with BLLs <20 µg/dL was generally not available.	Recent toxicological and prospective epidemiologic studies support and extend conclusions from the 2013 Pb ISA. Notably, prospective studies with baseline measures of renal function reduce uncertainty regarding potential reverse causality, providing additional evidence of Pb-associated decrements in renal function in adult populations with mean BLLs <5 µg/dL. The contribution of higher past Pb exposures remains an uncertainty. Recent animal toxicological studies include evidence for renal effects observed at concentrations <20 µg/dL.

BLL = blood lead level; ISA = Integrated Science Assessment; Pb = lead.

IS.7.3.5 Immune System Effects

The 2013 Pb ISA issued causality determinations for the effects of Pb exposure on different aspects of the immune system including atopic and inflammatory responses, decreased host resistance, and autoimmunity. The evidence in this ISA is organized based on the World Health Organization's *Guidance for Immunotoxicity Risk Assessment for Chemicals* (IPCS, 2012). As proposed in this guidance, this ISA restructures the available evidence into slightly different outcome groups than those in the 2013

Pb ISA, which include immunosuppression, sensitization and allergic responses, and autoimmunity and autoimmune disease. For comparison with the causality determinations issued in the 2013 Pb ISA, the evidence considered for "sensitization and allergic response" maps closely with "atopic and inflammatory disease," the "immunosuppression" section largely overlaps with "decreased host resistance," and the evaluation of "autoimmunity and autoimmune disease" includes consideration of the same endpoints as "autoimmunity." The recent evidence for autoimmunity and autoimmune disease remains "inadequate to determine the presence or absence of a causal relationship" (Appendix 6.7). The following sections focus on the evidence for immunosuppression (IS.7.3.5.1) and sensitization and allergic response (IS.7.3.5.2), which is also summarized in Table IS-6A and Table IS-6B.

IS.7.3.5.1 Immunosuppression

The 2013 Pb ISA concluded that "a causal relationship is likely to exist" between Pb exposures and decreased host resistance. This causality determination was based primarily on consistent evidence that exposure to relevant BLLs suppresses the delayed-type hypersensitivity (DTH) response and increases bacterial titers and subsequent mortality in rodents. Suppressed DTH response is one of the most consistently reported immune effects associated with Pb exposure in animals and has been reported following gestational and postnatal exposures to Pb acetate resulting in BLLs ranging from 6.75 to >100 μg/dL in rats, mice, and chickens. A limited number of epidemiologic studies reviewed in the 2013 Pb ISA (U.S. EPA, 2013a) indicated a positive association between BLLs and viral and bacterial infections in children. None of the studies considered potential confounders, however, and most analyzed populations with higher BLLs (means >10 μg/dL). Cross-sectional studies of cell-mediated immunity reported consistent associations between BLL and lower T cell abundance in children, while results from other studies on lymphocyte activation, macrophages, neutrophils, and natural killer cells were generally inconsistent or not sufficiently informative (e.g., cross-sectional study designs with limited or no consideration of potential confounding, and a lack of information on C-R relationship). Biological plausibility was provided by a number of studies demonstrating Pb-induced suppression of T helper (Th)1 cytokines production (e.g., interferon-gamma [IFN-γ]), and decreased macrophage function, both of which may lead to decreased DTH response and increased incidence of viral and bacterial infection.

Recent toxicological studies provide additional evidence for immunosuppression, including decreased serum levels of anti-tetanus toxoid (TT) specific immunoglobulin M (IgM) (but not IgG) antibodies in iron (Fe)-deficient rats exposed to Pb in drinking water (BLL = 16.1 μg/dL). Consistent with findings reported in the 2013 Pb ISA, recent studies show that Pb exposure suppresses the DTH response (BLL = 18.48 μg/dL). Recent epidemiologic studies investigating aspects of immunosuppression include populations with wider age-ranges and much lower mean and median BLLs than studies evaluated in the 2013 Pb ISA. Recent studies also adjust for a wide range of potential confounders, including extensive consideration of SES factors. Cross-sectional and case-control studies are coherent with the toxicological evidence, providing consistent evidence of associations between Pb exposure (mean, median, or

geometric mean BLLs: 1.4–3.15 μg/dL) and higher viral and bacterial infection prevalence and lower antibiotic resistance in children and adults. Notably, epidemiologic studies of viral and bacterial infection used concurrent blood Pb measures, raising uncertainty regarding the temporal sequence between Pb exposure and immunosuppression and the level, timing, frequency, and duration of Pb exposures that contributed to the observed associations. Vaccine antibody response, an endpoint that was not examined in studies evaluated in the 2013 Pb ISA, was evaluated in a birth cohort study and a few cross-sectional studies that demonstrate generally consistent evidence of an association between BLLs (mean or median <2 μg/dL) and decreased virus-neutralizing antibodies in children. Biological plausibility for the observed associations is provided by recent and previously evaluated 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.

Collectively, based on strong evidence from toxicological studies consistently demonstrating that Pb exposures suppress the DTH response and increase susceptibility to bacterial infection in animals and supporting evidence from epidemiologic studies demonstrating higher Pb-related susceptibility to viral and bacterial infection, reduced antibiotic resistance, and reduced vaccine antibodies in children. **Overall, there is sufficient evidence to conclude that there is *likely to be a causal relationship* between Pb exposure and immunosuppression**.

Table IS-6A Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and immune system effects

Immunosuppression: Likely to Be Causal (IS.7.3.5.1 and Appendix 6.3)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Animal toxicological studies were the primary contributors to the evidence for Pb-induced immunosuppression. Several studies in rodents show that dietary Pb exposure producing relevant BLLs (7–25 μg/dL) results in increased susceptibility to bacterial infection and suppressed DTH. A few cross-sectional epidemiologic studies indicated positive associations between Pb and respiratory infections, but these studies are limited by a lack of rigorous methodology or consideration for potential confounding.	Recent toxicological studies demonstrate the ability of Pb to alter antibody responses, providing additional evidence for the immunosuppressive effects of Pb. The relationship between Pb exposure and immunosuppression is further supported by recent epidemiologic studies, which expand the quantity and quality of the observational evidence base evaluated in the 2013 Pb ISA. A mix of recent prospective cohort, case-control, and cross-sectional studies that include more robust consideration for potential confounding report associations between low BLLs (<3.5 μg/dL) and susceptibility to viral and bacterial infection, reduced antibiotic resistance, and reduced vaccine antibodies in children.

BLL = blood lead level; DTH = delayed-type hypersensitivity; ISA = Integrated Science Assessment; Pb = lead.

IS.7.3.5.2 Sensitization and Allergic Response

The 2013 Pb ISA concluded that "a causal relationship is likely to exist" between Pb exposures and an increase in atopic and inflammatory conditions. This causality determination was supported by a prospective analysis reporting associations between BLLs and increased asthma incidence in children and

another longitudinal study that observed a positive association between cord BLLs and immediate-type allergic responses in children that were detected clinically using skin prick tests. Both studies had small sample sizes, however, and lacked precision (i.e., had wide 95% CIs), which increases the likelihood of chance findings. The associations observed in the prospective analyses were supported by a cross-sectional study of BLL-associated parental-reported asthma in children and population-based cross-sectional studies in children that reported associations between BLL and elevated serum IgE. Notably, many of the serum IgE studies had limited adjustment for potential confounders and included population mean BLLs >10 μg/dL. The epidemiologic findings were coherent with a large body of toxicological studies that reported physiological responses in animals consistent with the development of allergic sensitization, including increased lymph node cell proliferation, increased production of Th2 cytokines such as interleukin 4 (IL-4), increased total serum IgE antibody levels, and misregulated inflammation.

Recent animal toxicological studies relevant to sensitization and allergic response are limited in number. The available studies report effects of Pb on production of cytokines relevant to immediate-type hypersensitivity. However, the utility of these data for hazard identification is limited because changes in cytokine levels (particularly when measured in blood) can be associated with many different types of tissues and toxicities and may reflect an immune response to tissue injury but not necessarily an impact on or impairment of immune function. Recent epidemiologic evidence is inconsistent with studies evaluated in the 2013 Pb ISA. Specifically, whereas a few small prospective studies reviewed in the 2013 Pb ISA supported the presence of an association between BLLs and incident asthma in children, recent epidemiologic studies of atopic disease, including prospective cohort studies examining asthma, eczema, and food allergies were generally consistent in reporting a lack of an association in populations with low BLLs (mean or median BLLs <2 μg/dL). Similar to cohort studies evaluated in the 2013 Pb ISA, recent longitudinal analyses are limited in number and have limited statistical power because of low case numbers. Among other things, limited statistical power results in the reduced likelihood of detecting a true effect and a reduced likelihood that an observed result reflects a true effect. Notably, recent cross-sectional NHANES analyses also reported null associations between children's BLLs and asthma, eczema, and food allergies in much larger study populations. Additionally, recent studies provide inconsistent evidence for Pb-associated changes in immunological biomarkers involved in hypersensitivity and allergic response. Whereas there was coherence between the animal toxicological and epidemiologic evidence evaluated in the 2013 Pb ISA, the recent epidemiologic studies add considerable uncertainty to the line of evidence that previously provided support for the "likely to be causal" determination in the 2013 Pb ISA. Overall, given the strong body of toxicological evidence, but inconsistent results across epidemiologic studies, **the collective evidence is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and sensitization and allergic responses**.

Table IS-6B Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and immune system effects

Sensitization and Allergic Response: Suggestive (IS.7.3.5.2 and Appendix 6.4)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
A limited number of prospective studies in a few populations of children ages 1–5 yr reported associations of asthma and allergy with BLLs prenatal cord BLLs or BLLs. These studies had small sample sizes and lacked precision (i.e., had wide 95% CIs). The epidemiologic findings are coherent with a large body of toxicological studies that reported physiological responses in animals consistent with the development of allergic sensitization, including increased lymph node cell proliferation, increased production of Th2 cytokines such as IL-4, increased total serum IgE antibody levels, and misregulated inflammation.	Several recent epidemiologic studies of sensitization and allergic response, including prospective birth cohorts and cross-sectional studies with mean or median BLLs <2 μg/d, provide little evidence of an association between exposure to Pb and atopic disease, including asthma, eczema, and food allergies. Similar to the evidence in the 2013 Pb ISA, a considerable uncertainty in the evidence base is the limited number of children with asthma in the cohort studies evaluated. Recent toxicological evidence for effects of Pb exposure on biomarkers of allergic disease is sparse but provides some evidence of Pb-induced changes in IFN-γ, a Th1 cytokine known to play a role in the resolution of asthma.

BLL = blood lead level; CI = confidence interval; IgE = immunoglobulin E; IL-4 = interleukin 4; ISA = Integrated Science Assessment; Pb = lead; Th = T helper; yr = year(s).

IS.7.3.6 Hematological Effects

The effects of Pb exposure on RBC function and heme synthesis have been extensively studied over several decades in both human and animal studies. The 1978 NAAQS for Pb were established to prevent BLLs in most children from exceeding 30 μg/dL as such levels were associated with impaired heme synthesis, evidenced by accumulation of protoporphyrin in erythrocytes (U.S. EPA, 1978). The 2013 Pb ISA issued causality determinations for two hematological outcomes: RBC survival and function and altered heme synthesis. The evidence for both outcomes was "sufficient to conclude that there is a causal relationship" with Pb exposure. Given the interconnectedness of the effects of Pb on RBC survival and function and altered heme synthesis, this assessment presents a single causality determination for the combination of these outcomes. This approach allows for a more holistic evaluation of interrelated health endpoints, including a discussion of how all individual lines of evidence contribute to the overall hematological effects causality determination. The evidence available in the 2013 Pb ISA as well as evidence from recent studies is discussed in the ensuing subsections and summarized in Table IS-7. **Taken together, there is sufficient evidence to conclude that there is a *causal relationship* between Pb exposure and hematological effects, including altered heme synthesis and decreased RBC survival and function.**

IS.7.3.6.1 Red Blood Cell Survival and Function

A strong body of evidence from experimental animal studies reviewed in the 2013 Pb ISA demonstrated that Pb exposures alter several hematological parameters (e.g., hemoglobin [Hb],

hematocrit, mean corpuscular volume, mean corpuscular Hb), induce oxidative stress (e.g., alter antioxidant enzyme activities [superoxide dismutase, catalase, glutathione peroxidase], decrease cellular glutathione, and increase lipid peroxidation), and increase cytotoxicity in RBC precursor cells in rodents exposed to various forms of Pb via drinking water and gavage resulting in BLLs ≤30 μg/dL. Consistent results were observed in several additional studies in rodents that did not report BLLs. Results from epidemiologic studies were coherent with the toxicological evidence, including associations between BLLs and differences in hematological parameters, higher levels of oxidative stress, altered hematopoiesis, and higher prevalence of anemia. Notably, the epidemiologic evidence consisted of cross-sectional studies that were conducted in populations with higher mean Pb exposures (i.e., BLLs >10 μg/dL), did not thoroughly consider potential confounders, and lacked rigorous statistical methodology.

Recent toxicological evidence is limited, but studies continue to support the findings from the last review. The most consistent evidence comes from studies that report decreased Hb levels in rodents following Pb exposures (BLLs ranging from 7.5 to 14.7 μg/dL) (Appendix 7.3.2). Recent epidemiologic studies expand on the evidence presented in the 2013 Pb ISA and are coherent with the experimental evidence. Although the recent studies are also cross-sectional, they include populations with much lower BLL means (<10 μg/dL) and include more robust adjustment for potential confounding, addressing important uncertainties from the last review. The most consistent epidemiologic evidence indicates an association between higher BLLs and lower Hb levels in children (Appendix 7.3.1), which is in line with the evidence from recent experimental animal studies. While the clinical relevance of small mean decrements in Hb across exposure quintiles is unclear, a few of the recent epidemiologic studies observed increases in the odds of prevalent anemia in children associated with increasing quantiles of BLLs.

IS.7.3.6.2 Altered Heme Synthesis

As described in the 2013 Pb ISA, a small but consistent body of studies in adult animals reported that Pb exposures via drinking water and gavage for 15 days to 9 months (resulting in BLLs <30 μg/dL) decreased ALAD and ferrochelatase activities. The relationship between Pb exposure and altered heme synthesis was further supported by several toxicological studies that observed decreased Hb levels in laboratory animals exposed to Pb. Decreased Hb levels can be a direct indicator of decreased heme synthesis. Cross-sectional epidemiologic studies provided supporting evidence that concurrent elevated BLLs are associated with decreased ALAD and ferrochelatase activities and decreased Hb levels in both adults and children. However, the majority of these studies are limited by the lack of consideration of potential confounding. Although there were limitations in the epidemiologic evidence, some studies in children did control for or consider potential confounding, and effects in adults and children in these studies are coherent with effects observed in animal toxicological studies.

Recent PECOS-relevant studies are limited in number and focus mainly on Hb levels but continue to provide support for Pb-related alterations in heme synthesis. Notably, recent epidemiologic studies

indicate an inverse association between BLLs and Hb levels in children. These studies include more robust statistical methods, expanded consideration of potential confounders, and populations with much lower BLLs than the studies included in the previous reviews (mean or median BLLs ranging from 3.04 to 8.38 µg/dL; Appendix 7.3.1). The recent epidemiologic evidence is coherent with recent toxicological studies, which observed Hb decrements in Pb-exposed mice with BLLs relevant to humans.

Table IS-7 Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and hematological effects

Hematological Effects, Including Altered Heme Synthesis and Decreased Red Blood Cell Survival and Function: Causal
(IS.7.3.6.2 and Appendix 7)

Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
RBC Survival and Function: Experimental animal studies demonstrate that exposures resulting in BLLs relevant to humans alter several hematological parameters, increase measures of oxidative stress, and increase cytotoxicity in RBC precursor cells. Epidemiologic studies find associations in both adults and children between BLLs and altered hematological endpoints, higher measures of oxidative stress, altered hematopoiesis, and higher prevalence of anemia. The epidemiologic evidence consisted of cross-sectional studies that were conducted in populations with high mean Pb exposures and did not thoroughly consider potential confounders. Additional support for these findings was provided by toxicological and epidemiologic studies demonstrating increased intracellular Ca^{2+} concentrations, decreased Ca^{2+}/Mg^{2+} adenosine triphosphatase activity, and increased phosphatidylserine exposure, establishing biologically plausibility for Pb-induced changes in RBC survival.	*RBC Survival and Function*: Recent animal toxicological studies are limited in number, but consistent with evidence in the 2013 Pb ISA. The most consistent evidence comes from studies that report decreased Hb levels in rodents following Pb exposures (BLLs of 7.5 to 14.7 µg/dL). Recent epidemiologic studies include populations with much lower BLL means than studies in the 2013 Pb ISA (3.04 to 8.38 µg/dL) and more robust adjustment for potential confounding. The most consistent epidemiologic evidence indicates associations between higher BLLs and lower Hb levels and higher prevalence of anemia in children (birth to 11 yr).
Heme Synthesis: Altered heme synthesis (e.g., decreased ALAD and ferrochelatase activities, and decreased Hb levels) was demonstrated by a small, but consistent, body of epidemiologic and toxicological studies with relevant Pb exposures. Epidemiologic studies were all cross-sectional and the majority lacked consideration for potential confounding. Evidence for altered heme synthesis is also provided by a large body of toxicological and epidemiologic studies that report lower Hb concentrations in association with Pb exposure or BLLs.	*Heme Synthesis*: Recent epidemiologic studies indicate an inverse association between BLLs and Hb levels in children. These studies expanded consideration of potential confounders and include populations with lower BLLs (mean or median BLLs ranging from 3.04 to 8.38 µg/dL). The recent epidemiologic evidence is coherent with recent toxicological studies, which also observed Hb decrements in Pb-exposed mice with BLLs relevant to humans.

ALAD = δ-aminolevulinic acid dehydratase; BLL = blood lead level; Ca^{2+} = calcium ion; Hb = hemoglobin; ISA = Integrated Science Assessment; Mg^{2+} = magnesium ion; Pb = lead; RBC = red blood cell; yr = year(s).

IS.7.3.7 Reproductive and Developmental Effects

This ISA organizes the reproductive and developmental effects of Pb exposure into four outcome categories: effects on pregnancy and birth outcomes, effects on development, effects on female

reproductive function, and effects on male reproductive function. The collective evidence is sufficient to conclude that there is "likely to be a causal relationship" between Pb exposure and: 1) effects on pregnancy and birth outcomes, and 2) effects on female reproductive function. Evidence related to these outcomes is described in Sections IS.7.3.7.1 and IS.7.3.7.3, respectively. Effects on development (IS.7.3.7.2) and effects on male reproductive function (IS.7.3.7.3), for which evidence supports *causal relationships* with Pb exposure, are also discussed in more detail in the ensuing sections. Table IS-8A through Table IS-8D provide a summary of the evidence from epidemiologic and animal toxicological studies for reproductive and developmental effects, highlighting the recent evidence in comparison with the evidence available in the 2013 Pb ISA.

IS.7.3.7.1 Effects on Pregnancy and Birth Outcomes

The 2013 Pb ISA concluded that the available evidence was "suggestive of a causal relationship between Pb exposure and birth outcomes." The causality determination was supported by associations observed in epidemiologic studies of preterm birth and low birth weight/fetal growth. Notably, some studies reported associations between Pb and low birth weight in studies that used postpartum maternal bone Pb or air Pb concentrations. Although epidemiologic evidence was less consistent for associations between low birth weight and maternal blood Pb measured during pregnancy or at delivery, or with Pb measured in the umbilical cord and placenta, some inverse associations were observed between Pb biomarker levels and birth weight or other measures of fetal growth. The effects of Pb exposure during gestation in animal toxicological studies included similarly inconsistent findings, though most studies reported reductions in birth weight of pups or litters when dams were treated with Pb. Thus, although the evidence was inconsistent overall, there was some epidemiologic evidence supporting associations between Pb exposure and preterm birth and low birth weight or fetal growth that was supported by experimental animal evidence Pb-induced reductions in birthweight.

A recent quasi-experimental study used a difference-in-difference approach to demonstrate that reducing potential exposures to airborne Pb reduced the risk of preterm birth and several other birth-related outcomes. The study examined variation in potential airborne Pb exposure following the National Association for Stock Car Auto Racing's (NASCAR's) deleading of racing fuel and reported that removal of Pb from fuel was associated with increased birth weight as well as decreased probability of low birth weight, preterm birth, and small for gestational age for children born to mothers living within 4,000m of a racetrack relative to those residing at least 10,000m from the track. The difference-in-difference methodology controls for time-varying confounders, removing biases from comparisons over time in the treatment group that could be the result of trends due to other causes of the outcome. These findings provide support for the effects of airborne Pb exposures on birth outcomes and are coherent with experimental animal evidence from the 2013 Pb ISA indicating reductions in rodent birthweight following Pb exposure. Additionally, there were a few high-quality epidemiologic studies that reported associations with relevant BLLs and prenatal growth, birth defects, spontaneous abortion and pregnancy

loss, and placental function, but the overall findings were inconsistent. There continue to be uncertainties related to the specific biomarkers of exposure (maternal blood, maternal serum, maternal bone, maternal erythrocytes, cord blood, cord blood serum, placental tissue) associated with pregnancy and birth outcomes, the critical window of exposure, and potential confounding by co-occurring metals. Of note, the cohorts in the recent epidemiologic literature would generally be expected to have had appreciable past exposures to Pb; however, the extent to which adult BLLs in these cohorts reflect the higher exposure histories is unknown as is the extent to which these past Pb exposures (magnitude, duration, frequency) may or may not elicit effects on pregnancy and birth outcomes. Recent evidence from toxicological studies mostly reported no effects of Pb across pregnancy and birth outcomes, but this may be due to the exclusion of toxicological studies with exposures resulting in BLLs greater than 30 µg/dL, indicating the possibility that most pregnancy and birth outcomes are only affected in laboratory animals at levels higher than most environmentally relevant Pb exposure levels.

In summary, recent epidemiologic studies expand on findings presented in the 2013 Pb ISA, particularly supporting Pb effects on preterm birth and low birthweight and are coherent with previous studies in experimental animals. **The collective evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and effects on pregnancy and birth outcomes.**

Table IS-8A Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and reproductive and developmental effects

Pregnancy and Birth Outcomes: Likely to Be Causal (IS.7.3.7.2 and Appendix 8.3)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Epidemiologic evidence for pregnancy and birth outcomes was inconsistent, but those that examined postpartum maternal bone Pb or air Pb concentrations reported associations with preterm birth and low birth weight. Associations were less consistent for low birth weight with maternal blood Pb levels (measured during pregnancy or at delivery) or with Pb measured in the umbilical cord and placenta. Most experimental animal studies reported reductions in birth weight of pups or birth weight of litters when dams were treated with Pb.	A recent quasi-experimental study provides evidence for decreased preterm birth rates following NASCAR's phase out of leaded gasoline at races. Recent evidence from experimental animal studies generally reported no effects of Pb across pregnancy and birth outcomes, but this may be due to the exclusion of toxicological studies with exposures resulting in BLLs greater than 30 µg/dL.

BLL = blood lead level; mo = month(s); NASCAR = National Association for Stock Car Auto Racing; Pb = lead; yr = year(s).

IS.7.3.7.2 Effects on Development

The 2013 Pb ISA determined that the collective evidence was "sufficient to conclude that there is a causal relationship between Pb exposures and developmental effects." This determination was based on a strong body of evidence demonstrating delayed pubertal onset among males and females exposed to Pb. Cross-sectional epidemiologic studies reported consistent associations between BLLs and delayed pubertal onset (measured by age at menarche, pubic hair development, and breast development) among

girls (ages 6–18 years) with mean and/or median concurrent BLLs of 1.2–9.5 μg/dL. Although fewer studies were conducted in boys, associations between BLLs and delayed puberty onset in boys (ages 8–15 years) were observed in a longitudinal study and a few supporting cross-sectional studies (mean and/or median BLLs of 3–9.5 μg/dL). Limitations across most of the epidemiologic studies of BLLs and delayed puberty included a lack of adjustment for nutritional factors as a potential confounder and the use of cross-sectional study designs, which do not establish temporality. Additionally, because studies included older children and adolescents who likely had higher earlier childhood Pb exposures, there is uncertainty regarding the level, timing, frequency, and duration of Pb exposure that contributed to the observed associations. Experimental animal studies demonstrate that puberty onset in both males and females is delayed following exposure to Pb. Evidence for effects on postnatal growth was inconsistent.

Recent epidemiologic evidence continues to support an association between BLLs and delayed pubertal onset in girls (Appendix 8.4.2) and boys (Appendix 8.4.3). Notably, recent studies observe more consistent associations between Pb exposure and effects on puberty in girls. Although associations are reported in populations with lower mean BLLs (0.65–6.57 μg/dL), uncertainty regarding the role of potentially higher past exposures remains. Recent epidemiologic studies consider a wide range of confounders, including height, weight, and body mass index (BMI), and some studies were conducted among established longitudinal cohorts. No recent PECOS-relevant toxicological studies reported on the effects of Pb on male or female puberty, though some studies provide evidence for the biological plausibility of delayed pubertal onset. Specifically, Pb-induced disruptions of the hypothalamic-pituitary-gonadal axis, steroidogenic enzymes, and their sex steroid products provide plausible pathways through which Pb exposure could lead to the observed delays in pubertal onset reported in epidemiologic and toxicological studies. Recent toxicological and epidemiologic evidence for effects on postnatal growth is largely inconsistent, though epidemiologic studies that examined BLLs, as opposed to other biomarkers, provide more consistent patterns of inverse associations between Pb exposure and height and weight in children (8 months to 11 years).

Because of the strong body of evidence demonstrating delayed pubertal onset among males and females exposed to Pb, **the collective evidence is sufficient to conclude that there is a *causal relationship* between Pb exposure and effects on development.**

Table IS-8B Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and reproductive and developmental effects

Development: Causal Relationship (IS.7.3.7.2 and Appendix 8.4)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Epidemiologic studies reported associations between concurrent BLLs and delayed pubertal onset in boys and girls. Associations were observed in children and adolescents (6–18 yr) with low mean and/or median BLLs (1.2–9.5 μg/dL). A limitation across most of these studies is their cross-sectional design, which does not establish temporality between the exposure and outcome. Additionally, there is uncertainty with regard to the exposure frequency, timing, duration, and level that contributed to the associations observed in these studies. Experimental animal studies demonstrated that puberty onset in both males and females is delayed with Pb exposure.	Recent epidemiologic and toxicological evidence continues to support Pb-related delays in pubertal onset in boys and girls, including associations at lower BLLs in the epidemiologic studies (0.65–6.57 μg/dL). Results from recent studies examining the relationship between Pb exposure and postnatal growth are inconsistent, though epidemiologic studies that examined BLLs, as opposed to other biomarkers, provide more consistent patterns of inverse associations between Pb exposure and height and weight in children (8 mo to 11 yr).

BLL = blood lead level; mo = month(s); Pb = lead; yr = year(s).

IS.7.3.7.3 Effects on Female Reproductive Function

The 2013 Pb ISA concluded that the available evidence was "suggestive of a causal relationship between Pb exposure and female reproductive function." A small number of epidemiologic studies reviewed in the 2013 Pb ISA reported associations with concurrent BLLs and altered hormone levels in adults, but results were inconsistent, possibly due to the between study variation in hormones examined and the timing of measurements as related to menstrual and lifecycles. There was additionally some evidence of a potential inverse relationship between Pb exposure and female fertility, but findings were again inconsistent. There were a number of study limitations in the epidemiologic evidence. The majority of studies were cross-sectional and adjustment for potential confounders varied from study to study, with some potentially important confounders, such as BMI, not included in all studies. Further, most of the epidemiologic studies on female reproductive function reviewed in the 2013 Pb ISA had small sample sizes and were generally conducted in women attending infertility clinics. Toxicological studies often employed prenatal or early postnatal Pb exposures at relevant Pb levels and reported Pb-induced decreases in ovarian antioxidant capacity, altered ovarian steroidogenesis, and aberrant gestational hormone levels. Although epidemiologic and toxicological studies provide information on different exposure periods, both types of studies, including some high-quality epidemiologic and toxicological studies, supported the conclusion that Pb may affect some aspects of female reproductive function.

Recent studies expand on findings presented in the 2013 Pb ISA. The strongest line of evidence comes from recent epidemiologic studies examining the relationship between Pb exposure and effects on hormone levels and menstrual/estrous cyclicity (Table 8-1). Positive associations from a longitudinal cohort between bone Pb, a biomarker of cumulative Pb exposure, and both earlier age at menopause and risk of early menopause were supported by results from a cross-sectional NHANES study of concurrent

exposure of blood Pb with earlier age at menopause. Additionally, recent epidemiologic studies found consistent positive associations between blood Pb and follicle stimulating hormone and luteinizing hormone in women who were postmenopausal. Although these studies are limited by their cross-sectional study designs, they were conducted in well-established population-based surveys. These studies considered a wider range of potential confounders compared to studies evaluated in the 2013 Pb ISA, including coexposure to other metals, but not all studies adjusted for potentially important confounders such as age at menarche, pregnancy history, oral contraceptive use, and female hormone use. As with other studies in adults, the extent to which adult BLLs in these cohorts reflect potentially higher exposure histories is undiscernible as is the extent to which these past Pb exposures (magnitude, duration, frequency) may or may not elicit effects. While there were no recent PECOS-relevant toxicological studies that examined the effects of Pb on hormone levels in females or menstrual or estrous cyclicity, previous toxicological evidence supports epidemiologic study findings and indicate that Pb may disrupt reproductive hormones and menstrual and estrous cyclicity in females. **The collective evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and female reproductive function.**

Table IS-8C Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and reproductive and developmental effects

Female Reproductive Function: Likely to Be Causal (IS.7.3.7.2 and Appendix 8.5)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
A limited number of experimental animal studies conducted in nonhuman primates and rodents reported disrupted menstrual or estrous cyclicity and reduced progesterone following high levels of exposure to Pb (BLLs: 44–264 µg/dL), although another nonhuman primate study with lower BLLs than the other studies (<40 µg/dL) reported no effects on menstrual cyclicity. Cross-sectional epidemiologic studies with inconsistent adjustment for important confounders reported some associations between concurrent BLLs and altered hormone levels in women attending infertility clinics.	A recent cohort study reported associations between bone Pb, a biomarker of cumulative Pb exposure, and both earlier age at menopause and risk of early menopause. Cross-sectional studies provided supporting evidence of positive associations between concurrent exposure of blood Pb with earlier age at menopause. While there were no recent PECOS-relevant experimental animal studies that examined the effects of Pb on menstrual or estrous cyclicity, the results from recent epidemiologic studies are coherent with previous animal toxicological evidence.

BLL = blood lead level; mo = month(s); Pb = lead; yr = year(s).

IS.7.3.7.4 Effects on Male Reproductive Function

In the 2013 Pb ISA, the evidence was "sufficient to conclude that there is a causal relationship between Pb exposures and male reproductive function." Key evidence was provided by toxicological studies in rodents, nonhuman primates, and rabbits showing detrimental effects on semen quality, sperm, and fecundity/fertility with supporting evidence in epidemiologic studies of associations between BLLs and detrimental effects on sperm. Animal exposures resulting in BLLs from 5–43 µg/dL induced lower

sperm quality and sperm production rate, sperm DNA damage, and histological or ultrastructural damage to the male reproductive organs. These effects were found in animals exposed to Pb for 1 week to 3 months during peripuberty or as adults. Pb exposure of male rats also resulted in subfecundity in female mates and lower fertilization of eggs in vitro. Detrimental effects of Pb on sperm were observed in epidemiologic studies with concurrent BLLs of 25 μg/dL and greater among occupationally exposed men; however, these studies were limited because of their lack of consideration of potential confounding factors, including occupational exposures other than Pb. A smaller number of epidemiologic studies among men with lower Pb biomarker levels were limited to fertility clinic studies that may lack generalizability. Additionally, because of uncertainty regarding greater exposure to Pb earlier in life in these populations, the extent to which adult BLLs in these cohorts reflect potentially higher exposure histories as well as the extent to which these past Pb exposures (magnitude, duration, frequency) may or may not elicit effects is not discernible from the epidemiologic evidence. Biological plausibility for the observed associations was provided by animal toxicological studies that demonstrated Pb-induced oxidative stress within the male sex organs, increase apoptosis of spermatocytes and germ cells, and impaired germ cell structure and function.

Recent epidemiologic evidence continues to support an association between BLLs and decreased sperm/semen production, quality, and function. Results from analyses using other Pb biomarkers, including plasma, semen, and seminal fluid, were inconsistent. The evaluated studies were cross-sectional and conducted in males attending fertility clinics, which may have resulted in selection bias and limits the generalizability of the results. The studies were also limited by concurrent measurement of exposure and outcome, examination of different seminal parameters, and small sample sizes. Despite these limitations, a wide variety of potential confounders were considered, including adjustment for hormone levels, which could potentially impact sperm/semen production, quality, and function. Recent toxicological studies generally report that Pb exposure alters some aspects of sperm or semen quality, such as sperm density, motility, morphology, and viability, especially studies that include dosing during developmental periods or for periods 30 days or longer. The strongest line of evidence, including potential biologically plausible pathways, were reported for effects on sperm/semen production, quality, and function, while evidence for other effects on male reproductive function, including hormone levels, male fertility, and morphology and histology of male sex organs is either limited in quantity and/or inconsistent. **Overall, the collective evidence is sufficient to conclude that there is a *causal relationship* between Pb exposure and male reproductive function.**

Table IS-8D Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and reproductive and developmental effects

Male Reproductive Function: Causal Relationship (IS.7.3.7.3 and Appendix 8.6)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Animal toxicological studies in rodents, nonhuman primates, and rabbits reported that Pb exposures resulting in BLLs from 5–43 μg/dL induced lower sperm quality and sperm production rate, sperm DNA damage, and histological or ultrastructural damage to the male reproductive organs. These effects were found in animals exposed to Pb for 1 wk to 3 mo during peripuberty or as adults. There was some supporting epidemiologic evidence, but most studies examined occupationally exposed men with high BLLs (>25 μg/dL) and included limited control for potential confounders.	Recent epidemiologic studies reported consistent associations between BLLs and decreased sperm/semen production and quality. Results were inconsistent in studies that measured Pb in seminal fluid or seminal plasma. Epidemiologic studies also provided initial evidence of an association between BLLs and increased testosterone and morphological changes in male sex organs. The epidemiologic studies evaluated include non-occupationally exposed men with lower Pb exposures than studies included in the 2013 Pb ISA. Recent toxicological evidence is consistent with findings from the 2013 Pb ISA.

BLL = blood lead level; ISA = Integrated Science Assessment; mo = month(s); Pb = lead; wk = week(s); yr = year(s).

IS.7.3.8 Musculoskeletal Effects

The 2013 Pb ISA concluded that "a causal relationship is likely to exist between Pb exposure and effects on bone and teeth." In order to be more inclusive of other health effects related to bone and teeth (e.g., muscles, joints, and cartilage), this ISA expands the considered health outcomes to include effects on the entire musculoskeletal system. A summary of the evidence available in the 2013 Pb ISA as well as evidence from recent studies is provided in Table IS-9. Recent epidemiologic evidence continues to support an association between Pb exposure and effects on bone (e.g., increased prevalence of osteoporosis) and teeth (i.e., increased prevalence and incidence of dental caries and tooth loss in children and adults). There is also an emerging area of research on osteoarthritis, an endpoint that was not discussed in the 2013 Pb ISA. A few recent cross-sectional studies reported positive associations between BLLs and symptomatic and radiographic osteoarthritis and some biomarkers of joint tissue metabolism. The epidemiologic evidence base includes a larger number of studies and adult populations with lower mean, median, or geometric mean BLLs than studies included in the 2013 Pb ISA (1.03 to 4.44 μg/dL). Despite the evidence for associations at relatively low BLLs, these musculoskeletal outcomes were most often examined in adults who have been exposed to higher levels of Pb earlier in life, the extent to which adult BLLs in these cohorts reflect potentially higher exposure histories as well as the extent to which these past Pb exposures (magnitude, duration, frequency) may or may not elicit effects is not discernible from the epidemiologic evidence. Additionally, although the recent epidemiologic evidence is consistent with the findings highlighted in the 2013 Pb ISA, recent studies do not thoroughly address the unclear temporality of exposure and outcome resulting from mostly cross-sectional study designs. This uncertainty is particularly important for studies examining benchmark dose (BMD) and osteoporosis due to the possibility of reverse causality, where the observed associations could be driven by higher BLLs

due to increased bone turnover in individuals with low BMD or osteoporosis. 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 epidemiologic studies. **Overall, the collective evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and musculoskeletal effects.**

Table IS-9 Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and musculoskeletal effects

Musculoskeletal Effects: Likely to Be Causal (IS.7.3.8 and Appendix 9.5)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Strong toxicological evidence evaluated in the 2013 Pb ISA and the 2006 Pb AQCD (U.S. EPA, 2006) demonstrates 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 concentration-dependent trends. Systemic effects of Pb exposure included disruption of bone mineralization during growth, alterations in bone cell differentiation and function due to alterations in plasma levels of growth hormones and calcitropic hormones such as 1,25-dihydroxyvitamin D3, effects on Ca^{2+}- binding proteins, and increases in Ca^{2+} and phosphorus concentrations in the bloodstream. As in bone, Pb was found to easily substitute for Ca^{2+} in the teeth following exposure and was taken up and incorporated into developing teeth in experimental animals. These findings were coherent with results from a small body of epidemiologic studies that provided consistent evidence of associations between Pb biomarker levels and various effects on bone and teeth after adjusting for potential confounding by age and SES-related factors.	Recent epidemiologic studies continue to support associations between Pb exposure and effects on bone in adults and teeth in children and adults. The recent epidemiologic evidence is mostly from cross-sectional studies and does not thoroughly address the temporality of exposure and outcome. Additionally, uncertainty remains concerning the Pb exposure level, timing, frequency, and duration contributing to the observed associations in adult populations. Recent toxicological evidence is limited, but consistent with findings from the 2013 Pb ISA and coherent with the epidemiologic evidence.

AQCD = Air Quality Criteria Document; Ca^{2+} = calcium ion; ISA = Integrated Science Assessment; Pb = lead; SES = socioeconomic status.

IS.7.3.9 Mortality

In the 2013 Pb ISA (U.S. EPA, 2013a), 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 CVD chapter. Although this evidence contributed to the "causal relationship" between Pb exposure and CHD, there was no distinct causality determination for total or cause-specific mortality. A small number

of studies evaluated in the 2013 Pb ISA reported consistently positive associations between Pb biomarkers and total mortality. This evidence was further supported by consistent evidence of positive associations between BLLs and cardiovascular mortality in NHANES cohorts, including some studies that controlled for a wide range of potential confounders, tested for interactions between confounders and BLL, included evaluations of C-R relationships and extensive analysis of model evaluations, and examined specific causes of CVD mortality. In addition, an analysis of the NAS reported an association between bone Pb, a metric of cumulative Pb exposure, and increased total and cardiovascular mortality in older male veterans.

Several 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 and cardiovascular mortality (Table IS-10). A recent quasi-experimental study comparing time periods prior to and after the phaseout of leaded gasoline in professional racing series (i.e., NASCAR and the Automobile Racing Club of America [ARCA]) observed a decline in mortality rates in race counties relative to control counties following the phaseout of leaded gasoline. The novel study design utilized in this analysis is able to reduce concerns of potential confounding under a set of well-reasoned, but untestable assumptions. Other recent studies include nationally representative adult populations with low BLLs (mean <2.5 μg/dL), including an extended analysis of the NHANES III cohort. Notably, these analyses include study populations that were born prior to the phaseout of leaded gasoline and therefore likely had much higher past Pb exposures. Thus, the extent to which adult BLLs in these cohorts reflect potentially higher exposure histories as well as the extent to which these past Pb exposures (magnitude, duration, frequency) may or may not elicit effects is not discernible from the epidemiologic evidence. Studies that examined multiple causes of mortality in the same cohort generally reported effect estimates that were notably smaller in magnitude for total mortality compared to cardiovascular mortality. This suggests that the total mortality results may in large part be driven by the association between BLLs and cardiovascular mortality. There is extensive epidemiologic and toxicological evidence indicating pathways 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. Because cardiovascular morbidity, which comprises 33% of total (nonaccidental) mortality, is the most common contributor to total mortality (NHLBI, 2017), the progression demonstrated in the available evidence for cardiovascular morbidity supports potential biological pathways by which Pb exposure could result in cardiovascular mortality. There is also very limited evidence that Pb exposure is positively associated with other causes of mortality, including Alzheimer's disease (AD) and infection. Biological plausibility for these outcomes is demonstrated by pathways leading from Pb exposure to neurodegenerative disease (Appendix 3.3) and immunosuppression (Section IS.7.3.5), 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. A few uncertainties remain in the evidence base, including a limited number of independent studies (i.e., from non-overlapping study populations), and uncertainty regarding to the

specific timing, duration, frequency, and level of Pb exposure that contributed to the observed associations.

Given the strong epidemiologic evidence for Pb-associated all-cause and cardiovascular mortality and strong supporting evidence for Pb-associated cardiovascular effects, **there is sufficient evidence to conclude that there is a *causal relationship* between Pb exposure and total (nonaccidental) mortality.**

Table IS-10 Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and total (nonaccidental) mortality

Total (Nonaccidental) Mortality: Causal (IS.7.3.9 and Appendix 9.8)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Consistent evidence of positive associations between BLLs and total and cardiovascular mortality observed in NHANES cohorts, including some studies that controlled for a wide range of potential confounders. In addition, an analysis of the NAS reported an association between bone Pb, a metric of cumulative Pb exposure, and increased total and cardiovascular mortality in older male veterans.	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 and cardiovascular mortality. Recent studies include a quasi-experimental study and nationally representative populations with low BLLs (mean <2.5 μg/dL). Uncertainties remain regarding the specific timing, duration, frequency, and level of Pb exposure that contributed to the observed associations.

BLL = blood lead level; ISA = Integrated Science Assessment; NAS = Normative Aging Study; NHANES = National Health and Nutrition Examination Survey; mo = month(s); Pb = lead; yr = year(s).

IS.7.3.10 Cancer

The 2013 Pb ISA concluded that "a causal relationship is likely to exist between Pb exposure and cancer." This determination was based on strong evidence from animal toxicological studies demonstrating effects of Pb on cancer, genotoxicity, or epigenetic modification (Table IS-11). Carcinogenicity in animal toxicological studies with relevant routes of Pb exposure were reported in the kidneys, testes, brain, adrenals, prostate, pituitary, and mammary gland, albeit at high doses of Pb. Epidemiologic studies of cancer incidence and mortality reported inconsistent results; one strong epidemiologic study demonstrated an association between BLLs and increased cancer mortality, but other studies reported weak (i.e., small magnitude and/or imprecise 95% CIs) or null associations. The consistent evidence indicating Pb-induced carcinogenicity in animal models was substantiated by the mode of action findings from multiple high-quality toxicological studies in animal and in vitro models from different laboratories.

There are no recent toxicological studies conducted at concentrations deemed relevant to this ISA (i.e., BLLs <30 μg/dL). Recent in vitro studies add to our understanding of how Pb exposures may activate the mechanistic pathways that can result in cancer, including evidence for Pb activation of mechanistic pathways mediated by oxidative stress, genotoxicity, and inflammation, as well as changes in

cell cycle regulatory genes, epigenetics, apoptosis, and necrosis (Appendix 10.3). Additionally, new areas of research involving matrix metalloproteinases and metallothioneins have emerged and provide evidence of other potential mechanistic pathways through which Pb exposure could contribute to cancer. In the absence of any new cancer bioassay studies using animal models, uncertainty remains regarding the carcinogenic potential of low levels of Pb exposure. Recent epidemiologic evidence does little to address this uncertainty. Similar to the epidemiologic evidence evaluated in the 2013 Pb ISA, recent epidemiologic studies observed inconsistent associations between Pb exposure and overall cancer mortality (Appendix 10.4.2). A limited number of recent studies evaluating Pb exposure and site-specific cancers is also inconsistent. The small body of evidence across various site-specific cancer endpoints limits the ability to judge coherence and consistency across these studies. In general, recent studies control for a wide range of potential confounders, but studies were limited by a small number of cases resulting in limited power to detect an association, a relatively short time period between exposure and outcome, potential differences in Pb exposure histories based on study location, and the use of different biomarkers of exposure. Additionally, when associations were observed, study populations most often included adults who have been exposed to higher levels of Pb earlier in life, which produces uncertainty regarding the Pb exposure level, timing, frequency, and duration contributing to the observed associations.

Given the strong support from cancer bioassay studies using animal models with high exposure concentrations and in vitro studies of mechanistic pathways indicating the carcinogenic potential of Pb exposures, **the collective evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and cancer.**

Table IS-11 Summary of evidence from epidemiologic and animal toxicological studies on Pb exposure and cancer

Cancer: Likely to Be Causal (IS.7.3.10 and Appendix 10)	
Evidence from the 2013 Pb ISA	*Evidence from the 2024 Pb ISA*
Toxicological studies consistently reported cancer incidence following chronic exposure (i.e., 18 mo or 2 yr) to high concentrations of Pb, such as 10,000 ppm Pb acetate in diet or 2,600 ppm Pb acetate in drinking water. High-quality toxicological studies in animal and in vitro models from different laboratories also provided a biologically plausible pathway through which Pb exposure could lead to cancer. Epidemiologic studies of cancer incidence and mortality reported inconsistent results.	No recent cancer bioassay studies using animal models with relevant exposure levels are available. In vitro studies provide additional evidence supporting the Pb-induced activation of diverse mechanistic pathways that are typically associated with carcinogenesis. Recent epidemiologic studies add to the inconsistent epidemiologic evidence of an association between Pb exposure and cancer mortality.

ISA = Integrated Science Assessment; mo = month(s); Pb = lead; yr = year(s).

IS.7.4 At-Risk Populations

Interindividual variation in exposure or human responses to ambient air pollution can result in some groups or lifestages being at increased risk for health effects. The NAAQS are intended to protect public health with an adequate margin of safety. In so doing, protection is provided for both the population as a whole and those at increased risk for health effects in response to exposure to a criteria air pollutant [e.g., Pb; see Preamble (U.S. EPA, 2015)]. There is interindividual variation in both physiological responses and exposure to Pb in the environment. The scientific literature has used a variety of terms to identify factors and subsequently populations or lifestages that may be at increased risk of an air pollutant-related health effect, including susceptible, vulnerable, sensitive, at-risk, and response-modifying factors (U.S. EPA, 2015). Acknowledging the inconsistency in definitions for these terms across the scientific literature and the lack of a consensus on terminology in the scientific community, "at-risk" is the all-encompassing term used in ISAs for groups with specific factors that increase the risk of an air pollutant (e.g., Pb)-related health effect in a population, as initially detailed in the 2013 Pb ISA (U.S. EPA, 2013a). Therefore, this ISA takes an inclusive and all-encompassing approach and focuses on identifying those populations or lifestages potentially "at risk" of a Pb-related health effect.

As discussed in the Preamble (U.S. EPA, 2015), the risk of health effects from exposure to Pb may be modified as a result of intrinsic (e.g., preexisting disease, genetic factors) or extrinsic factors (e.g., sociodemographic or behavioral factors), differences in internal dose, or differences in exposure to Pb in the environment. Some factors may lead to a reduction in risk and are recognized as such during the evaluation. However, to inform decisions on the NAAQS, this ISA focuses on identifying those populations or lifestages at greater risk. While a combination of factors (e.g., residential location and SES) may increase the risk of Pb-related health effects in portions of the population, information on the interaction among factors remains limited. Thus, this ISA characterizes the individual factors that potentially result in increased risk for Pb-related health effects [see Preamble (U.S. EPA, 2015)].

IS.7.4.1 Approach to Evaluating and Characterizing the Evidence for At-Risk Factors

The ISA identifies and evaluates factors that may increase the risk of a population or specific lifestage to a Pb-related health effect; this approach is described in detail in the Preamble (U.S. EPA, 2015) and is illustrated in Table IS-12. Whereas Appendices 3–10 include a discussion of some populations and lifestages in order to explicitly characterize the causal nature between Pb biomarkers of exposure and health effects based on the body of evidence (e.g., children, minority populations), this section focuses on summarizing evidence that can inform the identification of such populations and lifestages.

Table IS-12 Characterization of evidence for factors potentially increasing the risk for Pb-related health effects

Classification	Health Effects
Adequate evidence	There is substantial, consistent evidence within a discipline to conclude that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, this evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.
Suggestive evidence	The collective evidence suggests that a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage, but the evidence is limited due to some inconsistency within a discipline or, where applicable, a lack of coherence across disciplines.
Inadequate evidence	The collective evidence is inadequate to determine whether a factor results in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. The available studies are of insufficient quantity, quality, consistency, and/or statistical power to permit a conclusion to be drawn.
Evidence of no effect	There is substantial, consistent evidence within a discipline to conclude that a factor does not result in a population or lifestage being at increased risk of air pollutant-related health effect(s) relative to some reference population or lifestage. Where applicable, the evidence includes coherence across disciplines. Evidence includes multiple high-quality studies.

The evidence evaluated in this section includes relevant studies discussed in Appendix 3–Appendix 10 of this ISA and builds on the evidence presented in the 2013 Pb ISA (U.S. EPA, 2013a). Using the approach developed in previous ISAs, (U.S. EPA, 2020, 2016a, 2013a, b) recent evidence is integrated across scientific disciplines and health effects, and where available, with information on exposure and dosimetry. In evaluating factors and population groups, greater emphasis is placed on the evidence for those health outcomes for which a "causal" or "likely to be causal" relationship is concluded in Appendix 3−Appendix 10 of this ISA (see Section IS.7.3).

As discussed in the Preamble (U.S. EPA, 2015), consideration of at-risk populations includes evidence from epidemiologic and animal toxicological studies, in addition to relevant exposure-related information. Regarding epidemiologic studies, the evaluation focuses on those studies that include stratified analyses to compare populations or lifestages exposed to similar air pollutant concentrations within the same study design along with consideration of the strengths and limitations of each study. Other epidemiologic studies that do not stratify results but instead examine a specific population or lifestage can provide supporting evidence for the pattern of associations observed in studies that formally examine effect measure modification.

Effect modification occurs when the effect of interest differs between subgroups or strata (Rothman et al., 2012). When a risk factor is an effect modifier, it changes the magnitude of the association between exposure to Pb and the outcome of interest across those strata or subgroups. For example, the presence of a preexisting disease or indicator of low socioeconomic status (SES) (e.g., educational attainment, household income) may act as an effect modifier if it is associated with

increased or decreased risk of Pb-related health effects. Thus, evidence of effect modification can help identify at-risk factors or potentially at-risk populations.[5]

Inference can be particularly strong from studies that consider the potential impacts of effect modification, especially when the modifying factors are coherent with information from other lines of evidence regarding the biological pathways connecting Pb exposures with particular health effects. Traditional modeling approaches, such as stratification and interaction terms, can identify individual effect modifiers (e.g., age groups or preexisting diseases), while emerging modeling approaches can identify a set of complex moderation functions. Preference in this section is given to studies articulating and justifying assumptions of effect modification and to studies with appropriate diagnostics (e.g., multiple comparisons) accounting for potentially spurious findings.

Similar to the characterization of evidence in Appendix 3−Appendix 10, the greatest emphasis is placed on patterns or trends in results across studies. Experimental studies in animals that focus on factors, such as genetic background or preexisting disease, are evaluated because they provide coherence and can support the biological plausibility of effects observed in epidemiologic studies. Also evaluated are studies examining whether factors may result in differential exposure to Pb and subsequent increased risk of Pb-related health effects. Additionally, physiologic factors that may influence the internal distribution of Pb are also considered. Conclusions are made with respect to whether a specific factor increases the risk of a Pb-related health effect based on the characterization of evidence using the framework detailed in Table III of the Preamble (U.S. EPA, 2015), and presented in Table IS-12.

IS.7.4.2 Summary of Population Characteristics and Other Factors Potentially Related to Increased Risk of Pb-Related Health Effects

The 2013 Pb ISA (U.S. EPA, 2013a) concluded that there was adequate evidence to classify children, minority populations, individuals in proximity to Pb sources, individuals living in residences with factors contributing to increased house dust Pb levels, and those with a certain nutritional status as populations at increased risk of Pb-related health effects. These conclusions were based on the consistency in findings across studies, as well as on coherence of results from different scientific disciplines. Some populations may be at increased risk of Pb-related health effects mostly due to increased Pb exposure. Recent studies provide additional evidence that minority populations, children, those in proximity to Pb sources, and those with certain nutritional excesses or deficiencies are at

[5]Effect modification may also inform causality determinations in several ways. Consistent evidence that at least one population subgroup is at risk of a Pb-related health effect provides strong support for causality determinations. Evidence for effect modification can also explain heterogeneity in results across studies, which could reduce uncertainties regarding inconsistent evidence. Finally, effect modification can provide supporting information on mechanisms (e.g., genetic polymorphisms or microbiome profiles) contributing to Pb-related health effects. Notably, the lack of evidence for effect modification where there is otherwise evidence of a Pb-related health effect in the general population does not weaken the overall evidence supporting a causality determination.

increased risk for Pb-related health effects. There is relatively little recent evidence to add to the evidence presented in the 2013 Pb ISA regarding individuals living in areas with certain residential factors (Table IS-13).

Several recent large epidemiologic studies, including some longitudinal studies, evaluated health effects among certain racial/ethnic groups or stratified results by race/ethnicity. Results from these studies expand the current knowledge base from the 2013 Pb ISA to provide further support of the relationship between Pb biomarkers and health effects (mainly increased concurrent BP and hypertension) among Black and Asian populations. However, there remains uncertainty regarding the level, timing, frequency, and duration of Pb exposure contributing to the observed associations. Similarly, recently available evidence among children further elucidates the increased risk children can experience from elevated exposures to Pb. Additionally, those living in proximity to a Pb sources (e.g., industrial sources of Pb) are not only at increased risk of elevated Pb biomarker levels, due to increased Pb exposure, but also increased risk of negative Pb-related health outcomes, as was demonstrated in the 2013 Pb ISA. Lastly, the recent evidence further supports and adds to the collective evidence presented in the 2013 Pb ISA that the presence of absence of certain nutrients (e.g., reduced intake of Ca^{2+} and Fe) may increase Pb-related health effects, while other nutrient deficiencies or surpluses may decrease the risk of a Pb-related health effect among certain populations.

Since the 2013 Pb ISA, recent research has expanded the evidence bases for several factors, which were originally classified as providing suggestive evidence of a population or lifestage that increases the risk of Pb-related health effects. Specifically, at the time of the 2013 Pb ISA there were a limited number of studies that evaluated genetic variants in relation to the effects of Pb exposure on a population. However, recent studies consider several additional genetic variants, and evidence collected as a whole further elucidates differential effects among certain segments of the population with genetic variants. Additionally, more evidence is available related to the impacts of stress on the health effects of Pb exposure. Taken together, recent studies, in combination with studies evaluated in the 2013 Pb ISA, provide adequate evidence that high stress levels modify the associations between Pb exposure and health effects.

Table IS-13 Summary of evidence for population characteristics and other factors potentially related to increased risk of Pb-related health effects

	Conclusions from 2013 Pb ISA	Conclusions from the 2024 Pb ISA
Adequate evidence (2024 Pb ISA)		
Race/ethnicity	Compared with white populations, minority populations were observed to be more at risk of Pb-related health effects. Studies of race/ethnicity provide adequate evidence that race/ethnicity is an at-risk factor based on the higher exposure observed among minority populations and some modification observed in studies of associations between Pb levels and health effects.	Recent exposure studies demonstrate that non-Hispanic Black children consistently have higher than average BLLs, particularly when compared with Hispanic and non-Hispanic white children, even though overall BLLs are dropping. Recent, large epidemiologic studies conducted in the United States expand upon previous evidence indicating that race/ethnicity is an effect measure modifier for Pb-related health outcomes.
Childhood	In consideration of the evidence base (e.g., stratified and longitudinal analyses) and integrating across disciplines of toxicokinetics, exposure, and health, there is adequate evidence to conclude that children are an at-risk population.	Recent evidence supports previous conclusions and extends findings among different childhood age groups.
Proximity to Pb sources	Epidemiologic studies report consistent positive associations between increased Pb exposure and associated health effects among those in proximity to Pb sources, including areas with large industrial sources.	Recent epidemiologic evidence further supports prior conclusions for both increased exposure and increased risk of health effects in proximity to Pb sources.
Nutrition	Epidemiologic and toxicologic studies provide consistent evidence that certain nutritional factors can increase or decrease the association between Pb exposure and certain Pb-related health effects.	Epidemiologic and toxicologic studies provide consistent evidence that certain nutritional factors can increase or decrease the association between Pb exposure and certain Pb-related health effects.
Residential factors	Findings suggest positive associations between increased blood Pb and increased house dust Pb levels.	Recent information does not inform or change prior conclusions.
Genetics	Few genetic variants have been observed in epidemiologic and controlled human exposure studies to affect the risk of Pb-related health outcomes and support is provided by animal toxicological studies of genetic factors.	Additional genetic variants, epigenetic modifications, and gene expression factors have been found to interact with Pb-related health outcomes.
Stress	Stress was evaluated as a factor that potentially increases the risk of Pb-related health effects (e.g., cognitive function in adults and hypertension), and while limited by the small number of epidemiologic studies, increased stress was observed to exacerbate the effects of Pb. Toxicological studies supported this finding.	Recent evidence informs prior conclusions and extends the results to children. Studies observed that high levels of maternal stress exacerbated the effect of prenatal Pb exposure on several neurodevelopmental domains, including language. Toxicological studies provide support for the interaction between maternal stress and Pb-related cognitive effects by sex.

	Conclusions from 2013 Pb ISA	Conclusions from the 2024 Pb ISA
Suggestive evidence (2024 Pb ISA)		
Older adulthood	Evidence, based on limited epidemiologic evidence but support from toxicological studies and differential exposure studies, is suggestive that older adults are potentially at risk of Pb effects. However, there are uncertainties related to the exposure profile associated with the effects in older populations.	Recent information does not inform or change prior conclusions.
Sex	Potential evidence suggests that adolescent and adult males typically demonstrate higher BLLs, although evidence regarding health outcomes is limited due to inconsistencies in whether males or females are at greater risk of certain outcomes in relation to Pb	Recent evidence informs prior conclusions, but still contains inconsistencies in presented results.
Preexisting disease	There are a limited number of epidemiologic studies that suggest preexisting diabetes modifies Pb effects on specific health effects (e.g., renal function or cardiovascular outcomes)	Recent information does not inform or change prior conclusions.
SES	Studies of SES and its relationship with Pb-related health effects are few and report inconsistent findings regarding low SES as a potential at-risk factor. Overall, the evidence is suggestive that low SES is a potential at-risk factor for Pb-related health effects.	Recent information does not inform or change prior conclusions.
Other metals	High levels of other metals, such as Cd and Mn, were observed to result in greater effects for the associations between Pb and various health endpoints (e.g., renal function, cognitive function in children), but overall, the evidence was limited.	Limited recent evidence informs prior conclusions. Hg and As were also found to interact with Pb-related cognitive functions.
Inadequate evidence (2024 Pb ISA)		
Smoking status	There are a limited number of studies and insufficient coherence for differences in Pb-related health effects by smoking status.	Recent information does not inform or change prior conclusions.
BMI	A small number of studies provide inadequate evidence that there may be BMI-related increase in risk of Pb-related health effects for some outcomes.	Recent evidence suggests modification of Pb-related health effects by overweight status.
Alcohol consumption	A small number of studies provide inadequate evidence that there may be alcohol-related increases in Pb-related health effects for some outcomes.	Recent information does not inform or change prior conclusions.

	Conclusions from 2013 Pb ISA	Conclusions from the 2024 Pb ISA
Maternal self-esteem	A small number of studies related to the relationship between Pb exposure and infant development suggested that maternal self-esteem modified the association, but the results were inconsistent, especially across other health outcomes.	Recent information does not inform or change prior conclusions.
Cognitive reserve	Limited epidemiologic evidence suggests that cognitive reserve may differentially impact the association between Pb exposure and Pb-related health outcomes. No additional evidence from the 2013 Pb ISA expanded the assessment of this factor.	Recent information does not inform or change prior conclusions.

As = arsenic; BLL = blood lead level; BMI = body mass index; Cd = cadmium; Mn = manganese; Hg = mercury; ISA = Integrated Science Assessment; Mn = manganese; Pb = lead; SES = socioeconomic status.

IS.7.4.2.1 Race/Ethnicity

Race is widely acknowledged to be a social construct, not a fixed biological (Payne-Sturges et al., 2021). Observed differences in exposures and/or outcomes across racial groups, therefore, are likely to reflect race as a proxy measure for a complex set of factors that result from these societal constructs (e.g., nutrition, housing opportunity, access/barriers to health care). This ISA evaluates and synthesizes existing research on the health and welfare effects of exposure to Pb, and many studies evaluated herein examine racial disparities in environmental exposure and human health, but do not empirically assess the underlying complexities that contribute to said disparities. Identifying racial disparities is an important step in recognizing populations at increased risk to the health effects of Pb but should also be considered in the context of the specific underlying factors that might explain these differences in exposures and/or outcomes. This section describes racial and ethnic disparities in Pb exposure and health effects, while some of the ensuing sections address other factors that may be impacted by social constructs of race (i.e., proximity to sources, nutrition, and stress).

Historically, racial and ethnic differences in exposures to environmental Pb have been evident. Both the 2006 Pb AQCD and the 2013 Pb ISA presented consistent evidence that Black populations have historically had relatively higher blood and bone Pb levels compared with white and other minority populations. While the 2013 Pb ISA reported that racial and ethnic gaps in mean blood and bone Pb levels have gradually narrowed over time, Black populations continue to typically have higher Pb exposures and body burdens compared with white populations. Recent evidence from 2011–2018 NHANES cycles indicates that non-Hispanic Black populations generally had BLLs higher than the national average, but in more recent years, average BLLs in non-Hispanic Black populations were lower than in non-Hispanic white populations (Appendix 2.4). Moreover, in some years, Asian populations had the highest mean BLLs when compared with other racial/ethnic groups. Nonetheless, non-Hispanic Black children are

consistently the group with the highest BLLs, although both overall differences and differences among groups are declining.

The 2013 Pb ISA concluded that minority populations, specifically non-Hispanic Black populations, are at an increased risk of health effects related to Pb exposure, compared with white populations. This conclusion is supported by several longitudinal and cross-sectional analyses. Recent large epidemiologic studies conducted in the United States expand on evidence from the 2013 Pb ISA and provide further support for an association between Pb exposure and health outcomes among minority populations. Specifically, several analyses using NHANES data reported increases in BP among non-Hispanic white individuals and non-Hispanic Black individuals (Appendix 4.3.1.1.1). However, increases in BP and hypertension prevalence were consistently larger among non-Hispanic Black individuals. These findings held true across several nationally representative cross-sectional studies. Taken together, the evidence suggests that in addition to having higher BLLs, associations between blood Pb and BP and hypertension are larger among non-Hispanic Black populations when compared with Hispanic or non-Hispanic white populations. However, due to the cross-sectional nature of these studies, the observed racial differences may also reflect a history of greater exposure to Pb among non-Hispanic Black populations that is not fully captured in the concurrent BLL metric. Racial differences were also noted for associations of Pb exposure and neurodevelopmental outcomes in children, but the evidence was limited to a single study. Overall, recent evidence confirms and extends the previous ISA's findings, indicating increases in Pb biomarker levels and a differential association between Pb exposure biomarkers and changes in BP or hypertension status, and potentially neurodevelopmental outcomes in children based on race/ethnicity.

IS.7.4.2.2 Childhood

Historically, children have been known to be at particularly higher risk for Pb-related health effects. The 2013 Pb ISA provided a plethora of evidence indicating a greater likelihood of Pb-related health outcomes among children. Previous toxicokinetic studies established that Pb can cross the placenta and disrupt the developing nervous system of the fetus. Additionally, studies have shown that children's behaviors and activities (including increased hand-to-mouth contact, pica behavior, crawling, and poor handwashing), differences in diets (e.g., consumption of breast milk), and biokinetic factors may place them at greater risk for exposure. There was strong evidence for Pb-related cognitive deficits and behavioral problems across gestation, childhood, and into adolescence. Among adolescents, Pb exposure was linked to delinquent or criminal behavior, delays in pubertal onset, and renal effects. However, uncertainty exists regarding the timing and duration of Pb exposure on observed health effects because of the high levels of Pb in the adolescent populations studied. Several studies reported evidence for Pb-related increases in immunosuppression, immune sensitization, and allergic responses in children. Associations were also found for increased anemia and reduced RBC function and survival. Children with higher BLLs were also reported to be at higher risk for dental caries.

Recent evidence extends support for Pb-related decrements in FSIQ, infant neurodevelopment, learning, memory, executive function, and academic performance/achievement in children. Several recent studies assessed timing of exposure by comparing associations between health outcomes and Pb levels measured during different exposure windows, including during gestation, birth, early-life, and concurrent exposures. There is no consistent pattern for critical exposure windows in the recent evidence base, which is consistent with the heterogeneity of results observed for different timing and duration of exposures in studies evaluated in the 2013 Pb ISA. Toxicological studies and epidemiologic studies examining modification by genetic/epigenetic factors, coexposure to other metals, or maternal stress indicate that time window sensitivities may be linked with biological, environmental, and psychosocial variables that operate at different timepoints during development. A few studies provide evidence for the persistence of effects of prenatal or early-life Pb exposure, noting early childhood cognitive deficits that continue into late adolescence. Furthermore, two animal studies reported Pb-induced cognitive function effects with longer exposure durations that spanned multiple developmental periods. Additionally, several epidemiologic studies indicated nonlinear C-R relationships between BLLs and cognitive function in children, which may be explained by unmeasured confounding or interaction by sex, genetics, underlying conditions, sociodemographics, and timing or duration of exposure. Most studies, however, generally supported dose-dependent cognitive function decrements at BLLs <30 μg/dL.

Additional recent studies find strong evidence for Pb affecting externalizing behaviors in children, including through influence on attentional deficits, impulsivity, hyperactivity, conduct disorders, aggression, and criminal behavior. Similarly, gestational, postnatal, adolescent, and average childhood (from birth to ages 4–5 or 11–13 years) Pb biomarker concentrations are associated with internalizing behaviors, such as anxiety and depression. Both gross and fine motor function are also affected, in line with previous findings involving oxidative stress, inflammation and Ca^{2+} signaling, impaired neuron development, synaptic changes, and neurotransmitter changes with increased Pb exposure. No clearly defined pattern exists regarding a specific sensitive exposure window regarding these health effects, although a few toxicological studies report greater decrements in motor function in association with gestational Pb exposure.

Although the 2013 Pb ISA found support for Pb-related immune effects in children, recent evidence was less consistent. Results for immunosuppression are consistent with previous findings, but the body of literature regarding immune sensitization and allergic responses was generally null. On the other hand, recent evidence supports results from previous studies, reporting associations between Pb exposures and decreased RBC survival and function, including increased prevalence of anemia among children with mean BLLs <10 μg/dL.

Recent epidemiologic studies also continue to report consistent associations between BLLs and delayed puberty among male and female adolescents. Some studies suggest that as BLLs decline, the association between blood Pb and age of menarche may be attenuated by potential confounders such as

body weight and adiposity. Of note, there is some evidence that childhood BLLs may affect the function of insulin-like growth factor, which could lead to delays in growth and pubertal onset in adolescent boys.

Although no recent toxicological studies have examined the relationship between Pb exposure and teeth, several recent epidemiological studies among large populations reinforce previous conclusions of increased dental caries in association with higher BLLs in early childhood.

Overall, substantial toxicokinetic, exposure, and health evidence continues to support the previous conclusion that children are at increased risk for the health effects of Pb.

IS.7.4.2.3 Proximity to Pb Sources

Studies from the 2013 Pb ISA provided sufficient evidence that living near Pb sources, including large industrial sources and urbanized areas with Pb-contaminated soils, is associated with increased Pb exposure. Additionally, aviation fuel was highlighted as a major source of Pb emissions in ambient air (Appendix 1.2). A study in North Carolina reported inverse associations of children's BLLs with proximity of their residence to airports (where leaded aviation fuel may be used). Recent evidence continues to support increased Pb biomarker levels associated with proximity to airports and other Pb sources. Additionally, recent evidence also implies that a reduction in environmental Pb at a particular source (e.g., superfund site) is associated with decreases in the BLLs of children in proximity to the original source.

In addition to increased biomarker Pb levels being associated with proximity to Pb sources, several recent epidemiologic analyses have reported increased Pb-related health effects among those in proximity to industrial sources of Pb. Specifically, studies comparing populations within certain distances of a Pb source indicated increases in BP and decreases in renal function, though they did not control for additional metals in their analyses. Additionally, recent studies have assessed child IQ and observed small reductions in child intelligence in closer proximity to Pb sources.

IS.7.4.2.4 Nutrition

The 2013 Pb ISA and prior AQCDs concluded that by limiting or outcompeting Pb for absorption in the gastrointestinal tract, diets rich in minerals including Ca^{2+}, Fe, and zinc give some protection from increased BLLs. Additionally, previous epidemiologic and toxicological investigations indicated that people with Fe deficits are at increased risk for Pb-related health consequences. Therefore, there are sufficient data from several fields showing certain nutritional factors affect the risk of Pb exposure and health effects in a population.

Recent epidemiologic studies continue to explore other modifications of Pb-related health effects by diet or nutritional intake. An evaluation of the impact of two different diet types (Prudent: high

amounts of fruit, legumes, whole grains, tomatoes, seafood, poultry, cruciferous vegetables, dark-yellow vegetables, leafy vegetables, and other vegetables; Western: high intake of processed meat, red meat, refined grains, butter, high-fat dairy products, eggs, and fries) was conducted on the relationship between bone Pb levels and cardiovascular outcomes. In this study, patella Pb measurements among those with low prudent diets were associated with a higher risk of coronary artery disease compared with those with a high prudent diet. This difference was not evident when assessing tibia Pb measurements.

Recent toxicological studies investigated the impact of various dietary factors on the effects of Pb on neurological outcomes. A recent study reported that in comparison with a standard diet, a high-fat diet exacerbated the effect of Pb on learning deficits during the first stages of learning. Another study, which supplemented Pb exposure in mice with green tea extract, reported that green tea ameliorated the negative impact of Pb exposure on both learning and memory. Additionally, one study reported probiotic supplementation partially mitigates the cognitive deficits observed in an active avoidance paradigm. Given the disparate dietary factors examined across these studies, conclusions on the modifying potential of any individual factor remains uncertain. However, when considered more generally, there is consistent toxicological evidence that dietary factors modify the cognitive effects of Pb exposure.

Adding on to previous evidence from the 2013 Pb ISA, recent studies have connected Fe deficiency to immune system effects in a few toxicological studies. A few studies that focused on different outcomes reported decreases in anti-TT-specific IgM and mucosal IgA levels in rats that were fed an Fe-deficient diet for 4 weeks and administered Pb acetate in drinking water for 4 weeks after confirming Fe deficiency. Taken together, these studies support a role for dietary factors in the immunotoxicity of Pb, but the diversity of nutritional factors investigated among a small number of studies makes it difficult to determine their relative importance. In summary, the evidence continues to indicate increased risk for populations with reduced intake of Ca^{2+} and Fe, and potential risk associated with other dietary factors.

IS.7.4.2.5 Genetics

Evidence from the 2013 Pb ISA suggested that various genetic variants may modify the relationship between Pb and various health effects. According to these previous epidemiologic and toxicological studies, populations with specific ALAD variants may have increased risk of Pb-related health effects. Variants of vitamin D receptor (VDR), dopamine receptor D4, glutathione S-transferase (GST) Mu 1, tumor necrosis factor α, endothelial nitric oxide synthase, and the hemochromatosis gene (HFE) were other genes studied, and presence of their variants may also affect the risk of Pb-related health effects. Overall, the potential for genetic variants to modify Pb-related health outcomes were investigated in a small number of studies. Therefore, despite some evidence that certain genetic variants may modify Pb-related health effects, there are still some uncertainties in the evidence.

Several recent studies in children add to the small body of previous evidence. The effect of Pb exposure on children's IQ was reported to be weaker (i.e., smaller magnitude) among those with the ALAD1 genotype (median BLL: 1.0 μg/dL). This study identified unique glutamate ionotropic receptor N methyl D aspartate-type subunit (GRIN)2A and GRIN2B variations that exacerbated Pb-related deficiencies in learning, memory, and executive function, with a greater impact observed in boys. Another recent study observed that prenatal Pb exposure was linked to DNA methylation in regions including genes involved in neurodevelopment. Overall, there is limited evidence of interactions and increased risk of relationships between genes and Pb exposure in children.

Several recent studies in adults have shown that certain genetic polymorphisms can be important in assessing the potential for increased risk of Pb biomarker levels and of Pb-related health effects. Specifically, VDR was evaluated in a longitudinal study examining the association between pulse pressure (PP) and bone and BLLs. Variations in VDR genes have the potential to influence Pb accumulation, absorption, and retention in the body. At the initial visit (baseline), an interquartile range increase in either tibia or patella Pb was associated with an increased PP among those with the variant (opposed to ancestral) genotype (single nucleotide polymorphisms [SNPs] in *Bsm1*, *Taq1*, *Apa1*, or *Fok1*). While the strength of the association between PP and tibia Pb diminished over time (10-year follow-up), the three-way interaction terms between bone Pb, VDR receptor type, and time-since-baseline was almost null, indicating that VDR consistently modifies the association between bone Pb and PP. In another recent study, several other genes and proteins were also evaluated as effect measure modifiers of the relationship between bone Pb measurements and incident CHD, including: ALAD, HFE, heme oxygenase-1 (HMOX1), VDR, apolipoprotein E (APOE), GSTs, and renin-angiotensin. These genes and the proteins they encode appear to play a role in influencing Pb uptake and retention, as well as altering Pb toxicity. The authors constructed two sets of genetic risk scores summing either all of the measured SNPs or a subset of SNPs that were observed to modify the relationship between Pb exposure and CHD. The association between patella Pb levels and incident CHD was notably stronger in participants in the highest tertiles of the two genetic risk scores compared with those in the lowest, suggesting that genetic loci may modify Pb-related CHD risk.

Recent epidemiologic studies on gene regulation during pregnancy are limited but provide insight on potential mechanistic pathways through which Pb may impact pregnancy. In one study, the association between maternal Pb levels in blood, patella, and tibial bone and microRNA (miRNA) expression in the cervix during the second trimester of pregnancy was assessed. Expression of two of the miRNAs were associated with maternal second trimester BLLs. Another study assessed the association of BLLs during pregnancy with mitochondrial DNA (mtDNA) content in cord blood, which is a sensitive marker of mitochondrial function and oxidative stress. Maternal Pb levels during the second trimester were associated with higher mtDNA content. As BLLs may differ by ALAD (aminolevulinic acid dehydratase) genotype, one study compared growth outcomes in children with ALAD1–1 and ALAD1–2/2–2. There were negative associations between baseline BLLs and height, knee height, and height-for-age z-score

(HAZ). The observed associations between BLLs and height, knee height, and HAZ were stronger (i.e., larger magnitude) in children with ALAD1–2/2–2 compared with ALAD1–1.

Overall recent studies have added to the body of evidence on genetic variants previously found to modify the risk of Pb-related health effects. Recent studies have also identified other variants – including but not limited to ALDA1, N-methyl D aspartate, HFE, VDR, HMOX1, and APOE – that may modify the relationship of Pb exposure and human health effects and predispose certain populations to greater risk of Pb-related health effects.

IS.7.4.2.6 Stress

The 2013 Pb ISA evaluated stress as a factor that could modify the association with Pb-related health outcomes. Specifically, these effects were most commonly evaluated within studies evaluating cognitive function. More recent evidence expands the knowledge base for stress as a factor that can increase the risk of Pb-related health effects.

Several recent studies among children evaluated cardiovascular outcomes associated with Pb biomarkers as a response to acute stressors. One study indicated that a higher level of Pb exposure during early childhood (mean age of 2.6 years) was related to a greater total peripheral resistance response to acute stress years later (at 9.5 years of age). Another study indicated significant decreases in HRV associated with BLLs, following an acute stressful stimulus in young (aged 3–5) children.

Maternal stress has also been evaluated within studies assessing the relationship between biomarkers of Pb exposure and neurologic and developmental outcomes among offspring. Maternal stress appeared to substantially modify the associations between Pb exposure biomarkers and neurodevelopment among children. Specifically, high maternal stress appeared to exacerbate the effect of prenatal Pb exposure on neurodevelopment in several domains, including language. However, epidemiologic and toxicological studies assessing birth outcomes did not observe an effect of maternal stress on relationships between Pb and adverse birth outcomes. Overall, the majority of recent evidence strengthens the previous conclusion that increased stress exacerbates the effects of Pb.

IS.8 Evaluation of Welfare Effects of Pb

Effects of Pb relevant to the secondary NAAQS are observed across ecological endpoints common to terrestrial, freshwater, and saltwater biota. Those endpoints include reproduction, growth, survival, neurobehavioral effects, hematological effects, and physiological stress, and occur at multiple scales of biological organization from the cellular to the ecosystem. The atmosphere and terrestrial and aquatic ecosystems are interconnected, with transfer of Pb taking place between each of these systems (Appendix 11.1.2). Although Pb is present in the natural environment, it has no known biological function

in plants or animals. In some instances, depending on the form of Pb and prevailing environmental chemistry at a particular geographic location, Pb is taken up by biota where it can lead to a biological response. Pb exposure of organisms can be via one or more pathways (e.g., uptake from soil or water, ingestion). For Pb to interact with a biological membrane and be taken up into an organism it must be bioavailable (Appendix 11.1.6). Generally, the greater amount of Pb available as the free Pb ion, the greater the bioavailability. Factors such as pH, dissolved organic carbon (DOC) or water hardness in aquatic environments, and pH, cation exchange capacity (CEC), or aging in terrestrial environments often interact strongly with Pb concentration to modify its effects, primarily through their influence on bioavailability, but also sometimes through direct modification of biotic effects. Uptake, subsequent bioaccumulation, and toxicity of Pb varies greatly between species and across taxa, as characterized in the 1977 AQCD (U.S. EPA, 1986b), the 2006 Pb AQCD (U.S. EPA, 2006), the 2013 Pb ISA (U.S. EPA, 2013a), and further supported in this ISA. In natural environments it is difficult to attribute observed effects solely to Pb due to the presence of confounding factors such as other pollutants, and additional modifying factors that affect Pb bioavailability and toxicity. Furthermore, the portion of Pb from atmospheric sources is usually not known. The welfare effects of Pb summarized in the following sections are presented in greater detail in Appendix 11, Effects of Lead in Terrestrial and Aquatic Ecosystems. Appendix 11 includes an overview of concepts related to ecosystem effects of Pb (Appendix 11.1) and evidence for effects of Pb on organisms inhabiting terrestrial (Appendix 11.2), freshwater (Appendix 11.3) and saltwater (Appendix 11.4) environments, especially since the 2013 Pb ISA.

Initial perturbations associated with exposure to Pb such as cytological or biochemical changes may lead to effects at higher levels of biological organization (i.e., from the subcellular and cellular level through the individual organism and up to ecosystem-level processes). The alteration of cellular ion status (including disruption of Ca^{2+} homeostasis, altered ion transport mechanisms, and perturbed protein function through displacement of metal cofactors) appears to be the major unifying mode of action underlying all subsequent modes of action of Pb toxicity in plants, animals, and humans (Lassiter et al., 2015; U.S. EPA, 2013a). Molecular mechanisms linked to oxidative stress may induce DNA damage and generation of reactive oxygen species leading to protein modification, lipid peroxidation, and altered enzyme response. For ecological endpoints in this ISA, biochemical (e.g., enzymes, stress markers) responses at the suborganism-level of biological organization are grouped under the broad endpoint of "physiological stress," while organism-level effects include reproduction, growth, and survival. These endpoints in turn have the potential to alter population, community, and ecosystem levels of biological organization (Suter et al., 2004). The definition of an ecosystem used in this ISA is "a functional unit consisting of living organisms, their nonliving environment, and the interactions within and between them" (Allwood et al., 2014). Ecosystems can be natural, cultivated, or urban (U.S. EPA, 1986b) and may be defined on a functional or structural basis (Appendix 11.1.4). Ecosystem structure includes species abundance, richness, distribution, diversity, evenness, and composition measured at the population, or, community scales, which may be further defined by spatial boundaries such as those relating to an ecosystem, region, or global scale. Pollutants, such as Pb, can affect the ecosystem structure at any of these scales, corresponding to levels of biological organization (Suter et al., 2005). Causality

determinations for ecological effects of Pb in this ISA use biological scale as an organizing principle to summarize effects on vegetation, invertebrates, and vertebrates in terrestrial, freshwater, and saltwater environments.

IS.8.1 Summary of Effects on Terrestrial Ecosystems

In terrestrial ecosystems, non-air media can receive Pb from atmospheric deposition or other sources. Once deposited, Pb can be resuspended into the air or transferred among other environmental media (Appendix 1.3). Since the 2013 Pb ISA (U.S. EPA, 2013a), evidence has continued to accrue for many of the effects of Pb on terrestrial ecosystems reported in that ISA and previous U.S. EPA assessments. In particular, effects previously documented were observed at exposures lower than in previous studies. This additional supporting evidence includes investigations of effects on species and communities that had not been previously studied, but the additional evidence is not sufficient to change any of the causality determinations for terrestrial ecosystems that were reached in the 2013 Pb ISA.

Studies published since the 2013 Pb ISA (U.S. EPA, 2013a) continue to support previous findings that plants generally sequester larger amounts of Pb in roots relative to shoots and that there are species, ecotype, and cultivar-dependent differences in the uptake of Pb from soil and the atmosphere, as well as in the translocation of sequestered Pb (Appendix 11.2.1). In the 2013 Pb ISA and previous assessments, Pb exposure was found to result in plant physiological stress and deficits in plant growth, whereas evidence of effects on plant survival and reproduction was mixed. Recent studies have continued to demonstrate various deleterious physiological effects of Pb exposure on plants, particularly oxidative stress. Strong uncertainties also remain regarding the concentrations at which these effects would be observed in the environment. Recent studies have examined the protective effects of mycorrhizae and of some plant nutrients when added in excess of the minimal requirements of the plants.

In terrestrial invertebrates, the 2013 Pb ISA (U.S. EPA, 2013a) and previous assessments reported evidence of effects on invertebrates that included responses of antioxidants, reductions in growth and survival, as well as decreased fecundity. Neurobehavioral aberrations and endocrine impacts were also found, as well as incomplete evidence of hematological effects. Second-generation effects were also observed. Evidence published since then provides additional support for the effects of Pb exposure on organismal and suborganismal responses including a decrease in survival as well as decreased growth and fecundity (Appendix 11.2.4.3). Recently published studies on physiological responses to Pb include decreases in protein and lipid content and increases in malondialdehyde in earthworms. Acetylcholinesterase activity decreased in response to Pb in snails and honeybees while the effects on protein, glycogen, other enzymes, and GST responses were variable depending on the site or species examined. Several new studies quantified changes in feeding and foraging behavior in bees following Pb exposure. Evidence also suggests that in earthworms, Pb exposure can have lasting effects on growth even postexposure and slow the time to maturation. Pb exposure delayed onset of the breeding season and

shortened duration in isopods, as well as influenced mate selection in fruit flies. Evidence published after the 2013 Pb ISA (U.S. EPA, 2013a) includes new organisms as well as modifying factors of organism response such as habitat, exposure history, and seasonality.

Effects of Pb observed in terrestrial vertebrates include decreased survival and reproduction, as well as neuro-behavioral effects and effects on development (U.S. EPA, 2006). The 2013 Pb ISA (U.S. EPA, 2013a) also provided evidence for Pb effects on hormones, blood, and other physiological and biochemical variables (U.S. EPA, 2013a). Evidence of effects on growth was limited. Studies published since the 2013 Pb ISA provide additional evidence for effects on suborganism- and organism-level endpoints, and specifically on hematological and physiological endpoints (Appendix 11.2.4.4). New studies have expanded upon the relationship between Pb exposure and ALAD activity by adding more species of birds, amphibians, and mammals to the evidence base. Additional evidence of oxidative stress has been gathered, as well as evidence of effects on corticosterone levels and immunity in birds. Recent literature continues to add to evidence relating to reproductive effects at both the organism and suborganism levels including effects on lifetime breeding success and some specific secondary sexual traits. New findings of behavioral effects of Pb included increased aggression in mockingbirds.

Systematic studies of the validity of using results of experiments with addition of soluble salts of Pb to soil for estimating effects of Pb exposure under field conditions have continued since the 2013 Pb ISA. As in previous work, recent experiments showed that the form of Pb, pH, CEC, organic carbon, Fe and Mn oxides, percolation, aging, and soil composition are all strong modifiers of toxicity. Recent studies demonstrated additional interactions among those variables and showed that their effects are at times mediated by additional variables, such as salinity. Those studies add support to the conclusion that data from exposure-response experiments in terrestrial environments conducted using spiking of soils with soluble salts of Pb are unlikely to generate accurate estimates of effects in contaminated natural environments (Appendix 11.2.5). However, Oorts et al. (2021) suggested that two corrections to the results of exposure-response experiments conducted with additions of soluble salts of Pb to soil may be sufficient to derive predicted no-effect concentrations according to the European Registration, Evaluation, Authorisation and Restriction of Chemicals Regulation (European Parliament and Council, 2006).

According to the 2013 Pb ISA (U.S. EPA, 2013a) and previous assessments, effects on terrestrial communities and ecosystems observed in contaminated natural environments have included decreased species diversity, changes in floral and faunal community composition, and decreasing vigor of terrestrial vegetation. In addition to impacts on soil microbial community function alone, interconnection of effects of Pb contamination among soil bacterial and fungal community structure, earthworms, and plant growth, have also been systematically documented. Some new evidence of the effects of Pb at the terrestrial community and ecosystem levels of biological organization has since been added. Many studies on the effects of Pb on microbial communities were reported in the 2013 Pb ISA (U.S. EPA, 2013a). Additional observational studies published since then (Appendix 11.2.4.1), many of which were anthropogenic environmental gradient studies, have continued linking Pb exposure and effects on microbial community

structure (e.g., abundance, diversity) and function (e.g., enzyme activities, respiration rates). Many found mixed (negative, positive, or null) relationships between total or bioavailable Pb soil concentration and the abundance of bacterial and fungal taxa. It remains difficult to disentangle the effects of Pb exposure on microbial communities from the effects of other soil contaminants using anthropogenic environmental gradients, as other heavy metals and soil physicochemical properties are significantly correlated with soil Pb concentration, and many of these factors also influence microbial processes. In addition to microbial communities, species interactions between tree species and their pests, and between herbaceous plants and nectar robbers, worms, and lepidopteran consumers were among the new community and ecosystem endpoints for which effects of Pb were observed (Appendix 11.2.6). Several studies found inverse relationships between Pb concentration along a pollution gradient and community structure of soil mites, potworms, nematodes, and invertebrates associated with kale plants. Although evidence for effects on growth, reproduction, and survival at the individual organism level and in simple trophic interactions makes the existence of effects at higher levels of organization likely, direct evidence is relatively sparse and difficult to quantify. The presence of multiple stressors, especially other metals, continues to introduce uncertainties in attributing causality to Pb at higher levels of organization.

IS.8.2 Summary of Effects on Freshwater Ecosystems

Freshwater organisms including algae, aquatic plants, microbes, invertebrates, vertebrates, and other biota with an aquatic lifestage (e.g., amphibians) may be exposed to Pb in aquatic environments. Inputs of Pb to freshwater ecosystems include air-related sources and non-air sources. Atmospherically derived Pb can enter aquatic systems through direct wet or dry deposition and erosional transport or resuspension of Pb from terrestrial systems (Appendix 11.1.2). Receiving water bodies include lakes (lentic systems) and rivers and streams (lotic systems). Freshwater wetlands, some of which may be inundated occasionally or constantly, also provide habitat for aquatic biota. Uptake of Pb by aquatic biota may occur via multiple exposure routes including direct absorption from the water column, ingestion of contaminated food and water, uptake from sediment porewater, or incidental ingestion of sediment (U.S. EPA, 2013a, 2006).

As described in previous U.S. EPA reviews of Pb, sensitivity to this metal can vary by several orders of magnitude across freshwater biota. Pb elicits responses in some freshwater invertebrate species at concentrations below 5 to 10 µg Pb/L (under some water conditions) while other freshwater organisms appear to be unaffected at concentrations greatly exceeding 1,000 µg Pb/L. Most of the available studies of Pb exposures in freshwater biota are laboratory toxicity tests on single species in which an organism is exposed to a known concentration of Pb, and the effect on a specific endpoint is evaluated. Concentration-response data from freshwater organisms indicate that there is a gradient of response to increasing Pb concentration and that some effects in sensitive species are observed at or near the upper limit of Pb concentrations quantified in U.S. surface waters (Appendix 11, Table 11-1). Freshwater invertebrate taxa that exhibit sensitivity to Pb include some species of gastropods, amphipods, cladocerans, and rotifers,

although the toxicity of Pb is highly dependent upon water quality variables such as DOC, hardness, and pH.

Physicochemical properties of surface waters such as hardness, DOC, and pH can be quantified, are directly related to the toxic effects, and are used in bioavailability models to predict acute and chronic toxicity (Appendix 11.1.6). As described in prior AQCDs, the 2013 Pb ISA, and this document (Appendix 11.3.2.1.1), the effect of water hardness is variable; generally, both the acute and chronic toxicity of Pb increases with decreasing water hardness as Pb becomes more soluble and bioavailable and less Ca^{2+} and Mg^{2+} ions are available to compete with Pb for binding sites. DOC has a protective effect on Pb toxicity in freshwater invertebrates and fish; newer studies generally continue to support these observations with some exceptions (Appendix 11.3.2.1.2). Since the 2013 Pb ISA, studies have further elucidated the relationship between the characteristics of humic substances and Pb bioavailability. As described in prior AQCDs and the 2013 Pb ISA, uptake and subsequent toxicity of Pb to freshwater biota can also be affected by pH, either directly or indirectly (Appendix 11.3.2.1.3). Generally, at low pH, there is more Pb^{2+} available to bind to the biotic ligand. As pH increases, there is increased formation of Pb organic (DOC) and inorganic (OH^-, CO_3^{2-}) complexes, which decrease Pb bioavailability. Since the 2013 Pb ISA, several studies have further characterized Pb complexation and adsorption under changing pH conditions, recent studies generally support the previous understanding that higher pH is protective; these findings vary by the duration of the toxicity bioassays and by taxa, however.

Biological factors that may influence freshwater organism response to Pb exposure include lifestage, genetics, and nutrition (see Section 7.2.3, 2006 Pb AQCD, Section 6.4.9, 2013 Pb ISA, and Appendix 11.3.2 of this ISA). These factors are more difficult to link quantitatively to toxicity than water chemistry variables. Often, species' differences in metabolism, sequestration, and elimination rates influence the relative sensitivity and vulnerability of exposed organisms. Uptake studies generally show that aquatic invertebrates and vertebrates accumulate Pb from water in a concentration-dependent manner and may reach an equilibrium depending on the organism's ability to eliminate or store Pb. Since the 2013 Pb ISA, several studies have examined how the activities of sediment-associated benthic invertebrates (sometimes called "bioturbators" because of the biological role they play in water column turbidity) influence Pb transfer to the water column and subsequent bioavailability to other aquatic organisms (Appendix 11.3.2.1.11). Overall, presence of these bioturbators can enhance Pb availability to organisms in the water column and potentially cause toxic effects in those organisms.

For freshwater plants and algae, studies on bioavailability and toxicity of Pb published since the 2013 Pb ISA (Appendix sections 11.3.2.2 and 11.3.4.2) continue to support previous findings that plants tend to sequester larger amounts of Pb in roots as compared with shoots and that there are species-specific differences in uptake of Pb, compartmentalization of that sequestered Pb, and plant response (U.S. EPA, 2013a, 2006). Most studies on effects of Pb in freshwater algal species reviewed in the 2013 Pb ISA and the AQCDs were conducted with nominal media exposures and effect concentrations greatly exceeded Pb reported in surface water. In the 1977 Pb AQCD, differences in sensitivity to Pb among different species

of algae were observed, and concentrations of Pb within the algae varied among genera and within a genus (U.S. EPA, 1977). The 1986 Pb AQCD (U.S. EPA, 1986b) reported that some algal species (e.g., Scenedesmus sp.) were found to exhibit physiological changes when exposed to high Pb concentrations in situ. Effects of Pb on algae reported in the 2006 Pb AQCD included decreased growth, deformation, and disintegration of algae cells, and blocking of the pathways that lead to pigment synthesis, thus affecting photosynthesis. New information since the 2013 Pb ISA includes studies on common reed (*Phragmites australis*) showing significant decreases in total biomass, photosynthesis, and rhizome growth as well as alterations in growth form and propagation strategy under Pb exposure and a study in freshwater algae based on analytically verified concentration of Pb (Appendix 11.3.4.2 and Table 11-5).

Freshwater aquatic invertebrates are generally more sensitive to Pb exposure than other taxa. Controlled studies at concentrations near the upper range of representative concentrations of Pb available from surveys of U.S. surface waters (median: 0.50 µg Pb/L; range 0.04 to 30 µg Pb/L, 95th percentile 1.1 µg Pb/L) (U.S. EPA, 2006), reviewed in the 1986 AQCD, the 2006 Pb AQCD, the 2013 Pb ISA, and this document provide evidence for the effects of Pb on reproduction, growth and survival in sensitive freshwater invertebrates, notably gastropods, cladocerans, rotifers, and amphipods. In studies reviewed in the 2013 Pb ISA the freshwater snail (*Lymnaea stagnalis*) was identified as one of the most sensitive species to Pb exposure, and more recent studies support these observations. Recent evidence further characterizes Pb effects on growth and reproduction at concentrations below 10 µg Pb/L in sensitive species of freshwater gastropods, cladocerans, rotifers, and amphipods, especially under chronic exposure scenarios (Appendix 11.3.5 and Table 11-5).

For freshwater vertebrates, early studies on waterfowl investigated exposure to Pb via accidental poisoning or ingestion of Pb shot (U.S. EPA, 1977). Studies on aquatic vertebrates reviewed in the 1986 Pb AQCD were limited to hematological, neurological, and developmental responses in fish (U.S. EPA, 1986b). In the 2006 Pb AQCD, effects on freshwater vertebrates included consideration of the role of water quality parameters on toxicity to fish, as well as limited information on the sensitivity of turtles and aquatic stages of frogs to Pb (U.S. EPA, 2006). Evidence in the 2013 Pb ISA supported the 2006 Pb AQCD conclusions that the gill is a major site of Pb uptake in fish and that there are species differences in the rate of Pb accumulation and distribution of Pb within the organism. Several studies in fish in which Pb concentration was analytically verified provide additional evidence for reproductive and developmental effects for freshwater vertebrates (Appendix 11.3.4.4.1.2). New studies continue to show distinct patterns of Pb tissue distribution in water versus dietary exposures (Appendix 11.3.2.4).

Reductions in species abundance, richness, and diversity associated with the presence of Pb in freshwater habitats are reported in the literature, usually in heavily contaminated sites where Pb (and other metal) concentrations are higher than typically observed environmental concentrations. Most evidence is from sediment-associated macroinvertebrate communities. New studies generally confirm findings in the 2006 Pb AQCD (U.S. EPA, 2006) and 2013 Pb ISA (U.S. EPA, 2013a) that transfer of Pb

through the food web is generally low (Appendix 11.3.2.5). Observational and experimental studies published since the 2013 Pb ISA continue to show negative associations between sediment and/or porewater Pb concentration and macroinvertebrate communities (Appendix 11.3.6). The evidence is expanded somewhat with studies reporting associations with Pb and periphyton abundance.

Approaches for characterizing the toxicity of Pb to freshwater biota since the 2013 Pb ISA include a proposal for updating aquatic life water quality criteria (Appendix 11.1.7.3). The existing U.S. EPA ambient water quality criteria (AWQC) for Pb for the protection of aquatic life are a criterion maximum concentration of 65 μg Pb/L (for acute exposure) and criterion continuous concentration of 2.5 μg Pb/L (for chronic exposure) at a hardness of 100 mg/L (U.S. EPA, 1985). Using the biotic ligand model (BLM) (Appendix 11.1.6) (Deforest et al., 2017) proposed acute BLM-based freshwater criteria ranging from 18.9 to 998 μg Pb/L and chronic BLM-based Pb freshwater criteria ranging from 0.37 to 41 μg Pb/L. The lowest criteria were for water with low DOC (1.2 mg/L), pH (6.7) and hardness (4.3 mg/L as $CaCO_3$), and the highest criteria were for water with high DOC (9.8 mg/L), pH (8.2) and hardness (288 mg/L as $CaCO_3$), which encompasses varying water quality conditions of North American surface waters. The updated data sets in Deforest et al. (2017) incorporated toxicity information for *L. stagnalis*, the cladoceran, *Ceriodaphnia dubia*, the amphipod, *Hyalella azteca*, and the rotifer, *Philodina rapida*; freshwater invertebrates that are relatively sensitive to Pb exposure. Compared to the number of genera used to develop the existing U.S. EPA AWQC for Pb (1984) for the protection of aquatic life, the number of genera with acute toxicity data for Pb increased from 10 to 32, and for chronic toxicity, from 4 to 13, which enabled the proposed chronic criteria to be based on bioassay data rather than an acute-to-chronic ratio. Additional advances in freshwater research since the 2013 Pb ISA have included development and evaluation of bioavailability models to predict the toxicity of acute and chronic metal mixtures, of which Pb is one component (Appendix 11.3.2.1.5). Considerable research beyond the scope of this document (Appendix 11.1.1) has focused on metal mixture assessment, including how uptake and bioaccumulation are affected in freshwater biota in the presence of multiple metals.

IS.8.3 Summary of Effects on Saltwater Ecosystems

Saltwater ecosystems encompass a range of salinities from just above that of freshwater (<1 ppt) to that of seawater (generally described as 35 ppt). These ecosystems may receive Pb from multiple sources such as contributions from direct atmospheric deposition and via inputs from terrestrial systems including runoff and riverine transport (Appendix 1). Habitats associated with coastal areas include salt marshes, estuaries, shallow open waters, sandy beaches, mud and sand flats, rocky shores, oyster beds, coral reefs, mangrove forests, river deltas, tidal pools, and seagrass beds (U.S. EPA, 2016b). Estuaries, where freshwater inflows gradually mix with salt water, are dynamic, heterogeneous environments characterized by physicochemical gradients of salinity. The Pb^{2+} ion, which is the most bioavailable form of Pb, is not common in seawater; rather, Pb primarily exists as a carbonate complex and to a lesser extent as a chloride complex (Appendix 11.4.1).

Factors affecting bioavailability of Pb to saltwater organisms (Appendix 11.4.2) are many of the same factors affecting bioavailability to freshwater biota, notably OM and pH. Since the 2013 Pb ISA, studies have further explored the effects of varying dissolved OM composition and changing pH on Pb uptake and bioaccumulation in saltwater biota. In contrast to freshwater, OM in saltwater systems does not necessarily demonstrate a protective effect and in some cases exacerbated toxicity of Pb to invertebrates (Appendix 11.4.2.1). Other factors, such as salinity, play a greater role in Pb fate, transport, and bioavailability in marine and estuarine systems, especially in dynamic estuarine environments characterized by physicochemical gradients of salinity (Appendix 11.4.2.3). Other factors that affect uptake and toxicity of Pb, such as biological adaptations by organisms, and the role of seasonality, metabolism, diet, and lifestage, are more difficult to link quantitatively to toxicity (Appendix 11.4.2).

For saltwater plants, there is relatively little information on biouptake and toxicity at concentrations of Pb typically encountered in the environment. Limited data on marine algae and saltwater plants reviewed in the 1986 Pb AQCD, 2006 Pb AQCD, the 2013 Pb ISA and a few new studies (Appendix 11, sections 11.4.2.10 and 11.4.4.2) provide evidence for species differences in Pb uptake, bioaccumulation rates and toxicity. As in freshwater plants, Pb is concentrated in root tissue, but sensitivity is species specific. Understanding of Pb effects in saltwater plants has not changed appreciably since the 2013 Pb ISA; observed effects occur at much higher Pb exposures than are found in the natural environment.

The majority of available studies of Pb effects on saltwater organisms are for invertebrate species. Uptake and subsequent bioaccumulation of Pb in marine invertebrates varies greatly between species and across taxa (U.S. EPA, 2006) (U.S. EPA, 2013a) and Appendix 11.4.2.11. In the 2006 Pb AQCD, a few effects were noted in saltwater invertebrates including differences in sensitivity to Pb in copepods, increasing toxicity of Pb with decreasing salinity in mysids, and effects on embryogenesis in bivalves (U.S. EPA, 2006). In the 2013 Pb ISA, several studies reported concentrations associated with reproductive effects in saltwater invertebrates including in a marine amphipod, a polychaete, and clams (U.S. EPA, 2013a). Several field monitoring studies with marine bivalves in the 2013 Pb ISA used ALAD as a biomarker for Pb exposure and correlated ALAD inhibition to increased Pb tissue content. Field and laboratory studies provide evidence for antioxidant response to Pb exposure; however, most effects are observed at concentrations of Pb that are higher than concentrations detected in marine environments. New information for saltwater invertebrates since the 2013 Pb ISA includes additional studies that report physiological perturbations associated with Pb exposure, including a few observations in previously untested taxa. Recent exposure-response data for saltwater invertebrates (Appendix 11.4.5 and Table 11-7) include reproductive and developmental bioassay results based on analytically verified concentration for mollusks and echinoderms, with effects reported at lower concentrations than studies included in the 2013 Pb ISA. Specifically, several embryo development bioassays for bivalves (48-hr exposure) and sea urchin (72-hr exposure) found effects at concentrations <50 µg Pb/L with no effects at concentrations <10 µg Pb/L for a few species (Markich, 2021; Romero-Murillo et al., 2018; Nadella et al., 2013).

For saltwater vertebrates, available information is largely for fish, with a few field-based studies in birds and sea turtles (Appendix 11.4.4.4). Studies published since the 2013 Pb ISA provide chronic toxicity data for several fish species, information that was previously lacking for evaluating longer-term effects of Pb on these organisms. Calculated chronic no-observed-effect concentrations (NOECs) for three saltwater fish species are <15 µg Pb/L with effects reported in the range of 15 to 30 µg Pb/L for survival (Appendix 11, Table 11-7). These studies in fish were conducted with juvenile lifestages.

For community- and ecosystem-level effects evidence from field studies in saltwater environments in the 2006 Pb AQCD and the 2013 Pb ISA, studies found either negative or null relationships between Pb and species abundance, richness, and diversity in saltwater macroinvertebrates; Pb is not the only contaminant in most observational studies, however, thereby making it difficult to separate the effects of Pb alone from other metal pollutants. Several experimental and observational studies since the 2013 Pb ISA reported negative relationships between sediment or saltwater Pb concentration and microbial abundance and diversity, while other studies found no relationship (Appendix 11.4.4.1). Additionally, some studies since the 2013 Pb ISA find reductions in foraminiferal and/or meiofaunal community richness, diversity, and/or abundance associated with higher concentrations of Pb in sediment and water, while others find positive or null correlations (Appendix 11.4.6). New observational studies in saltwater systems generally confirm findings in the 2006 Pb AQCD (U.S. EPA, 2006) and 2013 Pb ISA (U.S. EPA, 2013a) of little transfer of Pb through the food web, with Pb concentration decreasing with increasing trophic level (Appendix 11.4.2.13).

Since the 2013 Pb ISA, there are new toxicity data for saltwater biota that address some of the uncertainties at that time. There are new studies reporting effects of Pb on survival in saltwater vertebrates (Appendix 11.4.5) and additional evidence for reproductive and developmental effects in saltwater invertebrates (Appendix 11.4.5). Furthermore, in many of the studies supporting these effects, the concentration of Pb in the exposure media is analytically verified. This information reduces uncertainties identified in the previous review concerning a lack of exposure-response data for saltwater organisms, especially for chronic toxicity, and enables calculations of effect levels for saltwater biota based on experimental data. An increase in toxicological data for saltwater organisms over the last several years and availability of studies that analytically verify Pb exposure concentration has led to a study proposing updates to the acute and chronic AWQC for Pb (Church et al., 2017). For the acute criterion, the newly proposed value of 100 µg Pb/L is less than the current acute criterion of 210 µg Pb/L due to more recent acute toxicity data from relatively sensitive early lifestages of echinodermata and mollusca. The proposed chronic criterion for saltwater biota is 10 µg Pb/L. Finally, there is additional evidence for Pb association with changes in benthic invertebrate, microbial, and foraminiferal communities in coastal environments (Appendix 11.4.4.1 and 11.4.6).

IS.8.4 Summary of Welfare Effects Evidence

In the 2013 Pb ISA (U.S. EPA, 2013a), a series of causality determinations were made for effects of Pb on plants, invertebrates, and vertebrates in terrestrial, freshwater, and saltwater ecosystems (U.S. EPA, 2013a). Evidence published since that time supports or slightly expands the evidence for endpoints that were already established as causal in the 2013 Pb ISA (Table IS-14). A few studies report effects at lower effect concentration than in the 2013 Pb ISA. The new evidence is not sufficient to change any of the previous causality determinations for terrestrial and freshwater organisms and ecosystems**. New evidence for terrestrial (Appendix 11–2) and freshwater (Appendix 11–3) biota continue to support the existing causality determinations from the 2013 Pb ISA summarized in Table IS-14.**

At the time of the 2013 Pb ISA there were fewer studies on effects of Pb in saltwater biota compared with terrestrial and freshwater organisms and evidence was inadequate to infer causality relationships for many endpoints. Specifically, there was a lack of chronic toxicity data, and relatively few studies reported analytically verified Pb concentration in the experimental media. Several newer studies quantify Pb in water and/or sediment and report effects on endpoints at lower concentration than previously observed for saltwater biota, some of these studies are chronic exposure bioassays. Since the 2013 Pb ISA, the additional research for saltwater organisms supports a change in causality determinations for three endpoints (Table IS-14). Specifically, **the evidence is sufficient to conclude there is *likely to be a causal relationship* between Pb exposure and reproductive and developmental effects in saltwater invertebrates.** In addition, **the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and saltwater vertebrate survival,** and, **the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and saltwater community and ecosystem effects. Previous causality determinations for the remaining saltwater endpoints shown in Table IS-14 remain unchanged from the 2013 Pb ISA.**

Table IS-14 Summary of causality determinations for welfare effects of Pb

Level		Effect	Terrestrial[a]	Freshwater[a]	Saltwater[a]
Community- and Ecosystem		Community and Ecosystem Effects	Likely Causal	Likely Causal	↑Suggestive
Population-Level Endpoints	Organism-Level Responses	Reproductive and Developmental Effects – Plants	Inadequate	Inadequate	Inadequate
		Reproductive and Developmental Effects – Invertebrates	Causal	Causal	↑Likely Causal
		Reproductive and Developmental Effects – Vertebrates	Causal	Causal	Inadequate
		Growth – Plants	Causal	Likely Causal	Inadequate
		Growth – Invertebrates	Likely Causal	Causal	Inadequate
		Growth – Vertebrates	Inadequate	Inadequate	Inadequate
		Survival – Plants	Inadequate	Inadequate	Inadequate
		Survival – Invertebrates	Causal	Causal	Inadequate
		Survival – Vertebrates	Likely Causal	Causal	↑Suggestive
		Neurobehavioral Effects – Invertebrates	Likely Causal	Likely Causal	Inadequate
		Neurobehavioral Effects – Vertebrates	Likely Causal	Likely Causal	Inadequate
	Suborganismal Responses	Hematological Effects – Invertebrates	Inadequate	Likely Causal	Suggestive
		Hematological Effects – Vertebrates	Causal	Causal	Inadequate
		Physiological Stress – Plants	Causal	Likely Causal	Inadequate
		Physiological Stress – Invertebrates	Likely Causal	Likely Causal	Suggestive
		Physiological Stress – Vertebrates	Likely Causal	Likely Causal	Inadequate

[a]Based on the weight of evidence for causal determination in Table II of the ISA Preamble (U.S. EPA, 2015). Directional arrows denote a change in causality determination from 2013 Pb ISA.

Evidence used in determining causality for effects of Pb is presented below, with the order of effect categories reflecting an increasing scale of biological organization. In the presentation of the causality determinations below, rather than grouping determinations by ecosystem type, the sections are organized by endpoint (physiological stress, hematological effects, neurobehavioral effects, survival, growth, reproduction) and then community and ecosystem scale of biological organization.

IS.8.4.1 Physiological Stress

Physiological stress endpoints considered in the 2013 Pb ISA and previous AQCDs included changes in markers of enzyme function and oxidative stress. Although stress responses are correlated with Pb exposure, they are nonspecific and may be altered with exposure to any number of environmental stressors. There are no changes in this ISA to the causality conclusions from the 2013 Pb ISA for

physiological stress in terrestrial, freshwater, or saltwater biota (Table IS-15) At the time of the 2013 Pb ISA, evidence was sufficient to conclude that there is a causal relationship between Pb exposures and physiological stress in terrestrial plants, and new evidence has reinforced this conclusion. Evidence is sufficient to conclude that there is a likely to be causal relationship between Pb exposures and physiological stress in terrestrial invertebrates and vertebrates as well as freshwater plants, invertebrates, and vertebrates. Further evidence in saltwater invertebrates is suggestive of a causal relationship between Pb exposures and physiological stress. Evidence is inadequate to conclude that there is a causal relationship between Pb exposure and physiological stress responses in saltwater plants and vertebrates. Recent literature supports the previous evidence for Pb effects on enzymes and antioxidant activity in freshwater invertebrates (Appendix 11.3.4.3.1). New studies on physiological stress endpoints in freshwater invertebrates include changes in the activities of antioxidant defense enzymes such as superoxide dismutase, catalase, and glutathione peroxidase with aqueous exposure to Pb. A large body of evidence supports sublethal biomarker perturbations with Pb exposure in freshwater vertebrates; however, few studies were identified for this ISA that reported physiological response at more environmentally relevant concentrations of Pb (≤10 μg Pb/L; Appendix 11.1.1) or concurrently assessed response at organism-level endpoints (i.e., from the cellular and subcellular level to effects on growth, reproduction, or survival).

Table IS-15 Summary of evidence for effects of Pb on physiological stress endpoints in terrestrial and aquatic biota

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Plant Physiological Stress: Causal	
Several studies from the 2006 Pb AQCD report lipid peroxidation in plants; however, exposures in these studies were higher than would be found generally in the environment (U.S. EPA, 2006). Building on the body of evidence presented in the 2006 Pb AQCD, studies in the 2013 Pb ISA provide evidence of upregulation of antioxidant enzymes and increased lipid peroxidation associated with Pb exposure in many species of plants. Increased antioxidant enzymes with Pb exposure occur in some terrestrial plant species at concentrations approaching the average Pb concentrations in U.S. soils.	Recent studies continue to confirm increased antioxidant activity in plants in response to Pb stress as well as genotoxic effects of Pb exposure (Appendix 11.2.4.2).
Freshwater Plant Physiological Stress: Likely to Be Causal	
Increases of antioxidant enzymes with Pb exposure occur in algae, mosses, and floating and rooted aquatic macrophytes. Most available evidence for antioxidant responses in aquatic plants are from laboratory studies lasting from 2 to 7 d and at concentrations higher than typically found in the environment. However, data from transplantation experiments from nonpolluted to polluted sites indicate that elevated enzyme activities are associated with Pb levels measured in sediments.	Physiological stress response in freshwater vegetation is typically observed at much higher Pb exposures than are found in the natural environment. Studies reporting antioxidant processes upregulated in algae support previous findings of a likely to be causal relationship (Appendix 11.3.4.2).
Saltwater Plant Physiological Stress: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Invertebrate Physiological Stress: Likely to Be Causal	
Changes in enzyme activities and oxidative stress markers were reported in terrestrial invertebrates, including earthworms, snails, and nematodes.	Additional studies in a few terrestrial invertebrate species, notably earthworms, report altered enzyme activity and perturbations in other biomarkers of physiological stress associated with Pb exposure (Appendix 11.2.4.3.1).
Freshwater Invertebrate Physiological Stress: Likely to Be Causal	
Stress responses associated with exposure to Pb in aquatic invertebrates reported in previous AQCDs include elevated heat shock proteins, osmotic stress, lowered metabolism, and decreased glycogen levels. Although these stress responses are correlated with Pb exposure, they are nonspecific and may be altered with exposure to any number of environmental stressors. Evidence in the 2013 Pb ISA included upregulation of antioxidant enzymes, production of reactive oxygen species, and increased lipid peroxidation associated with Pb exposure.	Recent literature (Appendix 11.3.4.3.1) supports previous findings of Pb effects on enzymes and antioxidant activity in freshwater invertebrates. Physiological stress response was also observed in several invertebrates in chronic sediment bioassays conducted within the range of sediment Pb concentration measured in the environment.
Saltwater Invertebrate Physiological Stress: Suggestive	
Changes in antioxidant activity with Pb exposure are reported in some saltwater invertebrates. The 2013 Pb ISA included some evidence of invertebrate antioxidant responses in bivalves and crustaceans at Pb concentrations that are detected in the marine environment. Additional evidence from environmental monitoring studies that compared biomarker responses between reference and contaminated sites indicated a correlation between the amount of Pb with changes in antioxidant enzyme activity.	Studies published since the 2013 Pb ISA in saltwater invertebrates, primarily mollusks, continue to show perturbations to biomarkers of oxidative stress with Pb exposure, albeit at concentrations of Pb higher than typically countered in the environment (Appendix 11.4.4.3.1).
Terrestrial Vertebrate Physiological Stress: Likely to Be Causal	
Markers of oxidative damage are observed in terrestrial mammals in response to Pb exposure.	The evidence since the 2013 Pb ISA (Appendix 11.2.4.4.1) continues to support a likely to be causal relationship between Pb exposure and response in biomarkers of physiological stress. Most new studies are in birds.
Freshwater Vertebrate Physiological Stress: Likely to Be Causal	
Markers of oxidative damage are observed in fish and amphibians in laboratory studies. Across freshwater vertebrates, there are differences in the induction of antioxidant enzymes with Pb exposure that appear to be species-dependent.	Sublethal biomarker perturbations are associated with Pb exposure in freshwater vertebrates (Appendix 11.3.4.4.1.1). Few studies were identified that reported physiological stress response at ≤10 µg Pb/L or concurrently assessed response at organism-level endpoints.
Saltwater Vertebrate Physiological Stress: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality

AQCD = Air Quality Criteria Document; ISA = Integrated Science Assessment; Pb = lead.

IS.8.4.2 Hematological Effects

As reported in the 2013 Pb ISA, inhibition of ALAD enzyme activity, an important rate-limiting enzyme needed for heme production, is a recognized biomarker of Pb exposure (U.S. EPA, 2013a). The

causality determinations for Pb effects on hematological endpoints in terrestrial, freshwater, and saltwater organisms are unchanged from the 2013 Pb ISA (Table IS-16). Previous studies have indicated considerable species differences in ALAD activity in response to Pb. At the time of the 2013 Pb ISA evidence was sufficient to conclude that there is a causal relationship between Pb exposures and hematological effects in terrestrial vertebrates and inadequate to assess causality between Pb exposures and hematological effects in terrestrial invertebrates. Since the 2013 Pb ISA, additional species of birds, amphibians and mammals have been shown to experience decreased ALAD activity following exposure to Pb further supporting the existing causal relationship. For freshwater vertebrates, the evidence evaluated in the 2013 Pb ISA and Pb AQCDs was sufficient to conclude that there is a causal relationship between Pb exposures and hematological effects. Hematological effects of Pb on fish reported in the 2013 Pb ISA and AQCDs include a decrease in RBCs and inhibition of ALAD with elevated Pb exposure under various test conditions. Inhibition of ALAD is also reported in environmental assessments of metal-impacted habitats. In the 2013 Pb ISA it was determined that a causal relationship is likely to exist between Pb exposures and hematological effects in freshwater invertebrates. Limited evidence from saltwater invertebrates was suggestive of a causal relationship between Pb exposures and hematological effects while evidence for saltwater vertebrates was insufficient to assess causality. Evidence for hematological effects in saltwater invertebrates in previous AQCDs and the 2013 Pb ISA were primarily from field monitoring studies of marine bivalves that used ALAD as a biomarker for Pb exposure and correlated ALAD inhibition to increased Pb tissue content. Few new studies were identified since the 2013 Pb ISA that quantified ALAD response in terrestrial invertebrates or aquatic invertebrates or vertebrates; hence causality relationships for hematological effects of Pb are unchanged.

Table IS-16 Summary of evidence for effects of Pb on hematological endpoints in terrestrial and aquatic biota

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Invertebrate Hematological Effects: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality
Freshwater Invertebrate Hematological Effects: Likely to Be Causal	
In metal-impacted habitats, ALAD is a recognized biomarker of Pb exposure. Laboratory studies with freshwater invertebrates have indicated considerable species differences in ALAD activity in response to Pb. Field studies in freshwater bivalves report a correlation between Pb and ALAD activity.	No recent studies quantifying ALAD activity in freshwater invertebrates at environmentally relevant concentration of Pb were identified for inclusion in this ISA.
Saltwater Invertebrate Hematological Effects: Suggestive	
Field studies in saltwater bivalves report a correlation between Pb and ALAD activity.	Few additional studies have reported inhibition of ALAD activity in Pb-exposed saltwater invertebrates and the concentrations at which enzyme activity is affected appear to be much higher than Pb typically encountered in seawater (Appendix 11.4.4.3.1).

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Vertebrate Hematological Effects: Causal	
In the 1986 Pb AQCD, decreases in RBC ALAD activity were documented in birds and mammals near a smelter (U.S. EPA, 1986b). Additional evidence for effects of Pb blood parameters and their applicability as biomarkers of Pb exposure in terrestrial birds and mammals were presented in the 2005 Ecological Soil Screening Levels for Lead (U.S. EPA, 2005), the 2006 Pb AQCD (U.S. EPA, 2006), and the 2013 Pb ISA. Field studies include evidence for elevated BLLs correlated with decreased ALAD activity in songbirds and owls living in historical mining areas.	New evidence (Appendix 11.2.4.4.1) continues to support a causal relationship between Pb exposure and hematological effects in terrestrial vertebrates with most new evidence in birds. ALAD inhibition correlated with increased blood Pb concentrations in waterfowl, passerines, and scavengers as well as livestock and toads.
Freshwater Vertebrate Hematological Effects: Causal	
In the 1986 Pb AQCD, hematological effects of Pb exposure in fish included decrease in RBCs and inhibition of ALAD (U.S. EPA, 1986b). In fish, Pb effects on blood chemistry have been documented with Pb concentrations ranging from 100 to 10,000 µg Pb/L in studies cited in the 2006 Pb AQCD (U.S. EPA, 2006).	Few studies were identified since the 2013 Pb ISA that quantify ALAD response at concentrations considered for this ISA. (Appendix 11.3.4.4.1).
Saltwater Vertebrate Hematological Effects: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality

AQCD = Air Quality Criteria Document; ALAD = δ-aminolevulinic acid dehydratase; BLL = blood lead level; ISA = Integrated Science Assessment; RBC = red blood cell; Pb = lead.

IS.8.4.3 Neurobehavioral Effects

Organism-level endpoints include effects on behavior linked to Pb neurotoxicity. The causality determinations for neurobehavioral effects of Pb in terrestrial, freshwater, and saltwater organisms remain unchanged from the 2013 Pb ISA. Evidence for causality determinations for neurobehavioral endpoints are summarized in Table IS-17. The 2013 Pb ISA concluded that the neurobehavioral effects of Pb exposure on terrestrial and freshwater invertebrates are likely causal. In terrestrial invertebrates, the 2013 Pb ISA (U.S. EPA, 2013a) reported evidence of neurobehavioral aberrations such as impaired locomotion in nematode *Caenorhabditis elegans* that persisted over several generations while limited studies in freshwater invertebrates provided evidence of decreased ability to escape or avoid predation in worms and snails. Additional evidence since the 2013 Pb ISA in support of the likely to be causal relationship between Pb exposure and neurobehavioral effects in terrestrial invertebrates include studies quantifying alterations in foraging and feeding behavior in bees (Appendix 11.2.4.3.2). A few new studies including effects on locomotion in amphipods and bivalves, and alternation of neurotransmitter activity in bivalves and gastropods further support the 2013 finding of a likely to be causal relationship between Pb exposure and neurobehavioral endpoints in freshwater invertebrates (Appendix 11.3.4.3.2). Evidence is inadequate to assess causality between Pb exposure and neurobehavioral endpoints in saltwater invertebrates.

In the 2013 Pb ISA, the evidence was sufficient to conclude that the relationship between Pb exposure and neurobehavioral effects in terrestrial and freshwater vertebrates is likely to be causal. Diet

and injection studies in gull chicks and in lizards, designed to obtain Pb blood levels comparable to organisms exposed in the wild, resulted in a variety of abnormal behaviors. For aquatic vertebrates, evidence in prior AQCDs included behavioral impairment of a conditioned response in goldfish (U.S. EPA, 1977) and several studies in which Pb was shown to affect predator-prey interactions in fathead minnows (U.S. EPA, 2013a, 2006). Since the 2013 Pb ISA, there are additional studies on neurobehavioral response particularly in zebrafish (Appendix 11.3.4.4.1.2), which are used as an animal model for human health outcomes associated with Pb exposure. Endpoints assessed in zebrafish assays, such as decreased locomotor activity and altered social interactions used as surrogates for autistic behaviors in humans, can affect organism fitness in natural environments. Furthermore, some of these studies link changes in gene expression, neurotransmitter levels or other molecular and cellular responses to the observed behavioral outcomes. These new studies continue to support the likely to be causal relationship between Pb exposure and effects on neurobehavior in aquatic vertebrates.

Table IS-17 Summary of evidence for effects of Pb on neurobehavioral endpoints in terrestrial and aquatic biota

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Invertebrate Neurobehavioral Effects: Likely to Be Causal	
A few studies reported altered feeding rates in snails while others reported no effects. In limited studies available on nematodes, there is evidence that Pb may affect the ability to escape or avoid predation. Additional evidence of changes in the morphology of GABA motor neurons was also found in nematodes (*C. elegans*).	Nematode studies reported food preference, food finding ability, and feeding activity were altered by Pb exposure. New evidence in additional taxa include findings that Pb negatively affects foraging and feeding behavior as well as cognitive flexibility in bees (Appendix 11.2.4.3.2).
Freshwater Invertebrate Neurobehavioral Effects: Likely to Be Causal	
In the 2006 Pb AQCD, several studies were reviewed in which Pb was shown to affect predator-prey interactions. In limited studies available on worms and snails, there is evidence that Pb may affect the ability to escape or avoid predation.	A few studies further support the finding of a likely to be causal relationship between Pb exposure and neurobehavioral endpoints (Appendix 11.3.4.3.2). These endpoints include effects on locomotion in amphipods and alteration of neurotransmitter activity and foot movement in a freshwater bivalve.
Saltwater Invertebrate Neurobehavioral Effects: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality
Terrestrial Vertebrate Neurobehavioral Effects: Likely to Be Causal	
Limited behavioral studies in gull chicks experimentally exposed to Pb reported abnormal behaviors such as decreased walking, learning deficits, erratic behavioral thermoregulation, and food begging that could make them more vulnerable in the wild (Burger and Gochfeld, 2005). Lizards exposed to Pb through diet exhibited abnormal coloration and posturing behaviors. These results also cohere with findings in laboratory animals that show that Pb induces changes in learning and memory.	A few additional studies in birds since the 2013 Pb ISA reported a relationship between Pb exposure and neurobehavior or reported no effects (Appendix 11.2.4.4.2). In one study in mockingbirds, higher BLLs were correlated with increased levels of aggressive behavior (McClelland et al., 2019).

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Freshwater Vertebrate Neurobehavioral Effects: Likely to Be Causal	
In the 2006 Pb AQCD, exposure to Pb was shown to affect brain receptors in fish and may alter avoidance behaviors and predator-prey interactions. Studies cited in the 2013 Pb ISA included those that provided additional evidence for Pb effects on behaviors that may impact predator avoidance (swimming) and prey capture ability.	Several studies with larval zebrafish (*Danio rerio*) bolster the finding of a likely to be causal relationship from the 2013 Pb ISA. Some effects on behavioral endpoints such as locomotion and social interactions were reported at ≤20 µg Pb/L (Appendix 11.3.4.4.1.2).
Saltwater Vertebrate Neurobehavioral Effects: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality

AQCD = Air Quality Criteria Document; BLL = blood lead level; GABA = gamma-aminobutyric-acid; Pb = lead.

IS.8.4.4 Survival

Survival may have a direct impact on population size and can lead to effects at the community and ecosystem level of biological organization. Survival is commonly assessed in laboratory bioassays and reported as a toxicological dose descriptor (e.g., 50% lethal concentration [LC_{50}], LC_{20}) to facilitate comparison of effects across species and test conditions. In the 2013 Pb ISA the evidence was inadequate to conclude that there is a causal relationship between Pb exposure and survival in terrestrial, freshwater, or saltwater plants and this continues to be the case (Table IS-18). For invertebrates, the causality determinations for survival remain unchanged from the 2013 Pb ISA (Table IS-18). At that time, the evidence was sufficient to conclude that there is a causal relationship between Pb exposures and survival in terrestrial and freshwater invertebrates and inadequate for saltwater invertebrates.

Terrestrial invertebrates typically tolerate high concentrations of Pb relative to concentrations found in most uncontaminated soils. For freshwater invertebrates, key studies in amphipods reported in the 2006 Pb AQCD and 2013 Pb ISA indicate a response to Pb at <10 µg Pb/L under some water conditions. Several studies since the 2013 Pb ISA provide further characterization for known effects on survival in a few sensitive species of freshwater invertebrates, notably gastropods and amphipods, at ≤15 µg Pb/L in chronic exposures in which the concentration of Pb was analytically verified (Appendix 11.3.5).

Evidence is sufficient to conclude that there is likely to be a causal relationship between Pb exposure and survival in terrestrial vertebrates, with most of the direct evidence coming from studies of waterfowl and birds of prey conducted throughout the last 50 years. For freshwater vertebrates, studies in fish provided the basis for causal relationship for survival in the 2013 Pb ISA. Additional fish bioassays conducted in varying water chemistry conditions report effects on survival at Pb concentrations similar to those reported in the 2013 Pb ISA further supporting the causal relationship between Pb exposure and survival in freshwater vertebrates (Table IS-18). Several additional studies have considered the effects of Pb on native fish species including white sturgeon (*Acipenser transmontanus*), and westslope cutthroat

trout (*Oncorhynchus clarkii lewisi*) (Appendix 11.3.5). Other recent studies on freshwater vertebrates have further characterized the response to Pb under varying water conditions.

In the 2013 Pb ISA and previous assessments, the evidence for Pb effects on survival of saltwater vertebrates was inadequate. New evidence (Appendix 11.4.5) is limited to laboratory-based bioassays in a few fish species, toxicity data for other saltwater vertebrates remains lacking. Several recent chronic bioassays conducted with early lifestages of three saltwater fish species report NOEC in the range of 11–14 µg Pb/L (Appendix 11, Table 11-7). Furthermore, Pb in these bioassays was analytically verified. In the larval fish Topsmelt (*Atherinops affinis*), an LC_{50} = 15.1 µg Pb/L; NOEC <13.8 µg Pb/L was observed at a salinity of 14 ppt (Reynolds et al., 2018). Calculated chronic values for additional saltwater fish species that are consistent with the range reported above include grey mullet (*Mugil cephalus*) fingerling survival and Tiger perch (*Terapon jarbua*) fingerling survival (Hariharan et al., 2016)**.** Given these new chronic studies in saltwater fish, the causality determination for this endpoint has changed since the 2013 Pb ISA and **the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and saltwater vertebrate survival (Table IS-18).**

Table IS-18 Summary of evidence for effects of Pb on survival of terrestrial and aquatic biota

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Plant Survival: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality
Freshwater Plant Survival: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality
Saltwater Plant Survival: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality
Terrestrial Invertebrate Survival: Causal	
Survival of soil-associated invertebrates is adversely affected by Pb exposure, albeit at Pb concentrations associated with contaminated sites. In nematodes, the 2006 Pb AQCD reported LC_{50} values varying from 10 to 1,550 mg Pb/kg dry weight dependent upon soil OM content and soil pH (U.S. EPA, 2006). In earthworms, 14 and 28-d LC_{50} values typically fell in the range of 2,400 to 5,800 mg Pb/kg depending upon the species tested. More recent evidence has been consistent with these values and showed concentration-dependent decreases in survival in collembolans and earthworms under various experimental conditions.	Evidence continues to support a causal relationship between Pb exposure and invertebrate mortality, although most reported effects occurred at concentrations that greatly exceed environmental concentrations. Additional bioassays include studies in garden snails and earthworms (Appendix 11.2.4.3.2).

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Freshwater Invertebrate Survival: Causal	
Most of the evidence for Pb effects on survival in freshwater invertebrates is from sensitive species of gastropods, amphipods, cladocerans, and rotifers. In the 2006 Pb AQCD, Pb impacted the survival of some aquatic invertebrates at <20 µg/L dependent upon water quality variables (i.e., DOC, hardness, pH). Evidence in the 2013 Pb ISA also showed effects on survival in a few additional freshwater invertebrates at <20 µg Pb/L. Toxicity testing with amphipods under various water conditions indicate these organisms are sensitive to Pb at <10 µg Pb/L.	Several studies provide further characterization for known effects on survival in a few sensitive species of freshwater invertebrates at <20 µg Pb/L. In the gastropod *L. stagnalis,* survival was significantly decreased at 8.4 µg Pb/L after 21-d exposure and decreased survival was observed up to the end of a 56-d full lifecycle assessment (Munley et al., 2013). In a chronic 42-d bioassay with the amphipod *H. azteca*, survival was similar under two different experimental diets conducted concurrently (LC_{20} = 15 µg Pb/L and LC_{20} = 13 µg Pb/L) (Besser et al., 2016), and the results supported the previous findings of effects in amphipods in the low µg/L range (Appendix 11.3.5 and Table 11-5).
Saltwater Invertebrate Survival: Inadequate	
Limited evidence suggests that effects on survival are not observed in most saltwater invertebrates unless Pb concentrations greatly exceed those typically detected in seawater.	Evidence continues to show that effects on survival are typically not observed in bioassays unless Pb concentrations greatly exceed those typically detected in seawater.
Terrestrial Vertebrate Survival: Likely to Be Causal	
In terrestrial avian and mammalian species, toxicity is observed in laboratory studies over a wide range of doses (<1 to >1,000 mg Pb/kg body weight per day) as reviewed for the development of ecological soil screening levels (U.S. EPA, 2005), and subsequently reported in the 2006 Pb AQCD (U.S. EPA, 2006). The no-observed-adverse-effect level for survival ranged from 3.5 to 3,200 mg Pb/kg per day.	No new studies were available within the scope of this ISA reporting effects of Pb exposure on the survival of terrestrial vertebrates.
Freshwater Vertebrate Survival: Causal	
There is considerable historic information on Pb toxicity to freshwater fish. Early observations from highly impacted mining areas where Pb and other metals were present indicated local extinction of fish from streams (U.S. EPA, 1977). Several studies in the 2013 Pb ISA reported effects at <100 µg/Pb L in juvenile lifestages of a few fish species. In the 2013 Pb ISA, 96-hr LC_{50} values in fathead minnow tested in natural waters across the United States were as low as 41 µg Pb/L (Esbaugh et al., 2011).	Additional fish bioassays conducted in varying water chemistry conditions report effects on survival at Pb concentrations similar to those in the 2013 Pb ISA (Appendix 11.3.5 and Table 11-5). For larval zebrafish (*D. rerio*), 96-hr LC_{50} values varied with water hardness; in soft water LC_{50} = 52.9 µg Pb/L and in hard water LC_{50}=>590 µg Pb/L (Alsop and Wood, 2011). In 96-hr acute tests conducted with two lifestages of white sturgeon (*Acipenser transmontanus*), the lowest 96-hr LC_{50} was 177 µg Pb/L in 8-d post-hatch larvae (Vardy et al., 2014).

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Saltwater Vertebrate Survival: Suggestive (Inadequate in the 2013 Pb ISA)	
Insufficient evidence to assess causality	Additional evidence since the 2013 Pb ISA includes chronic bioassays with analytically verified concentrations of Pb conducted with early lifestages in three saltwater fish species that report NOECs in the range of 11–14 µg Pb/L (Appendix 11.4.5 and Table 11-7). In the larval fish Topsmelt (*Atherinops affinis*), survival was impacted to a greater extent at lower salinity (LC_{50} = 15.1 µg Pb/L; NOEC <13.8 µg Pb/L) than higher salinity (LC_{50} = 79.8 µg Pb/L; NOEC = 45.5 µg Pb/L) (Reynolds et al., 2018). Calculated chronic values for additional saltwater fish species include a NOEC = 14 µg Pb/L and LOEC = 29 µg Pb/L for grey mullet (*Mugil cephalus*) fingerling survival and a NOEC = 11 µg Pb/L and LOEC = 22 µg Pb/L for Tiger perch (*Terapon jarbua*) fingerling survival following 30 d exposure to Pb (Hariharan et al., 2016).

AQCD = Air Quality Criteria Document; d = day(s); DOC = dissolved organic carbon; hr = hour(s); ISA = Integrated Science Assessment; LC_{50} = 50% lethal concentration; LOEC = lowest-observed-effect concentration, NOEC = no-observed-effect concentration; OM = organic matter; Pb = lead.

IS.8.4.5 Growth

Alterations in the growth of an organism can impact population, community, and ecosystem-level variables. In plants, the 2013 Pb ISA concluded that the relationship between Pb exposure and reduced growth is causal in terrestrial plants and likely to be causal in freshwater aquatic plants. New evidence continues to support these findings (Table IS-19). Evidence was inadequate for growth endpoints for saltwater plants and algae in 2013 and this continues to be the case. There is evidence over several decades of research that Pb inhibits photosynthesis and respiration in terrestrial plants, both of which reduce growth (U.S. EPA, 2013a, 2006, 1977). Effects reported in plants are typically observed in laboratory or greenhouse settings with high exposure concentrations or in field studies near stationary sources and heavily contaminated sites, but studies that include multiple concentrations of Pb show increased response with increasing concentration. In the 2006 Pb AQCD, half maximal effect concentration (EC_{50}) values for growth inhibition in various freshwater algal and aquatic plant species were between approximately 1,000 and >100,000 µg Pb/L and were mostly based on nominal concentration data (U.S. EPA, 2006). An important advancement since the 2013 Pb ISA is the availability of bioassay data for algal growth rate in several freshwater species based on measured Pb concentration instead of nominal concentration, which strengthens confidence in the findings for the concentrations assessed (Appendix 11.3.5). In conclusion, most primary producers experience EC_{50} values for growth at concentrations that greatly exceed Pb concentrations typically found in U.S. soils and surface waters.

The 2013 Pb ISA concluded that the relationship between Pb exposure and decreased growth in freshwater invertebrates is causal, and likely to be causal in terrestrial invertebrates. Building upon the evidence for growth effects reported in the draft Ambient Aquatic Life Water Quality Criteria for Lead

(U.S. EPA, 2008) and the 2006 Pb AQCD (U.S. EPA, 2006), studies reviewed in the 2013 Pb ISA reported some effects at ≤10 µg Pb/L for growth endpoints in aquatic invertebrates (U.S. EPA, 2013a). The growth of the freshwater snail *L. stagnalis* was identified as one of the most sensitive organisms and endpoints for Pb toxicity. Since then, additional studies have supported previous findings of Pb effects on the growth of this species at <10 µg Pb/L [(Crémazy et al., 2018; Munley et al., 2013; Brix et al., 2012; Esbaugh et al., 2012); Appendix 11, Table 11-5]. The evidence remains inadequate to infer a causality relationship for Pb exposure and reduced growth in saltwater invertebrates, and terrestrial and aquatic vertebrates.

Table IS-19 Summary of evidence for growth effects of Pb in terrestrial and aquatic biota

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Plant Growth: Causal	
Effects of Pb on plant growth are typically observed in laboratory studies with high exposure concentrations or in field studies near stationary sources. In terrestrial plants, there is evidence over several decades of research that Pb inhibits photosynthesis and respiration, all of which can reduce the growth of the plant (U.S. EPA, 2006, 1986a, 1977). The 2006 Pb AQCD relied principally on evidence assembled in the Ecological Soil Screening Levels for Lead document (U.S. EPA, 2005), which concluded that growth (biomass) was the most sensitive and ecologically relevant endpoint for plants. In the 2013 Pb ISA, there was some evidence for exposure-dependent decreases in the biomass of some plant species grown in Pb-amended or Pb-contaminated soil.	Recent studies have continued to demonstrate growth effects, albeit at concentrations that greatly exceed Pb measured in soils. Growth endpoints include decreases in photosynthetic performance, damage to chlorophyll, increased antioxidant activity in response to Pb stress, as well as genotoxic effects of Pb. Studies of the effects of Pb on terrestrial plants published since the last ISA continue to support the previous known findings of declines in plant growth under controlled exposures of Pb (Appendix 11.2.4.2).
Freshwater Plant Growth: Likely to Be Causal	
There is a large body of evidence to support growth effects in plants at higher Pb concentrations. As reported in the 2013 Pb ISA and earlier AQCDs, there are documented effects on growth in algae and aquatic plants in laboratory studies. Most primary producers experience EC_{50} values for growth in the range of 1,000 to 100,000 µg Pb/L, concentrations that greatly exceed Pb concentrations typically found in U.S. surface waters.	Additional studies in algae and macrophytes continue to support a likely to be causal relationship (Appendix 11.3.4.1). A few new studies assessed the sensitivity of freshwater algal growth to Pb exposure and found a significantly negative effect in certain species. New information on Pb effects on common reed (*P. australis*) shows significant decreases in total biomass, photosynthesis, and rhizome growth as well as alterations in growth form and propagation strategy under Pb exposure.
Saltwater Plant Growth: Inadequate	
Saltwater species are historically underrepresented in toxicity testing. In studies reviewed in the 2013 Pb ISA, marine algae exhibited a range of sensitivity to Pb with a 72-hr EC_{50} reported for Chaetorceros sp. of 105 µg Pb/L. Other tested species were considerably less sensitive (72-hr EC_{50} = 740 µg Pb/L or higher).	Limited evidence for growth inhibition for marine algal species published since the 2013 Pb ISA, including a few longer-term studies, generally show effects at concentrations that greatly exceed environmental concentrations (Appendix 11.4.4.2).

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Invertebrate Growth: Likely to Be Causal	
A few studies cited in the 1986 Pb AQCD, the 2006 Pb AQCD, and the 2013 Pb ISA reported growth effects in terrestrial invertebrates and that effects were more pronounced in juvenile organisms, underscoring the importance of lifestage to overall Pb susceptibility. Some studies also showed concentration-dependent inhibition of growth in earthworms raised in Pb-amended soil.	Recent evidence continues to show growth-rate effects in organisms associated with soil and food Pb contamination including earthworms, snails, and nematodes, as well as new evidence for tobacco cutworm and fruit flies (Appendix 11.2.4.3.2).
Freshwater Invertebrate Growth: Causal	
Some studies in sensitive freshwater invertebrates reported inhibition of growth at or below 20 µg Pb/L. The lowest reported LOEC for growth in the 2006 Pb AQCD (16 µg Pb/L) was in amphipods (*H. azteca*) (Besser et al., 2005). In the 2013 Pb ISA, there was evidence for growth inhibition in one species of snail (L. stagnalis) at <4 µg Pb/L (Grosell and Brix, 2009; Grosell et al., 2006). The lowest genus mean chronic toxicity value for Pb was 10 µg Pb/L in a freshwater mussel (Wang et al., 2010).	Additional studies support previous findings of Pb effects on growth of the snail (*L. stagnalis*) at <10 µg Pb/L (Crémazy et al., 2018; Munley et al., 2013; Brix et al., 2012; Esbaugh et al., 2012) and a few other invertebrates at or near 25 µg Pb/L (Appendix 11.3.5 and Table 11-5).
Saltwater Invertebrate Growth: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality
Terrestrial Vertebrate Growth: Inadequate	
In AQCDs, growth effects of Pb have been reported in birds (changes in juvenile weight gain) at concentrations typically higher than currently found in the environment away from heavily exposed sites.	No new studies were available within the scope of this ISA reporting growth effects in terrestrial vertebrates from Pb exposure.
Freshwater Vertebrate Growth: Inadequate	
Evidence for growth effects of Pb is limited to a few studies in amphibians and fish. Reports of Pb-associated growth effects in freshwater fish are inconsistent; some studies have shown no effects. Growth effects of Pb were reported in frogs at concentrations typically higher than currently found in the environment.	A few additional fish studies assessed growth endpoints, with some reporting no effect (Appendix 11.3.4.4.1.2).
Saltwater Vertebrate Growth: Inadequate	
Insufficient evidence to assess causality	Few studies were identified since the 2013 Pb ISA that assessed growth in saltwater vertebrates.

AQCD = Air Quality Criteria Document; EC_{50} = half maximal effect concentration; ISA = Integrated Science Assessment; LOEC = lowest observed effect concentration; Pb = lead.

IS.8.4.6 Reproduction

Evidence from invertebrate and vertebrate studies from Pb AQCDs, the 2013 Pb ISA and in this review indicates that Pb is affecting reproductive performance in multiple species (Table IS-20). Various endpoints have been measured in multiple taxa of terrestrial and aquatic organisms to assess the effect of Pb on development, fecundity, and hormone homeostasis, and they have demonstrated the presence of adverse effects. Reproductive effects are important when considering effects of Pb because impaired fecundity at the organism level of biological organization can result in a decline in abundance and/or

extirpation of populations, decreased taxa richness, and decreased relative or absolute abundance at the community level (Suter et al., 2004). The evidence is inadequate to conclude that there is a causal relationship between Pb exposures and developmental and reproductive effects in either terrestrial or aquatic plants. In the 2013 Pb ISA the evidence was sufficient at that time to conclude that there is a causal relationship between Pb exposures and developmental and reproductive effects in terrestrial and freshwater invertebrates. New evidence suggests that in earthworms, Pb exposure slows the time to maturation and that in isopods, it delays onset of the breeding season and shortens its duration, and that it influences mate selection in fruit flies (Appendix 11.2.4.3.2). For freshwater invertebrates, recent evidence further supports previous observations of Pb effects on reproductive endpoints at low concentrations in sensitive species of gastropods, cladocerans and rotifers, especially under chronic exposure scenarios (Appendix 11.3.5 and see Table 11-5).

In the 2013 Pb ISA, evidence was suggestive of a causal relationship between Pb exposure and reproductive and developmental effects in saltwater invertebrates based on endpoints including delay in onset to reproduction in amphipods, impaired larval development and embryogenesis inhibition in bivalves, and a decrease in fertilization rate of eggs in a marine polychaete (U.S. EPA, 2013a). Since the 2013 Pb ISA, the evidence base for Pb effects on reproductive and developmental endpoints in saltwater invertebrates has expanded, primarily due to multiple new embryo-larval developmental assays in mollusca and echinodermata (Appendix 11.4.5 and Table 11-7). Several of these acute exposure bioassays analytically verify the concentration of Pb at which effects were observed (Markich, 2021; Romero-Murillo et al., 2018; Nadella et al., 2013) and report effects at lower concentrations than reported in the 2013 Pb ISA. Considering coherence of reproductive and developmental effects of Pb across species, observations in saltwater invertebrates are consistent with terrestrial and freshwater invertebrates (both "causal" in the 2013 Pb ISA). As a result of the newly available evidence since the 2013 Pb ISA the causality determination for this endpoint has changed and **the evidence is sufficient to infer *a likely to be causal relationship* between Pb exposure and reproductive and developmental effects in saltwater invertebrates.**

In the 2013 Pb ISA, the evidence was sufficient to conclude that there is a causal relationship between Pb exposures and developmental and reproductive effects in terrestrial and freshwater vertebrates, and this continues to be the case. For reproduction and development in freshwater vertebrates, the weight of evidence for the causal relationship in the 2013 Pb ISA was primarily from studies with fish. Previous Pb AQCDs have reported reproductive and developmental effects in fish, including brook trout (*Salvelinus fontinalis*), rainbow trout (*Oncorhynchus mykiss*), and fathead minnow (*Pimephales promelas*) (U.S. EPA, 2013a, 2006, 1977). Other supporting evidence for the causal determination in the 2013 Pb ISA for reproductive effects in aquatic vertebrates included alteration of steroid profiles and additional reproductive variables, although most of the available studies were conducted using nominal concentrations of Pb. New early lifestage fish studies, including several in zebrafish (*D. rerio*) in which the concentration of Pb in exposure water was analytically verified (Appendix 11.3.4.4.1.2) add to the

existing evidence for Pb effects on endocrine and developmental endpoints. These studies at analytically verified concentration of Pb include several developmental studies in amphibians (Appendix 11.3.4.4.3).

Table IS-20 Summary of evidence for reproductive effects of Pb in terrestrial and aquatic biota

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Plant Reproduction: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality
Freshwater Plant Reproduction: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality
Saltwater Plant Reproduction: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality
Terrestrial Invertebrate Reproduction: Causal	
The 2006 Pb AQCD reported effects on reproduction in collembolans and earthworms, with LOECs and NOECs typically well above Pb soil concentrations observed away from stationary sources of contamination. In the 2013 Pb ISA, studies in a few taxa expanded the evidence for Pb effects on developmental and reproductive endpoints for invertebrates at concentrations that generally exceed Pb levels in U.S. soils. Evidence of multigenerational toxicity effects of Pb is also present in terrestrial invertebrates, specifically springtails, mosquitoes, carabid beetles, and nematodes in which decreased fecundity in the progeny of Pb-exposed individuals was observed.	Studies published since the 2013 Pb ISA continue to support a causal relationship between Pb exposure and invertebrate reproductive endpoints including time to maturation and brood size (Appendix 11.2.4.3.2). In addition to new studies in earthworms and nematodes, additional new taxa demonstrating reproductive effects associated with Pb exposure include isopods and fruit flies. Several multigenerational fruit fly studies together report that Pb exposure influences female mate selection, oviposition site, and tolerance to Pb contamination is greater in populations with a history of Pb exposure.
Freshwater Invertebrate Reproduction: Causal	
Reproductive effects of Pb in freshwater aquatic invertebrates are well characterized in previous Pb AQCDs and the 2013 Pb ISA and have been observed at or near current ambient concentrations in some species in laboratory exposures. Results under controlled conditions have consistently shown reproductive effects of Pb in sensitive taxa, especially amphipods and cladocerans, at concentrations near Pb quantified in freshwater environments.	Recent evidence (Appendix 11.3.5) further characterizes Pb effects on reproductive endpoints at low (<10 µg Pb/L) concentrations in sensitive species of gastropods, cladocerans, and rotifers (Appendix 11, Table 11-5), especially under chronic exposure scenarios.
Saltwater Invertebrate Reproduction: Likely to Be Causal (Suggestive of, but Not Sufficient to Infer Causality in the 2013 Pb ISA)	
For saltwater invertebrates, there is limited evidence for effects on reproduction and early development. Reported effects included a delay in the onset to reproduction in amphipods (Ringenary et al., 2007), impaired larval development (Wang et al., 2009) and embryogenesis inhibition (Wang et al., 2009; Beiras and Albentosa, 2004) in bivalves and a decrease in the fertilization rate of eggs (marine polycheate annelid) (Gopalakrishnan et al., 2008). These effects were observed for Pb concentrations higher than typically detected in marine environments.	Multiple new embryo-larval developmental assays in mollusca (mussels, oysters) and echinodermata (sea urchin) (Appendix 11.4.5 and Table 11-7) have expanded the evidence for reproductive effects since the 2013 Pb ISA. Several of these acute exposure bioassays analytically verified the concentration of Pb at which effects were observed (Markich, 2021; Romero-Murillo et al., 2018; Nadella et al., 2013) and reported effects at lower effect concentrations than those reported in the 2013 Pb ISA. For example, the 48-hr EC_{10} was 9–10 µg Pb/L in two mussel species, and 72-hr EC_{10} was 19 µg Pb/L in sea urchin *Strongylocentrotus purpuratus* (Nadella et al., 2013).

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Vertebrate Reproduction and Development: Causal	
Effects reported in the 2006 Pb ISA included declines in clutch size, number of young hatched, number of young fledged, decreased fertility, and decreased eggshell thickness observed in birds near areas of Pb contamination and in birds with elevated Pb tissue concentration regardless of location (U.S. EPA, 2006). In the 2013 Pb ISA, studies in a few taxa expand the evidence for Pb effects on mammalian developmental and reproductive endpoints.	Recent studies, although limited, continue to support a causal relationship between Pb exposure and reproductive effects in terrestrial vertebrates. New studies provide additional evidence of Pb exposure causing decreased lifetime breeding success, lower nestling weight at birth, decreased eggshell thickness, and decreases in egg yolk antioxidant levels in birds (Appendix 11.2.3.4.2).
Freshwater Vertebrate Reproduction and Development: Causal	
The weight of evidence for reproductive and developmental effects in freshwater vertebrates is from fish. Pb AQCDs have reported developmental effects in a few fish species at or near 120 µg Pb/L (U.S. EPA, 1977) (U.S. EPA, 1986b) and reported effects on other reproductive endpoints including decreased spermatocyte development (U.S. EPA, 2006). Reproductive effects in fish are influenced by water chemistry.	Several studies in fish further support previous findings of Pb effects on reproductive endpoints in freshwater vertebrates (Appendix 11.3.4.4.1.2). A few of these studies report effects at lower concentrations than the 2013 Pb ISA or prior AQCDs. Specifically, hatching success rates in zebrafish embryos were reduced at 4.5, 9.6 and 18.6 µg Pb/L aqueous exposure; (Zhao et al., 2020). Endocrine disruption (significant reduction in thyroid hormones triiodothyronine (T3) and thyroxine (T4)) was observed in zebrafish larvae following exposure to 30 µg Pb/L (Zhu et al., 2014).
Saltwater Vertebrate Reproduction and Development: Inadequate	
Insufficient evidence to assess causality	Insufficient evidence to assess causality

AQCD = Air Quality Criteria Document; EC_{10} = effect concentration at 10% inhibition; hr = hour(s); ISA = Integrated Science Assessment; LOEC = lowest observed effect concentration; NOEC = no-observed-effect concentration; Pb = lead.

IS.8.4.7 Community and Ecosystem Effects

Endpoints relevant to assessing effects of Pb on communities and ecosystems include the alteration of species richness, species composition, and biodiversity. Uptake of Pb into aquatic and terrestrial organisms and subsequent effects on mortality, growth, development, and reproduction at the organism level can cascade to effects on populations and communities and lead to ecosystem-level consequences. Although the evidence is strong for the effects of Pb on growth, reproduction, and survival in certain species in experimental settings, considerable uncertainties exist in generalizing effects observed under experimental conditions and at a smaller scale to predicted effects at the community and ecosystem levels of biological organization. In many cases, it is difficult to characterize the nature and magnitude of ecosystem-level effects and to quantify relationships between environmental concentrations of Pb and ecosystem response due to the presence of multiple stressors, variability in field conditions, and differences in Pb bioavailability. In addition, although the presence of Pb is associated with shifts in biological communities, this metal rarely occurs as a sole contaminant in natural systems, making the contribution of Pb to the observed effects difficult to ascertain.

In the 2013 Pb ISA, the body of evidence was sufficient to conclude there is a likely to be causal relationship between Pb exposure and terrestrial and freshwater-community and ecosystem effects, and

recent evidence continues to support this determination (Appendix sections 11.2.6, 11.3.6, 11.2.4.1, and 11.3.4.1 and Table IS-21). In terrestrial habitats, communities and ecosystems exposed to elevated Pb concentration, typically from proximity to historically active metal extracting and processing point sources, have been shown to suffer from decreased species diversity and changes in species composition. These changes affect microbial, floral, and faunal communities. Since the 2013 Pb ISA, effects of Pb exposure on the interactions between trees and their pests, between herbaceous plants and insects, and plants, worms, and soils invertebrates have been added to the evidence (Appendix 11.2.6). Reductions in species abundance, richness, or diversity associated with the presence of Pb in freshwater habitats are reported in the literature, usually in heavily contaminated sites where Pb (and other metal) concentrations are higher than typically observed environmental concentrations. Most evidence is from sediment-associated microbial and macroinvertebrate communities. Since the 2013 Pb ISA (U.S. EPA, 2013a), several experimental and observational studies have examined the relationship between Pb concentration in the sediment and effects on freshwater microbes (Appendix 11.3.4.1). Several of these studies report negative relationships between sediment Pb concentration and microbial abundance or community structure, while some report no relationship or positive associations. Observational and experimental studies published since the 2013 Pb ISA continue to show negative associations between sediment and/or porewater Pb concentration and macroinvertebrate communities (Appendix 11.3.6).

For saltwater ecosystems, evidence was inadequate in the 2013 Pb ISA to assess causality between Pb exposures and community and ecosystem effects. Reduced species abundance and biodiversity of protozoan and meiofauna communities were observed in laboratory microcosm studies with marine water and marine sediments reviewed in the 2006 Pb AQCD as summarized in Table AX7 2.5.2 (U.S. EPA, 2006). In the 2013 Pb ISA, there were a few additional studies including effects on community structure and nematode diversity (U.S. EPA, 2013a). Since that time, there are new experimental and observational studies (Table IS-21) examining the relationship between Pb in sediment, and microbial abundance and/or diversity (Appendix 11.4.4.1), and Pb associations with saltwater foraminiferal communities (Appendix 11.4.6). Several of the benthic foraminifera studies report effects on community richness, diversity, and abundance. In other studies with foraminifera, there were changes in abundance of certain taxa associated with Pb, but not diversity metrics. Considering the new evidence, Pb quantified in sediment is a factor explaining variation in microbial diversity and foraminiferal species distributions and abundance in a variety of distinct geographic locations. In these studies, Pb is often correlated with other heavy metals. In addition to the available studies assessing Pb effects on saltwater communities, primarily foraminifera, the effects of Pb on reproduction and survival of early lifestages in sensitive saltwater invertebrates, especially when considered cumulatively, could impact populations, and community and ecosystem structure and function. Population, community, or ecosystem-level studies are typically conducted at sites that have been contaminated or adversely affected by multiple stressors (several chemicals alone or combined with physical or biological stressors), which increase the uncertainty of attributing observed effects to Pb. Therefore, additional evidence available since the 2013 Pb ISA indicates **the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and saltwater community and ecosystem effects**.

Table IS-21 Summary of evidence for community and ecosystem effects of Pb

Evidence from the 2013 Pb ISA	Evidence from the 2024 Pb ISA
Terrestrial Community and Ecosystem Effects: Likely to Be Causal	
Independent effects of Pb are difficult to interpret because of the presence of other stressors, including metals. The 1986 Pb AQCD (U.S. EPA, 1986a) reported shifts toward Pb-tolerant communities at 500 to 1,000 mg Pb/kg soil. In the 2006 Pb AQCD (U.S. EPA, 2006), decreased species diversity and changes in community composition were observed in ecosystems surrounding former smelters. In the 2013 Pb ISA, there was additional evidence for Pb effects on soil microbial communities.	Experimental studies have shown that trophic transfer of Pb can affect species interactions, nematode community composition, and bacterial abundance and/or activity (Appendix 11.2.4.1). Additional observational studies reported negative or null relationships between soil Pb concentration and microbial and invertebrate abundance and diversity (Appendix sections 11.2.4.1 and 11.2.6).
Freshwater-Community and Ecosystem Effects: Likely to Be Causal	
Effects of Pb are difficult to interpret because of the presence of other stressors, including metals. Most evidence of community and ecosystem-level effects is from near Pb sources, usually mining effluents. In the 2013 Pb ISA evidence for Pb effects on sediment-associated and freshwater aquatic plant communities added to the existing body of evidence of effects of Pb at higher levels of biological organization.	Several studies reported negative correlations between sediment Pb concentration and invertebrate community composition or ecosystem processes (Appendix 11.3.6). Additionally, observational and experimental studies have reported negative relationships between sediment and/or porewater Pb concentration and microbial abundance and/or community structure, while some reported no relationship or positive associations (Appendix 11.3.4.1)
Saltwater Community and Ecosystem Effects: Suggestive of, but Not Sufficient to Infer, a Causal Relationship (Inadequate in the 2013 Pb ISA)	
No studies on community and ecosystem-level effects of Pb in marine systems were reviewed in the 1977 Pb AQCD (U.S. EPA, 1977), or the 1986 Pb AQCD (U.S. EPA, 1986a). Observations from field studies reviewed in the 2006 Pb AQCD (U.S. EPA, 2006) included findings of a negative correlation between Pb and species richness and diversity indices of macroinvertebrates associated with estuary sediments. Evidence for community and ecosystem-level effects of Pb in saltwater ecosystems in the 2013 Pb ISA included a few laboratory microcosm studies as well as observations from field-collected sediments, biofilm, and plants in which changes in community structure were observed; however, evidence was inadequate to make a causality determination at the time.	Additional studies since the 2013 Pb ISA provide sufficient evidence for effects on saltwater communities and ecosystems to be suggestive of a causal relationship. Several studies report reductions in foraminiferal and/or meiofaunal community richness, diversity, and/or abundance associated with higher concentrations of Pb in sediment and water, while others found positive or null correlations (Appendix 11.4.6). In addition, several experimental and observational studies reported negative relationships between sediment and/or saltwater Pb concentrations and microbial abundance and/or diversity, while other studies found no relationship (Appendix 11.4.4.1).

AQCD = Air Quality Criteria Document; ISA = Integrated Science Assessment; Pb = lead.

IS.9 Policy-Relevant Issues

In the process of evaluating the current state of the science with respect to the effect of Pb exposure on health and welfare, studies that conducted analyses that address some of the key policy-relevant questions of this review were identified, as detailed in Volume 2 of the Pb IRP (U.S. EPA, 2022a), such as:

- To what extent has new information altered scientific conclusions regarding the relationships between Pb in ambient air and Pb in children's blood?

- To what extent does the newly available evidence alter our understanding of the C-R relationships between Pb in children's blood and reduced IQ?
- To what extent is there new scientific evidence available to improve our understanding of the health effects associated with various time periods of Pb exposures at various stages of life?
- Has new information altered our understanding of human populations that are particularly sensitive to the current low environmental Pb exposures, including air-related exposures?
- Does the newly available evidence identify new endpoints or indicate new exposure levels at which ecological systems or receptors are expected to experience effects?

The following sections summarize the evidence that can inform consideration of these policy-relevant questions, specifically: air Pb-to-blood Pb relationships (Section IS.9.1); C-R relationship between BLLs and IQ (Section IS.9.2); the level, timing, duration, and frequency of Pb exposure contributing to observed health effects (Section IS.9.3), and populations potentially at increased risk of a PM-related health effect (Section IS.9.4). A summary of recent evidence related to at-risk populations is provided in Section IS.7.4.

IS.9.1 Air Pb-to-Blood Pb Relationships

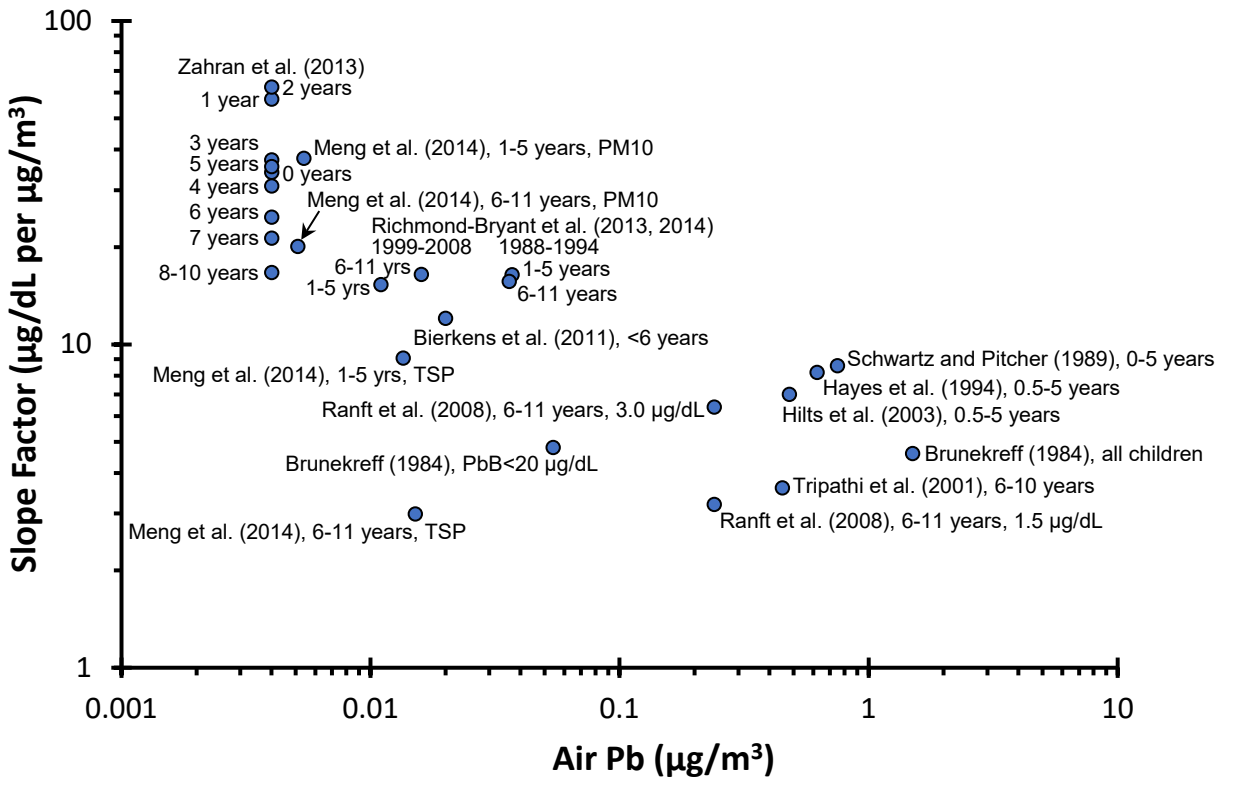
Multivariate regression models, commonly used in epidemiology, provide estimates of the variability in BLLs (or other biomarkers) explained by various exposure pathways (e.g., air Pb concentration, surface-dust Pb concentration). Models can provide estimates of the rate of change of blood or bone Pb concentration in response to an incremental change in exposure level (i.e., slope factor). Within the literature and U.S. EPA documents, the relationship between air Pb and blood Pb is commonly characterized in terms of a "slope factor" or "air-to-blood ratio." An air-to-blood ratio of 1:5 indicates that for every 1 $\mu g/m^3$ of air Pb, there is a 5 µg/dL increase in blood Pb. Synonymously, this is characterized by a slope factor of 5 µg/dL per $\mu g/m^3$. Air Pb-blood Pb relationships in children, described in Appendix 2.5.1, are summarized below.

The 1986 Pb AQCD (U.S. EPA, 1986a) described epidemiologic studies of relationships between air Pb and blood Pb. Drawing from the studies examined, the aggregate blood Pb-air Pb slope factor (when considering both air Pb and Pb in other media derived from air Pb) was estimated to be approximately double the slope estimated from the contribution due to inhaled air alone (U.S. EPA, 1986a). Much of the pertinent earlier literature (e.g., prior to 1984, when air Pb was dominated by the use of leaded gasoline in on-road motor vehicles) on children's BLLs was summarized by Brunekreef (1984) and found that the blood Pb versus air Pb slope was smaller at high blood and air levels. Most studies have empirically modeled the air Pb-to-blood Pb relationship using nonlinear regression (i.e., log-log), which itself gives an increasing slope with decreasing air Pb concentration.

In the 2008 final rule for the Pb NAAQS (73 FR 66964), the Administrator's decision on the revised level for the new primary standard was informed by an evidence-based framework for considering

air-related IQ loss for children living near Pb sources. U.S. EPA, recognizing uncertainty and variability in the air-to-blood relationships, interpreted the evidence as providing support for a range of estimates inclusive of 1:5 at the lower end and 1:10 at the upper end, with the ratio of 1:7 identified as a central estimate within the range supported by the evidence at the time (73 FR 67001−67002, 67005).

At the time of the 2013 Pb ISA (U.S. EPA, 2013a), there was uncertainty, due to the limited evidence, in projecting the magnitude of the air Pb-blood Pb relationship to ambient air Pb below 0.2 μg/m^3. There are studies since the 2013 Pb ISA that evaluate the air Pb-to-blood Pb relationship that are more reflective of current conditions with central tendency air Pb concentration (PbA) between 0.004 and 0.04 μg/m^3. As was the case for older data in the 1986 Pb AQCD (U.S. EPA, 1986a), newer data also show slope factors increasing with decreasing air Pb (Figure IS-4). Although saturable gastrointestinal absorption and saturation of Pb binding to RBC occur at relatively high rates of Pb intake leading to blood Pb concentration (PbB) of 20–30 μg/dL (see Section 2.2), the nonlinear relationship between PbA and PbB cannot be explained by a biokinetic mechanism.



Source: Figure based on Richmond-Bryant et al. (2014) with data from Table 2-13 (Appendix 2).

Figure IS-4 Slope factors for blood Pb as a function of air Pb.

In general, longitudinal studies conducted after phasing out leaded gasoline would best inform the current relationship of blood Pb to air Pb. Ideally, such studies would compare two populations for which air Pb concentrations differ while all other Pb sources are unchanged. In a nearly ideal study, Hilts (2003) reported the change in blood Pb from 1996 to 2001 for children under 5 years old associated with the emission reduction from a local smelter in Trail, BC, Canada. However, even in this study, the reduction in exposure from pathways other than air cannot be ruled out because of the "comprehensive education and case management programs." An advancement in analyses of the blood Pb-air Pb association came from leveraging the U.S. EPA Air Quality System (AQS) with NHANES surveys. The blood Pb-air Pb associations across different NHANES periods should reflect the change in this association for the U.S. population over time (Richmond-Bryant et al., 2014; Richmond-Bryant et al., 2013) because each NHANES cycle is a representative sample of the U.S. population. However, merging blood Pb results from multiple NHANES periods with the U.S. EPA AQS could introduce exposure measurement errors as well as uncertainties in terms of population representativeness and availability of covariates. Each single study presented in Table 2-13 (Appendix 2.5.1) deviates from the ideal design in one or more aspects. Collectively, all of these studies contribute to our understanding of how air Pb impacts blood Pb.

IS.9.2 Concentration-Response Relationships for Human Health Effects

In assessing the relationship between Pb exposure and human health effects, an important consideration is the shape of the C-R relationship across the full range of Pb biomarker levels and whether there is a threshold concentration below which there is no evidence of an effect. As described elsewhere in the document (Appendix 2.3), the interpretation of the epidemiologic study findings depends on the exposure history of the study populations and the choice of the biomarker in the context of what is known about that exposure history. Many of the adult populations examined in older and more recent epidemiologic studies are likely to have had higher past than recent Pb exposure. Given their longer exposure histories, there is uncertainty regarding the frequency, duration, timing, and level of exposure contributing to the blood Pb or bone Pb levels measured in adult and adolescent populations. Specifically, higher past exposures may bias C-R estimates based on later childhood, adolescent, and adult BLLs. Therefore, this section summarizes evidence relevant to thresholds and C-R relationships in studies of childhood Pb exposure. A summary of previous evidence regarding C-R relationships for exposure biomarkers in adolescents and adults is presented in Section 1.9.3 of the 2013 Pb ISA (U.S. EPA, 2013a), and a summary of recent evidence can be found within the health effects appendices.

With each previous assessment (U.S. EPA, 2013a, 2006), the epidemiologic and toxicological evidence demonstrated that progressively lower BLLs or Pb exposures are associated with cognitive deficits in children. The 2006 Pb AQCD found that cognitive effects in children were observed in association with BLLs of 10 µg/dL and lower, while the evidence assessed in the 2013 Pb ISA found that an association between BLLs and cognitive effects in children was substantiated to occur in populations with mean BLLs between 2 and 8 µg/dL. The conclusion of the 2013 Pb ISA was based on studies that

examined early childhood BLLs (i.e., age <3 years), considered peak BLLs in their analysis (i.e., peak <10 μg/dL), or examined concurrent BLLs in young children (i.e., age 4 years). A recent study of Canadian preschool children from generally middle- to upper-middle SES families with low Pb exposure (mean concurrent BLL = 0.70 μg/dL) did not find an association between concurrent Pb exposure and IQ at age 3−4 years (Desrochers-Couture et al., 2018). Although some other recent studies report associations between Pb exposure and cognitive effects in children with mean BLLs <2 μg/dL, recent studies generally include somewhat older children, or employ modeling strategies designed to answer relatively narrow research questions (e.g., the effect of joint exposure to Pb and other metals, or the effect of concurrent Pb exposure independent from prenatal exposure) and consequently do not have the attributes of the studies on which the conclusion of the 2013 Pb ISA was based (i.e., early childhood BLLs, consideration of peak BLLs, or concurrent BLLs in young children). Furthermore, studies that might extend the evidence related to exposure-response relationships (i.e., recent studies that reflect the lower early childhood Pb exposures now more common in the United States with an adequate range of Pb exposure [i.e., studies of subjects with BLLs <1 to 2 μg/dL measured during relevant time periods]) are limited. Overall, the recently available studies were not designed, and may not have the sensitivity, to detect (Cooper et al., 2016) the effect or hazard at these very low BLLs, nor do they provide evidence of a threshold for the effect across the range of BLLs examined.

Epidemiologic studies evaluated in the 2013 Pb ISA provided evidence of a larger decrement in cognitive function per unit increase in blood Pb among children with lower mean BLLs compared with children with higher mean BLLs. Key evidence was provided by an international pooled analysis of seven prospective cohort studies (Lanphear et al., 2019, 2005), as well as studies that examined prenatal or early childhood BLLs or considered peak BLLs in school-aged children or concurrent BLLs in young children (i.e., 2 years old). Recent studies that evaluate the shape of the C-R function for the relationship between Pb exposure and cognitive effects in children are limited in number, but continue to support the conclusions from the 2013 Pb ISA. In particular, a re-analysis of the pooled data set of Lanphear et al. (2005), Crump et al. (2013) corroborated the finding that there was evidence of a nonlinear C-R function over the range of the BLLs evaluated (e.g., 2.5–33.2 μg/dL, as 5th to 95th percentile concurrent BLLs) – i.e., a larger incremental effect of Pb exposure on IQ at lower blood Pb concentrations as indicated by a log-linear C-R function. Lanphear et al. (2005) also fit linear functions over stratified BLL ranges (e.g., < 7.5 μg/dL and ≥7.5 μg/dL) that similarly indicated statistically significantly larger Pb-associated cognitive function decrements across the lower range compared to the higher range. Individual studies also support this finding, showing greater decrements in cognitive function per unit increase in BLL among children in lower strata of BLLs compared with children in higher strata of BLLs [Figure 4-15, and Table 4-16 of U.S. EPA (2013a)]. Notably, uncertainty in the shape of the C-R relationship increases at lower BLLs due to a smaller number of observations. Previous assessments also noted attenuation of C-R relationships at higher exposure or dose levels in the occupational literature. Reasons proposed to explain the attenuation include greater exposure measurement error and saturation of biological mechanisms at higher levels, as well depletion of the pool of susceptible individuals at higher exposure levels (Stayner et al., 2003). Possible explanations specific to nonlinear relationships observed in studies of Pb exposure in children

include a lower incremental effect of Pb due to covarying risk factors such as low SES, poor caregiving environment, and higher exposure to other environmental factors (Schwartz, 1994), differential activity of mechanisms at different exposure levels, and confounding by omitted variables or misspecified variables (U.S. EPA, 2013a). Review of the evidence did not reveal a consistent set of covarying risk factors to explain the differences in the blood Pb-IQ C-R relationship across high and low Pb exposure groups observed in epidemiologic studies. Additionally, although evidence indicates a larger incremental effect of Pb exposure on IQ at lower BLLs, consistent findings of higher mean IQ at lower BLLs indicates that the absolute magnitude of the effect of Pb exposure on cognitive function declines with decreasing BLL.

IS.9.3 Lifestages and Timing of Pb Exposure Contributing to Observed Nervous System Effects

As discussed in Appendix 2.3.5, blood Pb may reflect both recent as well as past exposures because Pb is both taken up by and released from the bone. The relative proportion of BLLs resulting from recent versus past exposure is uncertain in the absence of specific information about the pattern of exposure contributing to observed BLLs, which is generally not ascertainable in epidemiologic studies. This uncertainty is greater in adults and older children, than in young children who do not have lengthy exposure histories. As a result, stronger conclusions can be reached regarding the timing of exposures that result in health effects in children. Several lines of evidence, which are summarized below, inform the interpretation of epidemiologic studies of young children with regard to the patterns of exposure that contribute to observed health effects.

The collective body of epidemiologic evidence reviewed in the 2013 Pb ISA did not provide strong evidence to identify an individual critical lifestage or timing of Pb exposure with regard to neurodevelopmental effects in children (U.S. EPA, 2013a). Specifically, epidemiologic studies reviewed in the 2013 Pb ISA consistently showed that BLLs measured during various lifestages and time periods (i.e., prenatal, early childhood, childhood average, and concurrent with the outcome) were associated with nervous system effects in children. Recent studies generally support this conclusion, though several studies indicate that increases in postnatal (earlier childhood, lifetime average, concurrent) BLLs were associated with larger cognitive function decrements in children ages 4–10 years than increases in prenatal BLLs. These results suggest that per unit increase, postnatal Pb exposures that are reflected in concurrent or cumulative BLLs or tooth Pb levels may have a larger magnitude of effect on cognitive function decrements as children age. Notably, however, exposure metrics that are based on blood Pb measurements at different ages in childhood are typically highly correlated. Consequently, the relative importance of various exposure metrics, which are measured during different lifestages and time periods, is difficult to discern in epidemiologic studies. Evidence in rodents and monkeys, however, indicates that Pb exposures during multiple lifestages and time periods, including prenatal only, prenatal plus lactational, postnatal only, and lifetime are observed to induce impairments in learning (Rice, 1992; Rice and Gilbert, 1990). Additionally, recent prospective epidemiologic studies observed associations between

childhood BLLs and decrements in IQ during late adolescence (18–19 years) and mid-adulthood (38–45 years). These findings provide insight into the persistence of Pb-associated cognitive function decrements and are consistent with the understanding that the nervous system continues to develop (i.e., synaptogenesis and synaptic pruning remains active) throughout childhood and into adolescence.

IS.9.4 Ecological Effects and Corresponding Pb Concentrations

Pb that is released into air, soil, or water is then cycled through any, or all, of these media before reaching an ecological receptor. When a plant, invertebrate, or vertebrate is exposed to Pb, the proportion of observed effects attributable to Pb from atmospheric sources is difficult to quantitatively assess because of a lack of information not only on deposition but also on bioavailability, as affected by specific characteristics of the receiving ecosystem, and on the kinetics of Pb distribution in long-term exposure scenarios. Although long-term trends in declining anthropogenic emissions of Pb are detected in some non-air media and biota, the connection between air concentration and ecosystem exposure continues to be poorly characterized for this metal, and measurements of the contribution of atmospheric Pb to specific sites is generally unavailable. Current evidence indicates that Pb is bioaccumulated in biota, however, the sources of Pb in biota have only been identified in a few studies, and the relative contribution of Pb from each source is usually not known.

No new endpoints were identified for Pb effects in terrestrial, freshwater, or saltwater biota since the 2013 Pb ISA. However, a few effects were reported at lower concentration than for the 2013 Pb ISA, primarily in chronic laboratory-based bioassays for endpoints that were already established as causal in the 2013 Pb ISA. The level at which Pb elicits a specific effect continues to be difficult to establish in terrestrial and aquatic systems. There are large differences in species sensitivity to Pb, and many environmental variables (e.g., pH, OM) determine the bioavailability and toxicity of Pb.

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