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Integrated Science Assessment for Lead

Appendix 3: Nervous System Effects

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Center for Public Health and 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

AA	atomic absorption
AAS	atomic absorption spectrometry
Aβ	amyloid beta
ABR	auditory brainstem response
AD	Alzheimer's disease
ADD	attention deficit disorder
ADHD	attention deficit/hyperactivity disorder
ADHD-RS	ADHD rating scale
ADOS	Autism Diagnostic Observation Schedule
ADRA2A	alpha−2A-adrenergic receptor
ALAD	aminolevulinic acid dehydratase
ALS	Amyotrophic Lateral Sclerosis
ALSPAC	Avon Longitudinal Study of Parents and Children
AOR	adjusted odds ratio
APP	amyloid precursor protein
AQCD	Air Quality Criteria Document
As	arsenic
avg	average
ASD	autism spectrum disorder
ASQ:I	Ages and Stages Questionnaire Inventory
ASSQ	Autism Spectrum Screening Questionnaire
ATP	adenosine triphosphate
BAARS	Barkley Adult ADHD-IV Rating Scale
BACE1	beta-secretase 1
BAEP	brainstem auditory evoked potential
BASC	Behavior Assessment System for Children
BASC-2	Behavior Assessment System for Children, second revision
BBB	blood-brain barrier
BDI	Beck Depression Inventory
BDNF	brain-derived neurotrophic factor
BKMR	Bayesian kernel machine regression
BKT	Binet Kamat Test
BLL	blood lead level
BMD	benchmark dose
BMDL	benchmark dose lower 95% confidence limit
BMI	body mass index
BMS	Baltimore Memory Study
BNT	Boston Naming Test
BPA	bisphenol A
BPAQ	Buss-Perry Aggression Questionnaire
BrainAGE	Brain Age Gap Estimation
BRIEF	Behavior Rating Inventory of Executive Functions
BRIEF-A	Behavior Rating Inventory of Executive Functions for Adults
BRIEF-P	Behavior Rating Inventory of Executive Functions for Preschool Children
BRS	behavioral rating scale
BSI	Behavioral Symptoms Index
BSID	Bayley Scales of Infant and Toddler Development
BSID-IIS	Bayley Scales of Infant and Toddler Development – Spanish Version
BT20+	Birth to Twenty Plus
Ca^{2+}	calcium ion(s)
CANTAB	Cambridge Neuropsychological Test Automated Battery
CAR	cortisol awakening response
CARES	Communities Actively Researching Exposure Study
CARS	Childhood Autism Rating Scale
CAT	catalase
CBCL	Child Behavior Check List
CBLI	cumulative blood lead index
CCAAPS	Cincinnati Childhood Allergy and Air Pollution Study
CCEI	Crown-Crisp Experiential Index
Cd	cadmium
CDIIT	Comprehensive Developmental Inventory for Infants and Toddlers
CDK5	cyclin-dependent kinase 5
Ce	cesium
CEM	Coarsened Exact Matching
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CHECK	Children's Health and Environmental Chemicals in Korea
CHEER	Children's Health and Environmental Research
CHMS	Child Health Monitoring System
CI	confidence interval
CIDI	Composite International Diagnostic Interview
CKD	chronic kidney disease
CKiD	Chronic Kidney Disease in Children
CLS	Cincinnati Lead Study

CNS	central nervous system
Co	cobalt
C-P	central-to-peripheral
cpd	cycles per degree
CPR	Conditioned Position Responding
CPRS	Conners' Parent Rating Scale
CPRS-R	Conners' Parent Rating Scale-Revised
CPT	Continuous Performance Test
C-R	concentration-response
CR	chromium
CREB	cyclic adenosine 3',4'-monophosphate response element binding protein
CRISYS-R	Crisis in Family Systems-Revised
CRP	C-reactive protein
CRS	Conners' Rating Scale
CRS-R	Conners' Rating Scale-Revised
CRT	Combined Raven's Test
CSF	cerebrospinal fluid
C-TRF	Caregiver-Teacher Report Form
CTRS	Conners' Teacher Rating Scale
CTRS-R	Conners' Teacher Rating Scale-Revised
C-V R^2	cross validated R-square
CVA	cerebrovascular accident
CVD	cardiovascular disease
CVLT	California Verbal Learning Test
CVLT-C	California Verbal Learning Test-Children's Version
d	day(s)
DAT1	dopamine transporter
DBD	Disruptive Behavior Disorder
DDE	dichlorodiphenyldichloroethylene
DI	deionized
DISC1	Disrupted-in-Schizophrenia−1
DMTS	Delayed Matching-to-Sample
DQ	development quotient
DRD2	Dopamine Receptor D2
DNAm	DNA methylation
DSC	Digit Symbol Coding
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSST	Digit Symbol Substitution Test
DTI	Diffusion Tensor Imaging
ECAT	elemental carbon attributable to traffic
ECDI	Early Child Development Inventory
EE	effect estimate
EEG	electroencephalogram
ELEMENT	Early Life Exposure in Mexico to Environmental Toxicants
EMOCI	emotional regulation
EOG	end of grade
EPM	elevated plus maze
EPN	early postnatal
EPSC	excitatory postsynaptic currents
ERG	electroretinography
ERP	event-related potential
ETS	environmental tobacco smoke
F	female
F#	filial generation
FA	fractional anisotropy
FBB-ADHS	Fremdbeurteilungsbogen für Aufmerksamkeitsdefizit/Hyperaktivität störungen
Fe	iron
FFQ	Food Frequency Questionnaire
FI	fixed interval
FLEHS	Flemish Environment and Health Study
FR	fixed ratio
FSIQ	full-scale intelligence quotient
FST	forced swim test
GABA	gamma-aminobutyric acid
GCNT1	glucosaminyl (N-acetyl) transferase 1
GD	gestational day
GDS	Gesell Developmental Schedules
GFAAS	graphite furnace atomic absorption spectrometry
GMR	geometric mean ratio
GRIN	glutamate ionotropic receptor N-methyl D-aspartate-type subunit
GSH	glutathione
GSI	Global Severity Index
GST	glutathione S-transferase
HCB	hexachlorobenzene
HDL	high-density lipoprotein
HFE	hemochromatosis gene
Hg	mercury
Hgb	hemoglobin
HHANES	Hispanic Health and Nutrition Examination Survey
HI	hyperactivity and impulsivity
HNES	Home Nurture Environment Scale
HNRS	Heinz Nixdorf Recall Study
HOME	Health Outcomes and Measures of the Environment
HPA	hypothalamic pituitary adrenal
hr	hour(s)
HR	hazard ratio
HR-ICP-MS	high resolution inductively coupled plasma mass spectrometry

HRR	hazard rate ratio
HRT	hormone replacement therapy
ICD	International Classification of Diseases
ICP-DRC-MS	dynamic reaction cell for inductively coupled plasma mass spectrometry
ICP-MS	inductively coupled plasma mass spectrometry
ICP-OES	inductively coupled plasma optical emission spectroscopy
ICP-SFMS	inductively coupled plasma sector field mass spectrometry
INMA	INfancia y Medio Ambiente
IQ	intelligence quotient
IQR	interquartile range
ISA	Integrated Science Assessment
ISAT	Illinois Standard Achievement Test
K6	Kessler Psychological Distress Scale
K-ABC	Kaufman Assessment Battery for Children
K-ARS	Korean ADHD Rating Scale
K-CBCL	Korean Child Behavior Check List
KEDI	Korean Educational Development Institute
KiTAP	Test of Attentional Performance for Children
KNHANES	Korea National Health and Nutrition Examination Survey
K-SADS	Kiddie Schedule for Affective Disorders and Schizophrenia
K-SADS-PL-K	Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime – Korean Version
K-XRF	K-shell X-ray fluorescence
LASSO	least absolute shrinkage and selection operator
ln	natural log
LOD	limit of detection
LTP	long-term potentiation
LURF	Land Use Random Forest
M	male
Mat	maternal
MAT	Metropolitan Achievement Test
MCU	mitochondrial Ca^{2+} uniporter
MDAT	Malawi Development Assessment Tool
MDI	Mental Development Index
mDISC1	mouse Disrupted-in-Schizophrenia−1
ME	maternal exposure
MEAP	Michigan Educational Assessment Program
MeHg	methyl mercury
MHI−5	Mental Health Index 5-item
MIREC	Maternal-Infant Research on Environmental Chemicals
MMSE	Mini Mental State Examination
Mn	manganese
mo	month(s)
MOCEH	Mothers' and Children's Environmental Health
MRI	magnetic resonance imaging
MrOS	Osteoporotic Fractures in Men Study
MRS	magnetic resonance spectroscopy
MSCA	McCarthy Scales of Children's Abilities
NaAc	sodium acetate
NAS	Normative Aging Study
NBAS	Neonatal Behavioral Assessment Scales
NBNA	Neonatal Behavioral Neurological Assessment
NCDS	Nunavik Child Development Study
NEI	National Emissions Inventory
NHANES	National Health and Nutrition Examination Survey
NHBCS	New Hampshire Birth Cohort Study
NHS	Nurses' Health Study
NMDAR	N-methyl-D-aspartate receptor
NPR	Norwegian Patient Registry
NR	not reported
NS	no stress
OD/CD	oppositional defiant and conduct disorder
OFT	open-field test
OLS	ordinary least squares
OR	odds ratio
ORIEN	orientation/engagement
OTB	operant test battery
Pb	lead
PbO	lead oxide
PC	primary caregiver
PCBs	polychlorinated biphenyls
PCNA	proliferating cell nuclear antigen
PD	Parkinson's disease
PDI	Psychomotor Developmental Index
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
PEG	Parkinson's Environment and Genes
PERI	perinatal
PHDCN	Project on Human Development in Chicago Neighborhoods
PIQ	Performance Intelligence Quotient
PIR	poverty-income ratio

$PM_{2.5}$	fine particulate matter
PND	postnatal day
PPI	Psychopathic Personality Inventory
PR	prevalence ratio
PROGRESS	Programming Research in Obesity, Growth, Environment and Social Stressors
PRP	post-reinforcement pause
PTA	pure-tone average
pts	points
p-tau	phosphorylated tau
PTSD	post-traumatic stress disorder
PW	postweaning
Q	quartile
RNS	reactive nitrogen species
RO DI	reverse osmosis deionized
ROS	reactive oxygen species
RR	relative risk
RSEI	Risk Screening Environmental Indicators
SCN	suprachiasmatic nucleus
SCWT	Stroop Color-Word Test
SD	standard deviation
SDQ	Strengths and Difficulties Questionnaire
Se	selenium
SE	standard error
SES	socioeconomic status
SGA	small for gestational age
SGPD	System Genomics of Parkinson's Disease
SMBCS	Sheyang Mini Birth Cohort Study
SMS	Social Maturity Scale
SOD	superoxide dismutase
Sp	specificity protein
SPHERL	Study for Promotion of Health in Recycling Lead
SPM	Standard Progressive Matrix
SQ	social quotient
SRP	self-report of personality
SRS	Social Responsiveness Scale
SWAN	Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale
T#	trimester #
TBD	to be determined
TBPS	Taiwan Birth Panel Study
TEACh	Test of Everyday Attention for Children
TMT	Trail Making Test
TOKS	tin-ore kilns and smelters
TRD	Temporal-Response Differentiation
TRF	Teacher Report Form
TSCD	Tohoku Study of Child Development
TST	Tail Suspension Test
TUNEL	terminal deoxynucleotidyl transferase dUTP nick end labeling
U.S. EPA	United States Environmental Protection Agency
USV	ultrasonic vocalizations
VA	visual acuity
VDR	vitamin D receptor
VEP	visual evoked potential
VIF	variance inflation factor
VIQ	Verbal Intelligence Quotient
VMI	visual-motor integration
WAIS	Weschler Adult Intelligence Scale
WASI	Wechsler Abbreviated Scale of Intelligence
wk	week(s)
WHO	World Health Organization
WIAT	Wechsler Individual Achievement Test
WISC	Wechsler Intelligence Scale for Children
WJTA	Woodcock-Johnson Test of Achievement
WMC	working memory capacity
WMH	white matter hyperintensities
WMS	Weschler Memory Scale
WPPSI	Wechsler Preschool and Primary Scale of Intelligence
WRAML	Wide Range Assessment of Memory and Learning
WRAT	Wide Range Achievement Test
XRF	X-ray fluorescence
yr	year(s)
YSR	youth self-report
Zn	zinc

APPENDIX 3 NERVOUS SYSTEM EFFECTS

Summary of Causality Determinations for Pb Exposure and Nervous System Effects

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

Outcome Group	Causality Determination
Nervous System Effects Ascertained during Childhood, Adolescent, and Young Adult Lifestages	
Cognitive Effects	Causal
Attention, Impulsivity and Hyperactivity	Causal
Conduct Disorders, Aggression, and Criminal Behavior	Likely to be causal
Internalizing Behaviors	Likely to be causal
Motor Function	Likely to be causal
Sensory Function	Suggestive of, but not sufficient to infer, a causal relationship
Social Cognition and Behavior	Suggestive of, but not sufficient to infer, a causal relationship
Nervous System Effects Ascertained during Adult Lifestages	
Cognitive Effects	Causal
Psychopathological Effects	Likely to be causal
Sensory Function	Suggestive of, but not sufficient to infer, a causal relationship
Neurodegenerative Disease	Suggestive of, but not sufficient to infer, a causal relationship

The Executive Summary, Integrated Synthesis, and all other appendices of this Pb ISA can be found at https://assessments.epa.gov/isa/document/&deid=359536

3.1 Introduction

While Pb affects nearly every organ system, the nervous system appears to be one of the most sensitive targets. The sections that follow provide an evaluation of the most policy-relevant scientific evidence relating to the effects of lead (Pb) exposure on the nervous system. To maximize transparency regarding the studies included in the appendix, the scope is defined in Section 3.2. Section 3.3, Biological Plausibility, provides an overview of the biological pathways that potentially underlie the nervous system effects discussed in subsequent sections of the appendix. Section 3.4 summarizes overt nervous system toxicity, including changes in brain structure and function. There is no causality determination in this section; rather, data presented in the section may be referenced in the outcome-specific "Summary and Causality Determination" discussions in later sections if they provide support for the conclusions. Sections 3.5 and 3.6 describe the epidemiologic and experimental animal evidence that pertains to specific endpoints or outcome groupings, which are organized by the lifestage at which they are ascertained (i.e., childhood, adolescence, and young adult [Section 3.5] and adult [Section 3.6] lifestages).

The strongest and most policy-relevant evidence within each section is discussed first. Within Section 3.5, which focuses on exposures and outcomes ascertained during childhood lifestages, including adolescence and early adulthood, the strongest evidence that is best substantiated at the lowest exposure levels relates to Cognitive Effects (Section 3.5.1) and Attention, Impulsivity, and Hyperactivity (Section 3.5.2) in children. Conduct Disorders are discussed in Section 3.5.3, followed by Anxiety and Depression (Section 3.5.4), Motor Function (Section 3.5.5), Sensory Organ Function (Section 3.5.6), and Social Cognition and Behavior (Section 3.5.7). The next section (Section 3.6) includes endpoints that are ascertained during adult lifestages. The section begins with an assessment of the evidence pertaining to Cognitive Effects in Adults (Section 3.6.1) followed by sections on Anxiety, Depression, and Psychopathological Effects (Section 3.6.2), Sensory Function (Section 3.6.3), and Neurodegenerative Diseases (Section 3.6.4). Within each section, the collective body of evidence is integrated within and across scientific disciplines, and issues relevant for interpreting the scientific evidence as well as the rationale for the causality determination are outlined for relevant endpoints or outcome groupings.

3.2 Scope

The scope of this appendix is defined by Population, Exposure, Comparison, Outcome, and Study Design (PECOS) statements. The PECOS statements define the objectives of the review and establish study inclusion criteria, thereby facilitating identification of the most relevant literature to inform the

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

Epidemiologic Studies:

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

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

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

Outcome: Nervous system effects including but not limited to cognitive function (e.g., intelligence quotient [IQ] decrement), externalizing and internalizing behaviors, psychopathological effects, sensory organ function, motor function, and neurodegenerative diseases; and

Study Design: Epidemiologic studies consisting of longitudinal and retrospective cohort studies, case-control studies, cross-sectional studies with appropriate timing of exposure for the health

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

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

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

endpoint of interest, randomized trials and quasi-experimental studies examining interventions to reduce exposures.

Experimental Studies:

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

Exposure: Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that results in a BLL of 30 µg/dL or below;[4,5]

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

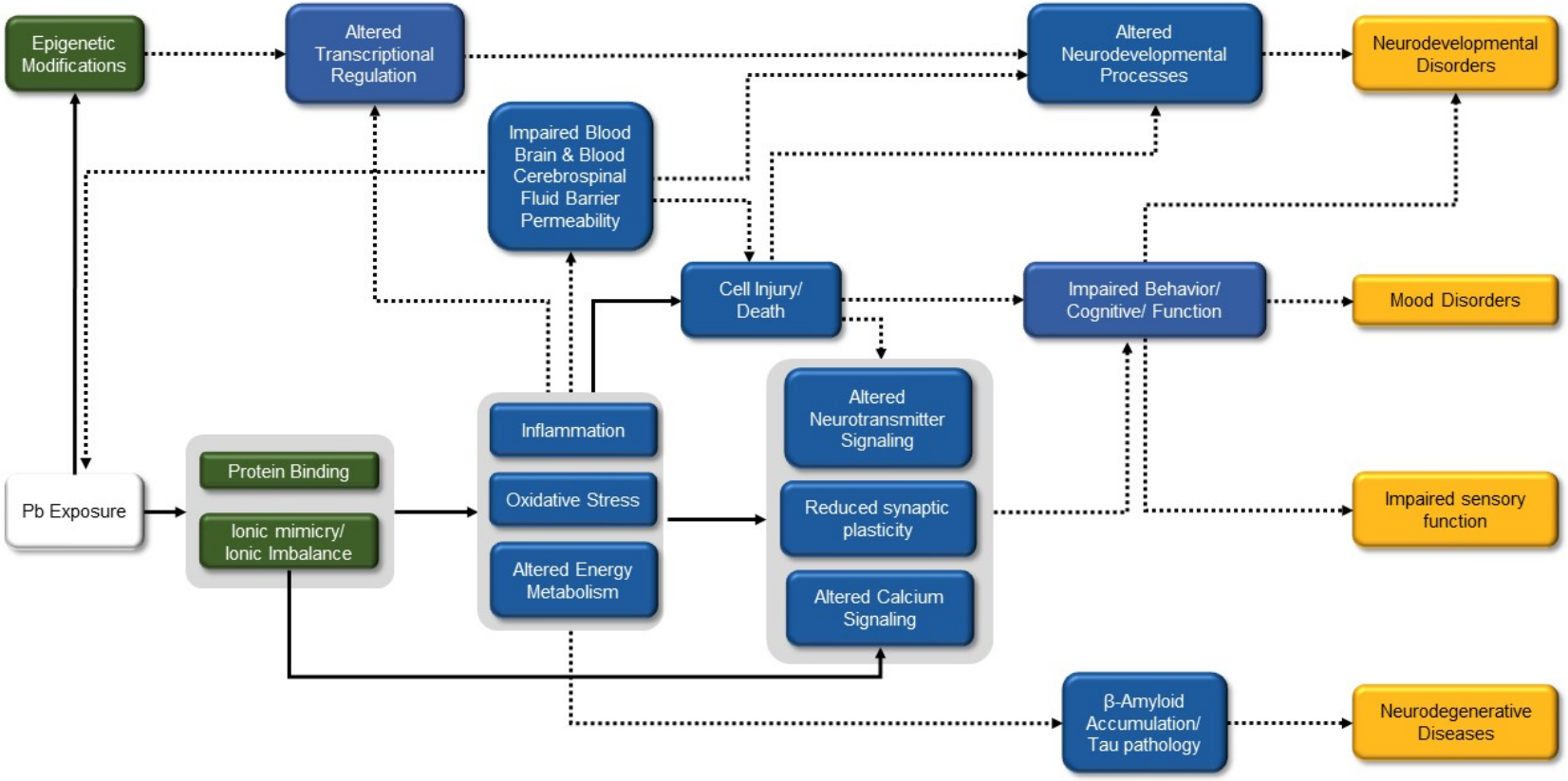
Outcome: Nervous System effects; and

Study Design: Controlled exposure studies of animals in vivo.

3.3 Biological Plausibility

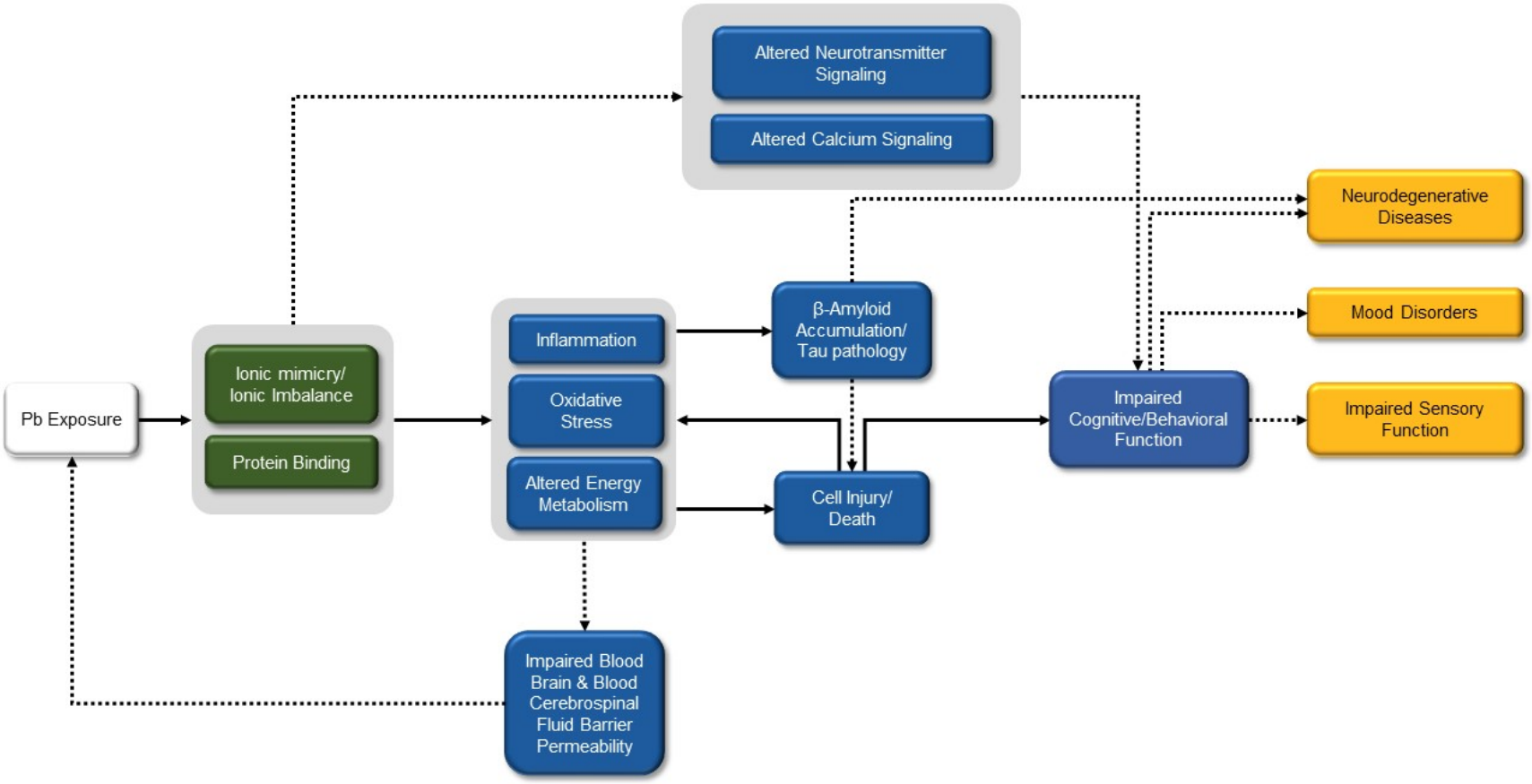
This section describes biological pathways that potentially underlie nervous system effects resulting from exposure to Pb. Timing of exposure is important for the health effects for Pb. Exposures during development can lead to improper formation and maturation of the nervous system and exposures to the mature nervous system can lead to neurodegeneration. Figure 3-1 and Figure 3-2 graphically depict these proposed pathways for health effects resulting from developmental exposure to Pb and later life exposures, respectively. Proposed pathways are presented as a continuum of responses, connected by arrows, which may ultimately lead to the apical nervous system health effects associated with exposures to Pb at concentrations observed in epidemiologic studies. This discussion of "how" exposure to Pb may lead to effects on the nervous system contributes to an understanding of the biological plausibility of epidemiologic results evaluated throughout this appendix. Most of the studies cited in this subsection are discussed in greater detail elsewhere in this appendix. The biological plausibility for Pb-induced effects on the nervous system is supported by evidence from the 2013 Pb ISA and by recent evidence. Note that the structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the current ISA are discussed in Section IS.7.2.

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



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence related to Pb exposure, and the arrows indicate a proposed relationship between those effects. Solid arrows denote evidence of essentiality as provided, for example, by an inhibitor of the pathway used in an experimental study involving Pb exposure. Dotted arrows denote a possible relationship between effects. Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color coded (white, exposure; green, initial effect; blue, intermediate effect; orange, effect at the population level or a key clinical effect). Here, population-level effects generally reflect results of epidemiologic studies. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below. The structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the 2022 Pb ISA are discussed in Section IS.7.2. Source: (Shadbegian et al., 2019).

Figure 3-1 Potential biological pathways for nervous system effects following developmental exposure to Pb.



Note: The boxes above represent the effects for which there is experimental or epidemiologic evidence related to Pb exposure, and the arrows indicate a proposed relationship between those effects. Solid arrows denote evidence of essentiality as provided, for example, by an inhibitor of the pathway used in an experimental study involving Pb exposure. Dotted arrows denote a possible relationship between effects. Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color coded (white, exposure; green, initial effect; blue, intermediate effect; orange, effect at the population level or a key clinical effect). Here, population-level effects generally reflect results of epidemiologic studies. When there are gaps in the evidence, there are complementary gaps in the figure and the accompanying text below. The structure of the biological plausibility sections and the role of biological plausibility in contributing to the weight-of-evidence analysis used in the 2022 Pb ISA are discussed in Section I.S.7.2. Source: (Shadbegian et al., 2019).

Figure 3-2 Potential biological pathways for nervous system effects following postweaning exposure to Pb.

Plausible pathways connecting Pb exposure to apical events resulting from developmental and later life exposures to Pb are proposed in Figure 3-1 and Figure 3-2, respectively. The proposed pathways supported by the strongest evidence include the direct actions of Pb on cellular protein function and subsequent initiation of oxidative stress-mediated pathways.

When Pb accumulates in the CNS, it can interfere with coordination of metal ions, which is essential for the structure and function of many cellular proteins. Pb ions can compete with and displace physiologically relevant ions (including Fe, Zn, Ca, and others) within proteins, leading to both altered protein structure and function. As described in the 2013 Pb ISA, there is evidence that this ionic mimicry and imbalance occurs in multiple organ systems, including the brain, and in proteins that perform diverse functions including metabolism, inflammation, and oxidative stress responses. For example, Pb treatment can disrupt Ca^{2+} signaling through interactions with calmodulin, voltage-gated Ca^{2+} channels, and various adenosine triphosphate (ATP)ases (U.S. EPA, 2013). There is also evidence that Pb can replace Zn ions in Zn finger-binding motifs, which are present in several transcription regulating proteins (U.S. EPA, 2013). Some research supports an interactive effect between Fe status and Pb exposure due to shared metabolic and physiological profiles. Lifetime exposure to Pb in rats has been shown to affect Fe status by increasing Fe content in the cortex and hippocampus of adult and aged animals and altering the expression of divalent metal transporters (such as divalent metal transporter 1 and ferroportin) in the brain (Zhu et al., 2013), suggesting that Pb may interfere with Fe trafficking in the brain. Often the effect of Pb can be reduced with exogenous supplementation of biologically relevant metals. Recent studies support the protective role of supplementation of Ca^{2+} (Basha and Reddy, 2015; Gottipolu and Davuljigari, 2014), Zn (Pedroso et al., 2017), Fe (Liu et al., 2013c) or essential metal mixtures (Basha et al., 2014) on neurologic alterations from Pb. These data support the hypothesis that direct competition of Pb with metals can cause neurologic effects.

The brain has the highest energy demand and metabolism of any organ. Because of this fact, energy homeostasis is critical and energy imbalance can increase the brain's susceptibility to stressors and cell death. Pb-induced alterations in energy production and metabolism have been measured in several ways. As discussed in the 2013 Pb ISA, Pb exposure can alter many aspects of energy metabolism, with animal models demonstrating effects following both developmental and adult exposures to Pb (discussed in Section 3.4.2.1). In recent studies of developmental Pb exposure, Pb-induced impairments in energy production throughout the body have been measured as reductions in the activity of glucose and glycogen metabolizing enzymes (Baranowska-Bosiacka et al., 2017) and alterations in the number and structure of mitochondria (Ouyang et al., 2019; Gąssowska et al., 2016a). Studies of Pb exposure in postweaning animals showed similar reductions of metabolizing enzyme activity (Yun et al., 2019; Verma et al., 2005; Yun and Hoyer, 2000; Sterling et al., 1982), altered mitochondrial structure (Ouyang et al., 2019; Dabrowska et al., 2015; Sun et al., 2014), and ATPase activity (Thangarajan et al., 2018), suggesting alteration of energy metabolism may occur regardless of the timing of Pb exposure.

Energy production involves the formation of reactive intermediate species including reactive oxygen (ROS) and nitrogen species (RNS). Disruptions in the mitochondria and energy metabolism result in increased levels of ROS and RNS. While ROS are a part of normal cellular functioning, uncontrolled production or reduced elimination of ROS by antioxidant systems can result in oxidative stress and cellular damage (for example, DNA damage, oxidization of cellular components). Evidence reviewed in the 2013 Pb ISA suggests that Pb may exert toxicity by disrupting cellular metabolism, increasing ROS/RNS concentrations, and depleting antioxidant capacity (U.S. EPA, 2013). Numerous recent studies have reported dysregulation of oxidative stress concurrent with altered mitochondrial function (Ahmad et al., 2020; Karri et al., 2018; Maiti et al., 2017; Kumar and Muralidhara, 2014; Baranowska-Bosiacka et al., 2011), adding to the body of evidence. A study by Yang et al. (2014) found that Pb downregulated the mitochondrial Ca^{2+} uniporter (MCU), resulting in increased ROS production in both SH-SY5Y cells and in newborn rats. Yang and colleagues found that in vitro activation or overexpression of MCU prevented Pb-induced oxidative stress whereas MCU inhibition or knockdown potentiated the effects suggesting that alterations in mitochondrial function were responsible for Pb-induced ROS production. In a similar manner, Pb has been shown to upregulate cyclophilin D, a protein that regulates mitochondrial membrane potential, and in vitro knockdown or inhibition of cyclophilin D prevents the Pb-induced loss of mitochondrial membrane potential (Ye et al., 2020; Ye et al., 2016a). Mitochondrial function is also thought to be dependent on a dynamic balance between mitochondrial fission and fusion. In a recent study, Pb reduced energy production and respiration while increasing mitochondrial ROS and altering the expression of genes involved with mitochondrial dynamics both in vitro and in vivo (Dabrowska et al., 2015). In this study, knockdown of the transcription factor peroxisome proliferator-activated receptor-γ coactivator 1α, which protects the mitochondrial fusion and fission balance, increased in vitro ROS production in response to Pb, further suggesting that altered mitochondrial activity results in ROS production in response to Pb. Together, these data provide evidence that mitochondrial dysfunction and altered energy metabolism is a source of oxidative stress.

Given their reactive nature, ROS and RNS can damage cellular proteins, lipids, and nucleic acids, which can lead to functional and downstream signaling impairment. As discussed in the 2013 Pb ISA, Pb exposure leads to elevated levels of ROS in neurons and other brain cells of exposed animals. Levels of oxidative species have also been assessed indirectly by the presence of oxidative damage to DNA and proteins as well as peroxidation of lipids. Studies assessed in the 2013 Pb ISA showed that Pb exposure increased signs of oxidative damage in the brains of a variety of animal species (U.S. EPA, 2013; Wu et al., 2008). Since publication of the 2013 Pb ISA, more recent studies have demonstrated Pb-induced increases in ROS production and oxidative damage in the brain both during development (Hossain et al., 2016; Lu et al., 2013) and postweaning (Singh et al., 2019; Liu et al., 2018a; Thangarajan et al., 2018; Singh et al., 2017; Kumar and Muralidhara, 2014; Flora et al., 2012). Proper regulation of oxidative stress requires a balance between the presence of oxidative species (i.e., ROS and RNS) and levels of antioxidant defense proteins (e.g., glutathione [GSH], catalase [CAT], and SOD). Along with increased ROS/RNS production, depletion of antioxidant proteins or reductions in antioxidant enzyme activity could contribute to an overall increase in oxidative stress. As discussed in the 2013 Pb ISA, animal

studies and human panel studies have shown that BLL is associated with an increased ratio of oxidized to unoxidized GSH (Mohammad et al., 2008; Diouf et al., 2006; Ercal et al., 1996; Sandhir and Gill, 1995). More recent studies showed similar impairment of antioxidant defenses in animal models of Pb exposure during developmental (Lu et al., 2013) and postweaning (Singh et al., 2019; Thangarajan et al., 2018; Singh et al., 2017; Flora et al., 2012) Pb exposures. Furthermore, changes in antioxidant status and oxidative stress can contribute to mitochondrial dysfunction, as described above. There is strong evidence that Pb exposure across the lifespan disrupts multiple aspects of energy metabolism and oxidative stress regulation.

Cellular damage caused by oxidative insults can trigger inflammation and vice versa; thus, it is often difficult to disentangle which occurs first. Given the interrelated nature of these factors, they are combined within the same gray box in the blood Pb diagrams (Figure 3-1 and Figure 3-2). Inflammation is a hallmark of many neurological conditions and neurodegenerative diseases. Inflammation can be triggered by the production of inflammatory mediators (e.g., cytokines) in response to cell or protein damage. As discussed in the 2013 Pb ISA, Pb exposure results in signs of inflammation including activation of inflammatory signaling pathways, inflammatory mediator production, and microglia cell activation (U.S. EPA, 2013). Several studies have observed increased inflammatory mediator levels and activation of inflammatory signaling pathways (for example, tumor necrosis factor-alpha) in the brains of animals exposed to Pb during development (Chibowska et al., 2020; Hossain et al., 2016; Ashok et al., 2015) and postweaning (Yang et al., 2019; Liu et al., 2018a). Proinflammatory markers interact with, and in some cases infiltrate, the BBB, initiating neuroinflammation, as indicated by altered gene expression, increased apoptosis, lipid and protein oxidation, and microglial activation (Saleh et al., 2018; Shvachiy et al., 2018; Sobin et al., 2013). Similarly, histologic and immunohistochemical signs of neuroinflammation in the dentate gyrus have been reported in rats exposed to Pb continuously from 7 days postconception to 28 weeks of age, which corresponded to behavioral changes (Shvachiy et al., 2018). In the same study, a similar neuroinflammatory phenotype was observed in mice that were given an 8-week Pb abstinence period between 12-week and 8-week Pb exposures (Shvachiy et al., 2018). In sum, recent evidence supports the plausibility of inflammation as an intermediate event in the development of neurological health effects regardless of the timing of Pb exposure.

While a robust immune response can protect the brain from certain insults, prolonged neuroinflammation is associated with several neurological and neurodegenerative diseases. AD, characterized by the accumulation of Aβ and p-tau, has been associated with increased markers of neuroinflammation. While neurodegenerative diseases are associated with old age, studies of developmental exposures to Pb have shown that early life exposures are associated with Alzheimer's-like pathology in adult animals. As discussed in the 2013 Pb ISA, Pb exposure in juvenile animals resulted in the increased production of APP and higher levels of p-tau in offspring. Similarly, early life Pb exposure of nonhuman primates led to Alzheimer's-like pathology later in adulthood (Wu et al., 2008). Studies published since the last ISA support and extend the findings that developmental exposures to Pb can lead to increased levels of misfolded proteins (e.g., abnormal APP processing, Aβ, tau protein) and

Alzheimer's-like pathologies (e.g., p-tau accumulation) (Ashok et al., 2015; Bihaqi and Zawia, 2013). Evidence from exposures during development suggests that early life may represent a sensitive window for insults associated with neurodegenerative disease (Liu et al., 2014a). Some studies with exposure of postweaning animals to Pb have shown increased inflammation associated with AD markers (Yang et al., 2019; Liu et al., 2018a; Zhang et al., 2012). In postweaning studies, treatment with molecules with anti-inflammatory and antioxidative properties were able to prevent Aβ accumulation and reversed cognitive and behavioral alterations in Pb-exposed mice (Liu et al., 2020; Yang et al., 2019; Liu et al., 2018a). Because of this, there is a solid line connecting the box containing inflammation, oxidative stress, and altered energy metabolism to the accumulation of Aβ in Figure 3-2. Evidence of effects of Pb on other neurodegenerative diseases are more limited. A recent study showed that exposure of postweaning rats to Pb resulted in increased accumulation of α-synuclein, a protein associated with PD, in the hippocampus that correlated with impaired learning and memory (Zhang et al., 2012). Overall, new data support the previous findings that Pb exposure can affect the development and progression of neurodegenerative pathologies in developmentally and postweaning exposed animals.

Beyond Pb's ability to produce neuroinflammation and oxidative stress and increase expression of disease-related proteins, excessive damage to cellular proteins or DNA can trigger cell death. While cell death and neuronal population loss in adulthood contribute to brain pathology, the developing brain is far more sensitive to disruption. Cell migration, differentiation, and pruning are all essential neurodevelopmental processes that need to be carefully timed and orchestrated. Thus, increased or aberrant cell loss results in improper nervous system development that could be responsible for the altered mood, sensory, or cognitive functions observed in Pb-exposed children and animals. The 2013 Pb ISA and Section 3.4.2.1 present several animal studies showing upregulation of apoptotic markers in various regions of the brain following Pb treatment, at various lifestages, which was supported by similar findings in in vitro experiments (U.S. EPA, 2013). Recent studies also reported activation of pro-apoptotic pathways in response to developmental Pb exposure (Ebrahimzadeh-Bideskan et al., 2016; Hossain et al., 2016; Su et al., 2016; Lu et al., 2013), supporting and extending the experiments reviewed in the 2013 Pb ISA. Another study showed histologic changes in the brain concomitant with increased markers of protein and lipid damage (Saleh et al., 2019), suggesting a relationship between cell death and structural changes in the brain with oxidative damage. Developmental Pb exposure caused dysregulated myelination in the brains of rats, which could be rescued with cotreatment with antioxidants (Nam et al., 2020; Nam et al., 2019a). Myelination is an essential step in nervous system development, as myelin sheaths facilitate quick and efficient electrical transmission along nerve cells to preserve nervous system function and connectivity. Several studies have also demonstrated that treatment with compounds with antioxidant capacity reduced the apoptotic signaling (Nam et al., 2018b; Ebrahimzadeh-Bideskan et al., 2016). Together, these data provide the justification for a solid line from the gray box containing oxidative stress and inflammation to the box containing cell injury/death in Figure 3-2.

Widespread cell loss in the mature nervous system can also lead to functional and structural changes that can contribute to behavioral and cognitive changes. Cell death is also a common element in

many neurodegenerative diseases. The animal studies showing upregulation of apoptotic markers in various regions of the brain following Pb treatment discussed in the 2013 Pb ISA are strengthened by similar findings in several new studies (Amedu and Omotoso, 2020; Liu et al., 2020; Abubakar et al., 2019; Singh et al., 2019; Yang et al., 2019; Liu et al., 2018a; Thangarajan et al., 2018; Maiti et al., 2017; Singh et al., 2016; Flora et al., 2012). In vitro exposure of neuronal cell lines to Pb resulted in reduced cell viability and increased apoptosis (Ye et al., 2020; Liu et al., 2017; Neelima et al., 2017; Meng et al., 2016; Su et al., 2016; Ye et al., 2016b; Ahmed et al., 2013). Additional discussion of apoptotic markers and brain structural changes following Pb exposure are discussed in Section 3.4.2.1. Like the developmental exposure studies, demyelination was observed in the spinal cord following postweaning exposure to Pb (da Silva et al., 2020; Villa-Cedillo et al., 2019). These data provide plausibility that adult Pb exposures contribute to cognitive and behavioral changes. Some studies therapeutically targeted RNS production in the mitochondria by treatment with fisetin, a polyphenolic compound with antioxidant properties to ameliorate the activation of pro-apoptotic signaling (Yang et al., 2019; Maiti et al., 2017). Their results suggest a role for oxidative stress in triggering the apoptotic cascade. In vitro treatment with the antioxidant genistein also protected against cell death (Su et al., 2016). Thangarajan et al. (2018) showed that treatment with an anti-inflammatory and antioxidative compound, morin, was able to largely restore proper brain architecture after Pb exposure. Together, these data provide the justification for a solid line from the gray box containing oxidative stress and inflammation to the box containing cell injury/death in Figure 3-2.

Inflammation and oxidative stress can also affect the integrity of the BBB, which provides a selective barrier for entry from the circulation to the brain and spinal cord. As discussed in the 2013 Pb ISA and 2006 Pb AQCD, Pb exposure in rodents was shown to increase permeability of the BBB and the blood-CSF barrier. Interestingly, Pb alone does not have a large effect on BBB integrity but can prolong BBB permeability in response to other stimuli (U.S. EPA, 2013, 2006). The effect of Pb on the BBB is also selective in that the permeability of all solutes is not affected equally (U.S. EPA, 2013, 2006). Disruption of the BBB could potentially promote increased Pb accumulation in the brain with prolonged or repeated exposure. Two new studies assessed the integrity of the BBB following Pb exposure and observed disruption of brain permeability with reduced levels of tight junction proteins and other important capillary proteins (Wu et al., 2020a; Song et al., 2014). In adult rats, 8 weeks of Pb dosing reduced expression of the tight junction proteins occludin and zonula occludens−1 at the BBB (Song et al., 2014). Pb has been implicated in alteration of the CSF barrier in rats (Zheng et al., 1996). The CSF can carry hormone signals important for brain development; thus, disruption of the cerebrospinal barrier could affect proper hormone signaling for brain development. Indeed, Pb exposure was reported to decrease transthyretin levels in the CSF, suggesting altered cerebrospinal barrier integrity (Zheng et al., 1996). There is likely interplay between Pb effects on endocrine and nervous system development. In conclusion, there is a potential for Pb to affect the BBB and blood spinal cord barrier, which could alter Pb availability and uptake into the nervous system.

While most data suggest that Pb acts through a mode of action involving oxidative stress and inflammation, additional signaling pathways are also affected by Pb exposure. Pb exposure can alter ion balance, which has particular importance with regard to the effect on Ca^{2+} signaling. Calcium signaling is vital for many fundamental neurological processes including membrane excitability, neurotransmitter release, synaptogenesis, transmission, and other processes. Of particular relevance for this review, neurotransmitter signaling is intimately connected with Ca^{2+} signaling. As discussed in the 2013 Pb ISA, developmental exposure to Pb interferes with the evoked release of neurotransmitters by inhibiting Ca^{2+} transport through voltage-gated ion channels (Cooper and Manalis, 1984; Suszkiw et al., 1984). Ca^{2+} is also a ubiquitous second messenger, which can regulate many neuronal physiologic processes like gene expression, membrane excitability, and dendrite development (Kawamoto et al., 2012). Interestingly, in the absence of stimulation, Pb has some Ca^{2+} mimetic activity that increases baseline neurotransmitter release (Cooper and Manalis, 1984; Suszkiw et al., 1984). In general, Pb exposure increased Ach levels, increased dopaminergic signaling, and reduced NMDAR expression (U.S. EPA, 2013). Animal models suggest that Pb exposure during development leads to inhibition of acetylcholinesterase (AchE), thereby increasing the levels of Ach and causing lasting neurodevelopmental changes that persist into adulthood (Basha and Reddy, 2015). The authors found that addition of Ca^{2+} restored cholinergic signaling (Basha and Reddy, 2015). These data help to justify the solid line from ionic mimicry to altered neurochemical signaling in Figure 3-1. Similar studies in animals postweaning have shown similar decreases in AchE activity (Galal et al., 2019; Okesola et al., 2019; Thangarajan et al., 2018; Andrade et al., 2017; Ferlemi et al., 2014; Phyu and Tangpong, 2013). Recent literature also supports altered dopaminergic signaling following postweaning Pb exposure (Sobolewski et al., 2020; Yousef et al., 2019; Amos-Kroohs et al., 2016; Stansfield et al., 2015; Basha et al., 2014; Weston et al., 2014; Cory-Slechta et al., 2012; Graham et al., 2011). Ca^{2+} gradients are also responsible for generating action potentials. Alteration of intracellular Ca^{2+} levels in neurons could cause deleterious effects on action potential generation and repolarization. Recent evidence shows that hippocampal slices from 50-day old rats exposed to Pb both pre and postnatally had enhanced pared pulse facilitation, suggesting Pb-induced dysregulation of Ca^{2+} signaling (Zhang et al., 2015b). This data support findings from a limited number of human MRI and MRS studies that provide evidence of physical and physiological changes in the brain corresponding to increased blood Pb that were discussed in the 2013 Pb ISA and 2006 Pb AQCD. Together there is evidence that Pb can alter neurotransmitter release and signal potentiation, which in turn could contribute to the changes in brain activity seen in various behavioral and cognitive diseases.

Beyond the actions of Pb discussed thus far, there is growing evidence of the effect of changes to the epigenome in mediating toxicity. Epigenetic changes refer to alterations in the mechanisms that regulate gene expression without altering DNA sequence. Epigenetic programming is a fundamental developmental process, and the complex relationships between the genome, epigenome, and environment can shape the health of present and future generations. Epigenetic alterations are often measured as changes in histone and DNA methylation patterns as well as the levels of the enzymes (e.g., methyltransferases, acetylases, deacetylases) responsible for regulating epigenetic modification in situ. Transcriptional regulators like microRNAs and long noncoding RNAs are also considered epigenetic

modifiers. As discussed in the 2013 Pb ISA, developmental Pb treatment in mice and monkeys decreased the activity of some DNA methyltransferases. Therapeutic treatment with a methyl donor improved Pb-induced decrements in LTP and Morris water maze performance (Cao et al., 2008). Gestational and postnatal exposure to Pb in rats increased histone acetylation in the hippocampus, which corresponded to a hyperactivity phenotype (Luo et al., 2014). The authors suggested this was due to upregulation of histone acetyltransferases, including p300. However, these changes occurred at BLLs in excess of 50 µg/dL; thus, the relevance of these findings to ambient exposure in humans is questionable. Other studies have reported changes in the expression of DNA methyltransferases (Schneider et al., 2013) and increased hypermethylation, especially in the hippocampus of female mice (Sánchez-Martín et al., 2015). The window of exposure, prenatal stress, and sex can all play a role in determining the epigenetic modifications (Sobolewski et al., 2018). While differences in epigenetic modifications and the effects of Pb on epigenetic enzymes have been reported and linked to behavioral effects in animals, there remains little evidence to connect epigenetic changes to alterations in specific pathways that have the potential to cause neurobehavior effects. As a result, the arrow for epigenetic changes in is represented as a dotted line when connecting to the box for neurodevelopmental disorders. Future research may elucidate a role for epigenetic modification in the etiology of neurological diseases. Most of the Pb literature on epigenetic changes has focused on heritable epigenetic changes during development; however, the effect of postweaning exposure to Pb on epigenetic mechanisms is not well known. Very few studies have evaluated epigenetic changes throughout the lifetime or with later life exposures. Individual studies have found changes in the expression of a long noncoding RNA (Nan et al., 2016) and a methyltransferase (Schneider et al., 2012), which might suggest that epigenetic modification could be affected during adult exposures; however, there are too few studies to draw reliable conclusions. The conclusion of epigenetic modification resulting in neurological effects is only plausible for developmental exposures with the present available data.

In summary, Pb exposure can result in a range of neurocognitive and behavioral health effects through a myriad of complex biological pathways. The pathways described here provide biological plausibility for associations between Pb exposure and nervous system effects in in children and adults. The developmental timing, sex, and presence of other stressors or enrichments alongside of Pb exposure can affect the resulting health effects. The identified pathways share many common features, including Pb interactions with cellular proteins, competing with and displacing other biologically relevant cations, increased oxidative stress, and inflammation, which can have widespread effects on brain structure and function. There is also evidence for disruptions of Ca^{2+} signaling, which can result in altered neurotransmitter signaling and contribute to the development of neurological health effects. Epigenetic modifications resulting from Pb developmental exposure have been reported but are still an area of active investigation. The role of these epigenetic changes in the progression of neurological health effects with later Pb exposures is unclear. Together the proposed pathways provide biological plausibility for epidemiologic evidence of neurological effects and were used to inform causality determinations throughout this appendix.

3.4 Overt Nervous System Toxicity

Overt nervous system toxicity refers to a diverse group of endpoints that inform brain structure and function, including brain histopathology changes, brain weight, electrophysiology, neuroinflammation, and neurotransmitter analyses. The collective body of epidemiologic and experimental animal studies assessed in the 2013 Pb ISA demonstrated the effects of Pb exposure on an array of nervous system outcomes. The evidence, including uncertainties, is summarized in Section 3.4.3. Study details that supplement the information provided in the text are in the evidence inventories (Table 3-1E and Table 3-1T in Section 3.7). Previous Pb assessments reviewed epidemiologic studies that found associations of Pb biomarkers with electrophysiologic or physical changes in the brains of adults assessed by imaging technologies. Biological plausibility for the effects of Pb on overt nervous system toxicity was provided by a small number of experimental animal study findings with dietary and lactational Pb exposure, with some evidence at BLLs relevant to humans. Recent epidemiologic studies support and extend the evidence pertaining to the association of lead exposure during childhood with brain structure and function in adolescence or adulthood. A smaller set of cross-sectional studies also report associations between childhood BLLs and overt nervous system outcomes. Multiple experimental animal studies report changes in the brains of rats and mice following exposure to Pb. These include changes in histology, neurotransmitter measures, brain weight, and electrophysiology measures, providing coherence for the epidemiologic studies that show associations with decrements in cognition, neurodegeneration, or increased behavioral problems. There is no causality determination for this section; rather, evidence in this section may be referenced in the outcome-specific "Summary and Causality Determination" discussions of Sections 3.5 and 3.6 if they provide biological plausibility or coherence for the observations in the epidemiologic studies.

3.4.1 Epidemiologic Studies of Brain Structure and Function

Previous Pb assessments (U.S. EPA, 2013, 2006) reviewed a small body of epidemiologic studies that found associations of Pb biomarkers with electrophysiologic and physical changes in the brains of young adults as assessed by magnetic resonance imaging (MRI) or spectroscopy (MRS). The implications of findings from most studies assessed in the 2006 Pb AQCD were limited by the small sample sizes (n = 12 to 45) and inadequate consideration of potential confounding. However, analyses cohort of adults (ages 20−23 years) reviewed in the 2013 Pb ISA included larger sample sizes and aimed to characterize potentially important lifestages of Pb exposures (Yuan et al., 2006), thus expanding the evidence pertaining to potential links between physiologic brain changes and functional neurodevelopmental effects. Overall, the small number of studies in a limited number of populations assessed in the 2013 Pb ISA showed physical and physiologic changes in areas of the brain associated with neurodevelopmental function, providing biological plausibility for the associations

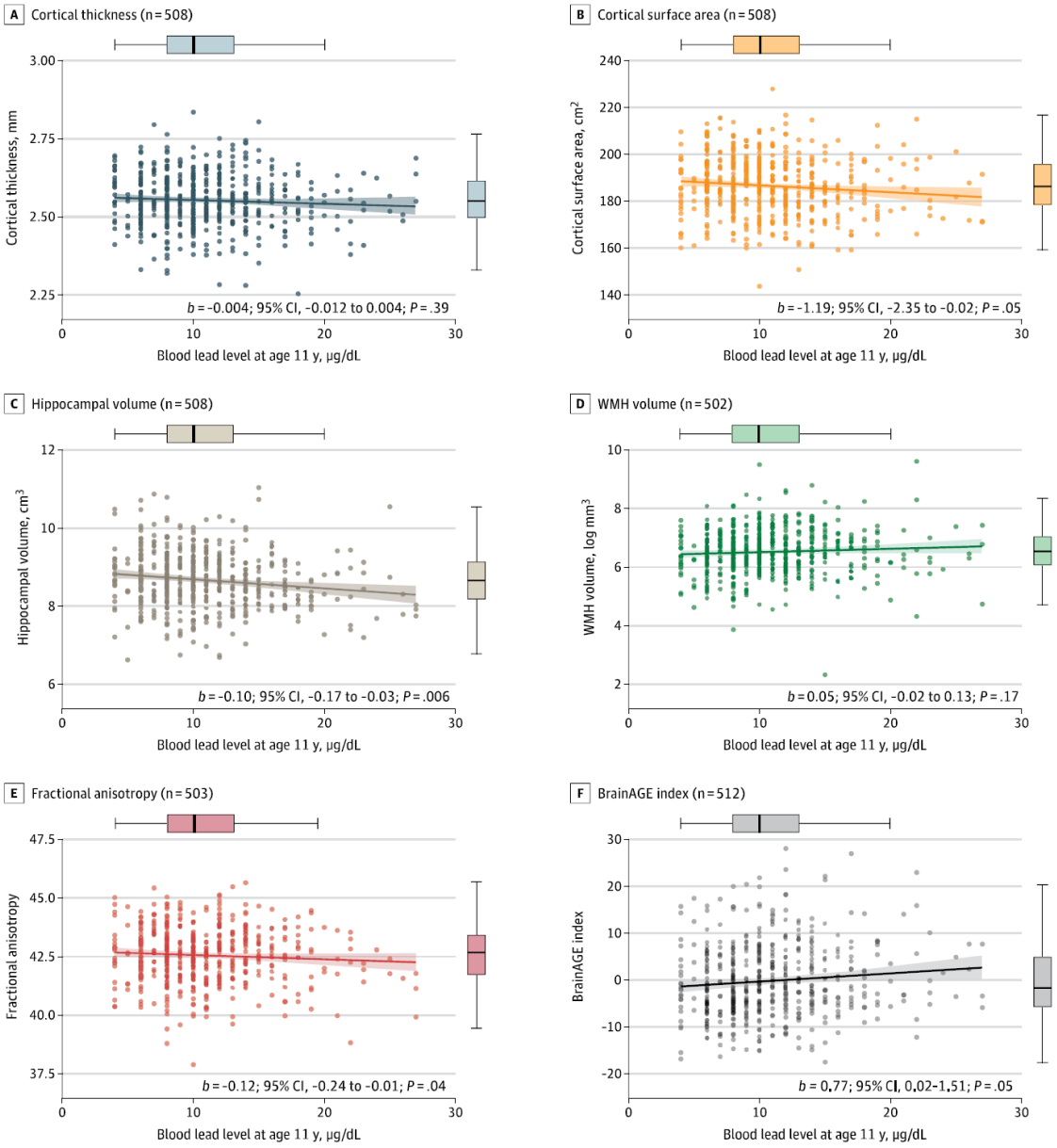
observed between Pb biomarker levels and cognitive function decrements and behavioral problems.

Several recent longitudinal studies add to the evidence characterizing the association of Pb exposure during childhood with brain structure and function during adolescence or adulthood. A smaller number of studies evaluated the cross-sectional association of childhood BLL with brain structure or function in childhood. These studies are summarized below, and key information from the studies is included in Section 3.7, Table 3-1E.

Reuben et al. (2020) conducted a study to examine the effect of childhood BLL, measured at age 11, on lower structural integrity of the brain at age 45. These investigators used data from the Dunedin Study in New Zealand, which enrolled participants beginning in 1972 and 1973 and followed them through April 2019. The mean early childhood BLL for the study participants was 10.99 μg/dL. MRI was used to assess multiple endpoints related to gray matter (cortical thickness, surface area, and hippocampal volume), white matter (white matter hyperintensities, fractional anisotropy [FA]), and the gap between chronological age and estimated brain age. In addition, cognitive function was estimated using the Wechsler Adult Intelligence Scale (WAIS)-IV, self-reports, and informant reports (see Section 3.6.1). A total of 564 of the original 1037 infants enrolled at birth were included in the analysis. Findings from the study are depicted in Figure 3-3. In models adjusted for sex, maternal IQ, and socioeconomic status (SES), associations were observed with cortical surface area, hippocampal volume, global FA, and the gap between each study member's chronological age at imaging and their MRI-predicted age, but not with all the MRI metrics assessed.

Two analyses of the Cincinnati Lead Study (CLS) have been conducted since the 2013 Pb ISA. Confounders considered in these analyses included child characteristics, Home Observation for the Measurement of Environment (HOME) score, maternal IQ, and SES (see Section 3.7, Table 3-1E for study-specific confounders). Cecil (2011) examined the association of childhood BLL (childhood [3–28 months] average) with volumetric MRI, MRS, diffusion tensor imaging (DTI), and functional MRI outcomes ascertained between ages 19 and 24 years old. This study found that childhood BLL was associated with decreased gray matter volume in several regions (i.e., medial and superior frontal gyri, inferior parietal lobule and cerebellar hemispheres). Higher childhood BLL was also associated with lower metabolite concentrations in several brain regions (white matter, left basal ganglia, left cerebellar hemisphere, and vermis). DTI and functional MRI findings also suggested injury and compensatory activity in specific brain regions. Overall, structural, organizational, and functional changes in the brain regions responsible for regulating behavior were indicated by this study. In another study of participants enrolled in the CLS, Beckwith et al. (2021) examined the relationships between childhood BLL (at 78 months), structural brain volume, and adult criminality. BLLs were associated with MRI-derived decreases in white and gray matter volumes in the frontal parietal and temporal lobes. Decreased gray matter volume in brain regions responsible for cognition and emotional regulation was also associated

with criminal arrests, potentially supporting associations observed between Pb exposure and conduct disorders that are described in Section 3.5.3.



BrainAGE = Brain Age Gap Estimation; CI = confidence interval; MRI = magnetic resonance imaging; SES = socioeconomic status. WMH = white matter hyperintensities; yr = year(s).
Regression lines and their 95% CIs are plotted. The box plots show the distribution of BLLs and brain outcomes.
Beta coefficients shown are for an incremental increase of 5 µg/dL in childhood BLL. Source: Reuben et al. (2020).

Figure 3-3 The relationship between blood Pb level at age 11 and brain outcomes in adulthood.

Lamoureux-Tremblay et al. (2021) examined the association between pre- and postnatal (measured concurrently to the MRI) BLLs and MRI findings in adolescents (mean age 18.3 years) enrolled in a longitudinal study of Inuit from Northern Quebec exposed to Pb, mercury (Hg), and polychlorinated biphenyls (PCBs). Functional MRI data were collected during fear conditioning and extinction tasks with the aim of understanding emotional dysregulation that could lead to anxiety disorders. These authors found higher differential activation in the right dorsolateral prefrontal cortex in association with higher postnatal BLL. Differential effects in the high Pb exposure group were observed during the fear extinction phase and maintained discrimination between the safety and threatening signals (CS+ > CS-). Activation of the dorsolateral prefrontal cortex has been associated with cognitive processes for regulating the affective state. The mean cord blood Pb was 4.56 µg/dL and the mean concurrent BLL was 1.78 µg/dL in this study. In an earlier study of this Inuit population, Ethier et al. (2012) measured visual evoked potentials (VEPs) using electrodes on the scalp to provide a direct measure of brain functions related to sensory function (i.e., visual contrast sensitivity and spatial vision) at age 5. The mean cord BLL in this study was 4.6 µg/dL. Amplitude and latency for standard VEP components were measured (i.e., N75 [negative deflection at approximately 75 ms], P100 [positive deflection at approximately 100 ms], and N150 [negative deflection at approximately 150 ms]) in this longitudinal study. Multiple tests were conducted, and associations were reported with significance levels. Cord Pb level was associated with a delay of the N150 component (e.g., $\beta = 0.06$ [95% CI: 0.01, 0.10]) and other latency metrics, which may indicate a deficit in early visual processing in Pb-exposed children. Confounders including child characteristics, maternal education, SES, drug and alcohol use, and other metals were considered in the analyses of Inuit children (see Table 3-1E for study-specific confounders considered). A subset of two separate studies was combined for this study, and participation rates based on the original number of participants enrolled in the study were not reported.

In a cross-sectional analysis of children, Kim et al. (2018a) examined the interaction between dopamine receptor D2 (DRD2) and BLL on the cortical thickness of 12 regions of the frontal lobe ascertained via MRI. The D2 receptor is located in the prefrontal cortex of the brain and may contribute to the pathology of attention deficit/hyperactivity disorder (ADHD). The authors relied on an age- and sex-matched sample of children ages 6 to 17 years old with and without confirmed ADHD for the analysis. This study found an interaction effect between a variant of DRD2 and BLL on reduced cortical thickness of several regions in the frontal lobe in the ADHD group, but not in the healthy controls in regression analyses adjusted for age, intracranial volume, and sex. A correlation between reduced cortical thickness and poorer inattention score on the parent-reported ADHD rating scale was also reported, supporting a link between Pb exposure, MRI findings, and functional decrements in attention. Results for Kim et al. (2018a) are found in Section 3.7, Table 3-1E.

3.4.1.1 Summary

Overall, multiple studies, including prospective studies following children through adolescence and adulthood, found associations between BLL and physiologic changes in regions of the brain responsible for cognition and behavior. The prospective studies considered important confounders including the HOME score (CLS only), SES, drug and alcohol use, and maternal IQ. A smaller number of studies indicated Pb-related changes in brain function or physiologic changes in children. Associations between Pb exposure and a large number of metrics and brain regions were evaluated in the epidemiologic studies, raising the likelihood of chance findings.

3.4.2 Experimental Animal Studies of Brain Structure and Function

Animal studies can offer insights into Pb-induced effects on brain structure and function through investigations that cannot be conducted on human subjects. Experimental animal studies provide evidence that Pb can cause alterations in brain development. The 2013 Pb ISA reviewed evidence that Pb exposure produced increased levels of oxidative stress and inflammatory response markers (U.S. EPA, 2013). These effects were observed in many regions of the brain and were associated with changes in neuronal and glial cell morphology, neurotransmitter levels, and brain electrophysiology. Additional discussion of the biological pathways that potentially underlie these nervous system effects are discussed in Section 3.3.

Recent studies (see Figure 3-3 and Table 3-1T) support the results summarized in the 2013 Pb ISA, showing increases in inflammatory responses and markers of oxidative stress in various regions of the brain. Most studies evaluated oral dosing of Pb via drinking water or gavage with exposure durations ranging from 14 days to 701 days depending on the study, with studies in both adult and developing animals. The specific dosing regimen varied by study, but the present review focuses on studies that resulted in a measured BLL ≤30 μg/dL. In studies with multiple time points, the magnitude or severity of effects generally increased with exposure duration. In addition, studies with developmental Pb exposure identified pregnancy and early development as sensitive windows for Pb toxicity. Several studies have examined brain architecture using histological methods following Pb exposure. In general, the magnitude and severity of the effects increased with longer exposure durations, and some studies found Pb-induced effects could be ameliorated by co-exposures with antioxidants (such as vitamins and specific lipids) or by environmental conditions (e.g., rearing condition or enrichment).

3.4.2.1 Histopathology

The nervous system is made up of the central and peripheral nervous systems, which include a diversity of cell types broadly grouped into neurons and glial cells. Neurons are the functional electrically excitable cells in the brain. Glial cells can be further divided into microglia and macroglia (astrocytes, oligodendrocytes, ependymal cells, Schwann cells, satellite cells, radial glia, and enteric glia), which are

neuronal support cells with diverse functions including innate immunity, phagocytosis, myelination, synaptic regulation, neuronal activity, and blood-brain barrier (BBB) integrity (Rea, 2015). In the central nervous system (CNS), astrocytes, oligodendrocytes, and microglia are the major types of glial cells. Normal brain development relies on coordination of all cell types across time. Pathology methods can be used to study alterations in brain cell morphology, function, and composition.

Short-term studies (<30 days) in adults evaluating Pb exposure and brain morphology after oral exposures in rats have observed abnormalities in treated animals and their offspring, including decreased numbers of neurons or synapses (Nam et al., 2018a; Saleh et al., 2018; Gąssowska et al., 2016a; Han et al., 2014; Rahman et al., 2012b), disorganized cells and lack of characteristic layering (Saleh et al., 2019; Saleh et al., 2018; Zhou et al., 2018), increased vacuolization (Saleh et al., 2019), effects on dendritic spines (Xiao et al., 2020; Saleh et al., 2018; Wang et al., 2016; Du et al., 2015; Rahman et al., 2012b), increased numbers of apoptotic cells (Saleh et al., 2019; Meng et al., 2016), and increased expression of various proteins and biochemical parameters related to oxidative stress (Saleh et al., 2018; Singh et al., 2017; Zhu et al., 2013) in multiple brain regions including the cerebellum, cerebral cortex, and hippocampus. In aggregate, this evidence suggests that Pb has the potential to disrupt the integrity of single neurons and populations, which may contribute to overt toxicity. Pb exposure has also been shown to interfere with the homeostasis of other essential metal ions, such as iron (Fe), in the brain (Zhu et al., 2013) and to inhibit various enzymes involved in energy production or glucose uptake (Zhao et al., 2021) and metabolism (reviewed in (ATSDR, 2020)). For all these studies, BLLs were below 30 µg/dL, and many were below 20 µg/dL (see Evidence Inventory Table 3-1T). Further discussion of these mechanisms is provided in Section 3.3.

Studies of long-term Pb exposure (>30 days) have also assessed brain morphology in adult mice and rats following oral dosing and observed neuronal damage including irregular shape, vacuolization, and cell degeneration in the cerebellum, hippocampus, and cerebral cortex (Liu et al., 2022c; Saleh et al., 2019; Singh et al., 2019; Saleh et al., 2018; Sun et al., 2014). Other histopathological lesions, including karyopyknosis (pre-apoptotic chromatin condensation of cell nuclei) (Nan et al., 2016) and swollen and distorted mitochondria (Ouyang et al., 2019; Gąssowska et al., 2016a; Sun et al., 2014) were observed in other studies. Several biochemical parameters related to oxidative stress were assessed including apoptosis using immunohistochemical methods like terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL staining) (Singh et al., 2019; Baranowska-Bosiacka et al., 2017; Meng et al., 2016; Nan et al., 2016; Su et al., 2016; Baranowska-Bosiacka et al., 2013) as well as caspase-3 (Wang et al., 2021a) and cell replication using proliferating cell nuclear antigen (PCNA) (Singh et al., 2019). In a 12-week rat dietary study, the authors reported neuronal damage and cognitive deficits accompanied by decreased levels of synaptic proteins as well as decreased levels of receptors and proteins related to synaptic plasticity regulation (N-methyl D-aspartate receptor [NMDAR], cyclic adenosine 3',4'-monophosphate response element binding protein [CREB], brain-derived neurotrophic factor [BDNF]) (Liu et al., 2022c). BLLs in all of these studies were below 30 µg/dL and many were below 20 µg/dL (see Evidence Inventory, Table 3-1T).

In the single available inhalation study, adult mice were dosed for 6 weeks via whole body inhalation of Pb oxide (PbO) nanoparticles. Hippocampal damage was observed including shrunken and damaged neurons, as well as increased Pb content in the brain (Dumková et al., 2017). The study reported BLLs of 13.99 µg/dL. However, exposure to PbO nanoparticles via inhalation did not impact markers of cell proliferation (PCNA) or cellular apoptosis (TUNEL) in the hippocampus (Dumková et al., 2017). Despite the limited evidence available for inhaled Pb, continuity of the effects (i.e., neuronal damage) has been reported across different routes of exposure. Toxicology studies of Pb inhalation remain a data gap that limits the evaluation of nervous system effects from inhaled Pb.

Brain morphology has also been assessed in developing animals with a variety of exposure contexts including pre-mating, during gestation, and during lactation. Pb is transferred across the placenta and through lactation (Silbergeld, 1991; Bhattacharyya, 1983). Some studies included cross fostering experiments to assess unique sensitivities at specific developmental windows, with some evidence indicating that the postnatal period is particularly sensitive to Pb neurotoxicity (Barkur and Bairy, 2016). Given the altricial nature of rodents, the postnatal period is roughly analogous to the third trimester of human brain development. Similar to results in adults, studies of developmental Pb exposures observed alterations in brain morphology including reduced numbers of neurons in the forebrain, hippocampus, hypothalamus, and amygdala (Long et al., 2022; Vigueras-Villaseñor et al., 2021; Wang et al., 2021a; Nam et al., 2018a; Shvachiy et al., 2018; Xiao et al., 2014), damaged neurons (Long et al., 2022; Wang et al., 2021a; Zhu et al., 2013), reduced numbers of glial cells (Dominguez et al., 2019; Sobin et al., 2013), changes in synapses (Sadeghi et al., 2021; Wang et al., 2021b; Gąssowska et al., 2016a; Gąssowska et al., 2016b; Zhang et al., 2015b; Xiao et al., 2014), reduced numbers of mitochondria (Zhang et al., 2015b), swollen and shrunken mitochondria (Ouyang et al., 2019; Gąssowska et al., 2016a; Baranowska-Bosiacka et al., 2013), altered levels of glycoconjugates (constituents of synaptic and neural membranes) (Sadeghi et al., 2021), and chromatin abnormalities (Ouyang et al., 2019; Baranowska-Bosiacka et al., 2013). BLLs in all of these studies were below 30 µg/dL and many were below 20 µg/dL. In a rat developmental study in which animals were dosed throughout pregnancy and lactation (gestational day [GD] 1 to postnatal day [PND] 21) with BLLs of 6.86 µg/dL, the authors reported pathological changes in synapses, including swelling of nerve endings, thickened synaptic cleft structure, and abnormalities in synaptic vesicle density (Gąssowska et al., 2016a). These changes in synapse morphology were accompanied by decreases in key synaptic proteins, as well as BDNF, a key neurotrophic factor that supports the differentiation, maturation, and survival of neurons in both development and adulthood (Gąssowska et al., 2016a). Additionally, studies in adult humans suggested that decreases in BDNF are associated with neurodegenerative diseases (Bathina and Das, 2015). These changes in synapses can result in synapse dysfunction, which would contribute to altered neurotransmission. Adverse changes in neuronal dendrite morphology were reported following developmental Pb exposures in multiple studies, including loss of dendritic spines, reduced spine density, decreased spine length, and impaired spine maturity and morphology at multiple developmental stages and brain regions (hippocampus, medial prefrontal cortex, dentate gyrus) (Xiao et al., 2020; Saleh et al., 2018; Zhao et al., 2018; Sepehri and Ganji, 2016; Wang et al., 2016; Du et al., 2015; Rahman et al., 2012b). Dendritic spines are the morphological and structural

basis for synaptic plasticity, learning, and memory (Frank et al., 2018), providing biological plausibility for altered learning and memory, as reported in Section 3.5.1.3.2.

The brain and CNS are separated from the blood by the BBB and the blood-cerebrospinal fluid (CSF) barrier, which allows for selective transport of materials into the CNS. The BBB is formed by several cell types including endothelial cells, astrocytes, pericytes, and microglia and plays an important immunological role in protecting the brain from circulating pathogens and toxic substances. Two studies assessed the integrity of the BBB following Pb exposure and observed disruption of brain permeability with reduced levels of tight junction proteins and other important capillary proteins (Wu et al., 2020a; Song et al., 2014). Increased permeability of the BBB may exacerbate neurotoxicity, as more toxicants can penetrate the brain with repeated or continuous exposure. Additional research is needed to fully elucidate the effects of Pb exposures on the BBB and the potential implications for CNS function and disease.

Neuroinflammation is a complex response that involves microglia and astrocyte activation, as well as other signaling proteins and cells (such as cytokines, reactive oxygen species, decreased antioxidant activity). Inflammation is protective against pathogens but can result in neuronal injury or neuronal loss in the CNS. Several studies in rodents evaluated and observed an effect of Pb exposure on markers of neuroinflammation, including microglia and astrocyte activation, and the promotion of cellular reactivity and inflammation (Wu et al., 2020a; Saleh et al., 2018; Shvachiy et al., 2018). Numerous studies also reported decreased numbers of microglia, which are glial cells that function primarily as immune cells with macrophage activity, clearing cellular debris and dead neurons from nervous system tissue (Dominguez et al., 2019; Sobin et al., 2013). Reduced numbers of microglia could indicate reduced capacity for clearing cellular debris and responding to pathogens, which could contribute to functional and morphological brain changes.

Experimental animal studies of rodents have also shown that Pb exposures affect measures of brain metabolism, including reduced glycogen concentrations in various brain regions (such as the forebrain, hippocampus, and cerebellum) (Baranowska-Bosiacka et al., 2017) and reduced rates of metabolism, which could indicate reduced glucose availability and poor metabolic cooperation between neurons and astrocytes (Baranowska-Bosiacka et al., 2017). A recent study directly measured decreased hippocampal glucose metabolism following developmental Pb exposure (pre-mating through PND 10) through reductions in glucose transporters (Zhao et al., 2021). Glucose cannot be synthesized or stored in neurons, hence glucose supply and transport are essential for neurophysiological processes with high glucose demands (such as learning and memory). Because the brain has the highest energy demand and metabolism of any organ, energy homeostasis is critical. In the above study, effects on glucose metabolism persisted at PND 30 when the blood Pb concentration had returned to control levels (BLL was 11.4 µg/dL at PND 10 and 1.8 µg/dL BLL at PND 30).

Taken together, animal studies provide strong evidence that Pb exposure impacts brain structure and function. Altered brain morphology, increased brain inflammation, oxidative stress, and associated

mitochondrial damage have all been consistently reported following Pb exposures. These effects were observed across multiple brain regions, on different levels of brain organization, across a variety of lifestages, and in both sexes.

3.4.2.2 Neurotransmitter Analysis

Neurotransmitters are molecules involved in the transmission of chemical signals between neurons and target cells and are involved in controlling a wide variety of brain functions, including motor function, learning, memory, metabolism, behavior, and hormone production. These neurochemical systems have been implicated in the initiation and maintenance of some brain diseases and disorders, e.g., Parkinson's disease (PD), depression, aggression, and dementia (Monday et al., 2018; Chichinadze et al., 2011; Haden and Scarpa, 2007; Webster, 2001). As described in the 2013 Pb ISA, exposures to Pb can induce changes in brain neurochemistry and signaling that vary by brain region, neurotransmitter type, and the sex of the animal. Pb can compete with calcium ions (Ca^{2+}) for common binding sites and second messenger system activation. When Pb activates a Ca^{2+}-dependent system in the nervous system, it can contribute to spurious neurotransmitter regulation and release because this system intimately relies on Ca^{2+} signaling for its homeostasis. Pb-related alterations in neurotransmission are discussed in further detail below.

A variety of neurotransmitters and their metabolites were evaluated in experimental animal studies of rodents, across multiple brain regions (hypothalamus, cerebral cortex, nucleus accumbens, frontal cortex, striatum, hippocampus, olfactory bulb, midbrain, cerebellum) and time points, including serotonin and its metabolite 5-hydroxylindolacetic acid (Weston et al., 2014; Mansouri et al., 2013; Graham et al., 2011), norepinephrine and its metabolite methoxyhydroxyphenylglycol (Long et al., 2022; Basha et al., 2014; Weston et al., 2014; Bijoor et al., 2012; Graham et al., 2011), dopamine and its metabolites dihydroxyphenylacetic acid and homovanillic acid (Sobolewski et al., 2020; Amos-Kroohs et al., 2016; Stansfield et al., 2015; Basha et al., 2014; Weston et al., 2014; Cory-Slechta et al., 2012; Graham et al., 2011), acetylcholine (Long et al., 2022; Mansouri et al., 2013), epinephrine (Basha et al., 2014), glutamate and its precursor glutamine (Long et al., 2022). The direction of changes depended on the brain tissue analyzed, time point, sex, and specific neurotransmitter assessed. However, multiple studies found significant effects of Pb exposure on the dopamine system (Sobolewski et al., 2020; Amos-Kroohs et al., 2016; Stansfield et al., 2015; Basha et al., 2014; Weston et al., 2014; Cory-Slechta et al., 2012; Graham et al., 2011). Some studies also reported Pb-induced changes in enzymes involved in neurotransmitter turnover and cycling, including monoamine oxidase (Basha et al., 2014) tyrosine hydroxylase (Sobolewski et al., 2020), glutamine synthase, and adenylate cyclase (Long et al., 2022).

Pb exposure has demonstrated effects on several neurotransmitters, which are important signaling molecules that control multiple brain functions. These effects were observed across multiple brain regions, across a variety of lifestages, and in both sexes. Altered neurotransmitter signaling can contribute

to multiple brain dysfunctions and disorders, providing biological plausibility for the health effects discussed in subsequent sections.

3.4.2.3 Brain Weight

Organ weights are a frequently assessed in experimental animal studies as they can easily be measured during animal necropsy. Importantly, brain weight is an indication of severe toxicity as the body goes to great lengths to spare the brain at the expense of other bodily systems. Brain weights were not reviewed in the 2013 Pb ISA. Several recent studies of rodents assessed brain weight following short and long-term Pb exposures, and most of these studies reported nonsignificant findings (Vigueras-Villaseñor et al., 2021; Mani et al., 2020; Wu et al., 2020a; Singh et al., 2019; Rahman et al., 2018; Saleh et al., 2018; Zhou et al., 2018; Singh et al., 2017; Barkur and Bairy, 2015a; Wang et al., 2013; Rahman et al., 2012b). However, two studies did find significant decreases in brain weight (16%–21% decrease): one reported a decrease after a 90-day oral exposure to Pb in juvenile rats, which resulted in a BLL of 28.4 µg/dL (Singh et al., 2019) and the other reported an 18% decrease in cerebellum weight in treated dams (27.7 µg/dL BLL), as well as reduced fetal brain weight at parturition following gestational exposure to Pb in drinking water (GD 1 to GD 20) (Saleh et al., 2018). In addition to gross measures of brain size and morphology (e.g., wet weight), studies using newer anatomical imaging methods have been conducted since the 2013 Pb ISA. Three-dimensional imaging technologies, such as MRI and ultrasound methods are being used for the analysis of neuroactivity and phenotypes in rodent toxicology studies (Turnbull and Mori, 2007). Brain volume and MRI morphometry were assessed in a single study of developing mice following dietary exposure to Pb (Abazyan et al., 2014). The authors reported no changes in lateral ventricle volume but did observe sex-specific changes in morphology including enlarged lateral ventricles. As the technologies improve, imaging technologies offer promising results for evaluating physiological functions like neural activity in whole intact animals. Study details are provided in Table 3-1T.

3.4.2.4 Electrophysiology

The effects of Pb exposure on brain electrophysiology were not reviewed in the 2013 Pb ISA. Several new studies in rodents have found that Pb exposure affects measures of brain electrophysiology, including long-term potentiation (LTP) and evoked excitatory postsynaptic currents (EPSCs). LTP is the process of signal transmission by which synaptic connections between neurons are activated and strengthened and may be one of the mechanisms underlying learning and memory processes. Recording of LTP is a recognized model for the study of memory (Lynch et al., 1990).

Presynaptic plasticity can be assessed using paired-pulse stimulation, wherein two stimuli occur in close succession. Hippocampal slices from rats were subjected to LTP induction and high-frequency

tetanic stimulations, and the magnitudes of EPSCs were measured. In developmentally Pb-exposed rats, the magnitudes of EPSCs were lower at PND 10, suggesting impaired hippocampal induction (Zhao et al., 2018). Other studies have also assessed EPSCs with a longer exposure duration and different conditions and found the ratios of EPSC responses between paired-pulse stimuli were significantly greater in hippocampal slices from Pb-exposed rats (Zhang et al., 2015b). These changes in EPSC responses were accompanied by inhibition of synaptic vesicular release (Zhang et al., 2015b). Depressed LTP following Pb exposures was measured in (Zhou et al., 2020a; Wang et al., 2016; Liu et al., 2012). These studies additionally reported increased neuronal free Ca^{2+} concentration and inhibition of various signaling proteins (Ca^{2+} calmodulin dependent protein kinase II and CREB), which were mediated by upregulation of the ryanodine receptor. Ryanodine receptors are ion channels that are critical for maintaining intracellular Ca^{2+} homeostasis. Changes in electrophysiological parameters affect neurotransmitter release and cell signaling, which can affect brain function (described in Section 3.4.2.2).

In addition to these effects, (Zhu et al., 2019a) reported alterations in cardiac sympathetic nerve activity in rats while evaluating nerve discharge as a potential contributor to other health effects discussed in the cardiovascular toxicity section (Appendix 4). The authors reported enhanced cervical sympathetic nerve discharge 1 year after Pb exposure ended, suggesting that Pb-induced alterations to autonomic nervous dysfunction can have lasting effects. This growing area of research recognizes the potential effect of Pb on electrophysiology in the nervous system.

3.4.2.5 Circadian Rhythms

Two recent studies evaluated the effects of Pb exposure on circadian rhythms using rodent models. The suprachiasmatic nucleus (SCN) of the hypothalamus is the primary regulator of circadian physiological processes and is synchronized daily by signals of light. Vigueras-Villaseñor et al. (2021) subjected male rats to chronic Pb exposure from conception to euthanasia. In these adult rats, under a standard 12:12-hour light-dark cycle, the authors observed daily delays in the nocturnal onset of locomotor activity. With a 6-hour photoperiod delay, the activity rhythms of Pb-exposed rats entrained to a new cycle faster than controls, and Pb treatment showed no significant effects when the photoperiod was advanced by 6 hours. Histochemical analyses of the hypothalamus in light-pulsed Pb-treated animals displayed decreases compared with controls in both photo-stimulated neurons (immunoreactivity to c-Fos) and the neuronal population in the SCN. Hsu et al. (2021) assessed disturbances in rodent sleep homeostasis by using electroencephalography and electromyography to score the sleep wake architecture of sleep cycles and found that adult rats with chronic Pb exposure showed disturbances in sleep patterns that were accompanied by altered clock gene expression and changes in the hypothalamus. These alterations in behavior, sleep cycles, brain structure, neuronal function, and gene expression warrant further investigations into the effects of Pb on the rhythm of vital circadian processes. The above studies reinforce the importance of considering the time of day in studies measuring the effects of Pb.

3.4.2.6 Summary

In conclusion, multiple studies measured a variety of nervous system endpoints in brains of rats and mice following exposure to Pb including histology, neurotransmitter analysis, brain weight, and electrophysiology measures. Histological analyses revealed reduced neuron counts, altered synapse morphology, and increased apoptosis, as well as oxidative damage in several brain regions, including the hippocampus, frontal cortex, and cerebellum. These regions were also found to have damaged mitochondria, vacuolization, and morphological changes. Pb concentrations ranged from 4.7 μg/dL to 28.4 μg/dL in these studies, which were conducted in a variety of animal models, sexes, and lifestages. These endpoints provide biological plausibility for effects on cognitive behavioral changes and diseases described in subsequent sections.

3.4.3 Integrated Summary of Overt Nervous System Toxicity

Overt nervous system toxicity refers to a diverse group of endpoints that inform brain structure and function, including brain histopathology changes, brain weight, electrophysiology, neuroinflammation, and neurotransmitter analyses. As described in Section 3.1, there are no causality determinations for this endpoint grouping. Instead, the evidence is considered supporting information that informs the health determinations in Sections 3.5 and 3.6.

Multiple studies measured nervous system endpoints in rats and mice following exposure to Pb including histological changes in brain structure and morphology, neuroinflammation, neurotransmitter analysis, brain weight, and electrophysiology measures. These findings that Pb exposures affect these endpoints provide biological plausibility for Pb to elicit human cognitive behavioral changes and diseases described in subsequent sections and are generally coherent with the epidemiologic studies of overt nervous system effects described in this section. The lack of toxicology studies examining Pb inhalation remains a data gap that limits the evaluation of nervous system effects from inhaled Pb.

Multiple epidemiologic studies, including prospective studies following children through adolescence and adulthood and a smaller number of cross-sectional studies of children, found associations between BLL and physiologic changes in regions of the brain responsible for cognition and behavior. These prospective epidemiologic studies considered important confounders; however, many Pb exposure metrics and brain regions were evaluated in the epidemiologic studies, raising the possibility of chance findings.

3.5 Nervous System Effects Ascertained during Childhood, Adolescent, and Young Adult Lifestages

The collective body of epidemiologic and experimental animal studies assessed in the 2013 Pb ISA demonstrated the effects of Pb exposure on an array of nervous system outcomes. Overall, the largest body of evidence assessed in the 2013 Pb ISA, as well as the outcome that was best substantiated to occur at the lowest Pb exposure levels, was related to cognitive effects in children. Multiple prospective studies conducted in diverse populations consistently demonstrated associations of higher blood and tooth Pb levels with lower full-scale IQ (FSIQ), executive function, and academic performance and achievement. The blood Pb biomarkers used in these studies reflect exposures during prenatal, postnatal and childhood lifestages. Tooth Pb generally reflects prenatal and early childhood exposure (or exposure up to the time that the tooth is shed depending on the specific tooth layers analyzed) (see Section 2.3.4.1.) Most studies examined representative populations and had moderate to high follow-up participation with no indication of selective participation among children with higher BLLs and lower cognitive function. Associations between BLL and cognitive function decrements were found with adjustment for several potential confounding factors, most commonly SES, parental IQ, parental education, and parental caregiving quality. In children aged 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. Although examined less extensively than cognitive effects, a strong body of evidence also indicated Pb-associated decrements in attention and increased hyperactivity.

3.5.1 Cognitive Function in Children

The 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 (U.S. EPA, 2013). Multiple prospective studies conducted in diverse populations consistently demonstrated associations of higher blood and tooth Pb levels with lower FSIQ, executive function, and academic performance and achievement. As noted above, these biomarkers reflect exposures during prenatal, postnatal and childhood lifestages (tooth Pb concentration may reflect exposure up to the time a tooth is shed depending on the layer analyzed [see Section 2.3.4.1]). Most studies examined representative populations and had moderate to high follow-up participation with no indication of selective participation among children with higher BLLs and lower cognitive function. Associations between BLL and cognitive function decrements were found with adjustment for several potential confounding factors, most commonly SES, parental IQ, parental education, and parental caregiving quality. In children aged 4–11 years, associations were found with prenatal (i.e., maternal or cord BLLs), early childhood, childhood average, and concurrent BLLs in populations with mean or group BLLs in the range of 2–8 μg/dL. No critical lifestage or specific duration of Pb exposure within childhood was uniquely associated with cognitive function decrements based on consideration of evidence from epidemiologic and toxicological studies. Several epidemiologic studies

found a supralinear concentration-response (C-R) relationship (i.e., larger incremental effect at lower BLLs). A threshold for cognitive function decrements was not discernable from the available evidence (i.e., examination of early childhood blood Pb or concurrent [with peak <10 μg/dL] blood Pb in the range of <1 to 10 μg/dL). Evidence in children was clearly supported by observations of Pb-induced impairments in learning and memory in juvenile animals. Several studies in animals indicated learning impairments with prenatal, lactational, post-lactational, and lifetime (with or without prenatal) Pb exposures that resulted in BLLs of 10–25 μg/dL. Biological plausibility for Pb-associated cognitive function decrements was supported by observations of Pb-induced impairments in neurogenesis, synaptogenesis and synaptic pruning, LTP, and neurotransmitter function in the hippocampus, prefrontal cortex, and nucleus accumbens.

The structure of the current assessment of cognitive effects in children is similar to that in the 2013 Pb ISA. Although the above measures of cognitive function are interrelated, the evidence for each of these categories of outcomes (i.e., FSIQ, Bayley Scales of Infant Development [BSID], neuropsychological tests of learning, memory, and executive function, and academic performance) was assessed separately, to the extent possible, in the order of strength of evidence. Studies assessing cognitive function of school-age children using instruments that measure FSIQ are described in Section 3.5.1.1, and studies assessing cognitive development in infants using the BSID and other instruments are described in Section 3.5.1.2. Studies examining the associations of Pb exposure with outcomes on neuropsychological tests of learning and memory and executive function in children as well as analogous endpoints in animals are discussed in Sections 3.5.1.3 and 3.5.1.4, respectively. These sections are followed by a discussion of studies that examine the association of Pb exposure with academic achievement and performance in Section 3.5.1.5. The final sections discuss issues relevant for the interpretation of the evidence base (Section 3.5.1.6) and the summary and causality determination (Section 3.5.1.7).

Because the conclusion from the 2013 Pb ISA was "causal," the PECOS statement for studies of cognitive effects in children (see Section 3.2) was refined to emphasize recent studies that examined lower BLLs more similar to those of current U.S. children (i.e., <5 μg/dL). Details of these studies are extracted into the evidence inventories (Section 3.7, Table 3-2E [FSIQ], Table 3-3E [Infant Development], Table 3-4E [Learning, Memory, and Executive Function], and Table 3-5E [Academic Achievement and Performance]). Studies with central tendency blood Pb concentrations that exceed 5 μg/dL are extracted into Table 3-6E of Section 3.7. In addition to refining the PECOS statement to focus on lower exposure levels, studies of younger children whose BLLs were less influenced by higher past Pb exposures are considered particularly informative. Controls for important potential confounders identified in the 2013 Pb ISA such as SES, parental education, quality of parental caregiving (often measured as the HOME score), nutritional status, and birth weight in studies of postnatal Pb exposure were considered attributes of high-quality studies (see section 4.3.13 of the 2013 Pb ISA (U.S. EPA, 2013)). A summary of the recent evidence, which is interpreted in the context of the entire body of evidence, is provided in

the subsequent sections. Overall, recent studies add to the evidence generally supporting the findings from the 2013 Pb ISA.

3.5.1.1 Full-Scale IQ in Children

A large number of studies evaluated in the 2013 Pb ISA found a consistent pattern of associations between higher BLL and lower FSIQ in children aged 4–17 years (see Figure 4-2 and Table 4-3 (U.S. EPA, 2013)). FSIQ has strong psychometric properties (i.e., reliability, consistency, validity), is among the most rigorously standardized cognitive function measures, is relatively stable in school-age children, and has been demonstrated to be predictive of educational achievement and life success. The strongest evidence was provided by prospective studies with analyses of the association of blood Pb levels measured in early childhood or tooth Pb level that generally reflect the early childhood Pb exposure (i.e., prospective studies where Pb exposure preceded the assessment of FSIQ). These prospective studies typically considered potential confounding by maternal IQ and education, SES, birth weight, smoking exposure, parental caregiving quality, and in a few cases, other birth outcomes and nutritional factors. Associations were found in diverse populations (e.g., Boston, MA; Cincinnati, OH; Rochester, NY; Cleveland, OH; Mexico City, Mexico; Port Pirie, Australia; and Kosovo, formerly of Yugoslavia) in studies that examined children recruited from prenatal clinics, hospital maternity departments, or schools. Studies generally reported high follow-up participation, which was supported by evidence that selection bias did not explain the associations observed. The few studies reporting weak or null associations (i.e., Cleveland, Sydney cohorts) were not stronger with respect to methodology or control for potential confounding and did not weaken the far larger body of supporting evidence (U.S. EPA, 2013).

The blood Pb-FSIQ association in children was further substantiated by an international pooled analysis of seven prospective cohorts (Lanphear et al., 2019, 2005) as well as multiple meta-analyses that combined results across various prospective and cross-sectional studies (Pocock et al., 1994; Schwartz, 1994a; Needleman and Gatsonis, 1990). Schwartz (1994a) additionally demonstrated the robustness of evidence to potential publication bias. The pooled analysis (Lanphear et al., 2019, 2005) examined several BLL metrics and demonstrated that early childhood and concurrent childhood BLLs explained more variation in FSIQ compared with the other blood Pb metrics, as indicated by the R-square values. The coefficient for concurrent BLL had a smaller standard error (SE) than the coefficient for early childhood BLL (Lanphear et al., 2019). Across studies, no clear indication that Pb exposure during one critical lifestage or time period within childhood was uniquely or more strongly associated with FSIQ (see Section 3.5.1.6.3). Blood Pb-associated FSIQ decrements at ages 4–17 years were found with concurrent, prenatal (maternal or cord), early childhood (e.g., age 2 or 4 years), multiple-year average, or lifetime average BLLs. Associations were also found with tooth Pb levels.

Key statistics associated with the international pooled analyses of seven cohort studies are presented in Table 3-1. The C-R function was nonlinear, with a larger incremental effect of Pb on IQ at lower blood Pb concentrations (Lanphear et al., 2019, 2005). The log-linear model coefficient (i.e., β

coefficient) for concurrent BLL was −2.65 (95% confidence interval [CI]: −3.69, −1.61) per unit change in natural log transformed BLL. The linear association observed for a subset of 103 children with peak BLLs <7.5 (mean concurrent BLL = 3.2 µg/dL) was −2.53 (95% CI: −4.48, −0.58). Linear coefficients for higher BLLs and using a peak BLL cutoff point of 10 µg/dL are included in Table 3-1, as are other key statistics, including R-square values for various models.

Table 3-1 Statistics associated with the international pooled analysis of data from seven cohort studies

Main Finding from Analyses of the Pooled Dataset	Quantitative Result[a]
Log-linear [b] model coefficient for blood Pb metrics and IQ, adjusted for site, HOME score, birth weight, maternal IQ, and maternal education	Early childhood: −2.21 (−3.38, −1.04) Peak: −2.86 (−4.10, −1.61) Lifetime average: −3.14 (−4.39, −1.88) Concurrent: −2.65 (−3.69, −1.61)[c]
IQ decrement over different concurrent blood Pb ranges based on the log-linear model	2.4 to 30 µg/dL: 6.7 IQ pts (4.1–9.3) 2.4 to 10 µg/dL: 3.8 IQ pts (2.3–5.3) 10 to 20 µg/dL: 1.8 IQ pts (1.1–2.6) 20 to 30 µg/dL: 1.1 IQ pts (0.7–1.5)
Linear coefficient,[d] sample size (n) and concurrent BLL measurements (mean, minimum, 5th and 95th percentiles, and maximum) for subset with peak BLLs <7.5 µg/dL	−2.53 (−4.48, −0.58) n = 118[e] (3.3, 0.9, 1.1, 6.7, 7.4 µg/dL)
Linear coefficient,[d] sample size (n) and concurrent blood Pb measurements (mean, minimum, 5th and 95th percentiles, and maximum) for subset with peak BLLs ≥7.5 µg/dL	−0.15 (−0.19, −0.11) n = 1215 (13.0, 0.1, 3.7, 34.2, 71.7)
Linear coefficient,[d] sample size (n) and concurrent blood Pb [d] measurements (mean, minimum, 5th and 95th percentiles and maximum) for subset with peak blood Pb <10 µg/dL	−0.77 (−1.65, 0.12) n = 258 (4.4, 0.1, 1.4, 8.0, 9.8)
Linear coefficient,[d] sample size (n) and concurrent blood Pb measurements (mean, minimum, 5th and 95th percentiles, and maximum) for subset with peak BLLs ≥10 µg/dL)	−0.13 (−0.22, −0.04) n = 1075 (14.0, 0.1,4.4, 35.5, 71.7)
Blood Pb metric with the largest R^2 for the relationship with IQ in the log-linear models	Early childhood R^2: 0.6433 = largest Peak R^2: 0.6401 Lifetime average R^2: 0.6411 Concurrent R^2: 0.6414

BLL = blood lead level; HOME = Health Outcomes and Measures of the Environment; IQ = intelligence quotient; Pb = lead; pts = points.
[a]Results reported by Lanphear et al. (2019) and/or Crump et al. (2013) and confirmed by Kirrane and Patel (2014).
[b]Coefficients are not standardized, i.e., coefficients indicate the decrement in full scale IQ per unit of natural log transformed blood Pb. Standardized estimates (i.e., standardized to a 1 unit increase for the 10th−90th percentile interval of the biomarker level and assumed to be linear within this interval) for this study are found in Evidence Inventory (Section 3.7, Table 3-2E).
[c]Slopes ranged from −2.36 to −2.94 in sensitivity analyses of concurrent blood Pb-IQ association, which omitted one cohort at a time.
[d]Linear coefficients are standardized to a 1 µg/dL increase in blood Pb
[e]The number of children from Boston cohort with peak BLLs <7.5 µg/dL was 28 after errors were corrected (Lanphear et al., 2019).

Several studies that conducted analyses stratified by BLL provide additional support for the findings of Lanphear et al. (2005) and Lanphear et al. (2019). These studies comprise a compelling body of evidence demonstrating a nonlinear C-R function (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) for the association between BLL and intelligence. This evidence is described in the 2013 Pb ISA (Section 4.3.12, Figure 4-15, and Table 4-16 of the U.S. EPA (2013)). Particularly compelling evidence was provided by analyses that examined prenatal or early childhood blood Pb levels or considered peak blood Pb levels in school-aged children (Schnaas et al., 2006; Bellinger and Needleman, 2003; Canfield et al., 2003a). The geometric mean Pb level in Schnaas et al. (2006) was 7.8 µg/dL and the mean blood Pb levels in Bellinger and Needleman (2003) and Canfield et al. (2003a) were 3.8 µg/dL and 3.3 µg/dL, respectively.

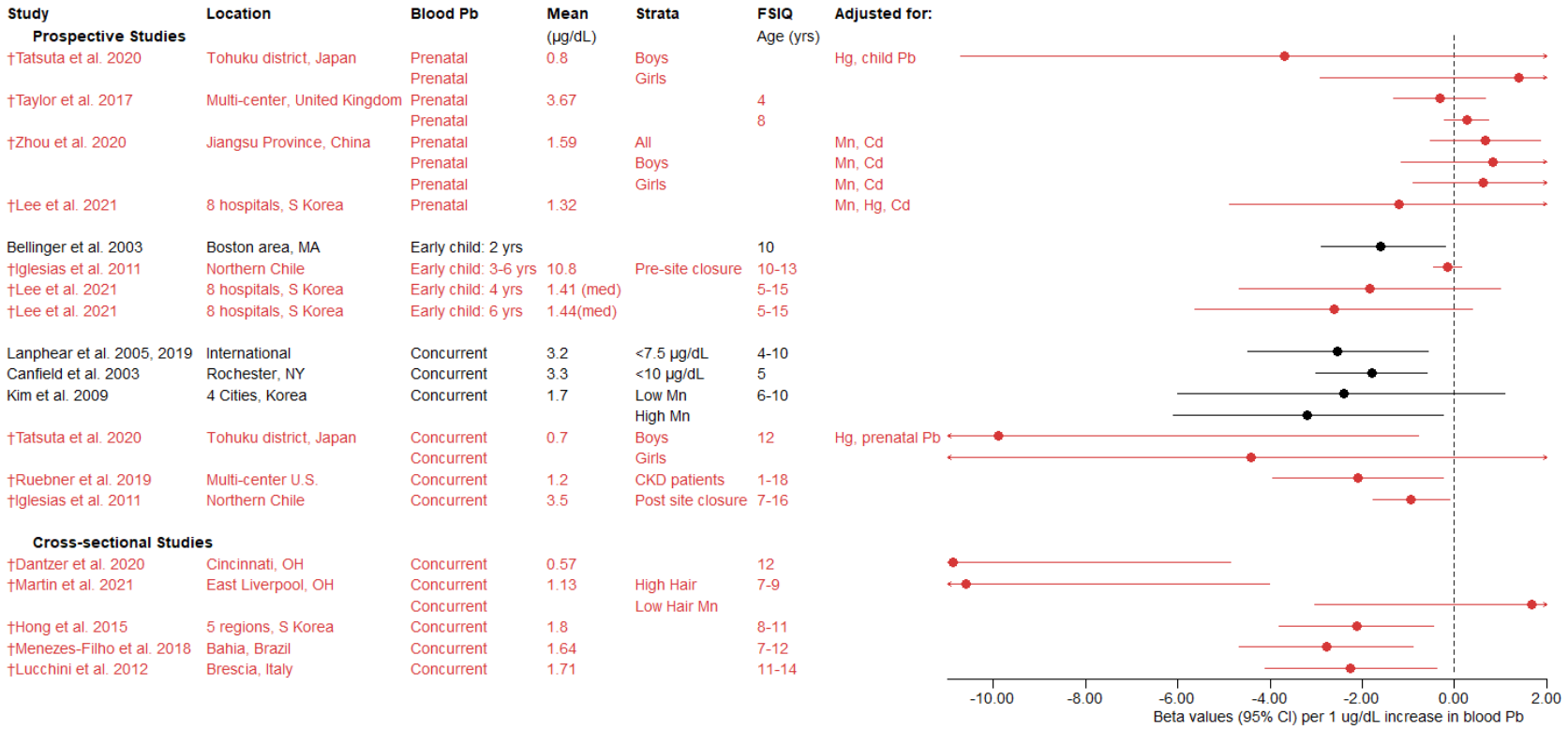
In a recent analysis, Crump et al. (2013) examined the shape of the C-R function for the pooled data using an alternative modeling strategy. Rather than model the natural log of BLL as was done in the original analysis (Lanphear et al., 2019, 2005), Crump et al. (2013) modeled the natural log (ln) of blood Pb + 1, which has the property of equaling zero when untransformed BLL equals zero. The authors applied F-tests to nested models containing both ln (BLL + 1) and non-transformed BLL and found that the linear coefficient did not improve the prediction of the model, indicating that ln (BLL + 1) was a better predictor across the full range of the data (e.g., 2.5–33.2, as 5th to 95th percentile concurrent BLLs). In addition, Crump et al. (2013) considered confounding by additional covariates, which were defined as site-specific in their final models. Despite the aforementioned differences in modeling approach, the Crump et al. (2013) analysis corroborated the findings of the original analysis, providing strong evidence in support of the nonlinear C-R function and the causal association between Pb exposure and cognitive effects in children. The coefficient for the Crump et al. (2013) log-linear association between concurrent BLL and IQ was −3.32 (95% CI: −4.55, −2.08), somewhat larger than that reported by Lanphear et al. (2019) (see Table 3-1).

Notably, the international pooled analysis (Lanphear et al., 2019, 2005) included data from seven longitudinal cohorts that were initiated before 1995. The median concurrent BLL was 9.7 µg/dL (5th and 95th percentiles: 2.5–33.2 µg/dL) with included studies reporting limits of detection of 1 µg/dL. Several other longitudinal and cross-sectional studies included in the 2013 Pb ISA, however, conducted analyses of children with mean BLLs ≤5 µg/dL, collectively providing strong evidence of an association between Pb exposure and FSIQ at lower BLLs (Kim et al., 2009; Chiodo et al., 2007; Surkan et al., 2007; Bellinger and Needleman, 2003; Canfield et al., 2003a) (see Figure 3-4).

Van Landingham et al. (2020) extended the analyses of the international pooled data described above that were first examined by Lanphear et al. (2005), Lanphear et al. (2019) and later by Crump et al. (2013). These authors identified "highly likely" confounders (HOME score, maternal education and maternal IQ) using a combination of correlation analysis and backward selection with a criteria of p = 0.15 to retain covariates in the model. Van Landingham et al. (2020) also included interaction terms

between BLL and each covariate. The results of their analyses were comparable to previous analyses that did not consider interactions. Specifically, the beta coefficient for concurrent blood Pb in the loglinear (blood Pb level +1) model with interaction terms was -4.945. Coefficients for the interactions of maternal IQ, maternal education and HOME score with Pb were negligible (i.e., -0.0003, -0.0051, and 0.0437, respectively). The authors also fit predictive models and calculated the IQ decrement for various increments of BLL, and across levels of each of the covariates. The interpretation of the covariates and the predicted IQ decrements at various combinations of BLL decrement and covariate levels that are presented in the paper, however, potentially conflate the interpretation of direct versus total effect estimates and may not inform causality (i.e., the table 2 fallacy) (Westreich and Greenland, 2013). As noted previously, there is a lack of data in the international pooled dataset for children with BLLs <1 microgram per dL and the data is sparse below <5 µg/dL; hence, uncertainty remains regarding the C-R function associated with this dataset in the range where the data are sparse and this uncertainty is not addressed by Van Landingham et al. (2020).

Several recent longitudinal studies add to the evidence informing the relationship between BLL and IQ in children. Heterogeneity in the magnitude and direction of the associations, which was potentially explained by race/ethnicity, sex, and modeling choices such as adjustment for other metals or chemicals was present. This heterogeneity did not weaken the larger body of supporting evidence. Overall, recent studies generally corroborated previous epidemiologic observations of associations between Pb exposure and IQ in children with relatively low blood Pb concentrations (≤5 µg/dL) (see Figure 3-4 and Evidence Inventory Table 3-2E).



Note: Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th−90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized. The "adjusted for" column indicates covariates that are not typically considered in multivariate models. The exhaustive list of confounders for individual studies is found Table 3-2E.
†Studies published since the 2013 Integrated Science Assessment for Lead.

Figure 3-4 Associations between blood Pb levels and full-scale intelligence quotient in children.

Several recent prospective epidemiologic studies were also conducted that examined the associations of prenatal or postnatal BLLs and effect measure modification by sex. Taylor et al. (2017) used data from the Avon Longitudinal Study of Parents and Children (ALSPAC) to study the association of maternal BLL and child IQ at ages 4 and 8 (i.e., Wechsler Preschool and Primary Scales of Intelligence [WPPSI] and Wechsler Intelligence Scale for Children [WISC]-III, respectively). Little evidence of an association with IQ was observed. The change in score on the WPPSI associated with maternal BLL was −0.32 (95% CI: −1.32. 0.68) per µg/dL and the change in score on the WISC-III was 0.26 (95% CI: −0.21, 0.73) per µg/dL. Sex-stratified analyses, however, indicated an association between maternal BLL and IQ decrement in boys (−0.29 [95% CI: −1.02, 0.44]), but not in girls, among whom positive associations were observed (0.73 [95% CI: 0.39, 1.33]). Models were adjusted for covariates including maternal education and indicators of SES. The mean prenatal and postnatal BLLs were 3.67 µg/dL and 4.22 µg/dL, respectively.

Tatsuta et al. (2020) examined the association of both cord BLL and postnatal BLL (at age 12) with IQ (WISC-IV) among boys and girls enrolled in the Tohoku Study of Child Development, a prospective birth cohort. In addition, the Boston Naming Test (BNT) was administered to assess language abilities. This study found decrements in FSIQ score in association with postnatal BLL [β = −9.88 (95% CI: −18.98, −0.78] among boys and a less precise association with IQ decrement that included the null value among girls [β = −4.41 (95% CI: −15.94, 7.13]). Confounders considered in the analysis included maternal IQ, parental SES (i.e., income) and Hg concentration in cord blood. Prenatal BLL was associated with a relatively weak and imprecise decrease in FSIQ score among boys [β = −3.68 (95% CI: −10.71, 3.35]. The association of prenatal BLL with FSIQ was slightly positive but with the CI including the null value among girls (β = 1.46 (95% CI: (−2.91, 5.83)]. Lower BNT scores (with cues) were associated with both prenatal and postnatal BLL among boys. The associations of pre- and postnatal BLLs with BNT were relatively weak or null in girls. The median postnatal BLL was 0.7 µg/dL and the median cord BLL was 0.8 µg/dL in this study.

Desrochers-Couture et al. (2018) studied the association between cord, maternal, and childhood (3–4 years old) BLLs with cognitive function (WPPSI-III at 3–4 years of age) among children enrolled in the Maternal-Infant Research on Environmental Chemicals (MIREC) Study. The analysis included mothers who participated in MIREC Chemical Study Plus (n = 610), which was conducted when the child reached the age of 3-4 years old. The cohort from which the study participants were drawn comprised Canadian preschoolers from mainly middle- to upper-middle SES families with low Pb exposure. The geometric mean concurrent blood Pb concentration was 0.70 µg/dL, and the geometric mean cord blood Pb concentration was 0.76 µg/d. Outcomes included FSIQ, verbal IQ, performance IQ, and a general language composite. The authors report standardized regression coefficients for the associations of cord blood Pb level and child blood Pb level with FSIQ. An association between cord blood Pb level and FSIQ was observed [β = −0.07 (95% CI: -0.143, 0.003)], while the association of childhood concurrent BLLs with FSIQ effectively null (β = 0.014 [95% CI: −0.071, 0.098]. These results describe a SD change in FSIQ (i.e., 13.5 points) per SD change in Log2-transformed blood Pb level (SD of Log2-transformed

BLLs not reported; results not depicted in Figure 3-4). The cord blood model adjusted for child age, sex, maternal education, evaluation site, and cord blood Hg, while the postnatal model adjusted for child age, sex, evaluation site, marital status, income, HOME score, Parenting Stress Index, and cord BLL. No pattern of Pb-associated cognitive function decrements emerged with the verbal or performance components of IQ or with the general language composite. An association (non-standardized beta coefficients) was observed between cord BLL and performance IQ in boys (β = −5.69 [95% CI: −9.97, −1.41] but not in girls (β = 0.29 [95% CI: −3.79, 4.36]). The study adjusted for several important confounders, including SES. Although maternal education was included in the model, maternal IQ, which is a strong predictor of child IQ, was not accounted for in the analysis.

Zhou et al. (2020b) conducted a study to examine the association of cord blood concentrations of trace elements, including Pb, manganese (Mn), and cadmium (Cd), with FSIQ, verbal IQ, and performance IQ components among children from an agricultural region in China who were enrolled in a prospective birth cohort. In models including each of these elements, cord BLL was not associated with FSIQ (β = 0.67 [95% CI: −0.51, 1.85]). A similar lack of association was observed with performance and verbal IQ and in sex-stratified analyses. Models were adjusted for covariates including maternal education and family income. Each of the trace elements were included in the models but interactions between the elements were not examined. The mean cord BLL among the children was 1.59 µg/dL. Liu et al. (2015) developed a predictive model to examine the association of Pb, Cd, and Hg in serum with FSIQ at age 5, dropping variables based on the variance inflation factor (VIF >10). The final model for FSIQ (i.e., WPPSI) did not include cord serum Pb level; thus, no results pertaining to the association of Pb concentration in serum with FSIQ were presented. Wang et al. (2022) investigated associations between cord and concurrent venous blood concentrations of Pb, selenium (Se), As, Cu, Mn, and Cr and FSIQ among children (6–8 years old) born in a hospital in Wujiang, Jiangsu Province. The geometric mean concentrations of cord and venous blood Pb were 2.83 µg/dL and 3.30 µg/dL, respectively. Cord blood Pb was weakly associated with reduced performance IQ (β = −0.11 [95% CI: −0.25, 0.03]) in boys, and concurrent venous blood Pb was associated with reduced verbal IQ in girls (β = –0.49 [95% CI: −0.86, −0.12]).

Lee et al. (2021) studied the association of Pb and other metals (i.e., Cd, Hg, and Mn) among mother and infant pairs from eight hospitals in South Korea. In multivariable models including each of the metals as well as covariates, imprecise negative associations of prenatal Pb exposure (β = −1.20 [95% CI: −4.87, 2.01]), child BLL at age 4 (β = −1.83 [95% CI: −4.66, 1.01]), and child BLL at age 6 (β = −2.61 [95% CI: −5.62, 0.40]) with FSIQ were observed. In another study of exposure to multiple trace metals conducted in Wujiang, China, imprecise associations of maternal cord and early childhood venous blood were observed with FSIQ (e.g., −4.77 [95% CI: −14.34, 4.79] comparing the upper quartile of venous child BLL with the reference quartile) (Wang et al., 2022). The geometric mean blood Pb concentration was 2.30 µg/dL (interquartile range [IQR]: 1.83–3.30 µg/dL), and the study included 113 children.

The recent body of evidence also includes a which evaluated the association of BLL in early childhood (3-6 years) and BLL later in childhood (10-13 years) when IQ was also measured. The BLLs that were measured later in childhood corresponded to the period when a major source of Pb exposure was eliminated (i.e., following the closure of a Pb storage facility) (Iglesias et al., 2011). The early childhood mean BLL was 10.8 µg/dL, and concurrent mean BLL was 3.5 µg/dL. This study found an FSIQ decrement associated with concurrent BLL (β = –0.94 [95% CI: (–1.77, –0.11)]) and a weaker, less precise association with early childhood BLL (β = –0.14 [95% CI: –0.45, 0.16]). Verbal IQ was more strongly associated with concurrent BLL than performance IQ. These associations were adjusted for important confounders including maternal IQ and education, HOME score, and SES; however, participation was moderately low with approximately 43 percent of the children with early childhood BLLs participating in the IQ assessment.

Braun et al. (2018) conducted a study to determine whether residential exposure interventions would reduce BLL in children and further result in improvements in the IQ score assessed using the WPPSI at 5 to 8 years of age. Eligible women were randomly assigned to either a Pb exposure reduction or injury prevention group. The geometric mean BLLs for children from 1 to 8 years of age was 1.6 µg/dL in the Pb exposure intervention group and 1.7 µg/dL in the control group. Dust Pb loadings were lower following the intervention, but no differences in BLL (i.e., risk of having blood Pb concentration >2.5 or 5 µg/dL) were observed among the children. The effect of the intervention on BLL differed depending on race/ethnicity, however. Specifically, the relative risk (RR) of having an elevated BLL (>2.5 µg/dL) indicated a protective effect of the intervention among non-Hispanic black children who received the Pb intervention (RR: 0.6 [95% CI, 0.4–1.0]), but not among non-Hispanic white children who received the Pb intervention (RR: 1.0; 95% CI, 0.5–1.9; race/ethnicity × intervention p-value = 0.06). No improvement in FSIQ was observed among children who received the Pb intervention, nor did race/ethnicity modify the effect of the intervention on FSIQ.

Several cross-sectional analyses were also conducted. Dantzer et al. (2020) analyzed data drawn from the Cincinnati Childhood Allergy and Air Pollution Study (CCAAPS), a longitudinal study that followed children beginning at age 1 and included their caregivers. Children were assessed using the WISC-IV at their age−12 study visit. BLL, toenail Pb concentration, and information on covariates were also ascertained at the age−12 visit. A strong but imprecise association between BLL at age 12, concurrently ascertained IQ -10.87 [95% CI: -16.89, -4.85]), and a relatively smaller association with toenail Pb concentration (−1.70 [95% CI: −4.27, −0.86]) were observed after adjustment for caregiver IQ, SES, BMI (sex was considered as a potential confounder). Toenail Pb concentration reflects blood Pb concentration approximately months to a year before concurrent BLL due to the time it takes toenails to grow. The concurrent BLL in this study was 0.57 µg/dL.

Martin et al. (2021) found interactions between blood Pb and blood Mn level with IQ decrement among children (n = 57-62 depending on the analysis) enrolled in the Communities Actively Researching Exposure Study (CARES) cohort in East Liverpool, Ohio. BLL was measured and FSIQ ascertained at

the first clinic visit, which occurred when the child was between 7 and 9 years of age. Stronger associations between BLL and FSIQ were observed with increasing Mn concentrations in hair and toenails. For example, the association of blood Pb with FSIQ ranged from 1.69 (95% CI: −3.04, 6.41) when ln hair Mn equaled 5 ng/g to −10.60 (95% CI: −17.17, −4.02) when ln hair Mn equaled 7 ng/g. In contrast, relatively imprecise associations between BLL and FSIQ at varying levels of blood Mn were observed. The mean BLL among children in this study was 1.13 µg/dL (range: 0.30–6.64). Haynes et al. (2015) examined the association of BLL and FSIQ among the same cohort of children. The primary objective of this study was to examine the effect of Mn on child intelligence. Associations between BLL and FSIQ were not reported, although a 1 µg/dL increase in blood Pb was associated with lower processing speed (β = –3.53 [95% CI: –6.95, –0.12]).

Ruebner et al. (2019) evaluated the association between BLLs and FSIQ among children with chronic kidney disease (CKD). FSIQ was assessed using several instruments depending on the child's age (i.e., Mullen Scales of Early Learning [age 12–29 months], WPPSI [30 months–5 years], and Wechsler Abbreviated Scale of Intelligence [WASI; 6–18 years]). Concurrent BLL assessment was associated with FSIQ decrement (β = −2.1 [95% CI: −3.9, −0.2]). Covariates considered as potential confounders included race, poverty, maternal education, and factors related to CKD (i.e., CKD stage, duration, glomerular versus non-glomerular diagnosis, hypertension, proteinuria, and anemia). The median BLL in this study was 1.2 µg/dL.

Hong et al. (2015) found an association between blood Pb concentration and lower FSIQ (−2.12 [95% CI: −3.79, −0.45] in a cross-sectional analysis of Korean school children from 8 to 11 years old. This association persisted in models adjusted for paternal education and income, ADHD rating scale score, Mn, and Hg (−1.95 [95% CI: −3.61, −0.29] per 10-fold increase). The mean BLL in this study was 1.80 µg/dL.

Menezes-Filho et al. (2018) examined the association of concurrent BLL with intelligence (WASI) among children from 7 to 12 years old. Mn in hair and toenails was also measured and the interaction between metals evaluated. Child IQ was associated with BLL in this study (−2.78 [95% CI: −4.66, −0.89]) in adjusted models. The mean BLL of children in this study was 1.64 µg/dL. The effect of BLL on child IQ was greater among children with higher toenail Mn concentrations.

Lucchini et al. (2012) conducted a cross-sectional analysis of children between the ages of 11 and 14 to examine the relationship between concurrent BLL and FSIQ as well as the potential interactions with Mn and the aminolevulinic acid dehydratase (ALAD) genotype. A decrement in FSIQ score was observed in association with BLL after adjustment for covariates including SES and maternal education (β = −2.24 [95% CI: −4.10, −0.37]). No interaction with Mn or ALAD was found. The mean BLL was 1.71 µg/dL in this study.

3.5.1.1.1 Summary

A large number of studies evaluated in the 2013 Pb ISA found a consistent pattern of associations between higher BLL and lower FSIQ in children aged 4–17 years (U.S. EPA, 2013). Multiple recent longitudinal studies add to the evidence informing the relationship between BLL and IQ in children. Heterogeneity in the magnitude and direction of the associations was present across studies. In a study of Canadian preschool children with low blood Pb levels, an association between cord blood Pb level and FSIQ was observed, while the association of childhood concurrent BLLs with FSIQ effectively null (Desrochers-Couture et al., 2018). In addition, associations were observed in boys but not in girls in several studies (Tatsuta et al., 2020; Taylor et al., 2017). There was some indication that the heterogeneity across studies could be explained by modeling choices such as confounder adjustment for other metals. For example, cross-sectional analyses found evidence that exposure to Mn may modify the association between Pb exposure and IQ in some populations (Martin et al., 2021; Menezes-Filho et al., 2018). However, studies that adjusted for multiple metals (e.g., Mn, Hg, Cd, and Pb) in regression models, without examining the interaction between metals, found little evidence of an association between cord or postnatal BLL and IQ (Zhou et al., 2020b; Liu et al., 2015), imprecise associations only in boys (Tatsuta et al., 2020), or large IQ decrements after adjustment for Mn, Hg, and ADHD rating score (Hong et al., 2015). Overall, recent studies generally corroborated the epidemiologic observations of associations between Pb exposure and IQ in children with relatively low blood Pb concentrations (≤5 μg/dL) among some populations of children (see Figure 3-4 and Evidence Inventory Table 3-2E). Consistent with findings from the 2013 Pb ISA, individual studies continue to report associations of FSIQ with prenatal BLL (maternal and cord blood Pb) and postnatal BLLs measured at various childhood lifestages. The heterogeneity in the observations across studies did not weaken the larger body of evidence supporting the association of Pb exposure with cognitive effects in children at BLLs <5 μg/dL.

3.5.1.2 Infant Development

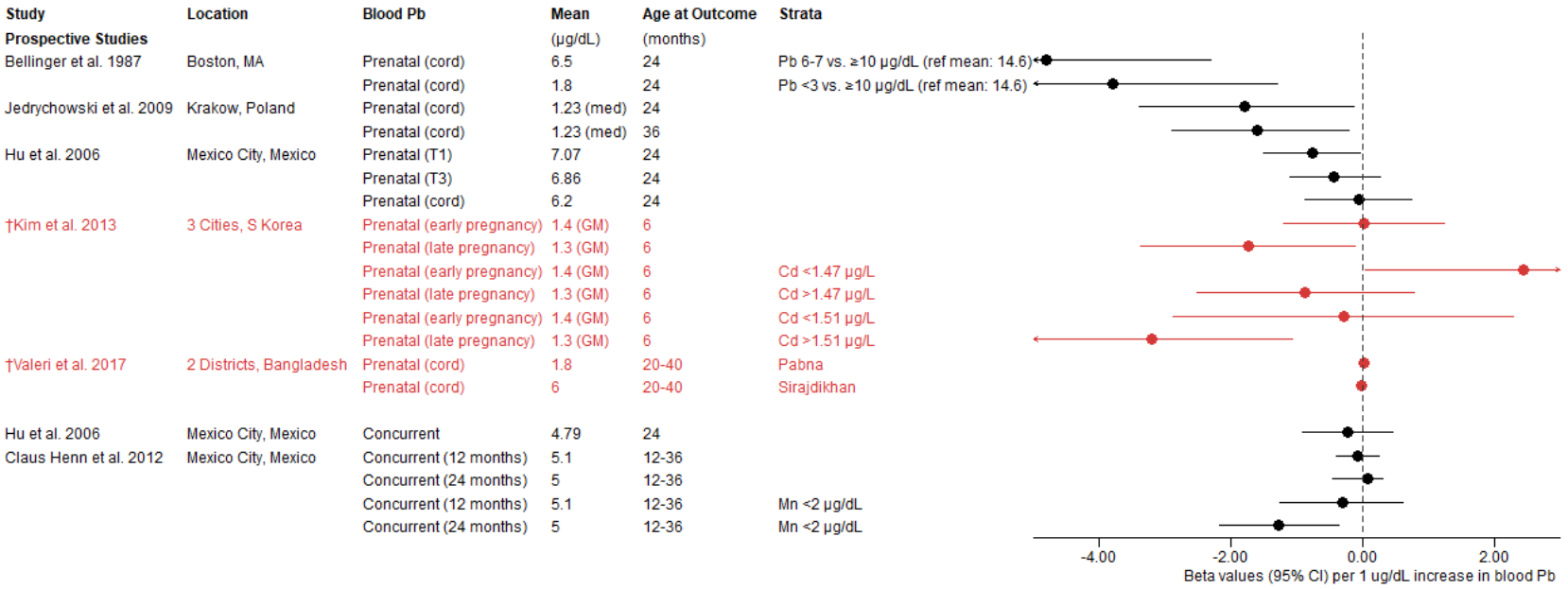
The BSID is an assessment instrument that was developed to identify children with developmental delays. The early versions (e.g., (Bayley, 1969)) have been expanded and refined, with subsequent versions incorporating three domains of development (i.e., cognitive, language, and motor), and parent-reported subtests that reflect social, emotional, and adaptive behaviors (Albers and Grieve, 2007). The current version of the BSID, the BSID-IV, retains the same number of domains but includes fewer questions within each domain and requires less time to complete (Balasundaram and Avulakunta, 2021).

This section focuses on the Mental Development Index (MDI) and the cognitive and language scales of later versions of the BSID. The MDI and cognitive/language scales are reliable indicators of the current development and cognitive function of infants, integrating cognitive skills such as sensory and perceptual acuities, discriminations, and response; acquisition of object constancy; memory learning and

problem-solving; vocalization and beginning of verbal communication; and basis of abstract thinking (McCall et al., 1972). However, the MDI test is not an intelligence test, and MDI scores, particularly before ages 2–3 years, are not necessarily strongly correlated with later measurements of FSIQ in children with normal development (U.S. EPA, 2013).

In the review of the MDI evidence in the 2013 Pb ISA, emphasis was placed on results from examinations at ages 2–3 years, which incorporate test items more similar to those in school-age IQ tests. Most of the prospective studies reviewed in previous ISAs (U.S. EPA, 2013, 2006) found associations of higher prenatal (cord and maternal BLL), earlier infancy, and concurrent BLL with lower MDI scores in children aged 2 to 3 years (see Table 4-4 of the 2013 Pb ISA). These blood Pb-associated decrements in MDI were observed in populations with mean BLLs of 1.3 to 7.1 µg/dL. Studies typically recruited participants before or at birth without consideration of Pb exposure or maternal IQ and reported high to moderate follow-up participation as well as nondifferential loss-to-follow-up. Most studies adjusted for birth outcomes, maternal IQ, and education. Cord BLLs were associated with MDI, with additional adjustment for SES and HOME score in the Boston cohort (Bellinger et al., 1987) and for HOME score in the Yugoslavia cohort (Wasserman et al., 1992). Some studies found a stronger association of MDI with prenatal BLLs than child postnatal BLLs (Hu et al., 2006; Gomaa et al., 2002; Bellinger et al., 1987).

Among the studies assessed in the 2013 Pb ISA, several included children with mean BLLs less than 5 µg/dL (Henn et al., 2012; Jedrychowski et al., 2009b; Hu et al., 2006; Bellinger et al., 1987). Recent longitudinal epidemiologic studies of populations or including groups with maternal, cord, or postnatal mean BLLs less than 5 µg/dL add to the overall body of evidence (see Section 3.7, Table 3-3E). These studies are presented in Figure 3-5.



Note: Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th −90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.
†Studies published since the 2013 Integrated Science Assessment for Lead.

Figure 3-5 Associations between biomarkers of Pb exposure and Bayley Score of Infant Development Mental Development Index.

Several studies were conducted using data from Mexico City birth cohorts that enrolled low and middle-income women seeking prenatal care at maternity hospitals belonging to the Mexican Institute of Social Security (Y Ortiz et al., 2017; Henn et al., 2012; Hu et al., 2006). Hu et al. (2006) and Sánchez et al. (2011) were designed to elucidate the time window during pregnancy when the effect of Pb exposure on neurodevelopment is most pronounced and are discussed in Section 3.5.1.6.3 and included in Table 3-6E, which includes studies with central tendency BLLs ≥5 μg/dL. Y Ortiz et al. (2017) examined the modification of the Pb-neurodevelopment association by prenatal stress using the Crisis in Family Systems-Revised (CRISYS-R) questionnaire, which assesses negative life events across several domains (i.e., financial, legal, career, relationships, community and home violence, medical problems, other home issues, discrimination or prejudice, and difficulty with authority). Using structural equation models, this study found that 3rd trimester maternal BLL (β = −6.60 [95% CI: −13.49, 0.29] per unit of log-transformed BLL) and the quadratic term for stress (β = −0.23 [95% CI: −0.45, −0.01] per unit of log-transformed BLL) were associated with lower scores on the cognitive component of the BSID. A weak more than multiplicative interaction between 3rd trimester maternal BLL and stress was also observed (β = 1.02 [95% CI: −0.78, 2.82]). Approximately 67% of the mother-infant pairs had complete information for covariates, which included maternal education, IQ, and HOME score. Henn et al. (2012) studied the interaction between postnatal blood Mn and Pb levels (age 12 and 24 months) and MDI score at five different time points between 12 and 36 months of age among the Mexico City mother-infant pairs. The coefficients for the association between BLL at 12 and 24 months with MDI score were –0.07 (95% CI: –0.39, 0.25) and–0.08 (95% CI: –0.46, 0.30), respectively. Interactions between the highest quintile of Mn and continuous BLL at 12 months were observed (β = –1.27 [95% CI: –2.18, –0.37]). The model was adjusted for covariates including hemoglobin, maternal IQ, and maternal education.

Kim et al. (2013b, 2013c) studied the combined effect of prenatal exposure to Pb and Cd on infant cognitive development at 6 months of age among participants in the Mothers' and Children's Environmental Health (MOCEH) study, which enrolled infant-mother pairs from maternity clinics in three Korean cities. Higher maternal BLL in late pregnancy was associated with lower MDI scores (β = −1.74 [95% CI: −3.37, −0.12]), while maternal BLL in early pregnancy was not (β = 0.02 [95% CI: −1.20, 1.24] per μg/dL). This association was found after adjustment for Cd and other covariates including maternal education and SES. A larger decrement in MDI was associated with late pregnancy maternal BLL among those with Cd levels above the median (β = −3.20 [95% CI: −5.35, −1.06]) compared with the decrement observed among those with Cd levels below the median (β = −0.29 [95% CI: −2.88, 2.30]). Further, an increase in MDI was observed in association with early pregnancy maternal BLL among those with Cd levels below the median (β = 2.44 [95% CI: 0.04, 4.83]), indicating the potential for random error, differential confounding, or other forms of bias to influence findings. In another study of mother-infant pairs in Korea, Kim et al. (2018b) evaluated the associations between MDI and various chemicals and metals, including Pb, in perinatal maternal whole blood and umbilical cord blood. The median maternal and cord blood Pb concentrations were 2.7 μg/dL and 1.2 μg/dL, respectively. Associations of blood Pb concentrations and MDI were assessed but not reported because they lacked statistical significance.

Valeri et al. (2017) examined the combined effect of cord blood concentrations of Pb, arsenic (As), and Mn with cognitive and languages scores on the BSID. This study enrolled infant-mother pairs from two birth cohorts in Bangladesh, which differed substantially regarding metal profiles and maternal characteristics including maternal education. This study presents results from multiple regression modes and also applied Bayesian kernel machine regression (BKMR) in a prospective analysis that considered covariates including maternal IQ, education, and HOME score. A weak association between increasing cord Pb level and decreasing cognitive score was observed in the group with lower Mn and As concentrations in cord blood (β = −0.01 [95% CI: −0.02, 0.00]) but not in the group with higher concentrations of these metals (β = 0.01 [95% CI: −0.05, 0.07]).

Koshy et al. (2020) analyzed data from a birth cohort following children living in a slum in Vellore, India. Blood Pb concentration at 15 and 24 months was averaged to determine the association with raw cognition score on the BSID at age 2 (β = –0.2 [95% CI: –0.2, –0.03]). These results were adjusted for covariates including SES, maternal IQ, and iron level. In another study, Shekhawat et al. (2021) obtained cord blood Pb data and BSID-III scores at 6.5 months on average in a prospective cohort study of mother-child pairs in western Rajasthan, India. The linear regression models showed no significant associations of Pb levels and cognitive or language scores.

Parajuli et al. (2015a) and Parajuli et al. (2015b) assessed the association of cord BLLs with MDI at 24 and 36 months of age, respectively, in a birth cohort of mother-child pairs recruited from a general hospital in Bharatpur, Nepal. The median blood Pb concentration was 2.06 µg/dL. Adjusting for in utero Pb, As, and zinc (Zn) levels, HOME score, mother's age, parity, mother's education level, family income, mother's body mass index (BMI) just before delivery, weight of the infant at birth and 24 months after birth, gestational age, and infant age at the time of BSID-II assessment, no association was observed between cord blood Pb and 24-month MDI (β = −4.21 [95% CI: −13.62, 5.20] per log-transformed BLL) or 36-month MDI (β = 4.05 [95% CI: −3.21, 11.31] per log-transformed BLL).

Several recent studies assessed neurodevelopment using other validated instruments (Nozadi et al., 2021; Nyanza et al., 2021; Zhou et al., 2017; Vigeh et al., 2014; Lin et al., 2013). Zhou et al. (2017) assessed 139 mother-child pairs from the Shanghai Stress Birth Cohort. Maternal whole blood and maternal prenatal stress levels were assessed at 28–36 weeks of gestation, and the Gesell Developmental Schedules (GDS) adapted for a Chinese population were administered to children at 24–36 months of age in the study. This instrument measures development quotients (DQs) in five domains (gross motor, fine motor, adaptive behavior, language, and social behavior) and has been validated for children 0–84 months old. For this section on neurodevelopment, only the language domain is relevant. The Symptom Checklist–90-Revised was used to produce a Global Severity Index (GSI) for evaluating overall maternal emotional stress. After controlling for child sex, age, maternal age, gestational week, birth weight, maternal education, and family monthly income, there was no association between prenatal maternal BLL and child cognitive development. However, the authors observed interaction effects such that high maternal stress appeared to exacerbate the effect of prenatal Pb exposure in several domains, including

language (β = −33.82 [95% CI: −60.04, −7.59] per log-10 transformed unit of BLL), while low maternal stress did not (β = −1.76 [95% CI: −13.03, 9.51] per log-10 transformed unit of BLL).

Vigeh et al. (2014) evaluated 174 children in Tehran, Iran up to 36 months postpartum in eight developmental areas (social, self-help, gross motor, fine motor, expressive language, language comprehension, letters, and numbers) using Harold Ireton's Early Child Development Inventory (ECDI). Items for these areas were combined to generate a general development ECDI score, with higher scores representing better development. This parent-reported measure is meant for use with children 15 months to 6 years old and includes 60 age-discriminating items from the Minnesota Child Development Inventory. To assess Pb exposure, three maternal whole blood samples and one umbilical cord blood sample were collected from each mother-child pair in the first, second, and third trimesters and at delivery, respectively. The authors observed increased odds (odds ratio [OR] = 1.74 [95% CI: 1.18, 2.57]) of a low ECDI score (<20% lower than expected for the children's age and sex) in the first trimester (BLL = 4.15 µg/dL), adjusting for hematocrit, maternal education, BMI, family income, gestational age, birth weight, and first born.

Lin et al. (2013) measured Pb and other metals (i.e., Mn, As, and Hg) in cord blood samples from 230 mother-infant pairs from the Taiwan Birth Panel Study (TBPS) and assessed development in cognition, language, motor, social, and self-care skills among 2-year-old children with the Comprehensive Developmental Inventory for Infants and Toddlers (CDIIT), which has been standardized for children 3 to 71 months old. The CDIIT uses DQs, and a score of 100 represents normal development. After adjusting for maternal age, maternal education, fish intake ≥2 times/week during pregnancy, infant gender, environmental tobacco smoke during pregnancy and after delivery, and HOME Inventory score, the linear regression models showed that highly Pb-exposed (≥75th percentile: 1.65 µg/dL) children had lower cognitive DQs (β = −5.35 [95% CI: −9.64, −1.06]) compared with those in the low-exposure (<75th percentile) group. The authors also observed an interaction with Mn such that children who were highly exposed to both Mn and Pb had larger deficits in cognitive (β = −8.19 [95% CI: −14.40, −1.98]) and language (β = −6.81 [95% CI: −12.16, −1.46]) DQs compared with those with low exposure to just one or both of these metals.

Nozadi et al. (2021) collected blood samples from pregnant mothers at the 36-week visit or at time of delivery and administered the Ages and Stages Questionnaire Inventory (ASQ:I) at 10–13 months of age to evaluate neurodevelopment. Trained staff scored children on five 65–70 item developmental domains: communication, gross motor, fine motor, problem-solving, and personal-social. A 1 µg/dL increase in prenatal blood Pb was associated with small, imprecise decreases in problem-solving (β = −0.67 [95% CI: −1.54, 0.20]) scores.

Nyanza et al. (2021) collected dried blood spots from a finger prick to measure Pb (in addition to Hg, Cd, and As) concentrations in pregnant mothers at 16–27 weeks of gestation from the Mining and Health study in Northern Tanzania. The authors used the Malawi Developmental Assessment Tool (MDAT) translated into Kiswahili to assess several functional domains, including social development, in

children between 6 and 12 months old. MDAT has been validated for children 0–6 years old in rural sub-Saharan Africa. Covariates in the Poisson regression model included maternal age, maternal education, maternal and parental occupation, number of under−5-year-old siblings at home, family socioeconomic wealth quintile, infant sex, infant age, birth weight, and height and weight at the time MDAT was administered. Concentrations of Pb were low (median: 2.72 μg/dL), and the German Environmental Survey for Children reference level of 3.5 μg/dL was used to dichotomize Pb exposure groups into low and high exposure groups. The authors did not observe significant associations between high Pb exposure and language impairment. However, children highly exposed to both Hg (≥0.08 μg/dL) and Pb were more likely to have global neurodevelopmental impairment (prevalence ratio [PR = 1.4 [95% CI: 0.9, 2.1]).

3.5.1.2.1 Summary

Most of the prospective studies reviewed in previous ISAs (U.S. EPA, 2013, 2006) found associations of higher prenatal (cord and maternal BLL), earlier infancy, and concurrent BLL with lower MDI score in children aged 2 to 3 years (see Table 4-4 of the 2013 Pb ISA). These blood Pb-associated decrements in MDI were observed in populations with mean BLLs of 1.3 to 7.1 μg/dL. Studies typically recruited participants before or at birth without consideration of Pb exposure or maternal IQ and reported high to moderate follow-up participation and nondifferential loss-to-follow-up. Recent studies continue to support associations between Pb exposure (i.e., maternal (Y Ortiz et al., 2017; Vigeh et al., 2014; Kim et al., 2013b, c), cord (Valeri et al., 2017), and postnatal exposure (Lin et al., 2013)) and poorer performance on tests of neurodevelopment among mothers and infants with mean BLLs <5 μg/dL (see Figure 3-5). Although Zhou et al. (2017) found no association overall, this study reported decrements in several domains of the GDS among infants of mothers reporting high maternal stress. Similarly, Y Ortiz et al. (2017) found some evidence of interaction between Pb exposure and maternal stress. Several studies found interactions between Pb, Mn, or Mn and As (Valeri et al., 2017; Lin et al., 2013; Henn et al., 2012) or Cd exposure (Kim et al., 2013b, c). The direction of the interaction was not consistent across studies. Overall, recent studies support findings from the 2013 Pb ISA and extend the evidence pertaining to modification of the association between Pb exposure and infant neurodevelopment by maternal stress and exposure to other metals.

3.5.1.3 Learning and Memory

The 2013 Pb ISA included many studies examining the associations of blood Pb levels with neuropsychological tests of memory and learning. These domains of cognitive function are related to intelligence, and several were evaluated in the subtests of FSIQ. Further, indices of memory and learning are comparable to endpoints examined in experimental animal studies.

3.5.1.3.1 Epidemiologic Studies of Learning and Memory in Children

The studies evaluated in the 2006 Pb AQCD and the 2013 Pb ISA did not clearly indicate associations between higher BLL and poorer performance on neuropsychological tests of memory or learning (i.e., acquisition of new information) in children 4–17 years of age (see Table 4-5 (U.S. EPA, 2013)). The studies used various tests (e.g., spatial span total errors on the Cambridge Neuropsychological Test Automated Battery [CANTAB], digit span or learning factor score on the WISC, Kaufman Assessment Battery for Children [K-ABC], memory score on the McCarthy Scale of Children's Abilities, California Verbal Learning Test [CVLT], and working memory on the Wide Range Assessment of Memory and Learning [WRAML]) to assess learning and memory, which may account for some of the heterogeneity observed in the findings. Notably, evidence for both memory and learning from prospective analyses of several established cohorts (i.e., Rochester, Boston, and Cincinnati) was mixed (Canfield et al., 2004; Ris et al., 2004; Stiles and Bellinger, 1993; Bellinger et al., 1991; Dietrich et al., 1991). These prospective studies examined blood Pb metrics including early childhood, lifetime average. Cross-sectional studies included in the previous ISA, however, generally found associations between higher concurrent BLLs and poorer learning and memory, including the large (n = 4,853) study of children aged 5–16 years who participated in the National Health and Nutrition Examination Survey (NHANES) III (Lanphear et al., 2000). Associations of higher concurrent BLL and poorer memory in children aged 5–16 years were also observed by Krieg et al. (2010) and Froehlich et al. (2007); however, some studies reporting such associations had limited implications because they lacked consideration for potential confounding (Counter et al., 2008; Min et al., 2007). Several studies included in the 2013 Pb ISA were conducted in populations with mean BLLs ≤5 μg/dL (Krieg et al., 2010; Surkan et al., 2007; Lanphear et al., 2000) and reported associations between increasing concurrent childhood blood Pb concentration and lower performance on tests of learning and memory.

A small number of recent studies examined the association of Pb exposure with children's performance on neuropsychological tests of learning and memory (see Section 3.7, Table 3-4E). Several such studies examined the association between Pb exposure and performance on tests of learning and memory in models that adjusted for several important confounders plus co-exposure to other metals or chemicals. Yorifuji et al. (2011) evaluated the association of cord BLL with several components of IQ at age 7 and age 14 in a Faroese birth cohort also exposed to methyl mercury (MeHg). IQ components including attention and working memory, language, visuospatial reasoning, and memory were assessed using the WISC-R and the children's version of the CVLT. The association of cord BLL with neuropsychological tests of cognition was reported without adjustment for cord Hg, with adjustment for cord Hg, and with a term for the interaction of cord blood Pb and cord Hg concentration. Poorer performance on the digit span components of the WISC-R, which measure short-term memory, were most consistently observed in association with cord BLL. The results for associations with performance on some of the tests indicated that the interaction between Pb and methyl Hg (MeHg) may be less than additive (i.e., the associations of cord blood with the neuropsychological test outcomes were most

discernable among children with hair Hg concentrations below 2.61 μg/g and among those with the lowest cord Hg concentrations (e.g., β = −0.27 (−0.42, −0.11) at age 14).

Another recent study by Tatsuta et al. (2014) also examined exposure to multiple chemicals including Pb, PCBs, and MeHg. The outcome in this study was performance on the K-ABC at 42 months of age. No associations with sequential processing speed score (−2.14 [95% CI: −12.80, 8.53]) or mental processing score (−3.32 [95% CI: −12.41, 5.77]) were observed after adjustment for variables including other chemicals, maternal IQ, and family income (associations per unit of log [base not reported] transformed BLL). Similarly, Oppenheimer et al. (2022) examined the association of cord BLL with working memory assessed using the WRAML among children (13–17 years old) living near a superfund site and thus exposed to multiple metals. Regression models were adjusted for prenatal concentrations of dichlorodiphenyldichloroethylene (DDE), hexachlorobenzene (HCB), PCBs, Pb, and Mn as well as other important confounders including HOME score and maternal IQ. The associations between verbal working memory, symbolic working memory and working memory index differences were 0.12 (95% CI: −0.20, 0.45), 0.09 (95% CI: −0.25, 0.42), and 0.59 (95% CI: −0.97, 2.15) respectively. The interaction of Pb exposure and sex was examined but no statistical evidence of the interaction was observed.

Summary

The studies evaluated in the 2006 Pb AQCD and the 2013 Pb ISA did not clearly indicate associations between higher BLL and poorer performance on neuropsychological tests of memory or learning (U.S. EPA, 2013). A small number of recent studies of children with mean BLLs <5 μg/dL add to the evidence informing the association of Pb exposure with performance on tests of memory and learning; however, the results from these recent studies do not enhance the consistency of the evidence as a whole. Some of the available studies consider co-exposure to other chemicals and metals as confounders (Tatsuta et al., 2014) although there is evidence that such co-exposures may interact with or modify the association between Pb and the outcome (Yorifuji et al., 2011). The evidence regarding the effect of Pb exposure on specific tests of learning and memory lacks consistency, overall.

3.5.1.3.2 Experimental Animal Studies of Learning and Memory

As described in the preceding sections, BLLs are consistently associated with decrements in FSIQ in children but show variable associations with performance on tests of learning and memory. A relationship between Pb exposure and cognitive function deficits is further supported by evidence for Pb-induced impairments in memory and learning in animal models. Critical evidence for the association of Pb with cognitive impairment comes from a series of studies describing the effects of lifetime Pb exposure on nonhuman primates (Rice, 1992; Rice and Gilbert, 1990a; Rice, 1990; Rice and Karpinski, 1988). Cynomolgus monkeys (*Macaca fascicularis*) were dosed continuously from birth and tested repeatedly throughout their lifetime. While these exposures yielded BLLs beyond values considered

relevant for the current assessment (>30 μg/dL), they provide key evidence of Pb-induced cognitive impairments in a translationally relevant species.

Learning and Memory – Morris Water Maze

In rodents, spatial learning and memory have been evaluated using several paradigms, including the Morris water maze. Typically, the Morris water maze task is separated into two distinct phases. During the training phase, spatial learning is assessed by measuring the time or distance required for a rodent to swim to a submerged platform using visual cues beyond the maze (e.g., basic shapes). Slower decreases in time to escape from the maze across training trials (i.e., escape latency) can be indicative of impaired spatial learning. After the animals have learned the location of the hidden platform (confirmed by steadily decreasing escape latencies across training trials), memory for the location of the platform is assessed in the probe phase by removing the platform and measuring the time each animal spends in that area of the maze. Decreased time spent or distance swam in the target zone can be indicative of a deficit in spatial memory. Although performance in both phases is primarily a function of learning and memory, other impairments, such as decreased motivation, motor deficits, or altered perceptual function may also influence the results. The impact of these factors is difficult to completely characterize, but some studies may include additional controls or tests (e.g., baseline swimming activity) to reduce this uncertainty. Because this ISA focuses on low exposure levels which typically do not cause overt toxicity, the impact of these factors is less likely to play a major role in the interpretation of these results.

The 2013 Pb ISA (U.S. EPA, 2013) reviewed the evidence suggesting that exposure to Pb produced learning and memory impairments in laboratory rodents using the Morris water maze. Several studies involved exposures to Pb of varying durations and across different developmental periods. Significant impairments in both learning and memory were reported for developmental exposures resulting in BLLs ranging from 23 to 70 μg/dL. For example, Kuhlmann et al. (1997) compared the effects of Pb exposure during various lifestages and reported impaired learning and long-term memory in adult Long-Evans rats exposed during gestation and lactation (via maternal diet) or over a lifetime from gestation through adulthood. Each of the exposure periods examined produced peak BLLs of 59 μg/dL. Exposure during adolescence only, which produced BLLs of 23 μg/dL, did not affect memory. In contrast with Kuhlmann, other studies reviewed in the previous ISA reported that postweaning Pb exposure (8 weeks via drinking water) in Sprague Dawley rats resulted in significant deficits in both learning and memory using the Morris water maze (Fan et al., 2010; Fan et al., 2009). Recent studies (see evidence inventory Table 3-4T) provide consistent evidence for Pb-induced impairments in learning and memory following developmental exposures with lower BLLs than covered in the previous ISA (≤30 μg/dL).

Evidence reviewed in the previous ISA indicated that development (i.e., preconception, during gestation, lactation) may be a critical window for Pb exposure to cause cognitive dysfunction later in life. Several recent studies examined the effects of long-term Pb exposure that began during development and continued into adulthood. In the study with the longest exposure duration that was relevant to this ISA,

Ouyang et al. (2019) developmentally exposed Sprague Dawley rats to Pb (0.05% Pb acetate in maternal drinking water) beginning on GD 0. After weaning, animals were maintained on drinking water containing (0.01% Pb acetate) until PND 679 (701 total days of exposure). This exposure resulted in a final mean BLL of 22 µg/dL. When assessed immediately following the end of exposure, exposed animals displayed both impaired learning and memory in the Morris water maze task (31% fewer crossings in the target zone during the probe trial compared with controls). Zhu et al. (2019b) exposed rats to Pb (0.5 g/L Pb acetate in maternal drinking water) for 387 days beginning at conception, which resulted in a final mean BLL of 29 µg/dL. In the Morris water maze, exposed animals showed significantly increased escape latencies on the last day of training only, suggestive of slightly impaired spatial learning. In the probe trial, exposed animals made 45% fewer crossings into the target zone than controls, strongly suggestive of impaired spatial memory. In another long-term study, Zhou et al. (2020a) developmentally exposed Sprague Dawley rats to Pb through maternal drinking water beginning at conception and continuing through lactation. After weaning, animals were maintained on Pb in drinking water (386 days). While this study examined several doses of Pb, only the lowest dose (0.5 g/L in water) produced BLLs that were relevant to this ISA. Learning and memory were tested via the Morris water maze during exposure at PND 21 (mean BLL 10 µg/dL) and later immediately following the end of exposure at PND 364 (mean BLL 15 µg/dL). At both time points, Pb-exposed animals took significantly more time to escape the maze during training and spent less time in the target zone during the probe trial, indicative of impaired learning and memory. The effect of Pb was slightly more pronounced at the earlier timepoint (number of crossings in target zone was 36% lower than that of controls at PND 21, compared with a 26% difference at PND 364), which may be due to improvement on the task with age.

In a study by Tartaglione et al. (2020), male and female Wistar rats were developmentally and lactationally exposed to Pb beginning 4 weeks prior to conception (GD −28) to PND 23 (50 mg/L in maternal drinking water), resulting in a final BLL of 26 µg/dL, and displayed increased escape latencies compared with controls. This effect was not sex-specific. Exposed animals showed mild memory deficits in the form of increased latency to target zone and increased distance to target zone relative to controls (no effect observed on crossings or time spent in target zone). While effects on memory were not sex-specific, the authors reported that Pb significantly decreased path efficiency (ratio of the shortest possible path length to the observed path length) in females only, which may indicate a sex-specific effect of Pb on the processes that govern spatial integration.

Xiao et al. (2014) compared the effects of Pb on two separate developmental windows in Wistar rats: one beginning prior to conception (2 mM Pb in maternal drinking water from GD −21 to PND 21, 57 days total) and the other beginning in adolescence (2 mM Pb in drinking water from PND 21 to 84, 63 days). The gestational exposure yielded a final BLL of 10 µg/dL at PND 21, while the adolescent exposure led to a final BLL of 4 µg/dL. Animals from both exposure groups were tested in the Morris Water Maze on PND 85. Exposed animals had significantly increased escape latencies and decreased target zone time relative to control animals, indicating cognitive dysfunction. No difference was observed between the exposure time frames, suggesting both may be similarly vulnerable to the cognitive effects of

Pb assessed by the Morris water maze. Similarly, Barkur and Bairy (2015b) employed a study design that examined multiple different time frames of exposure: pregestational, gestational, and combined gestation and lactation. All but the combined gestation and lactation group yielded BLLs that were relevant to this ISA. Pb exposure during each period of development had a significant negative effect on memory compared with the control groups (learning data were not reported). The gestation and lactation groups exhibited similar magnitudes of effects, with the pregestational group showing the smallest difference compared with the control. This study suggests that Pb affects memory following developmental exposure and that the periods of gestation and lactation may be more sensitive than the pregestational period alone.

Wang et al. (2021a) exposed Sprague Dawley rats to 0.05 and 0.1% Pb in drinking water from the beginning of gestation through the end of lactation. BLLs assessed on PND 21 resulted in BLLs of 24.9 and 30.4 μg/dL for the two dose groups, respectively. On PND 21, Pb-exposed rats displayed significantly increased escape latencies during acquisition, indicative of impaired learning. During the probe trial, only animals in the highest Pb concentration had significantly fewer crossings in the target zone. Betharia and Maher (2012) exposed Sprague Dawley rats starting at conception (10 μg/mL in maternal drinking water, GD 0 to PND 20) and assessed cognitive function via the Morris water maze at two points: end of exposure (PND 21, BLLs of 0.98 μg/dL) and later (PND 56, BLLs of 0.03 μg/dL). This study reported the lowest BLLs for animals tested in the Morris water maze paradigm. In contrast to many of the recent studies reviewed here, when assessed immediately following the end of exposure, no effects on learning or memory were observed. At the later time point, exposed females displayed significantly impaired memory relative to untreated controls. This minor discrepancy could be due to the lower dose used in the study. It is also possible that repeated experience with the paradigm across two sessions could "unmask" a subtle effect on learning and memory produced by low-level exposure to Pb, though data on cognitive function in animals with BLLs <1 μg/dL remain limited.

In Anderson et al. (2012), rats were exposed starting prior to conception and then continuing through lactation (GD −10 to PND 21) to a range of doses and assessed for learning after the end of exposure. Only the lowest Pb concentration (250 ppm in drinking water) yielded BLLs relevant to this ISA, with final levels of 19 μg/dL in males and 18 μg/dL in females. During the training phase, Pb exposure had no effect on escape latency in either sex; however, Pb-exposed females displayed significantly decreased path efficiency compared with untreated controls. While no effect on spatial memory was observed during the probe trials, exposed females once again exhibited lower path efficiency scores compared with untreated controls, suggesting that, in females particularly, Pb may influence pathfinding processes. This study also determined that Pb partially blunted the positive effects of an enriched environment on spatial learning, which may be relevant when considering how environmental factors (e.g., SES) may interact with Pb exposure in humans.

In Zhao et al. (2018), rats were developmentally and lactationally exposed to multiple doses of Pb from GD −14 to PND 10, resulting in final BLLs of 1 μg/dL for 0.005% Pb and 1.5 μg/dL for 0.01% Pb

on PND 30. The highest dose group (0.02% Pb in drinking water) yielded BLLs higher than relevant for this ISA. At the two relevant doses, Pb exposure led to significant impairments in both learning and memory. Additional recent studies provided evidence that developmental exposure to Pb resulted in learning and memory deficits that persisted later into adolescence and adulthood (Xiao et al., 2020; Li et al., 2016a; Zhang et al., 2014; Rahman et al., 2012b; Zhang et al., 2012) In one discrepant study, Wang et al. (2021b) exposed Sprague Dawley rats to Pb in drinking water (0.05–0.2% Pb) from 4 weeks prior to conception to PND 21. Only the lowest exposure concentration (0.05%) resulted in a mean BLL relevant to this ISA (21.1 µg/dL at PND 21). Learning and memory were also assessed via the Morris Water Maze on PND 21; the authors reported no significant effects of Pb during acquisition or testing in the 0.05% exposure group, though some effects on memory were seen at higher concentrations.

One recent study investigated the effects of Pb exposure on the cognitive function of adolescent rodents. Liu et al. (2022c) exposed 4-week-old Sprague Dawley rats to 0.2% Pb for 12 weeks, which yielded a mean BLL of 17.3 µg/dL. The authors reported no effect of Pb on learning during the acquisition phase; however, during the probe trial, Pb-exposed animals exhibited significantly fewer crossings relative to untreated controls, suggestive of memory impairment. These recent studies provide broadly consistent evidence that Pb produces learning and memory impairments, with developmental periods potentially representing a more sensitive window for exposure.

Learning and Memory – Novel Objection Recognition

Another commonly applied measure of long-term memory in animal models is the novel object recognition task. Following habituation to an empty arena, animals are placed in the arena with two identical mundane objects and allowed to explore freely. During the testing phase (~24 hours after training), animals are returned to the arena with one object from the first day and one novel object and allowed to explore. The time spent examining each object is recorded. Because rodents tend to explore unfamiliar objects, these durations can be used to calculate a recognition index, which serves as a measure of memory. Decreased recognition indices (less time spent with the novel object) suggest impaired memory. The previous ISA did not incorporate novel object recognition data, but one recent study used the paradigm to assess long-term memory following Pb exposure relevant to the current assessment.

Tartaglione et al. (2020) observed that long-term exposure to Pb via maternal drinking water (GD −28 to PND 23), which yielded relatively high BLLs of ~26 µg/dL, caused a significant decrease in novel object recognition index in females, but not males, when tested at PND 60–72. This study did not report results from the pre-test phase (i.e., habituation and familiarization), so the potential influence of activity differences or inherent place preference cannot be determined. However, the result of this single study is generally consistent with the pattern of memory impairment observed following developmental Pb exposure, though evidence from the novel object recognition paradigm remains limited. Sex, exposure timing, and behavioral history may also influence effects on long-term memory, yet the contribution of each of these factors remains unclear.

Learning and Memory – Y Maze

Another measure of spatial memory in rodents is the Y maze, which relies on the natural inclination of rodents to explore new areas rather than revisit previously explored areas. After the animal in placed in the Y-shaped maze, spontaneous alterations (i.e., entries into an arm different than the most recently visited arm) and total arm entries are recorded. Total arm entries reflect locomotor activity, and re-entries into the most recently visited arm from the center of the maze (decreased spontaneous alteration) may indicate dysfunction in working spatial memory. The previous ISA reviewed evidence from only one study that utilized the Y maze: (Niu et al., 2009) reported that Wistar rats exposed to Pb from lactation up to 12 weeks of age displayed learning impairments starting at 8 weeks of age. These exposures resulted in BLLs of 17 μg/dL, which are relevant to the current assessment.

Three recent studies utilized the Y maze to assess spatial memory following Pb exposures that produced comparable BLLs (Table 3-4T), and the results were inconsistent. Xiao et al. (2020) reported that female Sprague Dawley rats with long-term developmental exposure to Pb (125 ppm in drinking water from GD −7 to PND 68) displayed a significant decrease in spontaneous alterations compared with control females (70 versus 55%), which suggests a deficit in spatial working memory independent of locomotor function. In contrast, Tartaglione et al. (2020) did not observe any changes in spontaneous alterations following a shorter exposure in male and female Wistar rats (50 mg/L in drinking water from GD −28 to PND 23). Tartaglione et al. (2020) did report a significant decrease in arm entries made by exposed rats, which may indicate a Pb-induced alteration in exploratory behavior rather than an effect on memory. No sex effects were observed in this study. Similarly, Abazyan et al. (2014) conducted a dietary exposure to Pb from conception to adulthood (approximately 6 months), which yielded BLLs of 26 μg/dL in males and 35 μg/dL in females (not relevant to this ISA). The authors reported no significant effect of Pb on alterations in the Y maze in either sex. While these recent studies were focused on assessing memory rather than learning in the Y maze, the effects of Pb on Y maze performance and the influence of the developmental window remain unclear. Further investigation may be needed.

Learning and Memory – Fear Conditioning

Another measure of learning and memory, fear conditioning, is a task in which animals are trained to associate a particular conditioned stimulus (e.g., auditory tone) with an aversive unconditioned stimulus (e.g., mild foot shock). After repeated pairings of the conditioned and unconditioned stimuli (acquisition), animals are exposed to the conditioned stimulus and the conditioned response (e.g., freezing, defined as lack of non-respiratory movement) is recorded. Decreases in freezing behavior may indicate memory deficits, as the animal is no longer associating the tone with the aversive stimulus. Several variations on this procedure may be employed to interrogate different brain regions and processes, such as “trace” fear conditioning, wherein an interval occurs between the tone and the aversive stimulus. Though fear conditioning data were not incorporated in the previous ISA, four recent studies

examined the effects of Pb exposures that produced BLLs relevant to the current assessment on associative memory.

To assess the influence of exposure window on Pb-induced cognitive impairment, Anderson et al. (2016) exposed male and female Long-Evans rats to Pb (150, 375, and 750 ppm in chow) during three separate exposure windows (perinatal [GD −10 to PND 21], early postnatal [PND 0 to PND 21], and long-term postnatal [PND 0 to PND 55]), all of which resulted in BLLs <10 μg/dL (summarized in Table 3-4T). The authors used a "trace" fear conditioning paradigm with memory testing at 1, 2, and 10 days after conditioning. Anderson et al. (2016) reported significant effects of Pb that differed by sex, exposure window and dose. In females, learning impairments were observed only in the highest dose group of the perinatally exposed animals. Some memory deficits were noted in the early postnatal exposure group but only at lower doses. Interestingly, following long-term postnatal exposure, females only displayed memory problems at the lowest doses of Pb. This result is not easily explained by variation in BLL (i.e., the lowest dose group did not have higher BLLs than the other dose groups). In males, minor learning deficits were noted in the early postnatal and long-term exposure groups. Memory impairment was noted in perinatally exposed males at the lowest and highest doses only. The results of this experiment suggest that both sex and exposure window influence the effects of Pb on learning and memory, and that these effects may not follow the traditional dose-response relationship reported using other paradigms.

In a subsequent study by the same group, Verma and Schneider (2017) compared the effects of Pb on associative memory in two different rat strains using a design similar to the previous study (Anderson et al., 2016) to examine the influence of exposure window. There were no significant differences in BLL between Sprague Dawley and Long-Evans rats (Table 3-4T). The authors reported no Pb effects on acquisition across sex, indicating no effect on learning within the fear conditioning paradigm. In Long-Evans females, animals exposed during the early postnatal period showed a marked decrease in percent time freezing during the memory tests (day 1, control: 90% time freezing versus treated: 68% time freezing). Consistent with the previous study from this group, the effect was more pronounced after the initial acquisition trials (day 10, control: 70% time spent freezing versus treated: 29% time freezing). Conversely, in Long-Evans males, there was no effect in the postnatal exposure group, yet significant impairments were detected in the perinatal exposure group starting on the 2nd day after acquisition (day 2, control: 68% freezing versus treated: 48% freezing). Once again, the effect was more pronounced later in the experiment (day 10, control: 75% freezing versus treated: 39% freezing). Interestingly, no significant effect of Pb on learning or memory was observed in Sprague Dawley rats of either sex with BLLs of approximately 5 μg/dL.

Wang et al. (2016) exposed male Sprague Dawley rats to 100 ppm Pb in drinking water from PND 24 to 56 and then assessed memory using a context-dependent fear conditioning paradigm in which the rats were returned to the same test chambers without a tone or shock 24 hours after acquisition, and freezing was recorded. In this version of the test, environmental context serves as a cue that the animals associate with the aversive stimulus. The authors reported a dramatic decrease in % time spent freezing in

treated animals during the memory test 24 hours later (64% time spent freezing in controls compared with only 8% time spent freezing in treated animals). This long-term adolescent exposure, which produced BLLs of 13 µg/dL, resulted in significant memory dysfunction. The divergent results between Verma and Schneider (2017) and Wang et al. (2016) may be explained by variations in the paradigms used and the duration, timing of the exposures, and resulting BLLs.

Abazyan et al. (2014) conducted dietary exposure to Pb from conception to adulthood (approximately 6 months) in mutant (double transgenic) Disrupted-in-Schizophrenia−1 (DISC1; a genetic risk factor for schizophrenia) mice, which yielded BLLs of 26 µg/dL in males and 35 µg/dL in females (outside PECOS). Single transgenic mice that possessed the mouse DISC1 (mDISC1) transgene but did not express mDISC1 served as controls. Using a contextual fear conditioning paradigm, these authors reported no effect of Pb on fear extinction in mutant or control mice. These studies suggest developmental Pb may adversely affect learning and memory within the fear conditioning paradigm, but these effects may be sensitive to factors such as sex, strain or genetics, dose, and timing of exposure.

Learning and Memory – Avoidance

Another measure of learning and memory in animal models is the avoidance paradigm, which is a fear-aggravated test that relies on animals learning to avoid environments where they experienced an aversive stimulus. In the passive, "step-through" variation of the test, animals are placed in an arena with at least two compartments, separated by gates that allow passage between compartments. During training, animals will receive an aversive stimulus (foot shock) in the darkened chamber. The animals are later placed in an illuminated chamber and the time that elapses before the animals enter the dark chamber is recorded (entry latency). Shorter entry latencies are associated with impaired memory. The previous ISA did not incorporate any passive avoidance studies. Four recent studies examined passive avoidance behavior following Pb exposure.

Barkur and Bairy (2015b) compared the effects of Pb (0.2% in maternal drinking water) on associative learning in male Wistar rats across several different developmental exposure periods and durations, all but the longest of which produced BLLs <30 µg/dL. All exposed animals, except for the pregestation group (GD −30 to GD 1), displayed decreased entry latencies relative to controls, indicative of impaired memory. These effects persisted out to 48 hours after the initial exploration trial. Similarly, Barkur et al. (2011) observed that male Wistar rats exposed via maternal drinking water (0.2%) from GD 0 to PND 21 had significantly shorter entry latencies when assessed at PND 25 and again at PND 120. It should be noted that BLLs were >30 µg/dL when measured on PND 25 but the levels decreased to ~0.5 µg/dL by PND 120. Following long-term exposure to Pb via drinking water (50 ppm, GD 0 to PND 45), Bijoor et al. (2012) reported that male and female offspring displayed significantly shorter entry latencies than their untreated counterparts.

One study utilized a "step-down" version of the test, wherein animals are placed on a platform above a grid that delivers a mild electric shock. Over the course of training, animals should learn to associate the grid with the aversive stimulus and avoid stepping down off the platform. During testing, both latency (time elapsed before stepping down) and errors (number of times the animal stepped down onto the grid) are recorded to assess memory. Following long-term developmental exposure to Pb (0.4% in maternal drinking water from GD 0 to PND 21, BLLs of ~14 µg/dL), Kunming mice displayed significantly decreased step-down latency and increased errors relative to controls (Zhang et al., 2014), suggestive of both learning and memory impairment. These studies suggest that exposure to Pb during development results in negative effects on associative learning and memory that may persist into adulthood and that these effects are influenced by the developmental window during which exposure occurs.

Learning and Memory with Stress

The paradigm of combined Pb and stress exposure experienced by a laboratory animal has been examined by the Cory-Slechta laboratory with a focus on the common pathway of an altered hypothalamic pituitary adrenal (HPA) axis and brain neurotransmitter levels. Effects on learning varied, depending on the timing of stress, Pb exposure concentration, and sex of the animal. Pb-stress interactions were found with dietary Pb exposures that resulted in BLLs relevant to this ISA. The evidence additionally indicated that associations of Pb exposure and stress with learning deficits (multiple schedules of repeated learning and performance in females) may be related to aberrations in corticosterone and dopamine. Several recent studies with Pb exposures relevant to the current ISA included stress components in their experimental designs, providing further evidence that supports an interaction between stress experience and the effects of Pb on cognitive function.

The Cory-Slechta laboratory expanded upon their previous research by investigating the interaction between Pb and prenatal stress in males, with additional comparisons between maternal-only and lifelong exposure (Cory-Slechta et al., 2012). In contrast to previous reports on females, prenatal stress with Pb exposure was reported to enhance learning accuracy with a repeated learning and performance schedule. The authors postulated that this effect may be due to increases in the response rate, which have been observed in both Pb and stress independently. Thus, this seemingly positive result may reflect an increase in response rate or impulsivity.

In (Anderson et al., 2012), researchers examined the influence of differential rearing conditions (enriched or barren) on Morris water maze performance in Sprague Dawley rats exposed to Pb. The authors reported a significant positive effect of the environment on learning (decreased escape latencies) in males regardless of Pb exposure, though this effect was only present during the first two acquisition trials. The same trend was observed in female rats, though Pb was shown to dull the advantage provided by enrichment, with complete negation of the advantage observed at the high dose in females. While no consistent effect was noted on time spent in the target quadrant, Pb significantly impaired the path

efficiency relative to controls in both sexes, and this effect was ameliorated by an enriched environmental status. While these studies on the influence of Pb and stress on learning in rodents produced variable results, they provide evidence supporting the interaction between Pb and stress and suggest that these effects are further influenced by sex, age, and timing of exposure.

Summary

Several recent studies in laboratory animal models with exposures resulting in mean BLLs ≤30 µg/dL add to the substantial body of evidence indicating that Pb exposures can impair learning and memory. Compared with studies in the 2013 Pb ISA, more recent studies demonstrate that the relationship between Pb exposures and learning and memory impairments is present at lower BLLs. Recent studies provided evidence that early-life exposures were associated with learning and memory impairments later in adulthood, indicating that development is a critical window for the effects of Pb on cognitive function. Additionally, new evidence suggests that longer durations of Pb exposure (especially those encompassing developmental windows) produced greater learning and memory impairments. The few studies reporting weak or null effects were not stronger with respect to the design or methodology and did not weaken the much larger body of supporting evidence.

3.5.1.4 Executive Function in Children

The executive function domain of cognitive function is related to intelligence. Indices of executive function are generally comparable to endpoints examined in experimental animal studies.

3.5.1.4.1 Epidemiologic Studies

Epidemiologic evidence presented in the 2006 Pb AQCD and the 2013 Pb ISA indicated a consistent pattern of associations between higher childhood blood Pb (i.e., blood Pb metrics including early childhood, lifetime average and concurrent) or tooth Pb levels reflecting pre- or early postnatal Pb exposure, and poorer performance on tests of executive function in children and young adults (see Table 4-8 (U.S. EPA, 2013)). Associations were found with indices of executive function such as strategic planning, organized search, flexibility of thought and action to a change in situation, and control of impulses assessed by various tests including the Intra-Extra Dimensional Set Shift, Wisconsin Card Sorting Test, and Stroop Color-Word test (SCWT). The strongest evidence was provided by prospective analyses. These analyses included several birth cohorts in Boston and Rochester and examined BLLs that preceded the outcome assessment, with adjustment for several potential confounding factors (Canfield et al., 2004; Canfield et al., 2003b; Bellinger et al., 1994a; Stiles and Bellinger, 1993). Moderate to high follow-up participation that was not biased to those with higher BLLs and lower cognitive function was an additional strength of the studies. A small number of cross-sectional studies also found concurrent

blood Pb-associated decrements in executive function, including an analysis of the Rochester cohort (Froehlich et al., 2007), and some studies were limited due to their lack of consideration of potential confounding (Nelson and Espy, 2009; Vega-Dienstmaier et al., 2006). A cross-sectional analysis by Cho et al. (2010) with a concurrent child mean BLL of 1.9 μg/dL did not find an association with performance on SCWT.

A small number of recent studies expanded the evidence base pertaining to the effect of Pb on executive functions in children (study details can be found in Section 3.7, Table 3-4E). Most of these recent studies assessed executive function using parent-teacher ratings on the Behavior Rating Inventory of Executive Function (BRIEF) (Gioia et al., 2002). This instrument comprises three scales including a Behavioral Regulation Index, which has several components (i.e., emotional control, shift, and inhibit). Other scales of the BRIEF are the metacognition index and the global executive composite. Higher BRIEF scores indicate executive function-related behavioral dysfunction.

Fruh et al. (2019) studied mother-child pairs participating in Project Viva, a longitudinal birth cohort in eastern Massachusetts. Maternal blood Pb concentration in erythrocytes was measured during the second trimester of pregnancy and parents rated their child's behavior using the BRIEF in mid-childhood (median 7.7 years). The associations (i.e., β coefficients) with the parent and teacher-rated BRIEF Behavioral Regulation Index were imprecise, i.e., 1.15 (95% CI: −0.22, 2.52) and 0.77 (95% CI: −0.57, 2.10) per 1 μg/dL increase in maternal erythrocyte Pb, respectively. In another analysis of these data, Fruh et al. (2021) aimed to determine the association of joint exposure to Pb, Mn, Se, and MeHg with scores on the BRIEF and Strengths and Difficulties Questionnaire (SDQ) using BKMR and quantile g-computation. Individual beta coefficients for each metal from multiple regression models generally agreed with the original results. Specifically, maternal Pb concentration in erythrocytes (2nd trimester) was associated with worse parental ratings on the BRIEF global executive composite (β = 1.11 [95% CI: (−0.12, 2.34] per unit increase in maternal erythrocyte Pb). Notably, the mixture was also associated with poorer parent ratings on the BRIEF in BKMR models.

Sex-specific findings were observed in a study by Merced-Nieves et al. (2022). The researchers examined the association of prenatal BLL with behavioral tasks on the operant test battery (OTB) (i.e., Conditioned Position Responding [CPR], Temporal-Response Differentiation [TRD], Delayed Matching-to-Sample [DMTS], and Incremental Repeated Acquisition), which assess executive functions, at age 6–7 years. Maternal blood Pb in late pregnancy was not associated with greater response latencies in the CPR (β = 0.00 [95% CI: −0.08, 0.08]) and DMTS (β = 0.08 [95% CI: −0.04, 0.20]) tasks, although a small increase average latency to initiate a response in the TRD task (β = 0.14 [95% CI: −0.00, 0.29]). The association of blood Pb concentrations with two operant tasks were modified by child sex, indicating Pb-associated changes in the CPR task were more pronounced in girls, and Pb-associated changes in the TRD task were more pronounced in boys. The mean BLLs during the first trimester, second trimester, and delivery, in umbilical cord blood, and postnatal were 3.7, 3.9, 4.3, 3.4, and 2.4 μg/dL, respectively.

Ruebner et al. (2019) evaluated the association between BLLs and executive function among children with CKD. In addition to adjusting for important potential confounders including SES and maternal education, the author adjusted for clinical variables in their models (i.e., CKD stage, duration, glomerular versus non-glomerular diagnosis, hypertension, proteinuria, and anemia). Executive functioning was assessed with the Delis-Kaplan Executive Function System Tower Subset (subjects >6 years) and rated by parents using BRIEF for Preschool Children (BRIEF-P; 2–5 years) and the standard BRIEF (6–18 years) or self-reported by adults (18 years and older) using BRIEF for Adults (BRIEF-A). Associations between BLL and behavioral symptoms on BRIEF did not persist in models that controlled for potential confounders including race, poverty, maternal education, and clinical factors related to CKD (quantitative results not reported). The median BLL in this study was 1.2 μg/dL.

Summary

Strong evidence of associations between Pb exposure and indices of executive function was described in the 2013 Pb ISA. Studies included prospective analyses of several birth cohorts with moderate to high follow-up rates in Boston and Rochester that examined the BLLs that preceded the outcome assessment and adjusted for several potential confounding factors (Canfield et al., 2004; Canfield et al., 2003b; Bellinger et al., 1994a; Stiles and Bellinger, 1993). Recent studies that assessed executive functions using parent or teacher behavioral ratings on BRIEF are mixed; however, findings from these studies do not diminish the evidence from the earlier well-conducted studies that relied on neuropsychological testing.

3.5.1.4.2 Toxicological Studies of Executive Function

The epidemiologic evidence reviewed above indicated associations between higher childhood BLLs and poorer performance on tests of executive functions in children and young adults. Pb was associated with impaired strategic planning, organized search, flexibility of thought and action to a change in situation, and control of impulses (described in Section 3.5.1.4.1). In rodents, reversal learning is one of the main frameworks used to measure cognitive flexibility, an important component of executive function. Reversal learning tasks assess the ability of animals to actively suppress reward-related response and disengage from ongoing behavior when the conditions governing the response are altered. For example, if rodents are trained to press the leftmost of two levers to receive a reward, then the experimenters cease to reward presses of the left lever and begin rewarding right-lever presses, the animals must learn that the conditions have changed and adjust their behavior accordingly. Perseverance (i.e., continuing to press the left lever after the rules have changed) represents impaired cognitive flexibility and execution dysfunction. This basic paradigm can be expanded to parse specific components of executive function.

Two recent studies from the same group assessed executive function using an attention-set shifting task paradigm following relevant Pb exposures during development. Neuwirth et al. (2019c) compared performance in Long-Evans rats exposed to Pb during different windows of development. Briefly, rats were trained to dig for treats by relying on environmental cues that indicated which of two bowls contained a buried treat. Trained rats were run through a series of discrimination trials including interdimensional and extradimensional shifts to test cognitive flexibility. An interdimensional shift occurs when the relevant cue changes but remains within the same dimension (e.g., the baited bowl is still indicated by a scent, but the correct scent has changed from lavender to peppermint). More complicated extradimensional shifts require animals to recognize that the relevant cue has changed dimensions (e.g., the baited bowl is no longer indicated by scent but by the texture of the media).

Male rats exposed to Pb via lactation (150 ppm in maternal chow) during the early postnatal period (PND 0 to 22), which yielded BLLs of ~6 μg/dL, displayed substantial learning deficits in the form of increased Trials-to-criterion for the olfactory (the relevant dimension) discrimination component. Indeed, males exposed during the early postnatal period were unable to complete discrimination training and progress to the next task in the same manner as the control males, indicative of a substantial learning impairment as the result of Pb exposure. No effect was observed in female rats following exposure in the postnatal period, despite similar BLLs of ~5 μg/dL. Even though male rats perinatally exposed (GD −14 to PND 22, BLLs of ~6 μg/dL) successfully completed discrimination training, they struggled during testing and displayed significant increases in Trials-to-criterion across simple and complex discrimination tasks yet solved extradimensional shift tasks in a fashion comparable to control males. In contrast to males, perinatally exposed females performed poorly in extradimensional shift tasks and showed improved performance relative to controls in discrimination training and reversal (Neuwirth et al., 2019c).

In a subsequent study by the same group (Neuwirth et al., 2019b), the authors reported that perinatal exposure (GD 0 to PND 22), which resulted in BLLs ~10 μg/dL on PND 22, also produced sex-specific learning deficits in discrimination training and impaired reversal learning. These studies provide evidence that exposure to Pb during different developmental windows may produce differential patterns of executive dysfunction and that these changes may be sex-specific. While the previous ISA did not include any toxicological evidence that explicitly addressed executive function, the findings of (Neuwirth et al., 2019c) and (Neuwirth et al., 2019b) are consistent with the evidence reviewed in the previous ISA that indicated Pb exposure contributed to cognitive dysfunction and that the effects of Pb on cognition were often sex-specific.

Summary

The previous ISA did not incorporate any evidence of the relationship between Pb exposure and executive function in animal models. Two recent studies from the same group provided evidence that Pb exposure broadly impairs measures of executive function in a reversal learning paradigm. These effects were sex-specific, with greater effects reported in males. While these reports are consistent with one

another, evidence for the association between Pb exposure and impaired executive function in animal models with BLLs ≤30 µg/dL remains limited.

3.5.1.5 Academic Performance and Achievement in Children

Poorer academic performance and achievement is linked with lower FSIQ and may have important implications for success later in life (U.S. EPA, 2013). The 2006 Pb AQCD and the 2013 Pb ISA described associations of higher blood and tooth Pb levels, which reflected Pb exposure at various time periods and lifestages, in children aged 5–18 years with poorer performance on tests of math, reading, and spelling skills, lower probability of high school completion, lower class rank, and lower teacher ratings of academic functioning. Notably, associations were reported in prospective studies examining performance on academic achievement tests (Chandramouli et al., 2009; Min et al., 2009; Miranda et al., 2009) and an additional analysis of adolescents participating in NHANES (Lanphear et al., 2000). Several prospective studies (Min et al., 2009; Miranda et al., 2009) and cross-sectional studies (Krieg et al., 2010; Chiodo et al., 2007; Surkan et al., 2007; Lanphear et al., 2000) were conducted in populations with population or group mean BLLs ≤5 µg/dL. In addition, prospective studies in Boston and New Zealand found associations of tooth Pb levels collected at an earlier age (e.g., ages 6–8 years) and generally reflecting pre- or early postnatal Pb exposure, with school performance ascertained at age 18 from school records (Fergusson et al., 1997; Needleman et al., 1990), suggesting the effect of early exposure on Pb may be persistent. The strengths of the Fergusson et al. (1997) analysis included a low probability of selection bias, coherence with results indicating associations between higher tooth Pb levels and lower teacher ratings of math, reading, and writing abilities at ages 12–13 years (Fergusson et al., 1993), and consideration of important covariates including SES, parental education, and HOME score. The Needleman et al. (1990) study was relatively small with no adjustment for parental caregiving quality.

Recent prospective studies of groups or populations with mean BLLs ≤5 µg/dL add to the evidence supporting an effect of Pb exposure on academic achievement and performance (study details can be found in Section 3.7, Table 3-5E). Prospective studies have been conducted in Detroit, Chicago, North Carolina, and a 57-county region in New York State (all counties outside New York City).

Zhang et al. (2013) studied children enrolled in Detroit public schools to determine the association between childhood BLL measured before age 6 and performance on standardized tests for math, reading, and science in grades 3, 5, and 8. Compared with students with lower BLLs (defined as levels ≤1 µg/dL), students with higher BLLs (defined as levels between 1 and 5 µg/dL) had increased risk of scores that were classified as less than proficient (OR = 1.42 [95% CI: 1.24, 1.63] for math, OR = 1.33 [95% CI: 1.10, 1.62] for science, and OR = 1.45 [95% CI: 1.27, 1.67] for reading. Logistic regression models were adjusted for covariates including SES (i.e., free and reduced school lunch participation) and maternal education.

Evens et al. (2015) conducted a study in children enrolled in the Chicago public school system. The association between childhood BLLs measured before 72 months and failure on standardized tests for math and English in grade 3 was examined. This study found that a 1 μg/dL increase childhood BLL was associated with an increased risk of failure on the reading and math tests (RR = 1.06 [95% CI: 1.05, 1.07] and RR = 1.06 [95% CI: 1.05, 1.07], respectively) after adjustment for covariates including child characteristics, preterm birth, maternal education, and SES (i.e., participation in the free and reduced lunch program). The associations of BLL with reading failure in white, Black and Hispanic children were 1.14 (95%CI: 1.08, 1.20), 1.05 (95% CI: 1.04, 1.06) and 1.08 (95%CI: 1.05, 1.11), respectively. The associations of BLL with math failure were in white, Black and Hispanic children were 1.11 (95% CI: 1.05, 1.18), 1.05 (95% CI: 1.04, 1.06) and 1.09 (95% CI: 1.06, 1.12), respectively. The mean BLL was 4.81 μg/dL in this study. Blackowicz et al. (2016) extended this analysis through their examination of the association of BLL and failure on standardized tests for math or reading among Hispanic children enrolled in the Chicago school system. An association between 1 μg/dL change in BLL and failures in reading (RR = 1.07 [95% CI: 1.05, 1.10]) and math (RR = 1.09 [95% CI: 1.06, 1.12]) were observed. The mean BLL was 4.16 μg/dL in Hispanic children in this study.

In a statewide study of North Carolina school children (Shadbegian et al., 2019), children with higher BLLs had, on average, lower scores in both math and reading (averaged over grades 3 and 8) than children with lower BLLs. Compared with children with BLL ≤1 μg/dL, the authors reported a decrease in the test-score percentile of 0.95 (0.66, 1.24) for math and 1.41 (1.12, 1.70) for reading in children with a BLL of 5 μg/dL. Shadbegian et al. (2019) included interaction terms between BLL and the grade of testing that further indicated that the deficit in the test score persisted from grade 3 to grade 8.

Skerfving et al. (2015) studied the association of childhood BLL (age 7–12 years) with school performance in the ninth grade at age 16 among Swedish school children. School performance was based on a 1–5 point passing grade scale or a 4-level merit system in which 0, 10, 15, or 20 points were assigned for each increasing level of performance. This study found a 0.11-point decrease (95% CI: −0.18, −0.05) per 1 μg/dL increase in BLL for school performance using the grading scale and a −10.90 (95% CI: −15.49, −6.31) point decrease using the merit scale, among school children with BLLs ≤5 μg/dL. The models were adjusted for covariates including parent's income, education, and father's IQ score on the military conscription exam. The association with IQ (β = −0.20 [95% CI: −0.39, −0.02]) among those evaluated for military conscription at age 18 was also examined (see Section 3.6.1).

3.5.1.5.1 Summary

Associations of higher blood and tooth Pb levels, which reflect various time periods including earlier childhood lifestages, in children aged 5–18 years with poorer performance on tests of math, reading, and spelling skills, lower probability of high school completion and lower-class rank, and lower teacher ratings of academic functioning were observed in previous assessments (U.S. EPA, 2013).

Recent studies in populations of children (age 6–16 years) with BLLs ≤5 µg/dL support and extend these observations of poorer academic performance in association with increasing Pb exposure.

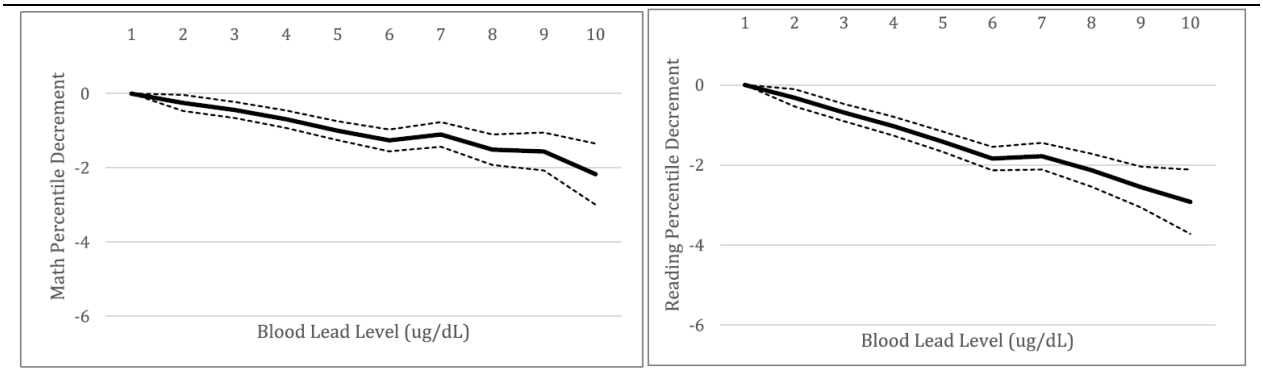
3.5.1.6 Relevant Issues for Interpreting the Evidence Base

3.5.1.6.1 Concentration-Response Function

With each previous assessment (U.S. EPA, 2013, 2006), the epidemiologic and toxicological study findings have shown that progressively lower BLLs or Pb exposures are associated with cognitive deficits in children. The 2006 AQCD found that cognitive effects in children were associated 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 of young children with mean BLLs between 2 and 8 µg/dL. The conclusions of the 2013 Pb ISA were based on studies that examined early childhood BLLs (i.e., age <3 years), considered peak BLLs in their analysis (i.e., peak BLL <10 µg/dL), or examined concurrent BLLs in young children (i.e., age 4 years). The lower bound of this mean BLL range was derived from Miranda et al. (2009), who examined the association between early childhood BLL and academic performance among school-aged (grade 4) children. A recent study of Canadian preschool children from generally middle- to upper-middle SES families with low Pb exposure (Desrochers-Couture et al., 2018) did not find an association between concurrent Pb exposure and performance on the WPPSI at age 3-4 years. Although some individual recent studies found associations of Pb exposure with cognitive effects in children with mean BLLs <2 µg/dL (e.g., (Martin et al., 2021; Dantzer et al., 2020; Hong et al., 2015)), the studies generally involved somewhat older children with lengthier exposure histories, or employed 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). Consequently, the studies did not provide evidence that would change the conclusion of the 2013 Pb ISA that cognitive effects in children are best substantiated in young children with mean BLLs between 2 and 8 µg/dL. Studies that might extend the evidence related to exposure-response relationships (i.e., recent studies that reflect the lower early childhood Pb exposures, which are now more common in the U.S.]) are limited. Overall, the recently available studies were not designed, and may not have the sensitivity (Cooper et al., 2016), to detect the effect or hazard at very low BLLs; however, recent studies generally corroborated the epidemiologic observations of associations between Pb exposure and IQ in children with relatively low blood Pb concentrations (≤5 µg/dL). Consistent with findings from the 2013 Pb ISA, studies do not provide evidence of a threshold for the effects across the range of BLLs examined. The finding of higher mean IQ with decreasing blood Pb concentration observed across epidemiologic studies, however, indicates that the absolute magnitude of the effect of Pb exposure on cognitive function is smaller with decreasing BLL.

Despite limitations, several recent studies describe the cognitive effects over the range of Pb exposure examined. Shadbegian et al. (2019) extended the analysis conducted by Miranda et al. (2009)

also using data from the statewide study of North Carolina school children while focusing on lower BLLs (<10 µg/dL) and characterized the persistence of Pb effects across grades. Among children with BLLs of 5 µg/dL or lower, a decrease in the test score percentile of 0.95 was found for math and a decrease of 1.41 was found for reading when comparing children with a BLL of 5 to those with a BLL ≤1 µg/dL. Figure 3-6 depicts the association of blood Pb levels with math and reading test score performance (average percentile decrement), with 95% CIs, among children across all grades.



Dotted lines denote 95% confidence intervals.
Source: (Shadbegian et al., 2019).

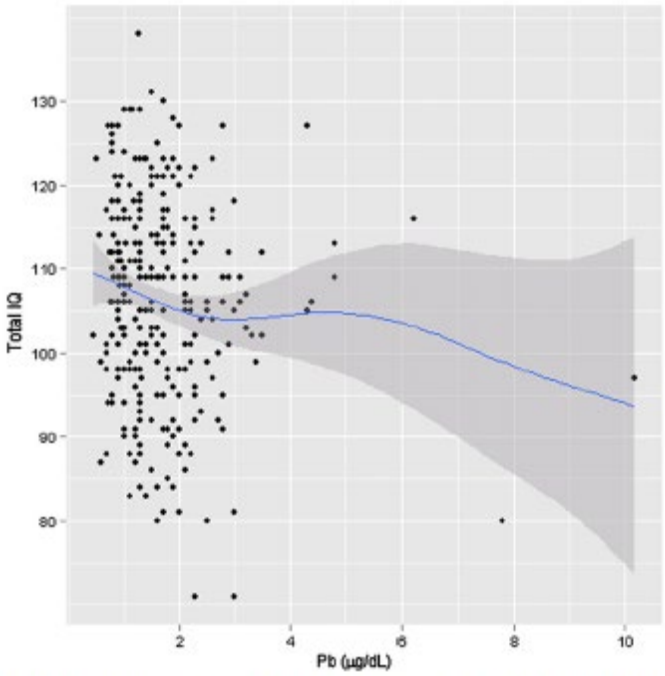
Figure 3-6 Association of blood Pb level with reading and math scores among North Carolina school children (average across all grades). Left panel displays impact of blood Pb level on math test score. Right panel displays impact of blood Pb level on reading test score.

Compelling evidence for a larger decrement in cognitive function per unit increase in blood Pb among children with lower mean blood Pb concentrations, compared with children with higher mean blood Pb concentrations, was presented in previous assessments (U.S. EPA, 2013, 2006). Individual studies as well as an international pooled analysis of seven prospective cohort studies by Lanphear et al. (2019, 2005) that examined prenatal or early childhood BLLs or considered peak BLLs in school-aged children or concurrent BLLs in young children <3 years old showed greater decrements in cognitive function per unit increase in BLL among children in lower strata of blood Pb levels compared with children in higher strata of blood Pb level (Figure 4-15, and Table 4-16 of U.S. EPA (2013) corroborated the finding of a nonlinear C-R function over the range of the BLLs evaluated (5th to 95th percentile BLL, 2.5 to 33.2 µg/dL), 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 (Crump et al., 2013). Notably the reanalysis by Crump et al. (2013) extended the findings of the original study by employing a different modeling strategy. Specifically, several covariates were defined in a site-specific manner (i.e., HOME score, maternal education, maternal IQ, ethnicity, maternal alcohol consumption, and maternal smoking), which enabled finer scale control for potential confounding factors (e.g., amount of alcohol consumed as opposed to a

binary variable for alcohol consumption). In addition, Crump et al. (2013) used more of the available blood Pb measurements by computing weighted averages for lifetime and early childhood BLLs. Further, the authors used formal methods (i.e., nested F-tests and splines) to decide between alternative specifications of BLL (linear versus log-linear) and chose to add 1 to the BLL prior to log transformation to ensure it would equal zero when BLL was zero. The key findings of Lanphear et al. (2005), Lanphear et al. (2019), and Crump et al. (2013) contribute to the strong evidence regarding the effect of low-level Pb exposure on cognitive function and the supralinear concentration relationship between Pb exposure and FSIQ. The beta coefficients from the log-linear models, which indicate larger incremental effects of Pb at lower blood Pb concentration, for (Lanphear et al., 2019, 2005) and Crump et al. (2013) were comparable (i.e., $\beta = -2.65$ [95% CI: –3:69, –1:61] per unit of natural log transformed BLL and $\beta = -3.32$ [95% CI: −4.55, −2.08] per unit of natural log transformed BLL + 1, respectively).

Attenuation of C-R relationships at higher exposure or dose levels has been reported 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, 1994a), differential activity of mechanisms at different exposure levels, and confounding by omitted or mis-specified variables (U.S. EPA, 2013). Review of the evidence did not reveal a consistent set of covarying risk factors to explain the differences in blood Pb IQ C-R relationship across high and low Pb exposure groups observed in epidemiologic studies. Recent studies in populations with mean concentrations of 2 µg/dL or lower indicated that some of the observed heterogeneity at lower BLLs may be explained by the underlying distribution in at-risk factors, including other metals. In addition, some recent studies with similarly low blood Pb concentrations reported effect modification by sex. These studies are discussed in more detail in Section 3.5.1.6.2.

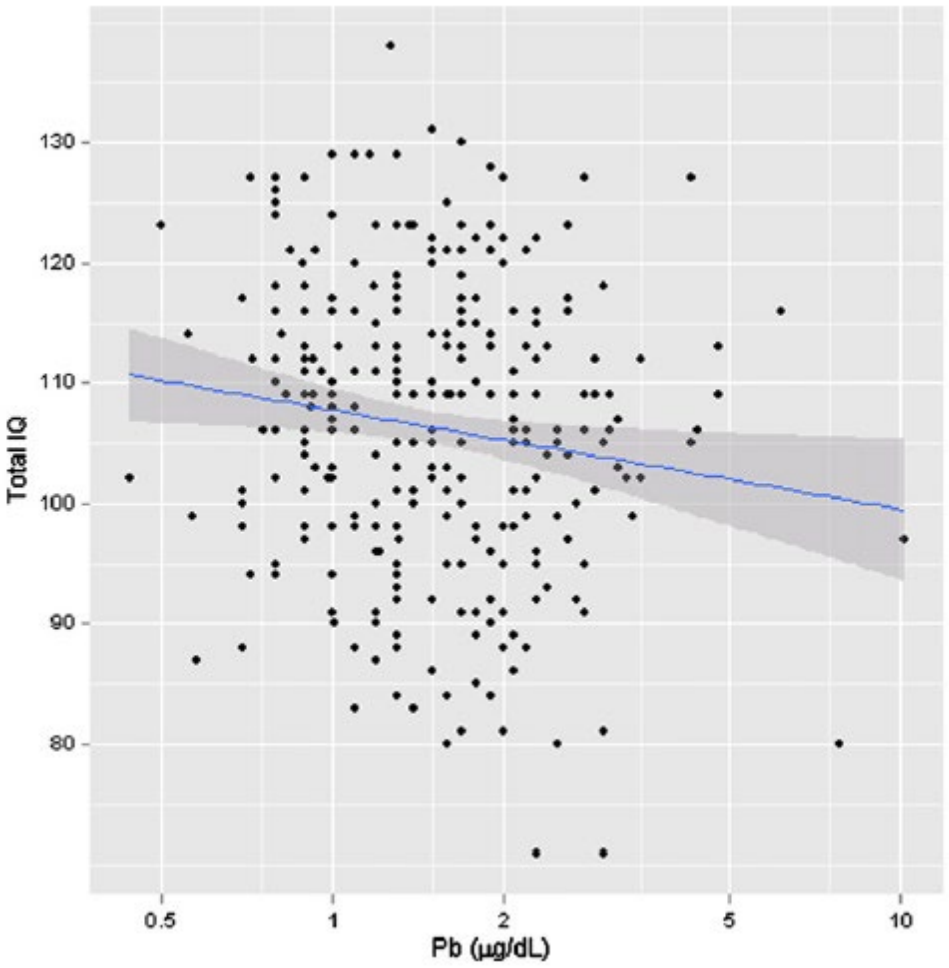
A limited number of recent studies examine the shape of the C-R function for the relationship between Pb exposure and cognitive effects in children. Lucchini et al. (2012) conducted a cross-sectional analysis of children between the ages of 11 and 14 to examine the relationship between concurrent BLL and FSIQ. The mean BLL was 1.71 µg/dL in this study. The relationship between BLL and IQ using a restricted cubic spline fit is plotted in Figure 3-7. As shown in the plot, the decrement in IQ is not constant over the range in BLLs (0.44–10.2 µg/dL). The study was conducted in an area where ferroalloy plants had operated and the extent to which the children in the study were exposed to higher Pb levels during early childhood was not clear from this cross-sectional analysis.



IQ = intelligence quotient.
Source: Lucchini et al. (2012).

Figure 3-7 Relationship between concurrent blood Pb level and intelligence quotient among Italian adolescents using a cubic spline fit.

Lucchini et al. (2012) also plotted relationship between the log-transformed BLL (ordinary least squares fit) and FSIQ (Figure 3-8). A decrement in FSIQ score was observed in association with ln concurrent BLL after adjustment for covariates including SES and maternal education (−2.24 [95% CI: −4.10, −0.37)]. Consistent with evidence reviewed in the 2013 Pb ISA, the log transformation of BLL implies a larger incremental decrement in IQ at lower BLLs. Lucchini et al. (2012) calculated the benchmark dose (BMD) for blood Pb, which is the dose that results in a specific IQ loss (i.e., a loss of one IQ point), and its lower 95% confidence limit (BMDL) using this C-R function. The BMDL calculated from these data is 0.11 µg/dL. As noted previously the older children in this study may have had higher past Pb exposure that was not reflected in their concurrent BLL.



IQ = intelligence quotient.
Source: Lucchini et al. (2012).

Figure 3-8 Relationship between log-transformed blood Pb level and intelligence quotient using an ordinary least squares fit.

Experimental animal studies support the findings in epidemiologic studies indicating the effect of Pb exposure on cognition at low exposures. Clear support from animal toxicological studies that demonstrated decrements in learning, memory, and executive function with dietary exposures resulting in relevant BLLs was assessed in the 2013 Pb ISA. Recent experimental animal studies further support impairments in cognitive function at BLLs <20 µg/dL. It is well-documented (and reviewed in the previous ISA) that Pb exposures resulting in BLLs ≥20 µg/dL consistently produced deficits in cognitive function. Recent evidence (reviewed in the current ISA; see Section 3.5.1.3.2) suggests that BLLs resulting from lower-level exposures (5–10 µg/dL) also lead to cognitive function deficits in animal models. For example, Zhou et al. (2020a); Zhao et al. (2018); Xiao et al. (2014); Betharia and Maher (2012); Cory-Slechta et al. (2012) all reported significant cognitive deficits following exposures yielding BLLs ≤ 10 µg/dL. Betharia and Maher (2012) reported the lowest BLLs for animals tested in the Morris

water maze (0.98 μg/dL at PND 21 and later 0.03 μg/dL at PND 56) which produced mild effects on memory in females at the later time point only.

The reader should be aware that BLLs reported in many of these studies were measured later during experimentation and do not necessarily reflect peak Pb burden or Pb burden during the most sensitive window of brain development for young animals and children; BLLs in toxicological studies should be interpreted in the context of both exposure time course and blood collection. Discussion of BLLs and cognitive function is further complicated by the exposure window. The evidence generally supports the notion that Pb exposures during brain development led to changes in cognition that persist after cessation of exposure and BLLs have decreased. For example, Barkur and Bairy (2015b) compared multiple different windows of exposure and reported the greatest decreases in learning and memory following gestational and lactational windows, consistent with the altricial nature of rodent brain development.

While nonlinear C-R relationships including U- or inverted U-shaped curves for various endpoints, including those related to cognitive impairment, were demonstrated in the toxicological literature discussed in the previous ISA, these toxicological findings are distinct from epidemiologic findings of supralinear relationships in that some U- or inverted U-shaped relationships do not indicate Pb-induced impairments at higher exposure concentrations (U.S. EPA, 2013). Recent animal studies do not provide evidence for an inverted dose relationship, rather increased Pb doses (and resulting BLLs) generally resulted in greater cognitive impairment. This may be related to the refined PECOS used in the current ISA, which did not incorporate studies reporting BLLs higher than 30 μg/dL, thus narrowing the range of doses integrated. Thus, recent evidence generally supports dose-dependent effects of Pb on cognitive function at relevant BLLs.

In summary, recent studies support and extend the evidence pertaining to the effect of Pb exposure on cognitive function in children at low BLLs. These effects are best substantiated to occur in study populations with mean BLLs between 2 and 8 μg/dL. Association between Pb exposure in populations of children below 2 μg/dL are reported, extending the evidence described in the 2013 Pb ISA; however, heterogeneity at lower exposure levels (i.e., not all studies report positive associations) has been observed. Recent experimental studies of rodents continue to support impairments in cognitive function at BLLs <30 μg/dL. Compelling evidence for a larger decrement in cognitive function per unit increase in blood Pb among children with lower mean blood Pb concentrations, compared with children with higher mean blood Pb concentrations, across a broad range of BLLs (e.g., 5th percentile of 2.5 μg/dL up to 95th percentile of 33 μg/dL) was supported by a reanalysis of a pooled international dataset Crump, 2013, 3838553}. Recent studies with an adequate range of Pb exposure measured during relevant time periods that would be required to evaluate exposure-response relationships are generally lacking. Considering the collective body of studies, no evidence of a threshold for cognitive effects in children across the range of BLLs examined in epidemiologic studies was reported.

3.5.1.6.2 Confounding

The 2013 Pb ISA described multiple factors that influence cognitive function and behavior in children including parental IQ and education, SES of the family, quality of the caregiving environment (i.e., HOME score), and other environmental exposures (U.S. EPA, 2013; Wasserman and Factor-Litvak, 2001). These other risk factors often are correlated with blood, tooth, and bone Pb levels, and thus, are considered as potential confounding factors in epidemiologic analyses. The collective epidemiologic evidence consistently demonstrates associations of higher blood and tooth Pb levels with cognitive function decrements and poorer behavior in children. These associations were observed in diverse populations in the U.S., Mexico, Europe, Asia, and Australia. Associations have been observed across studies that used different methods to control for confounding and adjusted for different potential confounding factors, commonly maternal IQ and education, SES, and HOME score. Several studies have found associations with additional adjustments for smoking exposure, birth outcomes, and nutritional factors. Multiple recent studies adjusted for exposure to other metals or environmental chemicals e.g., Zhou et al. (2020b) and Liu et al. (2015); however, there remains uncertainty regarding the appropriateness of the adjustment for other metals as confounders in some studies that did not examine the potential for interactions (see Section 3.5.1.6.5 for evidence related to interactions between Pb and other metals).

As noted in the 2013 Pb ISA, no single method to control for potential confounding is without limitation, and there is potential for residual confounding by unmeasured factors. However, the consistency of findings among different populations and study methods with consideration of several well characterized potential confounding factors as described above increases confidence that the associations observed between Pb biomarker levels and neurodevelopmental effects in children represented a relationship with Pb exposure. Recent studies expanded the evidence reporting associations between Pb exposure and nervous system effects in children after consideration of covariates including sex, maternal stress and race or ethnicity as potential effect modifiers as opposed to confounders (see Section 3.5.1.6.5). Biological plausibility was derived from extensive evidence provided by animal toxicological studies that are experimental in design and thus, not vulnerable to confounding. These experimental animal studies demonstrate the effect of Pb on cognition and behavior as well as changes in neurogenesis, synaptic pruning, and neurotransmitter function in the hippocampus, prefrontal cortex, and nucleus accumbens of the brain (U.S. EPA, 2013). Recent experimental animal studies support the evidence described in the 2013 Pb ISA, provide additional evidence for Pb-induced impairments in learning and memory (short and long-term) assessed by several methods not discussed in the 2013 Pb ISA, and extend the limited evidence related to Pb-induced impairment of executive functions. These experimental animal studies provide strong support that the effects observed in epidemiologic studies cannot be explained by confounding.

3.5.1.6.3 Lifestages

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 cognitive function decrements in children (U.S. EPA, 2013). Epidemiologic studies consistently pointed to inverse associations between FSIQ in school-aged children and BLLs measured at various lifestages and time periods (Table 4-14 U.S. EPA (2013)). In an analysis of data from seven prospective studies Lanphear et al. (2019) found that increases in early childhood (age 6–24 months on average), peak, concurrent, and lifetime average BLLs were associated with decreases in FSIQ in children at ages 4–10 years. The investigators reported that the best predictor of IQ decrement, as indicated by the model R^2 value, was early childhood blood Pb concentration (R^2 = 0.6433), although the R^2 value for the concurrent metric (0.6414) was nearly identical (Lanphear et al., 2019; Crump et al., 2013). These results illustrated the challenge of distinguishing a critical time period when exposures are highly temporally correlated. Epidemiologic studies that aimed to improve the characterization of important lifestages and time periods of Pb exposure by examining children in whom BLLs were not strongly correlated with exposure over time indicated FSIQ decrements in association with higher concurrent BLLs but did not conclusively demonstrate stronger findings for early versus concurrent BLLs (Table 4-15 of U.S. EPA (2013)). Considering the collective body of epidemiologic evidence reviewed in the 2013 Pb ISA, there was no clear indication of a single critical lifestage or duration of Pb exposure that is uniquely associated with the risk of neurodevelopmental effects in children. These observations in the epidemiologic literature were supported by experimental animal evidence. Consistent with findings from the 2013 Pb ISA, more recent studies continue to report associations with prenatal BLLs (maternal and cord blood Pb) and postnatal BLLs measured at various childhood lifestages despite some heterogeneity in the magnitude and direction of the associations at BLLs <5 μg/dL.

Maternal Pb exposure presents an exposure risk during gestation and early infancy, when important neurodevelopmental processes are known to occur. Substantial fetal Pb exposure may occur from mobilization of maternal skeletal Pb stores (Gulson et al., 2003; Hu and Hernandez-Avila, 2002) and its transfer across the placenta (Section 3.2.2.4 of U.S. EPA (2013)). Among studies that examined BLLs at multiple time periods, some found a larger decrement in MDI per unit increase in prenatal blood Pb than concurrent blood Pb ((Hu et al., 2006; Gomaa et al., 2002), Table 4-14 of U.S. EPA (2013)). Prenatal and early postnatal (age 6 months) BLLs were also associated with cognitive function in studies that included school-aged children (ages 5–17 years) (Table 4-14 of U.S. EPA (2013)). Sánchez et al. (2011) extended the analysis of Hu et al. (2006), which was designed to elucidate the time window during pregnancy that the effect of Pb exposure on neurodevelopment is most pronounced among participants in a birth cohort study in Mexico City. These authors compared methods to model exposure and found that the MDI score at age 2 was sensitive to the choice of method. A decrease in MDI score of 2.74 (95% CI –5.78 to 0.29) per natural log increase in BLL during the first trimester was observed, using a window-

specific regression, while the corresponding decrease was larger [β=–4.13 (95% CI, –7.54, –0.72) using a multiple informant model.

As described above, however, most of these studies also found cognitive function decrements in association with postnatal BLLs, and the results did not identify an individual critical postnatal time period of blood Pb measurement associated with cognitive function decrements. Maternal pregnancy-cord BLL correlations of 0.53–0.81, depending on the stage of pregnancy, were reported by Schell et al. (2003). Depending on the magnitude of child exposure, the contribution of maternal blood Pb to child BLLs appears to diminish rapidly over a period of a few months following birth, after which child BLLs may be influenced mainly by postnatal Pb exposures (Section 3.4.1 of U.S. EPA (2013)).

Recent studies observed associations between Pb exposure during prenatal and childhood lifestages (i.e., maternal (Y Ortiz et al., 2017; Vigeh et al., 2014; Kim et al., 2013b, c), cord (Valeri et al., 2017), and postnatal exposure (Lin et al., 2013)) and poorer performance on tests of neurodevelopment among mothers and infants with mean BLLs <5 µg/dL. The is some evidence indicating that there heterogeneity in the magnitude and direction of the observed associations in recent studies may be explained, in part, by co-exposure to other metals or maternal stress

Experimental animal studies demonstrated that prenatal or early postnatal or lifetime Pb exposure alters brain development via changes in synaptic architecture and neuronal outgrowth, leading to impairments in memory and learning (Sections 4.3.10.4, 4.3.10.10, and 4.3.2.3 of U.S. EPA (2013)). Gestational or infancy Pb exposures are not necessary to induce cognitive function decrements in juvenile animals, however. Studies of monkeys have found that Pb exposures during lifestages and time periods extending from infancy through the juvenile or adult periods resulted in impaired cognitive function (Rice, 1992; Rice and Gilbert, 1990a; Rice, 1990; Rice and Karpinski, 1988). These findings are consistent with studies of individuals aged 3 to 30 years, which showed that brain development ascertained using MRI continues throughout adolescence, indicating the potential for alterations to neurodevelopment later in childhood (Gerber et al., 2009; Lenroot and Giedd, 2006).

Additional recent animal studies support the notion that various exposure periods (i.e., preconception, gestation, lactation) may represent a critical periods during which Pb exposure can cause cognitive impairment later in life. In rodents, developmental exposure to Pb was consistently associated with persistent cognitive effects observed both early (Tartaglione et al., 2020; Zhao et al., 2018; Barkur and Bairy, 2015b; Anderson et al., 2012) and later in life (Liu et al., 2022c; Xiao et al., 2014; Betharia and Maher, 2012). Few studies were designed to compare exposures across multiple different developmental windows (Barkur and Bairy, 2015b; Xiao et al., 2014). These studies reported similar magnitudes of effects between developmental windows, suggesting that individual periods of development may be similarly sensitive to Pb. Generally, longer exposures that spanned multiple developmental periods (e.g., preconception through lactation) produced not only the highest BLLs but the largest effects on cognition (Zhou et al., 2020a; Zhu et al., 2019b).

Unlike other organ systems, the unidirectional nature of CNS development limits the capability of the developing brain to compensate for cell loss, and environmentally induced cell death can result in a permanent reduction in cell numbers (Bayer, 1989). Hence, when normal development is altered, the early effects have the potential to persist into adult life even in the absence of concurrent exposure, magnifying the potential public health effects. A limited number of studies examined the persistence of the effects of Pb on cognitive function. A recent study by Shadbegian et al. (2019) indicated that poorer performance on tests of reading and math associated with earlier childhood Pb exposure persisted from grade 3 to grade 8. Some epidemiologic evidence reviewed in the 2013 Pb ISA indicated associations of earlier childhood blood or tooth Pb levels in adolescents or adults with decreased cognitive function (Mazumdar et al., 2011; Ris et al., 2004; Stiles and Bellinger, 1993). Recent studies support and extend this evidence. Specifically, childhood Pb exposure was observed to have long-term cognitive consequences in young- (18–19 years) (Skerfving et al., 2015) or mid-adulthood (38 or 45 years of age) (Reuben et al., 2020; Reuben et al., 2017). These epidemiologic studies did not examine adult BLLs, thus the relative influence of adult Pb exposure was not ascertained. The persistence of effects of early exposures, however, is supported by findings of impaired learning in adult monkeys exposed to Pb only during infancy (Rice, 1992; Rice and Gilbert, 1990a; Rice, 1990). Additional recent studies in rodents provided support for the persistence of effects of early exposures of Pb (Xiao et al., 2020; Li et al., 2016a; Xiao et al., 2014; Zhang et al., 2014; Rahman et al., 2012b; Zhang et al., 2012; Kuhlmann et al., 1997).

There is some evidence that the effects of early Pb exposure on cognitive function are not fixed. Results indicated higher cognitive function in children at ages 1–8 years who had declines in BLL over durations of 6 months to 5 years compared with children with smaller declines, no change, or increases in BLLs in some studies (Hornung et al., 2009; Chen et al., 2005; Liu et al., 2002; Ruff et al., 1993; Bellinger et al., 1990). This evidence pertains to populations with declines from higher BLLs at baseline (20–55 μg/dL) or larger declines over time (i.e., 8, 14 μg/dL) than those expected for most of the current population of U.S. children. No recent studies that provided additional information on this topic were identified.

To conclude, 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, 2013). Recent studies support this conclusion. Evidence indicates that prenatal BLLs are associated with mental development in very young children aged <2 years. Several studies indicated that increases in postnatal (earlier childhood, lifetime average, concurrent) BLLs were associated with larger cognitive function decrements in children aged 4–10 years than were similarly sized 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 (U.S. EPA, 2013). The identification of critical lifestages and time periods of Pb exposure is complicated by the fact that BLLs in older children, although affected by recent exposure, are also influenced by Pb stored in their bone and maternal Pb stores. Thus, associations of neurodevelopmental effects with concurrent BLL in children

may reflect the effects of past and recent Pb exposures. Nonetheless, the epidemiologic evidence for associations of neurodevelopmental effects with multiple lifestages or time periods of Pb exposure, including more recent exposures, is supported by evidence in monkeys that Pb exposures in infancy, lifetime exposure starting from birth, or lifetime exposure starting during the juvenile period induce impairments in cognitive function when assessed between the ages of 6 and 10 years.

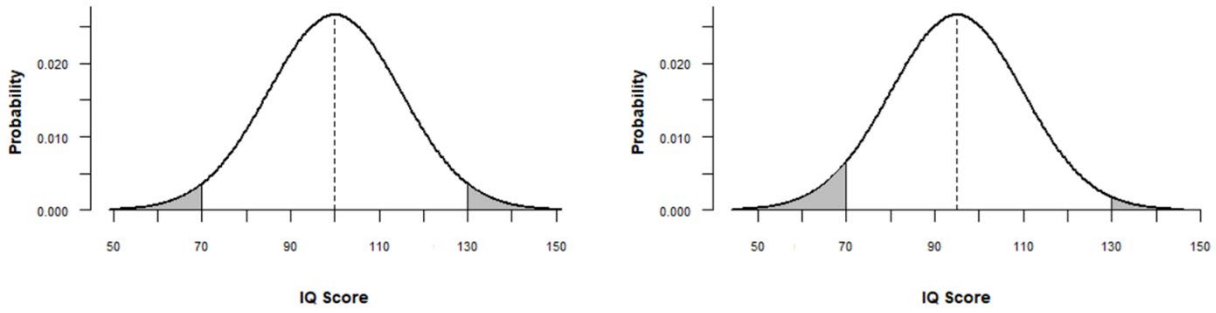
3.5.1.6.4 Public Health Significance

The 2006 Pb AQCD and the 2013 Pb ISA (U.S. EPA, 2013, 2006) concluded that neurodevelopmental effects in children were among the effects best substantiated as occurring at the lowest BLLs. Evidence from several cohorts of children indicated that there is a supralinear C-R relationship between blood Pb and FSIQ (i.e., larger incremental effect of blood Pb on FSIQ at lower levels) and no threshold was identified for Pb-associated neurodevelopmental effects in the range of BLLs examined. The evidence reviewed in the current assessment supports these conclusions and continues to clearly indicate that neurodevelopmental effects in children are among the greatest public health concern associated with Pb exposure.

Cognitive function in children has been assessed using a variety of tests, including FSIQ, BSID, academic performance, and academic achievement. As noted in the 2013 Pb ISA (U.S. EPA, 2013), FSIQ has strong psychometric properties (i.e., reliability, consistency, validity), is among the most rigorously standardized cognitive function measures, is relatively stable in school-age children, and has been predictive of educational achievement and life success. Variation in IQ score across different populations, however, may be influenced by differential access to resources in those populations (Shuttleworth-Edwards, 2016; Marks, 2010). In children aged 6 months to 3 years, the BSID is commonly used to assess mental development; however, the BSID MDI is not an intelligence test and MDI scores are not necessarily strongly correlated with later measurements of FSIQ in children with normal development. Lower FSIQ is also linked to poorer academic performance and achievement, both of which have important implications for success later in life including reduced earning potential and productivity (Lin et al., 2016; U.S. EPA, 2013; Salkever, 1995; Schwartz, 1994b). Analyses of end-of-grade tests from North Carolina indicated that early childhood BLL is associated with reduced performance on the tests, the cumulative effect of Pb and low SES is more pronounced at the lower end of the test score distribution (Miranda et al., 2009), and the effects of Pb exposure persisted from grade 3 to grade 8 (Shadbegian et al., 2019). Tests of academic achievement generally measure a child's understanding of a given curriculum that is developed and implemented through the school system; thus, because exams are typically specific to each state, data cannot be directly compared across states.

The World Health Organization (WHO) definition of "health" is "the state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" (WHO, 1948). By this definition, decrements in health status that are not severe enough to result in the assignment of a clinical diagnosis might reflect a decrement in the well-being of an individual. Further, deficits in subtle indices

of health or well-being may not be observable except in aggregate, at the population level; therefore, a critical distinction between population and individual risk is essential for interpreting the public health significance of study findings. This concept of population risk is relevant to the interpretation of findings regarding IQ in the assessment of their public health significance. Specifically, Weiss (1988) discussed the hypothetical effects of a small shift in the population distribution of IQ score. As shown in Figure 3-9, these authors anticipate that even a small shift in the population mean IQ may be significant from a public health perspective because such a shift, given a normal distribution, could yield a larger proportion of individuals functioning in the low range of the IQ distribution, which is associated with increased risk of educational, vocational, and social failure (Section 4.3.13), as well as reduce the proportion of individuals with high IQ scores. Although the change in population mean IQ score may be small relative to the standard error for the IQ measurement, a study that is large enough will have adequate statistical power to detect small changes at the population level. Bias may be introduced if the measurement error of the outcome is highly correlated with the exposure, but there is no evidence to suggest that individuals with higher BLLs test systematically lower than their true IQ.



IQ = intelligence quotient.
Note: Two distributions of intelligence test scores. (Left): Based on a mean of 100 (the standardized average, with SD of 15). (Right): Demonstrating a 5% reduction model, based on a mean score of 95. This is a conceptual model that assumes that the incremental C-R between Pb exposure and IQ is similar across the full range of IQ and is not based on actual data. The figure shows that the effect of a small shift in population mean IQ score may result in a larger proportion of individuals with IQ scores below 70 and a smaller proportion with IQ scores above 130.
Source: Reproduced with permission of Elsevier; from Weiss (1988).

Figure 3-9 Two distributions of intelligence test scores demonstrating the consequence in a small shift in the mean score.

3.5.1.6.5 Potentially At-Risk Populations

The 2013 Pb ISA described physiologic factors that influence the internal distribution of Pb (U.S. EPA, 2013). Blood and bone Pb measurements are influenced to varying degrees by biokinetic processes including absorption, distribution, metabolism, and excretion. These processes are affected by age,

genetics, diet, and co-exposures to other metals and chemicals, which are summarized in the Executive Summary and Integrated Synthesis (https://assessments.epa.gov/isa/document/&deid=359536). In addition to these physiological factors, several population characteristics that explain differential Pb exposure have been identified. These factors included age, sex, race and ethnicity, proximity to Pb sources, and residential sources and are also discussed in the Executive Summary and Integrated Synthesis (https://assessments.epa.gov/isa/document/&deid=359536). The factors potentially related to increased risk of Pb-induced cognitive effects (i.e., factors identified in epidemiologic studies that conduct stratified analyses and compare the magnitude of the observed association across stratum) are discussed below.

Age

This section on Potentially At-Risk Populations emphasizes stratified results described in some epidemiologic studies, as opposed to the large body of longitudinal studies following mothers and infants throughout childhood that comprises the most compelling body of evidence in support of conclusions regarding childhood as an "at-risk" factor. As noted in previous sections of the document (i.e., Section 3.5.1.1 and 3.5.1.6.1), recent evidence supports the finding from the 2013 Pb ISA that cognitive effects in young children is the outcome that best substantiated to occur at the lowest exposure levels. Strong evidence indicates increased risk of Pb-induced neurocognitive effects during several childhood lifestages throughout gestation, childhood, and into adolescence (see Section 3.5.1.6.3). Moreover, the integrated synthesis (Section 7.4.2.2) of this document concludes that, "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."

Sex

Multiple epidemiologic studies included in the 2013 Pb ISA examined Pb-related effects on cognition separately in males and females. Studies on cognition from the CLS cohort and a study in Poland reported larger magnitude Pb-associated cognitive effects in males (Jedrychowski et al., 2009a; Ris et al., 2004; Dietrich et al., 1987), whereas studies from Australia indicated that females were at increased risk of Pb-associated cognitive effects (Tong et al., 2000; Baghurst et al., 1992; Mcmichael et al., 1992). While toxicological evidence supporting sex-specific effects of Pb on cognitive function was summarized in the previous ISA (Virgolini et al., 2008; Yang et al., 2003; Mcgivern et al., 1991), the number of studies considering sex as a factor was limited. Recent evidence provides more support for the sex-biased effects. One study reported a male-specific effect (Anderson et al., 2016) and several studies demonstrated female-specific effects (Tartaglione et al., 2020; Verma and Schneider, 2017; Anderson et al., 2012; Betharia and Maher, 2012). The evidence supports a conclusion that there are sex-related differences in the effects of Pb on cognitive function, yet it remains difficult to parse the exact nature and

direction of sex-specific effects given the variation in outcomes examined, exposure timing and the considerable number of studies that only reported data from one sex at a time.

Several recent epidemiologic studies examined sex-stratified associations of Pb exposure with cognitive effects (Tatsuta et al., 2020; Zhou et al., 2020b; Desrochers-Couture et al., 2018; Taylor et al., 2017). Tatsuta et al. (2020) found a decrement in FSIQ score in association with postnatal BLL (β = −9.880 [95% CI: -2.905, 5.831]) among boys, with a smaller less precise association among girls (β = −4.406 [95% CI: -15.94, 7.129]). Prenatal BLL was associated with a smaller and less precise decrease in FSIQ score among boys (β = −-3.683 [95% CI: -10.714, 3.349]) but not among girls (β = 1.463 [95% CI: -2.905, 5.831]). A lower BNT score (with cues) was associated with both pre- and postnatal BLL among boys in this study. Desrochers-Couture et al. (2018) studied the association between cord, maternal and childhood (3–4 years old) BLLs with cognitive function (WPPSI-III at age 3–4 years) among preschool aged children in Canada. An association was observed between cord BLL and performance IQ in boys (β = −3.28 [95% CI: −5.31, −1.18] per doubling) that was not present in girls (β = 0.16 [95% CI: −1.76, 2.06] per doubling). Although associations were imprecise, Taylor et al. (2017) found an association between increased maternal BLL and IQ decrements in boys but not in girls enrolled in the ALSPAC study (e.g., −0.29 [95% CI: −1.02, 0.44] versus 0.73 [95% CI: 0.39, 1.33], respectively on the WISC). Using models that adjusted for co-exposure to metals (Mn and Cd), Zhou et al. (2020b) found no association between cord BLL and FSIQ in boys or girls. Further, using models that adjusted for other chemicals (i.e., DDE, HCB, PCBs, and Mn), Oppenheimer et al. (2022) found no statistical evidence of an interaction between prenatal Pb exposure and sex.

Maternal Stress

Toxicological studies assessed in the 2013 Pb ISA demonstrated that early life exposure to Pb and maternal stress can result in dysfunction of the HPA axis (U.S. EPA, 2013). Recent toxicological evidence provides further support for this interaction between maternal stress and Pb exposure during development. Anderson et al. (2012) demonstrated that exposure to Pb blunted the positive effects of environmental enrichment on learning in the Morris water maze paradigm. Interestingly, Cory-Slechta et al. (2012) reported that contrary to the effect previously reported in females, maternal stress improved the performance of Pb-exposed male offspring in a repeated performance and learning paradigm compared with Pb-exposed males without maternal stress. While this study supports the interaction between maternal stress and Pb exposure, it remains unclear whether stress would positively influence other facets of cognitive function.

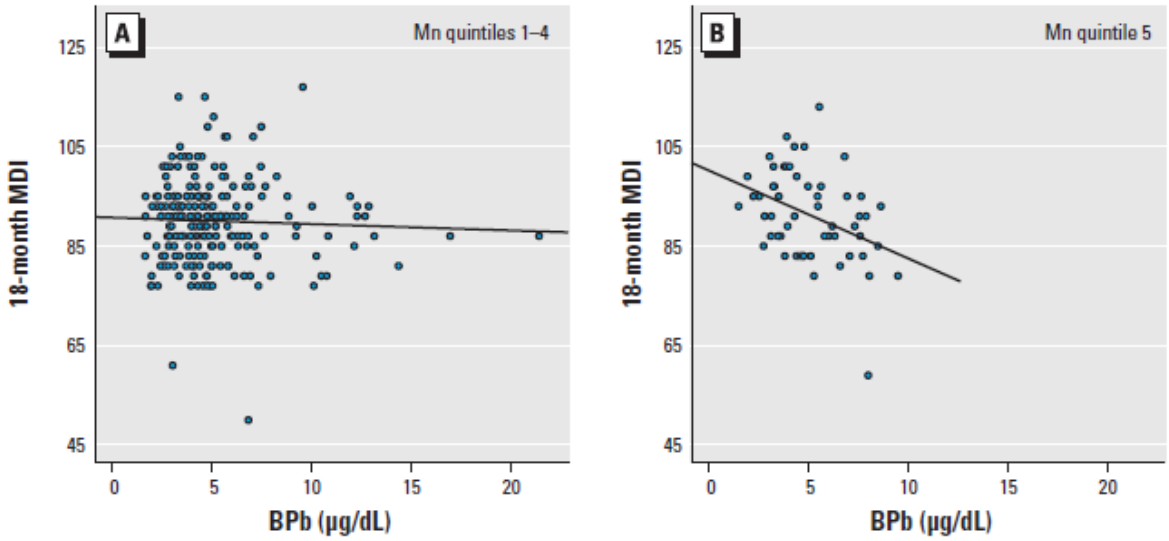
Recent epidemiologic studies examined maternal stress as a modifier of the association between Pb exposure and neurodevelopment. Y Ortiz et al. (2017) used the CRISYS-R questionnaire, which assesses negative life events across several domains (i.e., financial, legal, career, relationships, community and home violence, medical problems, other home issues, discrimination or prejudice, and difficulty with authority) to examine this effect. Third trimester maternal BLL was associated with the

cognitive component of the BSID in this study and a weak interaction (i.e., lower cognitive scores as BLL and stress increase) between log-transformed maternal blood Pb and stress was observed (β = 1.02 [95% CI: −0.78, 2.82]). In another study, Zhou et al. (2017) assessed mother-child pairs from the Shanghai Stress Birth Cohort. Maternal whole blood and maternal prenatal stress levels were assessed at 28–36 weeks of gestation, and the GDS adapted for a Chinese population were administered to children 24–36 months old in the study. No association between prenatal maternal BLL and child cognitive development was observed; however, an interaction effect was observed such that high maternal stress appeared to exacerbate the effect of prenatal Pb exposure in several domains, including language (β = −33.82 [95% CI: −60.04, −7.59] per log−10 transformed unit of BLL), while low maternal stress did not (β = −1.76 [95% CI: −13.03, 9.51] per log−10 transformed unit of BLL, p-interaction = 0.02).

Other Metal Exposure (Cd, Mn, Hg, As)

A limited number of studies included in the 2013 Pb ISA examined the modification of association between Pb exposure and cognitive function by other metals (U.S. EPA, 2013). Larger Pb-associated decrements in IQ (Kim et al., 2009) and neurodevelopment (Henn et al., 2012) were observed in children with higher Mn levels. Henn et al. (2012) also observed an interaction between the highest quintile of Mn and BLL at 12 months (Figure 3-10).

Several recent epidemiologic studies of the association of Pb exposure with FSIQ examined interactions between Pb exposure and other metals or modification of the Pb-FSIQ association by other metals. For example, some cross-sectional analyses found evidence that coexposure to Mn may heighten the effect of Pb in some populations (Martin et al., 2021; Menezes-Filho et al., 2018), while another study found no interaction between Pb exposure and Mn (or ALAD) (Lucchini et al., 2012). Several studies of the association between Pb exposure and infant development also point to possible interactions with other metals. Lin et al. (2013) observed an interaction with Mn such that children who were highly exposed to both Mn and Pb had larger neurodevelopmental deficits compared with those with low exposure to just one or both these metals. Kim et al. (2013b, 2013c) observed a larger decrement in MDI in association with late pregnancy maternal BLL among those with Cd levels above the median (β = −3.20 [95% CI: −5.35, −1.06]) compared with the decrement among those with Cd levels below the median (β = −0.29 [95% CI: −2.88, 2.30]). In contrast to the findings of Henn et al. (2012), Valeri et al. (2017) observed an association between increasing cord Pb level and neurodevelopmental decrements in children with lower cord blood Mn and As (β = −0.01 [95% CI: −0.02, 0.00]), but not in the group with higher concentrations of these metals (or metalloids) (β = 0.01 [95% CI: −0.05, 0.07]). Nyanza et al. (2021) also observed modification of maternal blood Pb and global neurodevelopmental status by blood Hg concentrations.



BPb = blood Pb; MDI = Mental Developmental Index; Mn = manganese.
Source: Henn et al. (2012).

Figure 3-10 Scatter plots and regression lines of blood Pb level and 18-month Mental Developmental Index among children in manganese (A) quintiles 1–4 and (B) quintile 5.

Only one recent animal study incorporated combined exposure to Pb and Mn at relevant levels (<30 µg/dL Pb). Betharia and Maher (2012) reported that both Pb and Mn individually impaired memory in the Morris water maze, but the effects of the mixture were not significantly different from those of the control. Interestingly, during the learning (acquisition) phase only, the mixture enhanced performance, suggesting a possible antagonistic effect of these two metals on the development of spatial learning processes. Given the lack of evidence available on combined metal exposures, the possible interaction between multiple metals at relevant levels in animals remains unclear.

Many recent toxicological studies provided evidence for the interaction of Pb and other metals (Mn, Cd, Ar, Hg, Fe) but were not PECOS-relevant (e.g., in vitro studies, high levels, non-mammalian models) and are summarized in the biological plausibility Section 3.3

Socioeconomic Status

SES has been examined as an effect modifier in multiple studies of Pb-induced cognitive effects (U.S. EPA, 2013, 2006). Larger blood Pb-associated decreases in cognitive function were found with lower SES in several studies (Ris et al., 2004; Tong et al., 2000; Bellinger et al., 1990). In contrast, a meta-analysis of eight studies found a smaller decrement in FSIQ for studies in disadvantaged populations than for studies in advantaged populations (Schwartz, 1994a). While the results indicate that BLL is associated with FSIQ deficits in both higher and lower sociodemographic groups, they do not

clearly indicate whether groups with different SES differ in Pb-related changes for cognitive function (Murphy et al., 2013).

No recent epidemiologic studies examined SES as a modifier of the association between Pb exposure and cognitive effects in children.

Race/Ethnicity

The evidence reviewed in the 2013 Pb ISA pertaining to the modification of the effect of Pb exposure on cognitive function in children by race or ethnicity was limited to one study (U.S. EPA, 2013). Miranda et al. (2007) presented data indicating that the association between early childhood exposure to Pb and declines in reading and mathematics scores was similar between Black and white children. In a recent study, Braun et al. (2018) examined the effects of residential exposure interventions on dust Pb loadings, BLL, and neurodevelopmental outcomes in children (4 to 8 years old). Although no intervention effect on BLL was found, overall, the geometric mean childhood BLLs for children 1 to 8 years old was lower in non-Hispanic Black children (See Appendix 2: https://assessments.epa.gov/isa/document/&deid=359536). No intervention effect on other neurodevelopmental outcomes (e.g., FSIQ, BSID, BRIEF) were observed.

Pre-existing Disease

Studies that examined the effect of Pb exposure on cognitive function in children across strata defined by pre-existing disease status were not reviewed in previous assessments (U.S. EPA, 2013, 2006).

A recent study examined the association of Pb exposure with IQ and executive functioning using BRIEF among children with CKD (Ruebner et al., 2019). Concurrent BLL assessment was associated with FSIQ decrement in adjusted models ($\beta = -2.1$ [95% CI: −3.9, −0.2] per 1 μg/dL increase in BLL). Associations between BLL and behavioral symptoms indicating executive function problems did not persist in models that controlled for potential confounders including race, poverty, maternal education, and clinical factors related to CKD.

Nutritional Factors

The 2006 Pb AQCD included studies that indicated individuals with Fe deficiency and malnourishment had greater inverse associations between Pb and cognition (U.S. EPA, 2006); nutritional factors were not examined as effect modifiers of the association between Pb exposure and cognitive effects in children in more recent studies reviewed in the 2013 Pb ISA (U.S. EPA, 2013).

No recent epidemiologic studies were available to inform this topic. Recent toxicological studies (that were PECOS-relevant) investigated the influence of different dietary factors on the effects of Pb. Liu et al. (2022c) exposed rats to 0.2% Pb in drinking water in combination with either standard rodent chow or a high-fat diet and then assessed cognitive function using the Morris water maze paradigm. High-fat diet increased the BLL of rats compared with Pb-exposed rats maintained on standard chow. High-fat diet enhanced the effect of Pb on learning during the acquisition phase compared with the Pb-control diet group. During the probe trial, Pb-exposed animals (both diets) had significantly fewer crossings into the target quadrant compared with untreated animals. Interestingly, a similar memory impairment was observed in the non-Pb + high-fat diet group, suggesting a role for high-fat diets in cognitive impairment independent of Pb exposure. The contribution of Pb versus high-fat diet remains unclear based on this one study.

Al-Qahtani et al. (2022) supplemented Pb exposure in mice with green tea extract and reported that green tea ameliorated the negative effects of Pb exposure on both learning and memory assessed in an active avoidance paradigm. Additionally, Long et al. (2022) reported that probiotic supplementation (*Limosilactobacillus fermentum*) in Pb-exposed rats partially mitigated the cognitive deficits observed in an active avoidance paradigm. These studies support a role for dietary factors in the neurotoxicity of Pb but the diversity of nutritional factors investigated and the small number of studies make it difficult to determine their importance.

Genetics

Polymorphisms in certain genes have been implicated in the absorption, retention, and toxicokinetics of Pb in humans (U.S. EPA, 2013, 2006). Studies assessed in the 2013 Pb ISA indicated that the presence of ALAD variants was associated with an increase in Pb-related cognitive effects in adults, but there was limited information for children. In studies of children, inverse associations with poorer rule learning and reversal, spatial span, and planning were exacerbated among those lacking the DRD4 gene (Froehlich et al., 2007). Two additional studies found no evidence that the methylenetetrahydrofolate reductase 677T allele or variants of the DRD2 or dopamine transporter (DAT1) genes modified the effect of Pb on neurodevelopment (Kordas et al., 2011; Pilsner et al., 2010).

Several recent studies add to the limited body of evidence in children. Bah et al. (2022) found that the effect of low Pb exposure on children's IQ was less among those with the ALAD1 genotype. Rooney et al. (2018) found interaction effects between variants of glutamate ionotropic receptor NMDA-type subunits 2A and 2B (GRIN2A and GRIN2B) and Pb exposure on performance on tests of learning, memory, and executive function, which were more pronounced in boys. Kordas et al. (2011) found that children with the DRD2 TT genotype (variant) scored higher than children with CC genotype (wild type) on the Bayley MDI and McCarthy memory scale. However, the variants did not modify the relationship between BLLs and MDI or McCarthy memory scale scores. Bozack et al. (2021) found that prenatal Pb exposure was associated with DNA methylation in regions annotated to genes involved in

neurodevelopment. Overall, the evidence pertaining to interactions between genes and Pb exposure in children remains limited.

Other Factors

No studies that examined maternal smoking as a modifier of the association between Pb exposure and cognitive effects were included in previous assessments (U.S. EPA, 2013, 2006). Recent studies did not examine maternal smoking as a modifier of the association between Pb exposure and cognitive effects in children.

BMI was not examined as an effect modifier of the association between Pb exposure and cognitive effects in children in studies reviewed in the 2013 Pb ISA (U.S. EPA, 2013). No recent studies have examined this factor as an effect modifier.

Maternal self-esteem modified the association between BLL and infant development in Surkan et al. (2008), which was assessed in the 2013 Pb ISA. No recent epidemiologic studies were available to inform this topic.

Cognitive reserve was not examined as an effect modifier of the association between Pb exposure and cognitive effects in children in studies reviewed in the 2013 Pb ISA (U.S. EPA, 2013). No recent epidemiologic studies were available to inform this topic.

3.5.1.7 Summary and Causality Determination: Cognitive Effects in Children

The evidence from epidemiologic and experimental evidence that supports the causality determination for cognitive effects in children is outlined in Table 3-2. **Overall, recent evidence supports the conclusion from the 2013 Pb ISA that there is a *causal relationship* between Pb exposure and cognitive effects in children**.

Studies evaluated in the 2013 Pb ISA found a consistent pattern of associations between higher BLLs and lower FSIQ in children aged 4–17 years (see Figure 4-2 and Table 4-3 (U.S. EPA, 2013)). The strongest evidence was provided by prospective studies with analyses of the association of blood Pb measured in early childhood before FSIQ was assessed or with tooth Pb levels typically measured in dentin reflecting prenatal or early childhood Pb exposure. These prospective studies typically considered potential confounding by maternal IQ and education, SES, birth weight, smoking exposure, parental caregiving quality, and in a few cases, other birth outcomes and nutritional factors. Associations were found in diverse populations (e.g., Boston, MA; Cincinnati, OH; Rochester, NY; Cleveland, OH; Mexico City, Mexico; Port Pirie, Australia; and Kosovo, Yugoslavia) in studies that examined children recruited from prenatal clinics, hospital maternity departments, or schools. Studies generally reported high follow-up participation supported by evidence that selection bias did not explain the associations observed.

Multiple recent longitudinal studies of children with mean BLLs <5 μg/dL add to the evidence informing the relationship between BLL and IQ in children. Heterogeneity in the magnitude and direction of the associations was present across these studies, however. In a study of Canadian preschool children with low blood Pb levels, an association between cord blood Pb level and FSIQ was observed, while the association of childhood concurrent BLLs with FSIQ effectively null (Desrochers-Couture et al., 2018). In addition, associations were observed in boys but not in girls in several studies (Tatsuta et al., 2020; Desrochers-Couture et al., 2018; Taylor et al., 2017). There was also some indication that the heterogeneity across studies could be explained by modeling choices such as confounder adjustment for other metals. For example, cross-sectional analyses found evidence that exposure to Mn may modify the association between Pb exposure and IQ in some populations Martin et al. (2021); (Menezes-Filho et al., 2018). However, studies that adjusted for multiple metals (e.g., Mn, Hg, Cd, and Pb) in regression models, without examining the interaction between metals, found little evidence of an association between cord or postnatal BLL and IQ (Zhou et al., 2020b; Liu et al., 2015), imprecise associations only in boys (Tatsuta et al., 2020; Desrochers-Couture et al., 2018), or large IQ decrements after adjustment for Mn, Hg, and ADHD rating score Hong et al. (2015). Overall, recent studies generally corroborated the epidemiologic observations of associations between Pb exposure and IQ in children with relatively low blood Pb concentrations (≤5 μg/dL) among some groups of children (see Section 3.5.1.1). Consistent with findings from the 2013 Pb ISA, studies continue to report associations with prenatal BLL (maternal and cord blood Pb) and postnatal BLLs measured at various childhood lifestages despite the aforementioned heterogeneity at BLLs <5 μg/dL. Overall, the heterogeneity did not weaken the larger body of supporting evidence.

In the review of the MDI evidence in the 2013 Pb ISA, emphasis was placed on results from examinations at ages 2–3 years, which incorporate test items more similar to those in school-age IQ tests. Among these studies, several included children with mean BLLs less than 5 μg/dL (Henn et al., 2012; Jedrychowski et al., 2009b; Hu et al., 2006; Bellinger et al., 1987). Most of the prospective studies reviewed in previous ISAs (U.S. EPA, 2013, 2006) found associations of higher prenatal (cord and maternal BLL), earlier infancy, and concurrent BLL with lower MDI scores in children aged 2 to 3 years (Figure 3-10). These blood Pb-associated decrements in MDI were observed in populations with mean BLLs of 1.3 to 7.1 μg/dL. Studies typically recruited participants before or at birth without consideration of Pb exposure or maternal IQ and reported high to moderate follow-up participation as well as nondifferential loss-to-follow-up. Most studies adjusted for birth outcomes, maternal IQ, and education. Cord BLLs were associated with MDI, with additional adjustment for SES and HOME score in the Boston cohort (Bellinger et al., 1987) and for HOME score in the Yugoslavia cohort (Wasserman et al., 1992). Some studies found a stronger association of MDI with prenatal than child postnatal BLLs ((Hu et al., 2006; Gomaa et al., 2002; Bellinger et al., 1987).

Recent studies continue to support associations between Pb exposure measured during prenatal or childhood lifestages and poorer performance on tests of neurodevelopment, among mothers and infants with mean BLLs <5 μg/dL (i.e., maternal (Y Ortiz et al., 2017; Vigeh et al., 2014; Kim et al., 2013b, c),

cord (Valeri et al., 2017), and postnatal (Lin et al., 2013) BLLs). Although Zhou et al. (2017) found no association overall, this study reported decrements on several domains of the GDS among infants of mothers reporting high maternal stress. Similarly, Y Ortiz et al. (2017) found some evidence of interactions between Pb exposure and maternal stress. Several studies found interactions between Pb and Mn or Mn and As (Valeri et al., 2017; Lin et al., 2013; Henn et al., 2012) or Cd exposure (Kim et al., 2013b); Kim et al. (2013c). Overall, recent studies support findings from the previous reviews and extend the evidence pertaining to modification of the association between Pb exposure and infant neurodevelopment by maternal stress and exposure to other metals. The MDI and other tests that measure neurodevelopment in infants and toddlers are not intelligence tests. Notably, MDI scores, particularly before ages 2–3 years, are not necessarily strongly correlated with later measurements of FSIQ in children with normal development and thus, are not weighted heavily in the consideration of causality (U.S. EPA, 2013).

Experimental animal studies evaluated in the 2013 Pb ISA demonstrated that prenatal and early postnatal or lifetime Pb exposure alters brain development via changes in synaptic architecture and neuronal outgrowth, leading to impairments in memory and learning (Sections 4.3.10.4, 4.3.10.10, and 4.3.2.3 of U.S. EPA (2013)). A small number of recent experimental animal studies were designed to compare exposures across multiple different developmental windows (Barkur and Bairy, 2015b; Xiao et al., 2014); these studies reported similar magnitudes of effects between developmental windows, suggesting that individual periods of development may be similarly sensitive to Pb. Generally, longer exposures that spanned multiple developmental periods (e.g., preconception through lactation) produced not only the highest BLLs but the largest effects on cognition (Zhou et al., 2020a; Zhu et al., 2019b). Overall, these studies provide strong support for observations in epidemiologic studies that Pb exposure during the prenatal, childhood, and adolescent lifestages is associated with cognitive effects. Recent animal studies also provide evidence to support the observation that development (i.e., preconception, gestation, lactation) may represent a critical window for Pb exposure to cause cognitive impairment later in life (see Section 3.6.1). In rodents, developmental exposure to Pb was consistently associated with persistent cognitive effects observed both early (Tartaglione et al., 2020; Zhao et al., 2018; Barkur and Bairy, 2015b; Anderson et al., 2012) and later in life (Liu et al., 2022c; Xiao et al., 2014; Betharia and Maher, 2012).

Learning, memory, and executive function are domains of cognitive function that are related to intelligence, and several are evaluated in the subtests of FSIQ. Additionally, indices of memory, learning, and executive function are comparable to endpoints examined in experimental animal studies. The studies evaluated in the 2006 Pb AQCD and 2013 Pb ISA did not clearly indicate associations between higher BLL and poorer performance on neuropsychological tests of memory or learning (U.S. EPA, 2013). The ascertainment of the outcomes varied across studies, potentially explaining the heterogeneity of the epidemiologic observations. Notably, evidence for both memory and learning decrements from prospective analyses of several established cohorts (i.e., Rochester, Boston, and Cincinnati) was mixed (Canfield et al., 2004; Ris et al., 2004; Stiles and Bellinger, 1993; Bellinger et al., 1991; Dietrich et al.,

1991). Cross-sectional studies included in the previous ISA, however, generally found associations between higher concurrent BLLs and poorer learning and memory. Several recent studies of children with mean BLLs <5 μg/dL add to the evidence informing the association of Pb exposure with performance on tests of memory and learning; however, these recent studies do not enhance the consistency of the evidence as a whole. Some of the available studies consider co-exposure to other chemicals and metals as confounders (Tatsuta et al., 2014) despite evidence that such co-exposures may interact with or modify the association between Pb and the outcomes (Yorifuji et al., 2011). Several recent studies of rodents with exposure resulting in mean BLLs ≤30 μg/dL add to the evidence indicating coherence between the epidemiologic and toxicological findings pertaining to learning and memory observed in the 2013 Pb ISA.

Strong evidence of associations between Pb exposure and indices of executive function was described in the 2013 Pb ISA. Studies included prospective analyses of several birth cohorts with moderate to high follow-up rates in Boston and Rochester that examined BLLs before the outcome assessment and adjusted for several potential confounding factors (Canfield et al., 2004; Canfield et al., 2003b; Bellinger et al., 1994a; Stiles and Bellinger, 1993). Recent studies relying on parent or teacher behavioral ratings on BRIEF did not generally report associations. The previous ISA did not incorporate any evidence of the relationship between Pb exposure and executive function in animal models. Recent studies from a single laboratory provided evidence that Pb exposure broadly impairs measures of executive function in a reversal learning paradigm. These effects were sex-specific, with greater effects reported in males. While these reports are consistent with one another, evidence for the association between Pb exposure and impaired executive function in animal models with BLLs ≤30 μg/dL remains limited.

As described in Sections 3.5.1.1 and 3.5.1.2 and summarized above, heterogeneity in the epidemiologic results for FSIQ and infant development at BLLs <5 μg/dL may be explained in part by sex, exposure to other metals, or maternal stress. Experimental animal studies offer some support for the observations regarding sex and maternal stress. The limited evidence evaluated in the 2013 Pb ISA (Virgolini et al., 2008; Yang et al., 2003; Mcgivern et al., 1991), combined with recent evidence, provides more consistent support for the sex-biased effects in both male (Anderson et al., 2016) and female (Tartaglione et al., 2020; Verma and Schneider, 2017; Anderson et al., 2012; Betharia and Maher, 2012) animals. The exact nature and direction of sex-specific effects given the variation in outcomes examined remains unclear, however. Toxicological studies assessed in the 2013 Pb ISA demonstrated the potential for Pb and maternal stress to result in dysfunction of the HPA axis (U.S. EPA, 2013). Recent toxicological evidence provides further support for the interaction between maternal stress and Pb exposure during the exposure period (Anderson et al., 2012; Cory-Slechta et al., 2012) but it remains unclear whether stress would positively influence some facets of cognitive function. Given the lack of evidence available on combined metal exposures, the possible interaction between multiple metals at relevant levels in animals remains unclear.

Poorer academic performance and achievement is linked with lower FSIQ and may have important implications for success later in life (U.S. EPA, 2013). In children aged 5 to 18 years higher blood Pb measured at various lifestages, including early childhood, and tooth Pb levels, which were generally measured in dentin and reflect Pb exposure during the prenatal or early childhood period, were associated with poorer performance on tests of math, reading, and spelling skills, lower probability of high school completion and lower-class rank, and lower teacher ratings of academic functioning (U.S. EPA, 2013). Recent studies in populations of children (age 6–16 years) enrolled in school districts including North Carolina, Detroit, and Chicago with BLLs ≤5 μg/dL support and extend these observations of poorer academic performance in association with increasing Pb exposure in populations with mean BLLs <5 μg/dL.

Recent studies support and extend the evidence pertaining to the effect of Pb exposure on cognitive function in children at low BLLs. Compelling evidence for a larger decrement in cognitive function per unit increase in blood Pb among children with lower mean blood Pb concentrations, compared with children with higher mean blood Pb concentrations, was supported by a reanalysis of a pooled international dataset (Crump et al., 2013). The larger incremental effect of Pb on cognitive effects at the lower (relative to higher) end of the study population Pb exposure distribution has been observed across biomarkers [i.e., bone (Wasserman et al., 2003; Wasserman, 2003), plasma (Hu et al., 2006) and blood (Section 4.3.12, Figure 4-15, and Table 4-16 of the 2013 Pb ISA U.S. EPA (2013))] and across different cognitive function endpoints [i.e., infant development (Hu et al., 2006), IQ (Wasserman et al., 2003; Wasserman, 2003) and academic achievement (Evens et al., 2015).] Crump et al. (2013) also supported the finding of Lanphear et al. (2019) that the C-R function in the pooled analysis of blood Pb level and IQ is adequately modeled as linear at BLLs < 10 μg/dL. Recent studies with an adequate range of Pb exposure measured during relevant time periods that would be required to further evaluate exposure-response relationships were limited. Considering the collective body of studies, no evidence of a threshold for cognitive effects in children across the range of BLLs examined in epidemiologic studies was reported.

The total body of evidence evaluated is sufficient to conclude that there is a *causal relationship* between Pb exposure and decrements in cognitive function in children. This causality determination is the same as the conclusion in the 2013 Pb ISA, reflecting the consistency of the results from epidemiologic studies of FSIQ, Bayley MDI, and academic performance and achievement, as well as the coherence of evidence across epidemiologic and toxicological studies of learning and memory. The pattern of associations consistently observed for tooth Pb levels and blood Pb levels measured at various lifestages or time periods reduces uncertainty regarding the temporal association observed in cross-sectional analyses of concurrent blood Pb levels with cognitive decrements in children. Notably concurrently measured tooth Pb levels in dentin generally reflect the prenatal or childhood Pb exposure that precedes the assessment of the outcome. 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. This interaction leads to increased oxidative stress and the

presence of inflammation, which can have widespread effects on brain structure and function, as well as disruptions of Ca^{2+} signaling. These disruptions can result in altered brain signaling and contribute to the development of neurological health effects. Recent studies support the conclusion of the 2013 Pb ISA that Pb-associated cognitive effects in children occur in populations with mean BLLs between 2 and 8 μg/dL. As noted in the 2013 Pb ISA, this conclusion 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). One recent study of Canadian preschool aged children from mainly middle- to upper-middle SES families with low Pb exposure (mean concurrent blood Pb level 0.70) did not find an association between concurrent Pb exposure and performance on WPPSI at age 3 to 4 years (Desrochers-Couture et al., 2018). Other recent studies found associations of Pb exposure with cognitive effects in children with mean BLLs <2 μg/dL; however, the studies with mean BLLs <2 μg/dL lack the aforementioned attributes (i.e., early childhood BLLs, consideration of peak BLLs, or examination of concurrent BLLs in young children) and exhibit heterogeneity in both the magnitude and precision of the associations at the lowest blood Pb concentrations. The observed heterogeneity may be explained in part by the underlying distribution and complex relationship between covariates in the populations studied, including sex, maternal stress, and co-exposures to other metals and neurotoxic chemicals, at relatively low BLLs (<5 μg/dL). Overall, epidemiologic and toxicological studies continue to strongly support the finding that exposure during multiple lifestages (prenatal through adolescence and early adulthood) is associated with cognitive effects in children. No evidence of a threshold for cognitive effects in children across the range of BLLs examined in epidemiologic studies was reported.

Table 3-2 Summary of evidence Indicating a causal relationship between Pb exposure and cognitive effects in children

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent associations from multiple, prospective epidemiologic studies with relevant BLLs	Evidence from prospective studies for decrements in FSIQ in association with prenatal, earlier childhood, peak, concurrent, lifetime average BLLs and tooth Pb levels in children ages 4–17 yr in multiple U.S. locations, Mexico, Europe, Australia.	U.S. EPA (2013) Section 4.3.2.1, Table 4−3	Blood Pb (various time periods and lifestages): Means 3–16 µg/dL
	Recent prospective studies observe associations of Pb with FSIQ; however, heterogeneity in the magnitude and direction of the associations is present.	Section 3.5.1.1	Blood Pb (various time periods and lifestages) <5 µg/dL (<2 µg/dL in some studies)
	Some recent epidemiologic studies indicate potential effect modification or interactions of Pb with sex, other metals, and maternal stress potentially explaining heterogeneity in the observed associations at BLLs <5 µg/dL.	Section 3.5.1.6.5	
	Evidence from prospective studies for lower scores on tests of executive function and academic performance in association with earlier childhood or lifetime average BLLs or tooth Pb levels in children ages 5–20 yr in multiple U.S. locations, U.K., New Zealand.	U.S. EPA (2013)	Blood Pb (various time periods and lifestages) <5 µg/dL
	Recent evidence generally relies on outcome ascertainment based on the BRIEF is inconsistent.	Section 3.5.1.4	
	The direction and magnitude of associations were not consistent for learning and memory. Recent evidence does not enhance the consistency.	U.S. EPA (2013) and Section 3.5.1.3	

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
	Supporting evidence from cross-sectional studies of children ages 3–16 yr, but most did not consider potential confounding by parental caregiving quality. Includes large NHANES III analysis.	U.S. EPA (2013)	Blood Pb (various time periods and lifestages) <5 µg/dL
	Several studies indicate supralinear C-R relationship, with larger decrements in cognitive function per unit increase in blood Pb at lower BLLs in children ages 5–10 yr. Reanalysis of international pooled analysis substantiates this finding.	U.S. EPA (2013) Section 3.5.1.6.1 Crump et al. (2013)	
Epidemiologic evidence helps rule out chance, bias, and confounding with reasonable confidence	Several epidemiologic studies found associations with adjustment for SES, maternal IQ and education, HOME score. Several adjust for birth weight, smoking. A few, nutritional factors.	U.S. EPA (2013) Section 3.5.1.6.2	
Experimental animal studies with relevant exposures provide coherence and help rule out chance, bias, and confounding with reasonable confidence	Impaired learning and associative ability in juvenile and adult animals as indicated by performance in tasks of visual discrimination, water maze, y maze, and operant conditioning with schedules of reinforcement with relevant dietary Pb exposure.	U.S. EPA (2013) Section 4.3.2.3	Blood Pb (after prenatal/ lactation, lactation only, prenatal/lifetime Pb exposure): 10–25 µg/dL
	Recent studies of executive function in rodents add to the evidence; however, evidence for impaired executive function in animal models with BLLs ≤30 µg/dL remains limited.	Section 3.5.1.4.2	
Experimental animal studies with relevant exposures provide coherence for epidemiologic observations of effect modification by sex or interactions of Pb with other metals or maternal stress	Recent studies in rodents suggest that factors such as sex and maternal stress may influence the effects of Pb on cognitive function.	Section 3.5.1.6.5	
Biological plausibility demonstrated	Pathways involving oxidative stress, inflammation and Ca^{2+} signaling result in impaired neuron development, synaptic changes, LTP, and neurotransmitter changes.	U.S. EPA (2013) Section 3.6	

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
	Recent studies support and extend findings related to overt nervous system effects.	Section 3.3	

BLL = blood lead level; BRIEF = Behavior Rating Inventory of Executive Functions; Ca^{2+} = calcium ion; C-R = concentration-response; FSIQ = full-scale intelligence quotient; HOME = Health Outcomes and Measures of the Environment; IQ = intelligence quotient; LTP = long-term potentiation; NHANES = National Health and Nutrition Examination Survey; Pb = lead; SES = socioeconomic status; yr = year(s).

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

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

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

3.5.2 Externalizing Behaviors: Attention, Impulsivity, and Hyperactivity in Children

The evidence evaluated 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 of blood Pb measured years before outcomes or tooth Pb levels, which were generally measured in dentin and reflect prenatal and early childhood Pb exposure, with attention decrements and hyperactivity in children (7–20 years) as assessed using objective neuropsychological tests and rated by parents and teachers. Most of the prospective studies examined representative populations with no indication of participation that was conditional on BLLs and behavior. The results from the prospective studies were generally 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. With respect to the timing of exposure discerned from prospective studies, blood Pb-associated attention decrements and hyperactivity were found in populations with prenatal (maternal or cord) or postnatal (i.e., 3–60-month average, age 6 years, or lifetime average through age 11–13 years) mean BLLs of 7 to 14 μg/dL and in groups with BLLs >10 μg/dL at 30 months of age. Biological plausibility for these observations in children was provided by experimental animal studies that demonstrated increases in impulsivity or impaired response inhibition with relevant postweaning and lifetime Pb exposures that resulted in BLLs of 11 to 30 μg/dL. Demonstrated Pb-induced impairments in neurogenesis, synaptic pruning, and dopamine transmission in the prefrontal cerebral cortex, cerebellum, and hippocampus also supported the biological plausibility of the associations observed in the epidemiologic studies. Although coherence across and within lines of evidence was demonstrated, the small number of studies of diagnosed ADHD were limited by their cross-sectional or case-control design, inconsistent adjustment for SES and parental education, and lack of consideration for potential confounding by parental caregiving quality.

There are three major domains of externalizing behavior disorders: (1) ADHD, (2) undersocialized aggressive conduct disorder, and (3) socialized aggressive conduct disorder (as reviewed in (Whitcomb and Merrell, 2012)). Although these domains are interrelated, to the extent possible, this Section (3.5.2) will maintain a similar structure as the 2013 Pb ISA by focusing on the ADHD domain, which encompasses characteristics including but not limited to short attention span, distractibility, impulsivity, and hyperactivity. Within the ADHD domain of externalizing behaviors, most epidemiologic studies of Pb exposure focus on attention, impulsivity, and hyperactivity. Some epidemiologic studies examined composite indices of multiple behaviors, and a few studies have examined physician-diagnosed ADHD. Domain-specific neuropsychological assessments of attention, impulsivity, and hyperactivity with strong psychometric properties and rigorous validation were emphasized in the 2013 Pb ISA and provide the strongest evidence for the causality determination. Studies that evaluated the association of Pb exposure with externalizing behaviors assessed using teacher and parent ratings, which are generally reliable and valid instruments that predict functionally important outcomes, contributed to the overall

evidence (Desrochers-Couture et al., 2019; Fruh et al., 2019; Nigg et al., 2016; Hong et al., 2015; Gittleman and Eskenazi, 1983).

Control for confounding is considered an attribute of a well-conducted, high-quality study. Greater weight is given to studies that consider important potential confounders in their design or statistical analyses. As noted in the 2013 Pb ISA (U.S. EPA, 2013), associations between Pb biomarker levels and externalizing behaviors may be confounded by parental SES, education, and IQ; nutritional status; and the quality and stability of the caregiving environment (often evaluated using the HOME score (Totsika and Sylva, 2004)). The research available for evaluation in the 2013 Pb ISA did not establish a direct relationship between parental psychopathology and child Pb exposure or one between parental psychopathology and poorer parental caregiving quality. Thus, parental psychopathology itself was not considered to be a potential confounder of associations between child Pb and externalizing behaviors. Although parental psychopathology was hypothesized to modify the association between Pb exposure and externalizing behavior, no studies available for evaluation in the 2013 Pb ISA evaluated parental psychopathology as an effect modifier. To the extent that parental psychopathology could affect child Pb exposure indirectly through parental caregiving quality, however, it was noted that confounder control would be achieved in studies that included an adjustment for the HOME score or similar metrics.

Greater emphasis is also placed on prospective studies with repeated assessments of BLLs and studies of children with BLLs that are less influenced by higher past Pb exposures (i.e., younger children). Studies assessing effects in populations with BLLs that are most relevant to current U.S. children (e.g., <5 µg/dL) are also emphasized, e.g., (Cho et al., 2010; Nicolescu et al., 2010; Chandramouli et al., 2009; Nigg et al., 2008; Chen et al., 2007; Chiodo et al., 2007). In the current ISA, when considering the causal relationship of Pb exposure with attention, impulsivity, and hyperactivity, PECOS statements (see Section 3.2) were refined to focus on the most informative studies. Longitudinal epidemiologic studies with mean (or central tendency) BLLs ≤5 µg/dL are highlighted in the text as are the most reliable biomarkers of Pb exposure (i.e., blood, bone, teeth, or nails). Consideration of potential confounding and modification of the observed associations by the aforementioned factors was evaluated when considering the overall quality of the study. Measures of central tendency for Pb biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in evidence inventory Table 3-7E (Epidemiologic Studies) and Table 3-7T (Toxicological Studies). In addition, studies with central tendency blood Pb concentrations that exceed 5 µg/dL are extracted into Table 3-8E of Section 3.7 (Evidence Inventories). An overview of the recent evidence is provided below. Overall, recent studies generally support findings from the 2013 Pb ISA.

3.5.2.1 Attention in Children

3.5.2.1.1 Epidemiologic Studies of Attention in Children

Attention is the ability to maintain a consistent focus on an activity or relevant stimuli and can be assessed by examining sustained attention, concentration, or distractibility. The preponderance of evidence pertaining to the externalizing behaviors included in the 2013 Pb ISA evaluated the association of Pb exposure with measures of attention (U.S. EPA, 2013). Most prospective studies found associations of blood or tooth Pb levels with decrements in neuropsychological tests of attention as well as parent and teacher ratings of attention. One strength of the prospective studies is that they characterized the sequence of Pb exposure (i.e., prenatal blood Pb, postnatal blood Pb before the outcome, concurrent, lifetime average blood Pb, and tooth Pb [i.e., generally measured in dentin, reflecting prenatal, early childhood or cumulative Pb exposure depending on the assessment method]), establishing the temporal relationship between exposure and outcome. In addition, the studies reported moderate to high follow-up participation that was not conditional on blood or tooth Pb levels and controlled for important confounders (i.e., parental education, IQ, and caregiving quality; SES). Overall, these studies showed a pattern of lower attention with higher blood or tooth Pb level (see Figure 4-9 and Table 4-11 of the 2013 Pb ISA (U.S. EPA, 2013)). Mean BLLs were generally within the range of 7–14 μg/dL for most of the prospective studies, and cross-sectional studies generally supported findings from the longitudinal analyses (see Section 4.3.3.1 of the 2013 Pb ISA (U.S. EPA, 2013)).

A small number of recent longitudinal epidemiologic studies of children with relatively low BLLs (i.e., ≤5 μg/dL) add to the evidence for associations between Pb exposure and decrements in neuropsychological tests of attention or parent and teacher ratings of behaviors that indicate attention problems (see Section 3.5.2.4).

Neugebauer et al. (2015) conducted an analysis of the Duisburg birth cohort data to examine the association of maternal BLLs at 32 weeks gestation with performance on neuropsychological tests of attention (Test of Attentional Performance for Children [KiTAP]) and parent-rated ADHD behaviors on the German Symptom Checklist for ADHD (Fremdbeurteilungsbogen für Aufmerksamkeitsdefizit/Hyperaktivitätstörungen [FBB-ADHS]) in childhood. Maternal blood Pb was most strongly associated with specific KiTAP subtests, i.e., number of omissions (geometric mean ratio [GMR] = 1.15 [95% CI: 1.00, 1.33]) and reduced performance speed (GMR = 1.14 [95% CI: 0.98, 1.33]). Maternal blood Pb concentration was positively associated with the inattention component of the FBB-ADHS indicating that inattention increases with increasing BLL (GMR = 1.05 [95% CI: 0.99, 1.12]).

In a study of a subset (n = 27) of Inuit children (Boucher et al., 2012b) (see Section 3.5.2.5) that used a modified Posner paradigm to assess the association between prenatal and concurrent childhood Pb exposure with visuospatial attention, vigilance, and impulsivity, Ethier et al. (2015) found that concurrent ln-transformed blood Pb was associated with some tests of attention including longer reaction times (β =

0.52 [95% CI: −0.10, 1.14] per SD increase in ln-transformed Pb) in a model adjusted for age, sex, and current PCB exposure. In another study, Tatsuta et al. (2014) adjusted for PCBs and MeHg (in addition to maternal IQ and family income) and found no associations with sequential processing score (−2.14 [95% CI: −12.80, 8.53] per unit of log transformed BLL [base not specified]) or mental processing score (−3.32 [95% CI: −12.4, 5.77] per unit of log transformed BLL [base not specified])). Yorifuji et al. (2011) found that cord blood Pb was associated with some neuropsychological tests of attention and working memory on the WISC-R (i.e., digit span) and that the interaction between cord blood Pb and cord Hg level may be less than additive. For example, the association of cord Pb with performance on the digit span forward at age 7 was β = −0.11 [95% CI: −0.29, −0.07] per log-transformed unit of BLL without accounting for the interaction between cord Pb and cord Hg concentration. This association was more pronounced when Hg exposure was lower. Specifically, the unstandardized associations of log-transformed cord BLL with the neuropsychological test outcomes were most discernable among children with hair Hg concentrations below 2.61 μg/g, which was the lowest cord Hg concentration. For example, a lower digit span forward score on the WISC-R (β = −1.70 [95% CI: −3.12, −0.28]) at age 7 and a lower digit span backward score on the WISC-R (β = −2.73 [95% CI: −4.32, −1.14]) at age 14 were observed among children with the lowest Hg exposure.

Ruebner et al. (2019) evaluated the association between BLLs and attention and hyperactivity among children with CKD. Attention was assessed using either Conners' Kiddie Continuous Performance (K-CPT; 4–5 years) or Conners' CPT II (≥6 years), which produce scores for omission and commission errors, correct detection rate, response variability, reaction time, and summary measures for sustained attention and inhibitory control. A 1.8 T-score point increase (i.e., worse performance) in CPT variability (95% CI: 0.2, 3.5), which indicates problems with sustained attention and attention regulation, was associated with childhood blood Pb (on average, ~2 years before outcome ascertainment) in this study. Covariates considered as potential confounders included race, poverty, maternal education, and factors related to CKD. The median BLL in this study was 1.2 μg/dL.

A small number of studies examined the gene-environment interaction between Pb exposure and genotypes associated with attention decrements. Rooney et al. (2018) studied children in Lisbon, Portugal to determine the association of baseline BLL (8–12 years old) and variants of GRIN2A and GRIN2B, which regulate neurodevelopmental processes, with performance on neuropsychological tests, including tests of attention, during the 7-year follow-up period. A pattern of association indicating poorer performance on tests of attention with increasing baseline Pb exposure was not observed. Choi et al. (2020) enrolled children (5–18 years old) with ADHD and healthy controls without ADHD to evaluate interactions between Pb exposure and noradrenergic pathway-related genotypes (i.e., [DAT1], dopamine receptor D4 [DRD4], and alpha−2A-adrenergic receptor [ADRA2A]). ADHD was assessed using the ADHD rating scale (ADHD-RS) and neuropsychological tests of attention (i.e., CPT and SCWT) were also administered. BLLs were associated with omission errors (β = 3.75 [95% CI; 0.09, 7.40]) in models adjusted for IQ, age, and sex, which were found to partly mediate the effect of Pb on ADHD symptoms in a path analysis model. An interaction effect was detected between the ADRA2A DraI genotype and Pb

levels on omission errors (β = 5.07 [95% CI: 0.20, 9.93]). Multiple comparisons were made in this analysis (e.g., associations with additional CPT components including commission errors, response time, and response time variability, ADHD-RS components and SCWT components were not observed), increasing the likelihood of chance findings.

Summary

Prospective studies in the 2013 Pb ISA showed strong support for an association between pre- and postnatal Pb exposure (range: 7–14 μg/dL) and decreased scores on neuropsychological tests and parent/teacher ratings of attention. Cross-sectional studies from the 2013 Pb ISA corroborated these observations. A small number of recent studies reported associations of maternal and cord BLLs ≤5 μg/dL with some measures of inattention; however, the results for multiple subtests were reported, potentially increasing the likelihood of chance findings. Recent studies add to the limited evidence regarding co-exposure to Hg and gene-environment interactions (see Section 3.5.2.6.3).

3.5.2.1.2 Toxicological Studies of Attention

In support of the associations described in the preceding sections for BLL with attention decrements in children, studies have found Pb-induced decreases in attention in animals, although results have not been consistent across studies. Although tests in animals often measure aspects of both attention and impulsivity, behaviors measured with signal detection tests with distraction can be inferred as predominately assessing sustained attention. In this test, animals earn food rewards by responding to a target stimulus and not responding to a distracting light. Poorer sustained attention and greater distractibility are indicated by lack of response to the target and increased response to the distracter light, respectively. The 2006 Pb AQCD (U.S. EPA, 2006) reported inconsistent effects of Pb exposure in animals on performance in this test. For example, postweaning Pb exposure that produced BLLs of 16 and 28 μg/dL induced small decreases in attention in adult rats, as indicated by small increases in omission and commission errors but only during sessions with long intervals between stimuli (Brockel and Cory-Slechta, 1999). Lifetime Pb exposure from birth (mean peak BLLs of 15 and 25 μg/dL for the 50 and 100 μg/kg/day groups, respectively) was found to induce distractibility in monkeys at age 9–10 years, as indicated by increased responses to irrelevant cues, i.e., distracting stimuli, in a spatial discrimination reversal task. Repeated reversal testing revealed that these deficits likely were not due to sensory or motor impairment (Gilbert and Rice, 1987).

In animals, Pb-induced decrements in attention have been inferred from tests designed to assess impulsivity but that have elicited behaviors that suggest deficits in attention. For example, a study reported that impaired performance on auditory threshold tasks in Pb-exposed monkeys was likely due to lack of attention (Laughlin et al., 2009). Rhesus monkeys were exposed to Pb acetate from gestation (drinking water of mothers, 3 months prior to mating) to birth or postnatally from birth to age 5.5 months

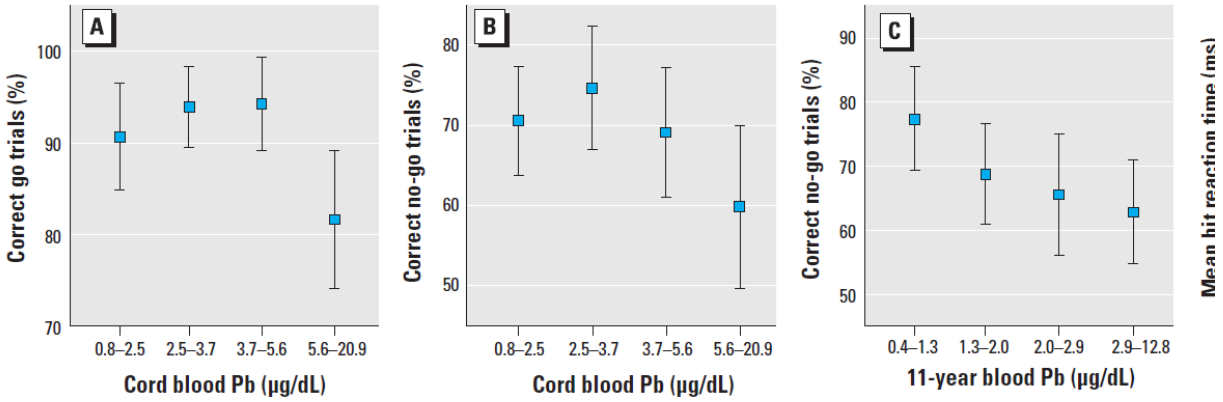
at weaning, resulting in bone Pb levels of 7 and 13 μg/g for prenatal and postnatal groups at 11 years of age, respectively, and average BLLs of 35 and 46 μg/dL, respectively, during Pb exposure. Animals were tested at age 13 years when BLLs had returned to baseline levels. The inability of some of the monkeys to engage or focus attention on the task at hand yielded fewer available measurements in Pb-exposed animals versus controls. These observations were made in monkeys with higher peak BLLs than those relevant to this ISA. No recent studies have evaluated attention in animals following exposure that resulted in BLLs relevant to the current ISA.

3.5.2.2 Impulsivity in Children

3.5.2.2.1 Epidemiologic Studies of Impulsivity in Children

Measures specific to impulsivity were examined in relatively few epidemiologic studies of children compared with measures of attention, and most studies including evaluations of impulsivity that were included in the 2013 Pb ISA were cross-sectional in design (U.S. EPA, 2013). The available evidence indicated Pb-associated poorer performance on tests of response inhibition. Response inhibition is a measure of impulsivity and has been assessed in children via stop signal tasks, which measure the execution of action in response to stimuli and the inhibition of that action when given a stop signal. Associations of blood and tooth Pb with parent and teacher ratings of impulsivity were also reported. These studies generally adjusted for potential confounding by SES, sex, parental education, and smoking; however, parental IQ or caregiving quality was not examined in most studies. The relatively small body of epidemiologic evidence (see Figure 4-9 and Table 4-11 (U.S. EPA, 2013)) was coherent with results from experimental animal studies (see Section 4.3.3.1 (U.S. EPA, 2013)).

Analyses of Inuit children have been conducted since the 2013 Pb ISA, examining Pb exposures and impulsivity. Boucher et al. (2012a) examined response inhibition deficits assessed with the Go/No-Go task and event-related potentials (ERPs) derived from electroencephalogram (EEG) recordings during task performance among Inuit school children residing in Arctic Quebec. Cord and concurrent blood Pb concentrations were associated with increased impulsivity after adjustment for covariates including child age, sex, SES, maternal nonverbal reasoning abilities, and Hg (Figure 3-11). In addition, Ethier et al. (2015) studied a subset of this population (n = 27) using a modified Posner paradigm to assess the association between pre- and concurrent childhood Pb exposure with visuospatial attention, vigilance, and impulsivity. The study found that cord Pb was associated with greater impulsivity (β = 0.42 [95% CI: 0.08, 0.76] per SD increase in ln-transformed Pb).



Source: Boucher et al. (2012a).

Figure 3-11 Mean ± standard deviation behavior performance in the Go/No-Go task according to quartiles of exposure for (A and B) cord blood Pb and (C) childhood blood Pb level at age 11 years.

Summary

Studies of impulsivity in children in the 2013 Pb ISA were limited by their quantity and lack of temporality but generally indicated associations of Pb exposure with worse scores on tests of response inhibition and on parent and teacher ratings of impulsivity. These studies also often lacked confounder control for parental IQ or caregiving quality, which are key potential confounders. Recent analyses of Inuit children add support for the relationship between Pb exposure and impulsivity with additional consideration of potential confounders including maternal nonverbal reasoning abilities (Boucher et al., 2012a).

3.5.2.2.2 Toxicological Studies of Impulsivity

The associations described between higher BLL and greater impulsivity in children are supported by findings in animals for Pb-induced increases in perseveration and impaired ability to inhibit inappropriate responses. In animals, these effects are supported by studies reviewed in the 1986 and 2006 Pb AQCDs (U.S. EPA, 2006, 1986) and studies incorporated into the 2013 Pb ISA. Animal studies provide more consistent evidence for the effects of Pb exposure on impulsivity than on sustained attention. As mentioned earlier, behaviors displayed by animals in a variety of tests can be identified as reflecting impulsivity. These include tests of differential reinforcement of low rates of responding, fixed interval (FI) schedule performance, FI with extinction, or fixed ratio (FR)/waiting-for-reward. Greater impulsivity is indicated by premature responses, decreased pause time between two scheduled events, and increased perseveration.

Behaviors observed in tests of operant conditioning with FI reinforcement schedules have also been used to indicate impaired learning in animals (Section 3.5.1.3.2), and the interactions observed between Pb exposure and maternal or offspring stress may also apply to effects on impulsivity. Maternal exposure to 150 ppm Pb with and without stress co-exposure was found to increase overall FI rate and decrease Post-reinforcement Pause (PRP) in rats. Lifetime (from gestation) Pb exposure resulting in BLLs of 11–16 μg/dL increased the overall FI rate without stress co-exposure and decreased PRP with stress co-exposure (Rossi-George et al., 2011), suggesting that stress may interact with Pb exposure to affect attention. Discrimination reversal learning has been shown to be affected by Pb exposure. In these tasks, an animal is trained to choose between two alternative responses and is then required to reverse the association. Perseveration or lack of inhibition of the original response can be interpreted to involve impulsivity. Spatial and non-spatial discrimination reversal was significantly affected in monkeys after Pb exposure during infancy, after infancy, or continuously from birth, and was exacerbated with distracting stimuli (Rice, 1990; Rice and Gilbert, 1990b; Gilbert and Rice, 1987). These monkeys had BLLs in the range of 15–36 μg/dL, which includes values relevant to this ISA. Hilson and Strupp (1997) found Pb exposure (Pb acetate in drinking water at GD 1–PND 28, yielding a BLL of 26 μg/dL in the lower dose group) in rats slowed reversal learning in an olfactory discrimination task. However, analysis of the response patterns showed that Pb exposure shortened the perseverative responding phase of reversal learning and lengthened the post-perseverative phase of chance responding, indicating impairments in associative ability, not response inhibition. Thus, it is more likely that Pb negatively affected associative learning rather than impulsivity in this study (Hilson and Strupp, 1997), which is inconsistent with the FI data in monkeys. Due to the small number of studies following relevant Pb exposures in rodents, it remains unclear whether Pb affects impulsivity in FI.

The effects of Pb exposure on impulsivity also have been demonstrated in a study reporting that Pb-exposed animals wait a shorter period of time for reward in FR/waiting for reward testing. In this test, animals can obtain food by pressing a lever a fixed number of times (FR component). Free food is then delivered at increasingly longer time intervals, so long as the animal inhibits additional lever presses. Animals can reset the schedule to return to the FR component at any time. Brockel and Cory-Slechta (1998) exposed male Long-Evans rats to 0, 50, or 150 ppm Pb acetate in drinking water from weaning, which produced respective BLLs of <5, 11, and 29 μg/dL after 3 months of exposure. After 40 days of exposure, the 150 ppm Pb-exposed rats responded more quickly in the FR component and reset the schedule (thus shortening the waiting period) more often than did the 50 ppm Pb-exposed rats and controls. In the waiting component, average wait time was significantly lower in both Pb exposure groups compared with controls. The rats exposed to 150 ppm Pb also had higher response rates and earned more reinforcers per session but had a higher response to reinforcement-ratio than did the 50 ppm Pb group and controls, which indicated less efficient responses.

Weston et al. (2014) used the delayed discounting paradigm following developmental exposure with or without prenatal restraint stress. The delayed discounting protocol offered animals the choice between a large reward after a long delay or a small reward after a short delay. Pb increased long-delay

responding, slowed acquisition of delayed discounting performance, and increased failures almost exclusively in males. Consistent with (Hilson and Strupp, 1997), these results more likely represent impaired learning or cognitive flexibility rather than simply increased impulsivity.

In summary, several studies in animals indicate that Pb exposure of rodents and nonhuman primates from birth or after weaning changes behavior in ways consistent with increased impulsivity, primarily as indicated by impaired response inhibition. It is also important to note that many of the measures of impulsivity discussed in this section are sensitive to disruption by impairments in learning and executive function, which is consistent with several of the studies summarized in Sections 3.5.1.3.2 and 3.5.1.4.2. Some observations of Pb-induced impulsivity in animals were made with BLLs considered relevant for this ISA. The observations for Pb-induced increases in impulsivity in animals provide support for associations found in children of higher blood and tooth Pb levels with lower response inhibition and higher ratings of impulsivity.

Transgenerational Effects of Pb on Impulsivity

The paradigm of combined Pb and stress exposure experienced by a laboratory animal has been examined with a focus on the common pathway of altered HPA axis and brain neurotransmitter levels. Studies investigating the interactions between Pb and prenatal stress on learning and memory are reviewed in Section 3.5.1.3.2. These findings were expanded on in a recent study that investigated the transgenerational effects of combined Pb and prenatal stress in mice (Sobolewski et al., 2020). The authors reported that Pb exposure in the gestating female (F0 generation) resulted in sex-specific effects in the third filial (F3) generation (no direct exposure to Pb), with F3 females displaying significantly elevated response rates in an FI schedule of reward compared with control lineages, suggesting an impulsive behavioral phenotype (Sobolewski et al., 2020). This and other transgenerational effects were accompanied by Pb-induced alterations in neurotransmitters, BDNF expression, and DNA methylation. The authors postulated that lineage effects may be mediated through some combination of maternal responses to pregnancy, maternal behavior, or epigenetic modifications (Sobolewski et al., 2020). While these findings were limited to a single study, they support the possibility that exposure to Pb may influence the behavior of subsequent generations.

3.5.2.3 Hyperactivity in Children

3.5.2.3.1 Epidemiologic Studies of Hyperactivity in Children

Studies reviewed in the 2006 Pb AQCD (U.S. EPA, 2006) indicated associations between higher concurrent BLLs or tooth Pb levels and higher parent or teacher ratings of hyperactivity in children aged 6–11 years in the U.S., Asia, and New Zealand (Rabinowitz et al., 1992; Silva et al., 1988; Gittleman and Eskenazi, 1983; Needleman et al., 1979; David et al., 1976). The case-control or cross-sectional design of

studies limited understanding of the temporal sequence between Pb exposure and hyperactivity. A prospective study (Chandramouli et al., 2009) included in the 2013 Pb ISA also found associations between BLL and hyperactivity as rated by teachers and parents. Overall, studies indicated associations in children 3–12 years old with mean concurrent BLLs of 3.7–12 μg/dL. Studies of recent hyperactivity symptoms as rated by parents and teachers are discussed in Section 3.5.2.4.

3.5.2.3.2 Toxicological Studies of Hyperactivity

The 2006 Pb AQCD (U.S. EPA, 2006) reviewed the evidence that developmental exposure to Pb could affect locomotor activity in laboratory animals. Findings summarized in this document included four studies showing increased activity with developmental Pb exposure and three studies showing no change in activity. The 2013 Pb ISA (U.S. EPA, 2013) only described one new study in this category, which showed a decrease in activity in mice after maternal Pb exposure (Leasure et al., 2008). Effects of developmental Pb exposure on rodent locomotor activity are commonly assessed using an open-field test. The activities examined vary across studies (e.g., distance traveled, counts of square crossings). Because there are myriad potential explanations for changes in rodent activity, it can be difficult to draw conclusions from "simple" tests like open-field. The results from such tests are best interpreted alongside additional behavioral assays, which, together, may better model the complexity of human behavior. Conclusions for an effect of developmental Pb exposure on locomotor activity were not reached in earlier United States Environmental Protection Agency (U.S. EPA) Pb reviews due to mixed results in these tests. Studies described in the 2013 Pb ISA (U.S. EPA, 2013) and 2006 Pb AQCD (U.S. EPA, 2006) as observing the effects of maternal Pb exposure, which resulted in mean BLLs no higher than 30 μg/dL, are Munoz et al. (1989), Rodrigues et al. (1996), Moreira et al. (2001), Trombini et al. (2001), De Marco et al. (2005), and Leasure et al. (2008).

Recent studies (see Table 3-11T) observed the activity of early postnatal rodents after developmental exposures to Pb with varying durations. Tartaglione et al. (2020) exposed rats to Pb from pregestation to offspring weaning and tested offspring. They observed a decrease in neonatal spontaneous activity on PND 10 and no change in spontaneous activity on PND 4, 7, and 12. Another group reported that two groups of CD1 mice exposed to either a high or low dose of Pb through lactation exhibited hyperactivity (PND 7, 11, 15, 19) compared with controls in open-field testing Duan et al. (2017). Interestingly, when locomotor data from early postnatal studies are pooled, nine out of nine sets of lactationally exposed animals (BLLs: 9.6–28.9 μg/dL) tested between PND 14 and 23 were hyperactive (Duan et al., 2017; De Marco et al., 2005; Moreira et al., 2001; Rodrigues et al., 1996). These sets consisted of both male and female rodents, except for one set of only males in Moreira et al. (2001).

Evidence inventory (Section 3.7) also includes recent studies that monitored the effects of developmental exposure to Pb on immature rodents postweaning. Basha and Reddy (2015) found decreased locomotor activity in male rats with gestational exposure to Pb when tested on both PND 21 and PND 28. Betharia and Maher (2012) studied open-field behavior in Sprague Dawley rats with

gestational and lactational exposure to Pb. There were no differences in total square crossings for both males and females tested at both PND 24 and PND 59. Flores-Montoya and Sobin (2015) saw no effects on open-field tasks (PND 28) in two groups each of male and female C57BL/6 mice after postnatal exposure (PND 0–28) to low levels of Pb acetate. Developmentally Pb-exposed rats from the Tartaglione et al. (2020) study described in the previous paragraph exhibited no change compared with control in open-field activity when tested on PND 30. Neuwirth et al. (2019a) observed no effect on locomotor activity in open-field tests (PND 36–45) for two groups of Long-Evans rats with different levels of in utero and lactational exposure to Pb. Zou et al. (2015) reported that exposure to Pb acetate in drinking water for 3 weeks (PND 37–58) increased spontaneous locomotor activity in juvenile ICR mice tested on PND 58. These recent studies do not indicate effects on the activity of rodents when tested in adolescence after Pb exposure from mothers, and they do not support the findings of hyperactivity in the similarly exposed and tested mice described by Trombini et al. (2001).

Faulk et al. (2014), Basha et al. (2014), and Wang et al. (2016) evaluated activity in adult rodents after developmental Pb exposure. Faulk et al. (2014) measured activity and horizontal movements along with ambulatory activity by adult offspring of dams (Agouti mouse) exposed to Pb for weeks from pregestation until weaning. Mean BLLs for offspring were not reported; however, maternal BLLs tested at weaning were below the limit of detection in the control group and 4.1, 25.1, and 32.1 μg/dL in the three respective exposure groups of 2.1, 16, and 32 ppm. Overall horizontal activity was different across Pb exposures in females but not in males. At 9 months, female offspring exposed to 2.1 ppm Pb had higher average horizontal activity compared with controls. There was a sex-specific difference in ambulatory measurement (subset of total horizontal activity), with only exposed females showing significant differences from controls. Ambulatory activity was lower in females at the 32-ppm exposure level at 3 months versus control offspring. Males did not exhibit significant differences at any time point or exposure level. Although there was suggestive evidence of differences in the life-course patterns of vertical activity by exposure among females, neither sex showed statistically significant differences between Pb-exposed and control offspring. Testing adult rats at 4, 12, and 18 months of age, Basha et al. (2014) found consistent decreases in locomotor activity associated with lactational Pb exposure. While mean BLLs at these testing periods were shown to be below the 30 μg/dL limit for PECOS relevance, it is notable that the mean BLL for this group of animals was determined to be 49.5 μg/dL at PND 45. Wang et al. (2016) measured distance traveled in the open field by Sprague Dawley rats aged 116–122 days after adolescent Pb exposure in drinking water from PND 24 to 56. They observed no effect of this exposure.

Evidence of Pb exposure-induced intergenerational effects on rodent behavior was also reviewed in the 2006 Pb AQCD (U.S. EPA, 2006). Trombini et al. (2001) observed increased open-field ambulation in F2 generation rats derived from female offspring of Pb-treated pregnant mothers. Recently, Sobolewski et al. (2020) exposed F0 mice to Pb during pregnancy and lactation, bred offspring with unexposed mates for two generations (F1 and F2), and then evaluated behavior in the F3 generation. F3 females demonstrated a small increase in locomotor activity, regardless of lineage.

Overall, there are still mixed indications on locomotor activity from Pb exposure studies with BLLs ≤30 μg/dL, which may be due to differential dosing, timing of exposures, and activity measurements. However, in a rare set of four individual studies wherein these critical factors were analogous, Pb exposure during lactation induced hyperactivity in rodents when tested within a PND 14 to 23 window (Duan et al., 2017; De Marco et al., 2005; Moreira et al., 2001; Rodrigues et al., 1996). Pb-induced hyperactivity in rodents provides some support for hyperactivity observed in children but may be more appropriately interpreted in the context of additional behavioral assays.

3.5.2.4 Parent and Teacher Ratings of ADHD-related Behavior

In addition to finding associations with attention, impulsivity, and hyperactivity, epidemiologic studies also found associations between higher concurrent BLLs and higher parent and teacher ratings of ADHD-related behaviors, calculated as a composite of the various behaviors evaluated in the diagnosis of ADHD (see Section 4.3.3.1 of the 2013 Pb ISA (U.S. EPA, 2013)). Most of these studies were limited due to their cross-sectional design and lack of validation of ADHD ratings with clinical diagnosis. Although diagnostic guidelines for ADHD exist, the exact criteria or specific behaviors required can vary. Thus, within studies, there were variations among subjects in the types of behaviors they displayed that led to a diagnosis of ADHD. Further the available studies considered age, sex, and SES or parental education but generally not both as potential confounders, and none of the studies considered parental caregiving quality.

Recent longitudinal studies add to the body of evidence examining the association between prenatal and childhood Pb exposure and parent/teacher-rated ADHD symptoms in populations with relatively low blood Pb concentrations (≤5 μg/dL). This group of studies includes some that found associations with hyperactivity using the SDQ, which is a screening questionnaire that includes five domains. Sioen et al. (2013) analyzed data from the Flemish Environment and Health Study (FLEHS I, 2002–2006), a birth cohort comprising mother-infant pairs to examine the association between cord blood Pb and ADHD-related behaviors for 281 infants whose parents returned the SDQ (26.4%). A positive association of cord blood Pb concentration with hyperactivity score ≥7 was observed (OR: 2.94 [95% CI: 1.17, 7.38 per log ug/dL increase in BLL]). In another study using this assessment instrument, Fruh et al. (2019) analyzed data from mother-child pairs participating in Project Viva, a longitudinal birth cohort in eastern Massachusetts. Maternal blood Pb concentration in erythrocytes was measured during the second trimester of pregnancy and parents rated their child's behavior using the SDQ in mid-childhood (median 7.7 years). The associations (i.e., β coefficients) with the parent and teacher-rated hyperactivity component of the SDQ were 0.10 (95% CI: −0.21, 0.41) and 0.20 (95% CI: −0.24, 0.64), respectively. While behavior assessments and maternal blood Pb measurements were available for fewer than half of Project Viva participants, important confounders including HOME score, maternal IQ, and parental education were considered in this study.

Several of these longitudinal epidemiologic studies used the Behavior Assessment System for Children (BASC) to assess both the behaviors and emotions of children (Reynolds and Kamphaus, 2015). BASC-2 includes individual subscales for attention and hyperactivity as well as an overall behavioral skills index (BSI) composite score. Specific rating scales and forms related to attention, hyperactivity, and impulsivity are emphasized in this section (e.g., clinical scales such as "attention problems" or "hyperactivity" on the teacher or parent rating scale forms).

Horton et al. (2018) analyzed data from the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) Project birth cohort in Mexico City to determine the association of weekly tooth Pb concentration (prenatal through 1 year postnatal) with BASC-2 scores assessed between 8 and 11 years old. Distributed lag models were used to identify specific time windows of increased risk due to Pb exposure. Tooth Pb concentration estimated to correspond with the 8 to 11 months postnatal period was associated with parent-rated behavioral symptoms overall ($\beta = 0.22$ units [95% CI: 0.06, 0.38] per natural log unit increase in dentine Pb concentration), and hyperactivity ($\beta = 0.19$ units [95% CI = 0.02, 0.37] per natural log unit increase in dentine Pb concentration) after adjustment for gestational age and maternal education. Approximately 12% of the original cohort was enrolled in this study; participants differed with respect to several characteristics including child birth weight and maternal IQ. Rasnick et al. (2021) conducted a study that estimated monthly air Pb exposure. The authors also aimed to identify sensitive time windows of exposure; however, they attempted to distinguish exposure to Pb in air by controlling for concurrent BLL (age 12 years) in their analysis of the Cincinnati Study of Allergy and Air Pollution study data. Air Pb exposure was estimated using validated land use regression models and behavioral outcomes, including attention and hyperactivity, were assessed using BASC-2 administered at age 12. Distributed lag models to predict outcome responses based on current and past (i.e., lagged) predicted air Pb exposures did not identify associations during any of the lifestages examined. Models were adjusted for community deprivation, residential greenspace, and elemental carbon attributable to traffic (ECAT), in addition to concurrent BLL.

In addition to examining attention using Conners' (Section 3.5.2.1.1), Ruebner et al. (2019) evaluated the association of BLLs with parent-rated attention and hyperactivity symptoms on BASC-2. This study was unique in that it enrolled children with CKD. Associations with parent ratings did not persist in models that controlled for potential confounders including race, poverty, maternal education, and clinical factors related to CKD. The median BLL in this study was 1.2 µg/dL.

Several other instruments, including FBB-ADHS, the Child Behavior Checklist (CBCL), the Disruptive Behavior Disorder (DBD) rating scale, the Barkley Adult ADHD-IV Rating Scale (BAARS), Conners' Rating Scale (CRS), the Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale (SWAN), and DuPaul's ADHD rating scale were used to assess total ADHD in recent prospective or case-control studies. These rating scales are generally reliable and valid instruments that predict functionally important outcomes (Desrochers-Couture et al., 2019; Fruh et al., 2019; Nigg et al., 2016; Hong et al., 2015; Gittleman and Eskenazi, 1983).

Neugebauer et al. (2015) conducted an analysis of the Duisburg birth cohort data to determine the association of maternal BLL at 32 weeks gestation with parent-rated ADHD behaviors in childhood (average age 9.5 years old) assessed using FBB-ADHS. Maternal blood Pb was associated with overall ADHD symptoms (β = 1.06 [95% CI: 1.01, 1.12]), with the strongest association observed for the impulsivity component (β = 1.13 [95% CI: 1.06, 1.22]). These associations were observed after adjustment for confounders including parental education, but not SES.

Liu et al. (2014b) examined the association of early childhood blood Pb concentration at 3, 4, or 5 years old (mean: 6.8 µg/dL) with parent and teacher ratings of ADHD behaviors among Chinese school children at age 6 using CBCL and the Caregiver-Teacher Report Form (C-TRF). The outcome was modeled as a continuous and also as a dichotomous variable (i.e., clinically significant behavior problems when T-score ≥60). The associations (i.e., β) between increased blood Pb concentrations (per µg/dL) and ADHD behavior problems were 0.001 (95% CI: –0.002, 0.002) for problems reported on CBCL and 0.07 (–0.18 to 0.32) for behavior problems reported on C-TRF. The associations (i.e., OR) with clinically significant ADHD behavior reported by parents on CBCL were 1.08 (95% CI: 0.99, 1.18) among children overall, 1.04 (95% CI: 0.94, 1.16) among boys, and 1.15 (95% CI: 0.98, 1.35) among girls. The participation rate was 81% in this study. Models were adjusted for confounders including parental caregiving quality but not SES. Another prospective study evaluated the association of Pb exposure with caregiver ratings on CBCL. In this study of adolescents, Winter and Sampson (2017) examined the relationship between average BLLs in childhood (6 years old or younger) with impulsivity between 16 to 18 years old. These authors found a 0.06 SD (95% CI: 0.01, 0.12) increase in impulsivity score, after adjustment for caregiver education and SES. Participants were originally enrolled in the mid−1990s and a random sample of those that continued to participate in 1999 and 2002 was randomly selected for this study, with 67% of those selected agreeing to participate.

Choi et al. (2016) investigated the association of childhood BLLs (geometric mean BLL = 1.56 µg/dL) with parent-rated ADHD symptoms later in childhood assessed using DuPaul's ADHD rating scale. Approximately 72% (n = 2,159) of 2,967 eligible participants provided blood Pb measurements and ADHD assessments, and 2052 were free of ADHD symptoms at baseline. A positive association between childhood blood Pb and the development of ADHD symptoms at the 2-year follow-up visit was observed in this study (RR: 1.55 [95% CI: 1.00, 2.40] >2.17 versus ≤2.17 µg/dL) after adjustment for residential area, household income, parental marital status, family history of psychiatric disorders, preterm birth, and birth weight. A stronger association was observed among children with higher BLLs and who resided in a single parent home (RR: 3.57 [95% CI 1.60, 7.98]).

Another longitudinal analysis examined the association of both cord BLL (mean: 4.7 µg/dL) and childhood (mean 2.7 µg/dL) BLL with ADHD symptoms among Inuit children in Quebec (Boucher et al., 2012b). In this study, teachers completed the DBD rating scale to indicate Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV symptoms of ADHD inattentive type and ADHD hyperactive-impulsive type. Associations between child concurrent log-transformed BLL and hyperactive/impulsive-

type ADHD symptoms assessed using DBD were observed (OR = 4.01 [95% CI: 1.06, 5.23] tertile 2 versus tertile 1; OR = 5.52 [95% CI: 1.38, 22.12] tertile 3 versus tertile 1). Inattentive-type ADHD symptoms on the DBD were not associated with Pb exposure. (Desrochers-Couture et al., 2019) extended this study by conducting a mediation analysis to estimate the direct and indirect associations of childhood BLLs with adolescent externalizing behaviors, including ADHD symptoms assessed using BAARS. The study found an association between childhood BLL and child hyperactivity and impulsivity, assessed by teachers on CBCL (β = 0.45 [95% CI: 0.13, 0.78]). Neither a direct (β = 0.09 [95% CI: −0.11, 0.28]) nor an indirect (β = −0.02 [95% CI: −0.06, 0.03]) association with adolescent ADHD symptomology assessed using BAARS was observed. A wide array of covariates was considered as potential confounders including both maternal education and SES.

Hong et al. (2015) found an association between blood Pb concentration and higher parent and teacher-rated ADHD-RS symptoms (β = 1.04 [95% CI: 0.18, 1.90] and β = 1.90 [95% CI: 0.74, 3.05], respectively) in a cross-sectional analysis of Korean school children from 8 to 11 years old after adjustment for demographic factors (age, sex, residential region, paternal education level, and SES). This association remained positive but was attenuated in models additionally adjusted for FSIQ, Mn, and Hg (β = 0.68 [95% CI: −0.20, 1.56] and β = 1.49 [95% CI: 0.32, 2.67], parent- and teacher-rated symptoms, respectively). The mean BLL in this study was 1.80 µg/dL. Associations indicating an increase in commission errors on CPT were also observed.

Nigg et al. (2016) conducted a case-control study of children from Michigan (mean BLL = 0.74 µg/dL (cases) and 0.94 µg/dL controls). In this study, ADHD composite indices were derived for (1) inattention/disorganization and (2) composite hyperactivity-impulsivity using relevant scales of the DuPaul, Conners', and SWAN scales. This study found an interaction between the hemochromatosis gene (HFE) C282Y genotype, which is involved in iron metabolism, and BLL in predicting parent and teacher reports of hyperactivity-impulsivity but not inattention. For example, the association between z scores of BLL and hyperactivity was significantly stronger among those with the HFE C282Y mutation (β = 0.74, [95% CI: 0.52, 0.96]) compared with those with the wild type genotype (β = 0.28 [95% CI: 0.15, 0.41]). This study also found an interaction between z scores of $\log_{10}$-transformed BLL and sex (association larger in boys) in predicting parent and teacher-rated hyperactivity and impulsivity but not attention.

3.5.2.4.1 Summary

Cross-sectional studies in the 2013 Pb ISA found associations between higher concurrent BLL and higher parent and teacher ratings of ADHD-related behaviors, calculated as a composite of the various behaviors that are evaluated in the diagnosis of ADHD (U.S. EPA, 2013). The evidence from prospective studies was limited to Chandramouli et al. (2009), which found associations between BLL and hyperactivity as rated by teachers and parents. Parent and teacher ratings generally considered SES or parental education, but typically not both, as potential confounders. None of the studies considered parental caregiving quality. Recent longitudinal studies that established the temporality between the

exposure and the outcome add to the body of evidence examining the association between prenatal and childhood Pb exposure and parent/teacher-rated ADHD symptoms in populations with relatively low blood Pb concentrations (≤6 μg/dL). Across studies, associations were observed with tooth Pb concentration that were measured in dentin and generally reflect early childhood Pb exposure, childhood BLLs, and maternal or cord (2–5 μg/dL) BLLs. Studies of caregiver-reported ADHD symptoms generally report associations with composite indices (Choi et al., 2016; Hong et al., 2015; Neugebauer et al., 2015; Liu et al., 2014b; U.S. EPA, 2013), and there is some evidence indicating that the associations with impulsivity and hyperactivity symptoms (Desrochers-Couture et al., 2019; Fruh et al., 2019; Horton et al., 2018; Winter and Sampson, 2017; Nigg et al., 2016; Neugebauer et al., 2015; Sioen et al., 2013; Boucher et al., 2012b) are stronger than the associations with inattention symptoms. The majority of recent studies were prospective and generally reported moderate or high participation rates. Some studies addressed the validity of caregiver assessed outcomes by evaluating internal consistency (Rasnick et al., 2021; Desrochers-Couture et al., 2019), and Nigg et al. (2016) addressed reliability and 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 (Desrochers-Couture et al., 2019; Fruh et al., 2019; Nigg et al., 2016; Hong et al., 2015; Gittleman and Eskenazi, 1983). Confounder adjustment remains somewhat inconsistent across studies, although Liu et al. (2014b) and Fruh et al. (2019) adjusted for the quality of parental caregiving, Choi et al. (2016) adjusted for family history of psychiatric disorders, and several considered both SES and parental education (Desrochers-Couture et al., 2019; Ruebner et al., 2019; Horton et al., 2018; Winter and Sampson, 2017; Boucher et al., 2012b). There is uncertainty regarding the patterns of exposure that are associated with BLLs in older children because they may be influenced by higher past exposure.

3.5.2.5 Clinically Diagnosed ADHD

In the 2013 Pb ISA, results from a small body of cross-sectional studies indicated associations between concurrent BLL and the prevalence of ADHD symptom ratings (Section 3.5.2.4) and clinically diagnosed ADHD in children aged 4–17 years. The temporal relationship between Pb exposure and ADHD was not established in these studies, and concurrent blood Pb concentrations in older children may reflect higher past exposures. Additionally, some ADHD symptom rating studies lacked outcome validation, and confounding was inconsistently addressed across studies. Therefore, the evidence specifically for these total ADHD index ratings and clinically diagnosed ADHD were emphasized less in the 2013 Pb ISA (U.S. EPA, 2013) than evidence for individual behaviors when drawing conclusions about the effects of Pb exposure on attention, impulsivity, and hyperactivity.

Recent studies add to the evidence and address some of the uncertainties pertaining to the studies included in the 2013 Pb ISA. Notably, Ji et al. (2018) analyzed data from the Boston Birth Cohort (1479 mother-infant pairs) to examine the association of early childhood Pb exposure (i.e., earliest (< age 4)

blood Pb concentration recorded during routine screening) with the development of ADHD later in childhood. ADHD was assessed using electronic medical records (International Classification of Diseases [ICD]-9 codes: 314.0, 314.00, 314.01, 314.1, 314.2,314.8, and 314.9, or ICD−10 codes: F90.0, F90.1, F90.2, F90.8, and F90.9). Several important potential confounders (i.e., parental education, SES but not quality of parental caregiving) were controlled for in the analysis, and child sex, maternal high-density lipoprotein (HDL), and maternal stress were considered as potential effect modifiers. Ji et al. (2018) analyzed the association modeling blood Pb concentration as continuous and as categorical variables. When blood Pb was analyzed using three categories, the OR comparing children with BLLs between 2 and 4 μg/dL to children with BLLs <2 μg/dL was 1.08 (95% CI: 0.81–1.44). The OR comparing children with BLLs between 5 and 10 μg/dL to children with BLLs <2 μg/dL was 1.73 (95% CI: 1.09–2.73). When blood Pb was modeled as a continuous variable, the OR was 1.12 [95% CI: 1.00, 1.25) per ug/dL increase in BLL. Sex-stratified analyses comparing children with BLLs between 5 and 10 μg/dL to children with BLLs <5 μg/dL indicated no association among girls (OR = 0.68 [95% CI: 0.27, 1.69]) and a strong association among boys (OR = 2.49 [95% CI: 1.46–4.26]). Joint analyses indicated a 10-fold increase in the magnitude of the association between childhood blood Pb concentration and ADHD diagnosis among those with multiple risk factors (i.e., male sex, inadequate maternal HDL, higher maternal stress).

Several additional recent studies also extend the evidence. Park et al. (2016) conducted a hospital based case-control study in Busan, South Korea comparing the odds of higher blood Pb concentration among diagnosed ADHD cases, which were confirmed using the Korean version of the Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime (K-SADS-PL-K), to the odds of higher blood concentration among controls that were frequency matched by age and sex and adjusted for other potential confounders. Blood Pb was measured when the cases and controls were recruited into the study. Higher blood Pb concentration was associated with increased risk of ADHD (OR: 1.60 [95 % CI: 1.04–2.45] per unit increase in log BLL); however, blood Pb concentrations were not associated with ADHD-RS score or CPT profiles among the ADHD cases. In a smaller case-control study that examined the association of childhood Pb exposure with diagnosed ADHD among children living near a former smelter in Omaha, Nebraska, Kim et al. (2013a) found a positive association (OR: 2.52 [95% CI: 1.07, 5.92] per unit increase in natural log BLL).

In a recent cross-sectional analysis of NHANES (2003–2004) data, Geier et al. (2018) examined the association of concurrent blood Pb concentration with self-reported doctor diagnosed attention deficit disorder (ADD) among children and adolescents 10–19 years old. This study observed a positive association between concurrent blood Pb concentration and ADD after adjusting for age, race, sex, and SES (OR: 1.29 [95% CI: 1.03, 1.55]). In a previous analysis Braun et al. (2006) found an association in children aged 4–15 years participating in NHANES (1999–2002). ADHD ascertained by the parent report of ADHD diagnosis is subject to reporting bias; however, the examination of multiple risk factors and outcomes in NHANES reduces the likelihood of biased participation and reporting of ADHD by parents of children specifically with higher Pb exposure.

3.5.2.5.1 Summary

The 2013 Pb ISA assessed a small body of cross-sectional studies that examined the associations between concurrent BLLs and the prevalence of clinically diagnosed ADHD. The temporal relationship between Pb exposure and ADHD was not established in these studies and it was noted that concurrent blood Pb concentration in older children potentially reflects higher past exposures. As noted in the 2013 ISA, clinically diagnosed ADHD was emphasized less than evidence for individual behaviors in drawing conclusions about the effects of Pb exposure on attention, impulsivity, and hyperactivity in the 2013 Pb ISA (U.S. EPA, 2013). Further, the available studies did not consistently adjust for SES, parental education, and quality of parental caregiving. A small number of recent studies add to the evidence showing consistent associations between Pb exposure and diagnosed ADHD. One recent epidemiologic study (Ji et al., 2018) addressed several of the uncertainties identified in the literature included in the 2013 Pb ISA. Specifically, this study employed a prospective design, and adjusted for parental education and SES (although not quality of parental caregiving). Notably, ADHD was ascertained using ICD codes recorded on electronic records and ADHD type was not distinguished in this study.

3.5.2.6 Relevant Issues for Interpreting the Evidence Base

3.5.2.6.1 Lifestages

Environmental exposures during critical lifestages spanning from childhood into adolescence can affect key physiological systems that orchestrate brain development and plasticity (see Section 3.4.1.6.4 of U.S. EPA (2013)). Epidemiologic studies examined in the 2013 Pb ISA consistently showed that BLLs measured during various lifestages and time periods, including the prenatal period, early childhood, later childhood, and averaged over multiple years, are associated with attention decrements, impulsivity, and hyperactivity in children. These observations of Pb-associated elevated risk are well supported by findings in animals that prenatal and early postnatal or lifetime Pb exposures alter brain development via changes in synaptic architecture (Section 4.3.10.4 of U.S. EPA (2013)) and neuronal outgrowth (Section 4.3.10.10 of U.S. EPA (2013)), potentially leading to increases in impulsivity (Section 4.3.3.1 of U.S. EPA (2013)). Potential mechanisms of lifestage-specific sensitivities are further reviewed in Section 3.3. Recent studies support this conclusion from the 2013 Pb ISA.

A limited number of epidemiologic studies employed methods designed to further elucidate critical lifestages for Pb exposure but did not change the overall conclusion in the 2013 Pb ISA. Horton et al. (2018) used distributed lag models to identify specific time windows of increased Pb-associated externalizing behaviors. This study found that tooth Pb concentration corresponding with the 8 to 11 months postnatal period was associated with parent-rated behavioral symptoms overall (0.22 units [95% CI: 0.06, 0.38] per natural log unit increase in dentine Pb concentration), and hyperactivity (β = 0.19 units [95% CI = 0.02, 0.37] per natural log unit increase in dentine Pb concentration) after adjustment for

gestational age and maternal education. In another study, Rasnick et al. (2021) also aimed to distinguish critical windows of exposure to Pb, focusing on Pb concentration in air by controlling for concurrent BLL (age 12 years). Air Pb exposure was estimated using validated land use regression models and behavioral outcomes, including attention and hyperactivity, were assessed using BASC-2 administered at age 12. Distributed lag models to predict outcome responses based on current and past (i.e., lagged) predicted air Pb exposures did not identify associations during any of the lifestages examined.

3.5.2.6.2 Public Health Significance

The strongest evidence indicating a causal relationship between Pb exposure and attention, impulsivity, and hyperactivity assessed in the 2013 Pb ISA was derived from studies that relied on neuropsychological testing (U.S. EPA, 2013). Domain-specific neuropsychological assessments of attention, impulsivity, and hyperactivity have strong psychometric properties and rigorous validation; however, deficits on these neuropsychological tests do not directly correspond to a diagnosis of ADHD nor do they necessarily predict long-term consequences that might be associated with some types of ADHD. Studies that evaluated the association of Pb exposure with behavioral symptoms of ADHD assessed using teacher and parent ratings contributed to the overall evidence in the 2013 Pb ISA, but the limitations of these studies were noted. The bulk of the recent evidence comprises prospective studies of parent or teacher ratings of ADHD behavioral symptoms. The recent studies addressed some uncertainties in the previous ISA related to the temporal association of the exposure with the outcome and controlled for potential confounding. Studies of diagnosed ADHD are also subject to limitations. Although diagnostic guidelines for ADHD exist, the exact criteria or specific behaviors required for diagnosis may vary across studies. The recent study by Ji et al. (2018) addressed several of the uncertainties regarding the association of Pb exposure with clinical ADHD. This study was prospective in design, assessed early childhood BLL (<4 years old), and adjusted for parental education and SES (although not quality of parental caregiving); however, ADHD was ascertained using ICD codes recorded on electronic records and ADHD type was not distinguished.

3.5.2.6.3 Potentially At-Risk Populations

Sex

Studies examining sex as an at-risk factor for attention, hyperactivity and impulsivity outcomes were not assessed in the 2013 Pb ISA. A recent study by Nigg et al. (2016) found an interaction between BLL and sex in predicting parent and teacher-rated hyperactivity and impulsivity but not attention. The association was larger in boys in this study.

Maternal Smoking

Maternal smoking during pregnancy was examined in a study of children's concurrent BLLs and the prevalence of ADHD among children aged 8–15 years. An interaction was observed between children's current BLLs and prenatal tobacco smoke exposure; those children with high Pb levels and prenatal tobacco smoke exposure had the highest odds of ADHD (Froehlich et al., 2009). Recent studies have not examined maternal smoking as an at-risk factor.

Co-exposure to Other Metals or Chemicals

Studies examining other metals as an at-risk factor for attention, hyperactivity and impulsivity outcomes were not assessed in the 2013 Pb ISA. Some recent studies adjusted for other metals or chemicals (e.g., PCBs) (Ethier et al., 2015; Tatsuta et al., 2014), and effect modifications were observed in other studies (Yorifuji et al., 2011). For example, Yorifuji et al. (2011) found a less-than-additive interaction between cord Pb and Hg concentrations. Specifically, a lower digit span forward score on the WISC-R ($\beta = -1.70$ [95% CI: −3.12, −0.28] per log-transformed BLL) at age 7 and a lower digit span backward score on the WISC-R ($\beta = -2.73$ [95% CI: −4.32, −1.14] per log-transformed BLL) at age 14 were observed among children with the lowest Hg exposure.

Gene-Environment Interactions

Studies examining gene-environment interactions in the context of attention, hyperactivity and impulsivity outcomes were not assessed in the 2013 Pb ISA. Interactions between child BLL and genes that regulate neurodevelopmental processes were observed in studies of attention (Choi et al., 2020; Rooney et al., 2018). Genes that were implicated included variants of GRIN2A and GRIN2B and genotypes involved in the regulation of noradrenergic pathways. In addition, Nigg et al. (2016) found an interaction between the HFE C282Y genotype and BLL in predicting parent and teacher reports of hyperactivity-impulsivity but not inattention. Specifically, the association between z scores of BLL and hyperactivity was significantly stronger among those with the HFE C282Y mutation ($\beta = 0.74$ [95% CI: 0.52, 0.96]) compared with those with the wild type genotype ($\beta = 0.28$ [95% CI: 0.15, 0.41]).

3.5.2.7 Summary and Causality Determination: Attention, Impulsivity, and Hyperactivity

Attention, hyperactivity, and impulsivity are included within the ADHD domain of externalizing behaviors. Although not studied as extensively as cognitive function, several epidemiologic studies have examined the relationship between Pb exposure in children and attention, impulsivity, and hyperactivity in children and young adults.

The majority of these studies examined attention, and some also examined impulsivity or hyperactivity. Thus, the focus of the evaluation is on the evidence related to attention, but the evaluation also draws on coherence with evidence for impulsivity and hyperactivity, including evidence in animals and that suggesting potential modes of action. The collective epidemiologic evidence base for attention in children comprises many prospective and cross-sectional studies, which were also reviewed in the 2006 Pb AQCD and the 2013 Pb ISA and some recently published studies. Most of these studies reported associations between childhood blood Pb or tooth Pb levels, that reflected early postnatal Pb exposure, and attention decrements, impulsivity, and hyperactivity (Table 3-7E). A small number of recent longitudinal studies contributed to this evidence. Not all results were uniform with regard to precision and the magnitude of the association, but results mostly showed a pattern of attention decrements, impulsivity, and hyperactivity with higher blood or tooth Pb levels.

Whether prospective, cross-sectional, or longitudinal, most studies relied on population-based recruitment from prenatal clinics, hospitals at birth, or schools and reported moderate to high participation. Several of the studies reviewed in the previous ISA demonstrated increased loss-to-follow-up in certain groups (e.g., lower SES or HOME scores), which has the potential to introduce selection bias and reduce the generalizability of findings. A strong indication that participation in the study was biased to those with higher BLLs and greater deficits in attention, hyperactivity, or impulsivity was not observed. Recent studies incorporated adjustments for these and other covariates. Repeated testing in children was common but the consistent pattern of association observed across the ages, BLL, and behavioral outcomes examined increases confidence that the evidence is not unduly biased by the increased probability of finding associations by chance alone. Coherence with animal studies, which are less vulnerable to confounding, further supports the pattern of associations described in the preceding sections.

The strongest epidemiologic evidence indicating an association of Pb exposure with inattention and hyperactivity is described in the 2013 Pb ISA U.S. EPA (2013). Prospective studies showed strong support for an association between Pb exposure (range: 7–14 μg/dL) and decreased scores on neuropsychological tests and parent/teacher ratings of attention and hyperactivity. Cross-sectional studies from the 2013 Pb ISA generally corroborated these observations. Studies of impulsivity in children in the 2013 Pb ISA were limited by their quantity and lack of temporality but generally indicated associations of Pb exposure with worse scores on tests of response inhibition and on parent/teacher ratings of impulsivity in cross-sectional analyses. A small number of recent prospective studies with mean maternal and cord BLLs ≤5 μg/dL report associations with some measures of inattention (Ethier et al., 2015; Neugebauer et al., 2015). In addition, recent analyses of Inuit children add support for the relationship between child and cord BLL and impulsivity (Boucher et al., 2012a).

Most of the aforementioned studies of parent and teacher ratings of ADHD-related behaviors in the 2013 Pb ISA were largely cross-sectional in design. The evidence from prospective studies was limited to Chandramouli et al. (2009), which found associations between BLLs and hyperactivity as rated

by teachers and parents. The available studies considered SES or parental education but generally not both as potential confounders, and none of the studies considered parental caregiving quality. 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 concentration, childhood (<6 μg/dL), and maternal or cord (2–5 μg/dL) BLLs. Studies of caregiver-reported ADHD symptoms generally reported associations with composite indices, and there is some evidence that the associations with impulsivity and hyperactivity symptoms are stronger than the associations with inattention symptoms. The majority of the recent studies were prospective and generally reported moderate or high participation rates. Some studies addressed the validity of caregiver assessed outcomes by evaluating internal consistency (Rasnick et al., 2021; Desrochers-Couture et al., 2019), and Nigg et al. (2016) addressed reliability/validity concerns by using structural equation modeling to create latent factors for inattention and hyperactivity-impulsivity for each informant. Confounder adjustment has become more consistent across recent studies. In addition to the studies relying on parent and teacher behavior ratings, a small number of recent studies add to the evidence showing consistent associations between Pb exposure and diagnosed ADHD. One recent epidemiologic study (Ji et al., 2018) addressed several of the uncertainties identified in the literature included in the 2013 Pb ISA. Specifically, this study employed a prospective design, assessed early childhood BLL, and adjusted for parental education and SES (although not quality of parental caregiving). Notably, in this study, ADHD was ascertained using ICD codes recorded on electronic records and ADHD type was not distinguished. Uncertainty remains regarding the patterns of exposure associated with BLLs in older children because they may be influenced by higher past exposures.

The findings from epidemiologic studies are generally coherent with findings of studies in experimental animals. Available evidence in animals supports the effect of developmental Pb exposure in rodents and nonhuman primates on behavioral measures consistent with increased impulsivity, primarily indicated by impaired response inhibition. Measures of impulsivity are additionally sensitive to disruption by impairments in learning and executive function, which is consistent with several of the studies summarized in Sections 3.5.1.3.2 and 3.5.1.4.2. While no recent animal toxicological studies of attention are available, evidence from the 2013 Pb ISA demonstrates Pb-induced decreases in attention in rodents and monkeys, although results are not entirely consistent across studies. Pb has been observed to have mixed effects on locomotor activity in rodents, but several studies have demonstrated Pb-induced hyperactivity in rodents during the postnatal phase, which provides some support for the epidemiologic findings.

In summary, the total body of evidence evaluated in this and previous assessments is sufficient to conclude that there is a *causal relationship* between Pb exposure and attention, impulsivity, and hyperactivity. This conclusion reflects the consistency of the results from epidemiologic studies of externalizing behaviors in children and young adults, incorporating various objective neuropsychological tests and reporting from teachers and parents, which are generally reliable and valid instruments that predict functionally important outcomes. The conclusion also incorporates the

coherence of evidence across epidemiologic and toxicological studies of externalizing behaviors and biological plausibility provided by studies that outline pathways by which Pb may interfere with the proper development, connectivity, and function of systems underlying externalizing behaviors.

Table 3-3 Summary of evidence indicating a causal relationship of Pb exposure with attention, impulsivity, and hyperactivity

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent associations from multiple prospective epidemiologic studies with relevant BLLs	Evidence from prospective studies for attention decrements and hyperactivity in association with prenatal (maternal or cord), early childhood, and lifetime blood Pb and tooth Pb levels in children ages 7–17 yr and young adults 19–20 yr in the United States, United Kingdom Australia, New Zealand.	Burns et al. (1999) Ris et al. (2004) Fergusson et al. (1993) Bellinger et al. (1994a) Chandramouli et al. (2009) Leviton et al. (1993) Section 4.3.3.1, U.S. EPA (2013) Neugebauer et al. (2015) Ethier et al. (2015)	Blood Pb: Means 2 to 8.3 µg/dL (prenatal maternal or cord), 8.3 µg/dL (age 6 yr), 13.4 µg/dL (age 3–60 mo), 14 µg/dL (lifetime avg to age 11–13 yr) Group with age 30 mo >10 µg/dL Tooth Pb (ages 6–8 yr): Means: 3.3, 6.2 µg/g
	Evidence from prospective studies of parent or teacher-rated ADHD composite symptom indices derived from widely used, structured instruments.	Choi et al. (2016) Neugebauer et al. (2015) Liu et al. (2014b)	Childhood BLL <6 µg/dL; maternal and cord BLL 2–5 µg/dL.
	Ratings for impulsivity and hyperactivity more strongly associated with Pb exposure	Sioen et al. (2013) Fruh et al. (2019) Horton et al. (2018) Neugebauer et al. (2015) Winter and Sampson (2017) Desrochers-Couture et al. (2019) Boucher et al. (2012b) Nigg et al. (2016)	Childhood BLL <6 µg/dL; maternal and cord BLL 2–5 µg/dL.
	Prospective analysis found associations with impulsivity in Inuit children	Boucher et al. (2012a)	Mean 4.7 (cord), 2.7 (concurrent, average age 11.3 yr)

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
	Prospective analysis find association with attention decrements in children with CKD	Ruebner et al. (2019)	Child blood Pb ~2 yr before outcome assessment at age 4–18 yr
Limited evidence evaluates the potential modification of Pb associations to other metals or genes	Co-exposure to Hg modified the risk of Pb-associated effects on attention (less than additive effect observed)	Yorifuji et al. (2011)	
	Interactions between BLL and genes that regulate neurodevelopmental processes observed.	Nigg et al. (2016) Rooney et al. (2018) Choi et al. (2020)	
	Association observed in prospective study of clinical ADHD diagnosed before age 6, with adjustment for parental education and SES.	Ji et al. (2018)	Mean: 2.2 µg/dL (<4 yr of age)
	No association found with ratings of attention problems in children ages 4–5 yr in whom ratings may be measured less reliably.	Wasserman et al. (2001)	Blood Pb: Mean 7.2 µg/dL for lifetime (to age 4–5 yr) avg
Supporting evidence from cross-sectional studies	Associations of concurrent BLL with attention decrements, impulsivity, and hyperactivity in children ages 5–7.5 yr. Some populations had high prenatal drug or alcohol exposure.	Section 4.3.3.1, U.S. EPA (2013)	Concurrent (ages 5–7.5 yr) blood Pb: Means 5.0–5.4 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Epidemiologic studies help rule out chance, bias, and confounding with reasonable confidence	Most prospective and some cross-sectional studies found associations with adjustment for SES, maternal education, and parental caregiving quality (HOME score). Some also considered parental IQ, smoking, birth outcomes. A few considered substance abuse, nutritional factors, and family history of psychiatric disorders. Studies had population-based recruitment with moderate to high follow-up participation not conditional on blood or tooth Pb level.	Section 4.3.3.1, U.S. EPA (2013) **HOME score**: Liu et al. (2014b) Fruh et al. (2019) **Family history of psychiatric disorders**: Choi et al. (2016) **SES and parental education**: Horton et al. (2018) Ruebner et al. (2019) Winter and Sampson (2017) Boucher et al. (2012b) Desrochers-Couture et al. (2019)	
Consistent evidence in animals with relevant exposures	Several studies report increased open-field activity in rodents following developmental Pb exposure, consistent with hyperactivity.	Rodrigues et al. (1996) Moreira et al. (2001) De Marco et al. (2005) Duan et al. (2017)	Blood Pb: 19–28 µg/dL in mice with lactational exposure (tested PND 15–19); 10–29 µg/dL in rats with lactational exposure (tested PND 14–23)
Evidence from lifetime Pb exposure in nonhuman primates suggests that Pb produces attention decrements, which supports the findings in humans	Lifetime Pb exposure in nonhuman primates was reported to increase distractibility in a spatial discrimination task.	Gilbert and Rice (1987)	Blood Pb: 15–25 µg/dL
	Evidence from lifetime Pb exposure in nonhuman primates suggests that Pb increased perseveration and errors of commission in a spatial discrimination reversal task	Rice (1990) Rice and Gilbert (1990b) Gilbert and Rice (1987)	Blood Pb; 15–36 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Evidence describes biologically plausible pathways	Both in vitro and in vivo evidence suggests that Pb exposure may influence brain development, neurotransmission, connectivity, neuronal integrity, all of which may underlie the observed alterations in externalizing behaviors.	Section 3.3	

ADHD = attention deficit/hyperactivity disorder; avg = average; BLL = blood lead level; CKD = chronic kidney disease; Hg = mercury; HOME = Health Outcomes and Measures of the Environment; mo = month(s); Pb = lead; PND = postnatal day; SES = socioeconomic status; yr = year(s).
[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.

3.5.3 Externalizing Behaviors: Conduct Disorders, Aggression, and Criminal Behavior in Children, Adolescents, and Young Adults

There are two domains of conduct disorders that are considered in the ISA: undersocialized aggressive conduct disorder, and socialized aggressive conduct disorder (Whitcomb and Merrell, 2012). As discussed in the 2013 Pb ISA (U.S. EPA, 2013), these domains are combined in this assessment because they cannot be disentangled based on the available epidemiologic literature. This section also considers evidence for criminal offenses, which are associated with conduct disorders (U.S. EPA, 2013). Although not described explicitly as a part of either domain of conduct disorders, evidence for criminal offenses is reviewed with conduct disorders because conduct disorders can be predictors of subsequent delinquency and criminality (Soderstrom et al., 2004; Babinski et al., 1999; Pajer, 1998).

The evidence reviewed in the 2013 Pb ISA is sufficient to conclude that a "causal relationship is likely to exist" between Pb exposure and conduct disorders in children and young adults (U.S. EPA, 2013). Prospective studies consistently indicated that earlier childhood (e.g., age 30 months 6 years) or lifetime average (to age 11–13 years) BLLs or tooth Pb levels (shed between ages 6–8 years and typically measured in dentin, which reflects prenatal and/or child Pb exposure depending on the tooth layer analyzed, see Section 2.3.4.1.) were associated with criminal offenses in young adults aged 19–24 years, and with higher parent and teacher ratings of behaviors related to conduct disorders in children ages 7–17 years (see Table 4-12 of (U.S. EPA, 2013) and (U.S. EPA, 2006)). Pb-associated increases in 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. Supporting evidence was provided by cross-sectional studies of children participating in NHANES, e.g., (Braun et al., 2008), and a meta-analysis of prospective and cross-sectional studies (Marcus et al., 2010). In addition, there was coherence across related measures of conduct problems in epidemiologic studies. Evidence for Pb-induced aggression in animals was mixed, however, with increases in aggression found in some studies of adult animals with gestational plus lifetime Pb exposure but not juvenile animals. The strongest evidence for the 2013 causality conclusion was provided by prospective epidemiologic studies, with support from cross-sectional studies of criminal offenses and ratings of behaviors related to conduct disorders. Associations with lower BLLs that were not influenced by higher earlier Pb exposures as in older children and adults were not well characterized, however.

Studies published since 2013 from both cohort and cross-sectional studies add to this evidence base, which continues to support a "likely to be causal" relationship, as described in Table 3-4 and below. The central tendency Pb levels, study-specific details, and selected effect estimates are highlighted in Table 3-9E.

3.5.3.1 Epidemiologic Studies of Conduct Disorders, Aggression, and Criminal Behavior in Children and Adolescents

The 2013 Pb ISA describes cohort and cross-sectional studies demonstrating associations of Pb exposure with behaviors related to conduct disorders, including criminal offenses (U.S. EPA, 2013). Collectively, the evidence from prospective cohort studies indicated associations of aggressive, antisocial, delinquent, and criminal behavior with biomarkers of Pb exposure. Cross-sectional studies also provided evidence on these associations, though there is more uncertainty in data from this study design due to limitations in assessing temporality.

Recent studies have evaluated associations between Pb and conduct disorders, aggressive behavior, and other related measures of externalizing behavior. Most of these studies were prospective cohort studies (Tlotleng et al., 2022; Desrochers-Couture et al., 2019; Reuben et al., 2019; Beckwith et al., 2018; Nkomo et al., 2018; Nkomo et al., 2017; Liu et al., 2014b; Sioen et al., 2013; Boucher et al., 2012b; Tatsuta et al., 2012). Several utilized self-report tools (e.g., Youth Self-Report [YSR], Buss-Perry Aggression Questionnaire [BPAQ], Psychopathic Personality Inventory [PPI], Antisocial Behavior Interview) to assess aggression, violence, or other socio-behavioral problems among adolescents and young adults aged 14–24 years. These studies reported central tendency BLLs at ages 6.5–13 years ranging from 2.3 to 8 μg/dL or mean bone Pb of 8.7 μg/dL (Tlotleng et al., 2022; Desrochers-Couture et al., 2019; Beckwith et al., 2018; Nkomo et al., 2018; Nkomo et al., 2017). In analyses adjusted for most key confounders, associations were observed for: physical violence (β: 0.05; 95% CI: 0.04, 0.05) (Nkomo et al., 2017); direct aggression (β [95% CI] comparing those with BLLs ≥10 μg/dL to those with BLLs <5 μg/dL: 0.43 [0.08, 0.78]) (Nkomo et al., 2018); anger aggression (β = 0.25 [95% CI: 0.04, 0.37]) (Tlotleng et al., 2022); and PPI (overall β = 0.22 [95% CI: 0.06, 0.38]; female β = 0.16 [95% CI: −0.05, 0.37]; male β = 0.22 [95% CI: −0.02, 0.47]) (Beckwith et al., 2018) (Table 3-9E). Although the PPI serves as a measure of psychopathic personality traits, psychopathy more generally includes behavioral factors such as aggression and criminal conduct, in addition to personality traits. As discussed in the 2013 Pb ISA (U.S. EPA, 2013), an analysis of this same cohort reported associations between BLLs and criminal and violent criminal arrests at ages 19–24 (Wright et al., 2008). (Beckwith et al., 2018) also noted that BLLs were associated with volumetric reductions in gray matter in the frontal lobe and white matter in several brain regions. Considered together, these studies provide support for an association between childhood Pb exposure and psychopathy in adolescents and young adults that may stem from changes in brain morphology. In addition to these studies examining total effects, one prospective study of Pb and self-reported behavioral outcomes conducted mediation analyses and reported an association between Pb and adolescent externalizing behavior mediated through child externalizing behavior (β: 0.18, 95% CI: 0, 0.36) (Desrochers-Couture et al., 2019). There was also evidence of a small but imprecise direct effect, though there was likely limited power to detect a direct effect given the small sample size and correlation between child and adolescent externalizing behavior. The observed association between BLLs and adolescent externalizing behavior is at least partially mediated through child externalizing behavior in this study population.

Other prospective cohort studies used observer assessments (e.g., parent or teacher ratings) to assess conduct disorders, aggression, and related behaviors among children with central tendency blood or cord blood Pb ranging from 0.4 to 14.3 μg/dL (Fruh et al., 2019; Ruebner et al., 2019; Liu et al., 2014b; Sioen et al., 2013; Boucher et al., 2012b; Tatsuta et al., 2012). Some of these studies focused on the prenatal period as a potentially sensitive period of exposure: three of these studies evaluated Pb levels in cord blood (Sioen et al., 2013; Boucher et al., 2012b; Tatsuta et al., 2012) and one evaluated second trimester maternal BLLs (Fruh et al., 2019). All but two (Ruebner et al., 2019; Boucher et al., 2012b) of these studies evaluated the outcome in children with mean age <8 years. These analyses reported generally null associations (Table 3-9E). It is possible that behavioral ratings are less reliable at younger ages or that these outcomes manifest at later ages (Blair, 2001).

There were also some cross-sectional evaluations of blood Pb and behavioral problems (e.g., aggression, oppositional, externalizing, antisocial) covering children with central tendency BLLs ranging from 0.7 to 11.08 μg/dL (Liu et al., 2022b; Desrochers-Couture et al., 2019; Reuben et al., 2019; Barg et al., 2018; Rodrigues et al., 2018; Boucher et al., 2012b; Naicker et al., 2012; Nigg et al., 2010). These analyses utilized a mix of self-report and observer assessment tools to evaluate the outcomes of interest in children aged 6–13 years. Positive associations were reported in most studies, including for child externalizing behavior (β: 0.23; 95% CI: 0.08, 0.38) and child oppositional defiant and conduct disorder (OD/CD) (β: 0.37; 95% CI: 0.06, 0.69) (Desrochers-Couture et al., 2019); "attacking people" (boys only, see table for unstandardized estimate; (Naicker et al., 2012)); teacher-reported aggressive and rule-breaking behavior (referred to in the paper as "externalizing behavior") (log-transformed concurrent Pb β: 0.14; 95% CI: 0.01, 0.26) (Boucher et al., 2012b); parent-reported externalizing composite (β for SD increase in symptoms scores per SD increase in log10 transformed BLL = 0.21 [95% CI: 0.05, 0.37]) and oppositional behavior (β for SD increase in symptoms scores per SD increase in log10 transformed BLL = 0.09 [95% CI: −0.09, 0.27]) (Nigg et al., 2010); antisocial behavior (β = 0.02 [95% CI: 0.00, 0.04]) (Reuben et al., 2019); and antisocial/aggressive behavior factor (Parent-reported β = 0.20 [95% CI: 0.05, 0.34]; Child-reported β = 0.20 [95% CI: 0.04, 0.35]) (Liu et al., 2022b). Both of the null studies evaluated the outcome in groups of children that included individuals aged <8 years (Barg et al., 2018; Rodrigues et al., 2018); it is possible that behavioral ratings are less reliable at younger ages or that these outcomes manifest at later ages (Blair, 2001). More research is needed to disentangle these issues. Overall, cross-sectional studies were less of a consideration in drawing conclusions on the effects of Pb, given their inherent limitations with regard to temporality (given exposure assessment using BLLs).

Among studies published since the 2013 Pb ISA, there were also evaluations of the association between Pb and suspensions, arrests, juvenile delinquency, and crime (including violent crime) (Wright et al., 2021; Emer et al., 2020; Beckley et al., 2018; Boutwell et al., 2017; Amato et al., 2013). The strongest evidence comes from three prospective studies. Using data from the CLS on multiple measures of BLLs (from prenatal to age 6 years; mean = 14.4 μg/dL) and arrests from ages 18–33, (Wright et al., 2021) observed numerous positive associations, including for adult arrests (RR = 1.01 [95% CI: 1.00, 1.03]), lifetime arrests (RR = 1.02 [95% CI: 1.00, 1.03]), arrests for violent crime (RR = 1.02 [95% CI: 0.99,

1.04]), and arrests for drug crime (RR = 1.03 [95% CI: 1.01, 1.06]) (Wright et al., 2021). In a cohort based in Milwaukee, Wisconsin, (Emer et al., 2020) reported that elevated mean and peak BLL prior to age 6 was associated with increased risk of firearm violence perpetration (RR for mean BLL = 1.03 [95% CI: 1.02, 1.04]; RR for peak BLL = 1.02 [95% CI: 1.01, 1.02] (Emer et al., 2020). Additionally, (Amato et al., 2013) reported that Pb exposure during the first 3 years of life (based on a BLL ≥10 μg/dL and <20 μg/dL) increased the odds of school suspensions in fourth grade, compared with those without Pb exposure during the first three years of life (based on a BLL <5 μg/dL) (OR: 2.66; 95% CI: 2.12, 3.32) (Amato et al., 2013).

Supporting evidence comes from a prospective study with limitations that affect interpretation and confidence as well as one ecologic study. Criminal offending, comprising both criminal conviction and self-report offending, was evaluated in a prospective cohort study based in Dunedin, New Zealand in which the mean 11-year-old BLL was 11.01 μg/dL (Beckley et al., 2018). In sex-adjusted analyses of convictions, the authors reported that increased childhood BLL was associated with increased odds of at least one nonviolent criminal conviction for ages 15–38 years (OR: 1.05; 95% CI: 1.00, 1.10). However, sex-adjusted analyses of other criminal conviction endpoints (e.g., any criminal conviction, recidivistic conviction, one-time conviction, violent offense) were inconclusive (see Table 3-9E). While this study had extensive follow-up (27 years) and both subjective and objective measures of the outcome, the limited adjustment for potential confounders is a concern. Analyses were adjusted for sex, age was controlled in the study design, and SES was evaluated as a potential confounder but determined not to be associated with BLL; however, important covariates (i.e., parental IQ or education and HOME score) were not considered, leaving open the possibility of residual confounding. In an ecologic study of 106 census tracts in St. Louis, Missouri, United States, (Boutwell et al., 2017) reported that a 1% increase in the proportion of elevated blood Pb tests (≥5 μg/dL) among children within a census tract was associated with increased RRs for firearm crimes (RR: 1.03; 95% CI: 1.03, 1.04), assault crimes (RR: 1.03; 95% CI: 1.02, 1.03), robbery crimes (RR: 1.03; 95% CI: 1.02, 1.04), and homicides (RR: 1.03; 95% CI: 1.01, 1.04). The association with rape was inconclusive (RR: 1.01; 95% CI: 0.99, 1.03). While ecologic studies can be useful for hypothesis generation and understanding patterns among groups, the lack of control for individual-level confounding factors in such studies leaves concern for risk of bias.

3.5.3.1.1 Summary

Overall, recently published epidemiologic studies support the findings from the previous ISA. The strongest evidence published since 2013 comes from prospective cohort studies of 1) self-reported conduct and aggression-related outcomes (Tlotleng et al., 2022; Desrochers-Couture et al., 2019; Beckwith et al., 2018; Nkomo et al., 2018; Nkomo et al., 2017), and 2) external measures of delinquency (e.g., criminal arrests, school suspensions) (Wright et al., 2021; Amato et al., 2013). These studies evaluated outcomes among individuals aged 7–33 years in relation to earlier (or cumulative) Pb levels. BLLs were <10 μg/dL in the studies of self-reported conduct and aggression-related outcomes and higher

in studies of external measures of delinquency (e.g., (Wright et al., 2021); mean 14.4 µg/dL). These studies controlled for most relevant confounders, and the prospective study design inherently ensured appropriate temporality between the exposure and outcome. Additional supporting evidence comes from cross-sectional studies using either self-report or observer-reported outcome measures among individuals aged 6–13 years with concurrent BLLs ranging from 0.7–11.08 µg/dL (Liu et al., 2022b; Desrochers-Couture et al., 2019; Reuben et al., 2019; Boucher et al., 2012b; Naicker et al., 2012; Nigg et al., 2010).

3.5.3.2 Toxicological Studies of Aggression

There are no recent PECOS-relevant studies examining the relationship between Pb exposure and aggression. Available toxicological studies of aggression were described in the 2006 Pb AQCD (U.S. EPA, 2006) and 2013 Pb ISA (U.S. EPA, 2013). The evidence supported effects of Pb exposure on changes in social behavior of rodents and nonhuman primates. In animals, the social behavior most comparable to conduct disorders in children is aggression; however, the effects of Pb on aggression in animals were inconsistent. In animals, aggression was assessed as threats, attacks, bites, chases, and offensive posture in encounters with other animals. Pb exposure was found to have no effect on aggression in some studies as well as to decrease and increase aggression in others. Pb exposure generally was not found to affect aggression in juvenile animals; however, increased aggression was found in adult animals with high concentrations of gestational plus postnatal dietary Pb exposure. Recent PECOS-relevant studies have not further examined the effects of Pb on aggression. Additional reported effects on social behaviors described in the 2006 Pb AQCD (U.S. EPA, 2006) and 2013 Pb ISA (U.S. EPA, 2013) included Pb-induced increases in social and sexual investigation, as indicated by sniffing, grooming, following, mounting, and lordosis behavior. Despite the limited new evidence, observations for Pb-induced changes in aggression in animals provide support for associations of altered aggression outcomes in children. Furthermore, many of the more general overt nervous system toxicology studies discussed in Sections 3.4.2 and 3.3 assessed a variety of endpoints, including brain structural changes and neurotransmitter analysis, that can contribute to understandings of the mechanistic underpinning of observed behavioral changes providing additional biological plausibility.

3.5.3.3 Relevant Issues for Interpreting the Evidence Base

3.5.3.3.1 Concentration-Response Function

The evidence base for this outcome is more limited compared with that for cognitive deficits, and the shape of the C-R function cannot be determined from available studies. However, it is important to highlight that in studies reviewed for the 2013 Pb ISA, effects were observed at central tendency BLLs of 5–10 µg/dL (Nigg et al., 2008; Wright et al., 2008; Chiodo et al., 2007; Wasserman et al., 2001) and <5

µg/dL (Braun et al., 2008). Among studies published since 2013, effects on conduct disorder, aggression, and crime were observed at central tendency BLLs of 5–10 µg/dL (Tlotleng et al., 2022; Beckwith et al., 2018; Nkomo et al., 2018; Nkomo et al., 2017; Naicker et al., 2012) as well as at central tendency BLLs <5 µg/dL (Liu et al., 2022b; Desrochers-Couture et al., 2019; Boucher et al., 2012b; Nigg et al., 2010). However, it should be noted that there is less confidence in these studies of BLLs <5 µg/dL as they were all cross-sectional analyses (Liu et al., 2022b; Desrochers-Couture et al., 2019; Boucher et al., 2012b; Nigg et al., 2010). Further work is needed to better understand whether the potential effects of Pb on this outcome persist at BLLs <10 µg/dL.

3.5.3.3.2 Potentially At-Risk Populations

Sex

The 2013 Pb ISA identified one study that evaluated the role of sex as an at-risk factor. Wright et al. (2008) examined early life BLLs and criminal arrests in adulthood and reported that risks attributable to Pb exposure were greater among males than females (Wright et al., 2008).

Several new studies evaluated the role of sex as an at-risk factor through sex-stratified analyses of Pb exposure and conduct disorders. The results were generally inconclusive regarding sex as an at-risk factor. In a prospective study of blood Pb concentrations at 3–5 years and teacher-rated behavioral problems at age 6 years, sex-stratified results were similar to non-stratified results, with null associations for conduct disorder and aggression-related outcomes (Liu et al., 2014b). In a prospective study of Pb exposure and self-reported aggressive behavioral characteristics, associations for some outcomes (e.g., ”attacks people”) were observed in boys (but not observed or reported for girls); the authors suggested this may be due to lower BLLs in girls compared with boys (Naicker et al., 2012).

In a cross-sectional study of first grade children (mean 6.7 years) and teacher-rated behavioral problems, sex-stratified results were generally null and similar to the non-stratified results. However, some analyses indicated stronger associations among females (e.g., Behavioral Regulation Index (PR [95% CI]: girls = 1.03 [1.00, 1.05]; boys = 0.99 [0.97, 1.01]), though the sample size was limited (n = 83 for girls) (Barg et al., 2018). The authors suggested these results could be explained by teacher expectations and perceptions of girls compared with boys, with effects on girls being more noticeable due to gender norms and expectations rather than greater susceptibility to Pb exposure (Barg et al., 2018).

Finally, in a study of BLLs measured at age 6.5 years and PPI between ages 19 and 24, sex-stratified models indicated stronger associations in males, though associations were also present in females (Beckwith et al., 2018). Sex-stratified analyses indicated that Pb-associated gray matter volume loss was only present in females, while Pb-related white matter loss was more widespread in males, including an overlap in frontal white matter loss associated with both PPI scores and BLLs (Beckwith et al., 2018).

Pre-existing Conditions

One study evaluated the association between Pb (median BLL 1.2 µg/dL) and aggression/conduct problems among children with CKD, a population at elevated risk of neurocognitive dysfunction (Gerson et al., 2006; Gipson et al., 2004). No associations were observed (Ruebner et al., 2019).

3.5.3.3.3 Confounding

The 2013 Pb ISA described multiple factors that influence conduct disorder and related outcomes including sex, race, SES, parental education, parental IQ, and quality of the caregiving environment (i.e., HOME score) (U.S. EPA, 2013). These risk factors are often correlated with blood, tooth, and bone Pb levels, and thus, are considered as potential confounding factors in epidemiologic analyses. As noted in the 2013 Pb ISA, no single method to control for potential confounding is without limitation, and there is potential for residual confounding by unmeasured factors. However, consistency of results across studies utilizing different approaches to control for confounding can increase confidence across the body of evidence.

Recent studies demonstrate associations between Pb exposure and conduct disorder after controlling for different combinations of the aforementioned key covariates as well as additional relevant covariates. However, it should be noted that in the current evidence base, the vast majority of studies that identified associations did not specifically adjust for HOME score (Liu et al., 2022b; Tlotleng et al., 2022; Desrochers-Couture et al., 2019; Reuben et al., 2019; Barg et al., 2018; Beckley et al., 2018; Nkomo et al., 2018; Rodrigues et al., 2018; AbuShady et al., 2017; Boutwell et al., 2017; Nkomo et al., 2017; Liu et al., 2014b; Amato et al., 2013; Sioen et al., 2013; Boucher et al., 2012b; Naicker et al., 2012; Tatsuta et al., 2012; Nigg et al., 2010). Yet, most of these studies did adjust for other potentially related covariates such as social adversity, house crowding, family violence, and SES, which mitigates some of the concern about residual confounding due to exclusion of HOME score. Additionally, as highlighted in the previous ISA, a meta-analysis by Marcus et al. indicated that the lack of adjustment for variables such as SES or HOME score does not warrant limiting inferences from a particular study (U.S. EPA, 2013; Marcus et al., 2010).

When there is uncertainty in epidemiologic evidence due to potential confounding, it is often helpful to consider associated toxicological data. Aggressive behavior in rodents is mediated by several brain regions, including the hypothalamus, prefrontal cortex, dorsal raphe nucleus, nucleus accumbens, and olfactory system (Takahashi and Miczek, 2014) along with other neurochemical systems including neurotransmitters, neuropeptides, and neuromodulators (i.e., serotonin, dopamine, vasopressin, oxytocin, testosterone, estrogen, corticotrophin releasing factor, opioids, neuronal nitric oxidate synthase, and monoamine oxidase A) (Takahashi and Miczek, 2014). Pb-induced changes on many of these neurochemical endpoints has been reported and are described in Section 3.3, which lends some limited yet relevant biological plausibility from the animal evidence without influence of potential confounding

factors. While no new studies on Pb-induced aggressive behavior in mammals were identified with BLLs of relevance to this ISA, the previous experimental animal studies support the evidence described in the 2013 Pb ISA.

3.5.3.3.4 Lifestages

Environmental exposures during critical lifestages spanning from childhood into adolescence can affect key physiological systems that orchestrate brain development and plasticity (see Section 3.5.1.6.4). Epidemiologic evidence assessed in the 2013 Pb ISA indicated associations of earlier childhood blood or tooth Pb levels with behaviors related to conduct disorders in adolescents or adults (Fergusson et al., 2008; Wright et al., 2008); however, these epidemiologic studies did not examine adult BLLs, thus the relative influence of adult Pb exposure cannot be ascertained.

Recent studies observed associations of Pb exposure assessed via blood, cord blood, or bone between delivery and age 13 years with outcomes evaluated among children, adolescents, and young adults aged 7–33 years (Liu et al., 2022b; Tlotleng et al., 2022; Wright et al., 2021; Desrochers-Couture et al., 2019; Reuben et al., 2019; Beckwith et al., 2018; Nkomo et al., 2018; Nkomo et al., 2017; Amato et al., 2013; Naicker et al., 2012). Evidence published since 2013 is weaker for exposures that occur during the prenatal period (Fruh et al., 2019; Sioen et al., 2013; Tatsuta et al., 2012) and for most studies assessing outcomes prior to the age of 8 years (Fruh et al., 2019; Liu et al., 2014b; Sioen et al., 2013; Tatsuta et al., 2012). It is possible that outcome assessment tools that measure conduct disorder and related aggressive traits are less reliable in this age group, aggressive patterns have not yet stabilized, or the particular type of aggression associated with Pb exposure does not manifest until later years (Blair, 2001). Overall, Pb exposure during lifestages spanning childhood and into adolescence may confer risk for conduct disorders and related outcomes.

3.5.3.3.5 Public Health Significance

The global prevalence of conduct disorders in 2019 was estimated to be 40.1 million (95% CI: 29 million, 52 million), with the highest burden experienced by individuals 0–14 years of age (GBD 2019 Mental Disorders Collaborators, 2022). Early life conduct disorders and other "antisocial behaviors" are an important public health issue due to their persistence within an individual (Lynam et al., 2009), their costs (both social and economic) to society (Sumner et al., 2015; Mccollister et al., 2010), and their association with risk-taking behaviors, comorbid mental health conditions, and premature mortality (Reyes, 2015; Maughan et al., 2014; Glenn et al., 2013). For example, in one recent study based in New Zealand, children with conduct problems accounted for 9.0% of the population but 53.3% of convictions, 15.7% of emergency department visits, 20.5% of prescription fills, 13.1% of injury claims, and 24.7 % of welfare benefit months (Rivenbark et al., 2018).

3.5.3.4 Summary and Causality Determination: Conduct Disorders, Aggression, and Criminal Behavior

The 2013 Pb ISA concluded that the relationship between Pb exposure and conduct disorders was "likely to be causal" (U.S. EPA, 2013). This causality determination was primarily based on epidemiologic evidence. In particular, prospective cohort studies provided key evidence of the association between blood or tooth Pb levels and 1) parent or teacher ratings of delinquent, aggressive, and antisocial behavior (Chandramouli et al., 2009; Dietrich et al., 2001; Burns et al., 1999), and 2) criminal offenses (Fergusson et al., 2008; Wright et al., 2008) in children and adolescents across diverse locations. Supporting evidence was provided by cross-sectional studies of these outcomes (Braun et al., 2008; Chiodo et al., 2007).

Recent epidemiologic studies support the findings from the previous ISA. The strongest evidence published since the 2013 Pb ISA comes from prospective cohort studies of 1) self-reported conduct and aggression-related outcomes (Tlotleng et al., 2022; Desrochers-Couture et al., 2019; Beckwith et al., 2018; Nkomo et al., 2018; Nkomo et al., 2017), and 2) external measures of delinquency (e.g., criminal arrests, school suspensions) (Wright et al., 2021; Amato et al., 2013). BLLs were <10 μg/dL in studies of self-reported conduct and aggression-related outcomes and higher in studies of external measures of delinquency (e.g., (Wright et al., 2021); mean 14.4 μg/dL). These studies controlled for most relevant confounders, and the study design inherently ensured appropriate temporality between the exposure and outcome. Additional supporting evidence comes from cross-sectional studies using either self-report or observer-reported outcome measures among individuals aged 6–13 years with concurrent BLLs ranging from 0.7–11.08 μg/dL (Liu et al., 2022b; Desrochers-Couture et al., 2019; Reuben et al., 2019; Boucher et al., 2012b; Naicker et al., 2012; Nigg et al., 2010). Although the evidence generally suggests positive associations, null results may be explained by age at outcome or exposure. For example, many studies with null associations evaluated the outcome in groups of children that included individuals <8 years of age. It is possible that behavioral ratings are less reliable among this younger age group and/or abnormal behaviors do not manifest until later in childhood. It should also be noted that both studies focusing exclusively on newborn exposure (i.e., measurement of Pb in cord blood) were null, which potentially indicates that the prenatal period may not be a relevant sensitive period of exposure for this outcome. Studies that provide information on sensitive periods of exposure are limited.

Despite the growing epidemiologic evidence, the central uncertainty present in the 2013 Pb ISA database remains: there is limited and inconsistent evidence from animal toxicological studies. Available toxicological studies of aggression were described in the 2006 Pb AQCD (U.S. EPA, 2006) and 2013 Pb ISA (U.S. EPA, 2013). No new PECOS-relevant studies examining the relationship between Pb exposure and aggression have been reported. Despite the lack of new PECOS-relevant studies, Pb-induced changes on many neurochemical endpoints that contribute to aggressive behaviors have been reported and are described in Section 3.3, which lends biological plausibility from the animal evidence.

In summary, **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**. This causality determination is based on positive associations observed across various populations and based on multiple outcome assessment approaches at relevant Pb exposure levels across recently published prospective and cross-sectional epidemiologic studies. However, limitations remain in the animal toxicology database, given the inconsistent evidence described in the 2013 Pb ISA and the lack of relevant studies published since then. Yet, biological plausibility for these associations is supported by human evidence linking early life Pb exposure to later life volumetric reductions in gray matter in the frontal lobe and white matter in several brain regions (Beckwith et al., 2018) and experimental animal studies demonstrating Pb-induced changes on neurochemical endpoints relevant to this set of outcomes.

Table 3-4 Summary of evidence for a likely to be causal association between Pb exposure and conduct disorders, aggression, and criminal behavior in children and adolescents

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent results from epidemiologic studies with relevant blood or bone Pb levels, adequate control of relevant confounders	Evidence from prospective studies (demonstration of a temporal sequence) using self-report measures of aggressive or related externalizing behavior among individuals ages 14–24 yr in relation to earlier average blood Pb or bone Pb	Nkomo et al. (2017) Nkomo et al. (2018) Beckwith et al. (2018)	Blood Pb: age 6.5–13 mean = 5.6–8 µg/dL
		Tlotleng et al. (2022)	Bone Pb: age 9 mean = 8.7 µg/g
	Evidence from prospective studies (demonstration of a temporal sequence) of arrests (ages 18–33 yr) and suspensions (ages 9–10 yr) in relation to earlier average blood Pb	Wright et al. (2021) Amato et al. (2013)	Blood Pb: prenatal to age 6 mean = >10 µg/dL
	Supporting evidence from cross-sectional studies using both self-report and observer-reported measures of aggressive or externalizing behavior among individuals ages 6–13 yr	Desrochers-Couture et al. (2019) Naicker et al. (2012) Liu et al. (2022b) Boucher et al. (2012b) Nigg et al. (2010) (Reuben et al., 2019)	Blood Pb (concurrent): age 6–13 mean = 0.7–11.08 µg/dL
	Supporting evidence from a mediation analysis from a prospective cohort study indicating indirect association of BLL on adolescent externalizing behavior via child externalizing behavior	Desrochers-Couture et al. (2019)	Blood Pb: age 11 geometric mean = 2.3 µg/dL
	Supporting evidence from a prospective study demonstrating association between early life BLL and volumetric reductions in gray matter in the frontal lobe and white matter in several brain regions (mean age 26.8 yr)	Beckwith et al. (2018)	Blood Pb: age 6.5 mean = 8.0 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
	Most studies had sufficient adjustment for relevant confounders. While most did not adjust for HOME score specifically, they did consider other related variables, such as income, parental IQ, parental education, SES, and/or neighborhood safety Evidence strongest for outcomes assessed among children ≥9 yr		
Experimental animal studies with relevant exposures provide coherence and help rule out chance, bias, and confounding with reasonable confidence	Supporting evidence from animals exposed prenatally and postnatally	U.S. EPA (2013)	
Biological plausibility demonstrated	Changes in key brain regions and neurochemical systems implicated in behavioral changes.	U.S. EPA (2013)	

BLL = blood lead level; HOME = Health Outcomes and Measures of the Environment; IQ = intelligence quotient; SES = socioeconomic status; yr = year(s).
[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.

3.5.4 Internalizing Behaviors: Anxiety and Depression in Children

The evidence evaluated in the 2013 Pb ISA was sufficient to conclude that a "causal relationship was likely to exist" between Pb exposure and internalizing behaviors in children (U.S. EPA, 2013). Prospective studies in a few populations found associations of higher lifetime average blood Pb (mean: ~14 μg/dL) or childhood tooth Pb (shed between ages 6–8 years and generally reflecting prenatal or early child Pb exposure depending on the tooth layer analyzed, see Section 2.3.4.1) levels with higher parent and teacher ratings of internalizing behaviors such as withdrawn behavior and symptoms of depression and anxiety in children aged 8–13 years. There was no strong indication of biased reporting of behaviors for children with higher BLLs. The few cross-sectional associations in populations with mean concurrent BLLs of ~5 μg/dL were inconsistent. Pb-associated increases in internalizing behaviors were found with adjustment for maternal education and SES-related variables. Consideration for potential confounding by parental caregiving quality was inconsistent. Despite some uncertainty in the epidemiologic evidence, the biological plausibility for the effects of Pb on internalizing behaviors was provided by a small number of experimental animal study findings with dietary lactational Pb exposure, with some evidence at BLLs relevant to humans. Additional toxicological evidence demonstrating Pb-induced changes in the HPA axis and dopaminergic and gamma-aminobutyric acid (GABA) systems provided additional support. Overall, the strongest evidence was from prospective studies in a few populations of children and the coherence with evidence from a small number of experimental animal studies with relevant Pb exposures. Some uncertainty related to potential confounding by parental caregiving quality remained.

Measures of central tendency for Pb biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 3-10E (Epidemiologic Studies) and Table 3-7T (Toxicological Studies). An overview of the recent evidence is provided below. Overall, recent studies generally support findings from the 2013 Pb ISA.

3.5.4.1 Epidemiologic Studies of Internalizing Behaviors in Children

Several epidemiologic studies evaluated in the 2013 Pb ISA linked biomarkers of Pb exposure in children with internalizing behaviors characterized by directing feelings and emotions inward, i.e., withdrawn behavior, symptoms of depression, fearfulness, and anxiety. These studies did not clearly indicate that Pb exposure affected a particular domain of internalizing behaviors, i.e., withdrawn behavior, somatic symptoms, anxiety, and depression. However, a consistent pattern of associations with BLLs was observed across ages and across multiple internalizing behaviors. The strongest evidence was provided by prospective studies conducted across multiple locations, i.e., Boston, Port Pirie, Australia, and Yugoslavia (Wasserman et al., 2001; Burns et al., 1999; Wasserman et al., 1998; Bellinger et al., 1994b). Collectively, these studies found associations between internalizing behaviors in children (ages 3–13 years) and Pb levels based on cord blood, concurrent blood (age 3 years), lifetime average blood,

and teeth. Moderate to high follow-up rates in most studies increased confidence that selection bias did not explain the pattern of associations observed in the studies. Factors, which were well documented to be correlated with both Pb exposure and internalizing behaviors, including SES, parental caregiving quality (speculated to mediate the potential correlation between parental psychopathology and Pb exposure), and parental education, were considered as potential confounders across most studies. Although internalizing behaviors are likely to have a strong familial component, the available evidence did not support parental psychopathology as a direct confounder of the child Pb-internalizing behavior association. Studies that included both teacher and parent ratings were emphasized. The most common instrument used to assess internalizing behaviors was CBCL. Summary scores for internalizing behaviors, associated syndromes, and DSM-IV scales (e.g., anxiety and depression) can be derived using CBCL.

Recent studies also analyze the association of Pb exposure with internalizing behaviors assessed using CBCL. Using community survey data from the Project on Human Development in Chicago Neighborhoods (PHDCN), Winter and Sampson (2017) examined the relationship between average BLL in childhood (6 years old or younger) and anxiety or depression in adolescence (mean age 17 years old). These authors found a 0.09 SD (0.03, 0.16) increase in anxiety or depression score, after adjustment for covariates including caregiver education and SES. Participants were originally enrolled in the mid–1990s and a random sample of those continuing to participate in 1999 and 2002 was randomly selected for this study, with 67% of those selected agreeing to participate. Liu et al. (2014b) examined the association of early childhood blood Pb concentration (3, 4, or 5 years old) with both parent and teacher ratings of internalizing behavior at age 6 using CBCL and C-TRF, respectively. The outcomes were modeled as both continuous and dichotomous variables (i.e., clinically significant behavior problems with T-score ≥60) and adjusted for potential confounders including parent's educational level, father's occupation, and child IQ. The emotional reactivity syndrome component of the teacher-rated internalizing problem scale and the DSM-IV oriented anxiety were associated with child BLL when scores were modeled as continuous terms (β = 0.32 [95% CI: 0.06, 0.59] and β = 0.25 [95% CI: 0.02, 0.50], respectively). The ORs were 1.10 (95% CI: 1.03, 1.18) for the association of child BLL with clinically significant teacher-reported internalizing behavior and 1.10 (95% CI: 1.01, 1.19) for clinically significant anxiety problems. The participation rate was 81% in this study. The mean BLL of the children in this study was 6.4 µg/dL and the study had a high participation rate and included both teacher and parent ratings of internalizing behavior.

Joo et al. (2018) analyzed data from the MOCEH study, a Korean prospective birth cohort of mother-child pairs that were followed for 5 years. Maternal (early and late pregnancy), cord, and multiple postnatal blood Pb concentrations were measured, and internalizing behaviors were assessed by the parent using the Korean-CBCL at age five. The interaction between Pb exposure and child sex was evaluated with further model adjustment for covariates including maternal educational level, and SES. Late pregnancy and cord BLLs were associated with increasing internalizing behavior ratings in boys (β = 2.55 [95% CI: 0.22, 4.88] and β = 2.44 [95% CI: −0.74, 5.63], respectively), while postnatal (ages 2 and 5) BLL was associated with increasing internalizing behavior ratings in girls (β = 2.94 [95% CI: 0.36, 5.52]

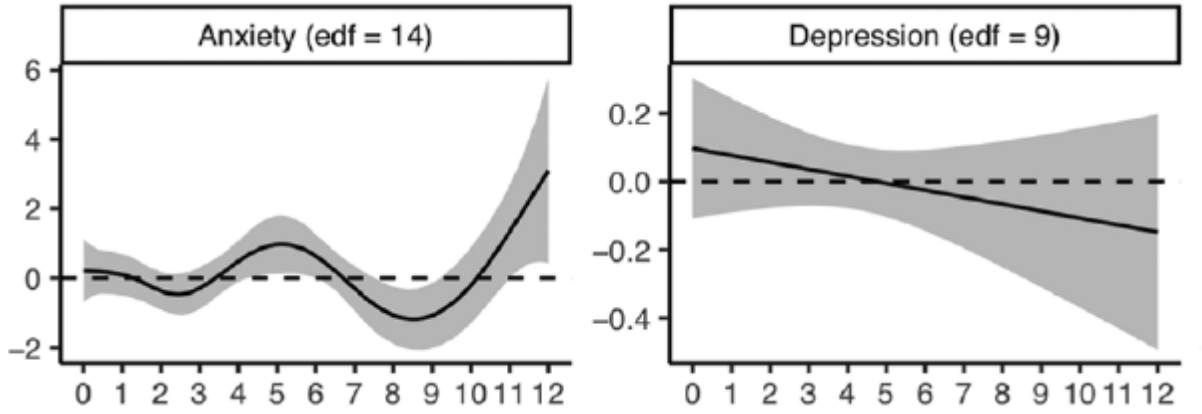
and β = 5.65 [95% CI: 0.5, 10.8]). A total of 579 women of the 1751 originally enrolled in the cohort provided data for this study.

Recent studies also examined the association of Pb exposure with internalizing behaviors using SDQ. SDQ includes five scales (i.e., peer relationship problems, hyperactivity, emotional problems, conduct problems and prosocial behavior) with the results for emotional problems discussed in this section. Fruh et al. (2019) studied mother-child pairs participating in Project Viva, a longitudinal birth cohort in eastern Massachusetts. Maternal blood Pb concentration in erythrocytes was measured during the second trimester of pregnancy and parents rated their child's behavior using the SDQ (see also Sections 3.5.1, 3.5.2, 3.5.3) in mid-childhood (median 7.7 years). The associations (i.e., β coefficients) with the parent- and teacher-rated emotional components of the SDQ were 0.30 (95% CI: 0.05, 0.55) and 0.07 (95% CI; −0.22, 0.35), respectively. A stronger association with the emotional component of the SDQ for girls compared with boys was reported by parents (β = 0.52 [0.18, 0.86] for girls versus β = 0.17 [95% CI: −0.17, 0.50] for boys). Note that the higher scores on the emotional problem scale indicate worse performance. Behavior assessments and maternal blood Pb measurements were available for fewer than half of study participants; however, important confounders including HOME score, maternal IQ, and parental education were considered in this study. Sioen et al. (2013) analyzed data from a birth cohort (FLEHS I, 2002–2006) comprising mother-infant pairs born in the Netherlands. This study examined the association of cord blood for 281 infants whose parents returned the SDQ (26.4% response rate). No association of cord blood Pb concentration with emotional symptom score ≥5 was observed (OR: 0.90 [95% CI: 0.52, 1.55] per doubling of BLL on log-scale).

Rokoff et al. (2022) used Conners' Parent and Teacher Ratings Scales (CPRS and CTRS) at age 8 years and the BASC-2 self-report of personality (SRP) at age 15 years to assess internalizing behaviors among children enrolled in a birth cohort study in New Bedford, MA. This study examined the association of cord blood Pb with internalizing behaviors and also considered exposure to organochlorines (hexachlorobenzene, p,p'-dichlorodiphenyl dichloroethylene, polychlorinated biphenyls) and Mn, which were also measured in cord blood. BKMR analysis indicated linear associations and no interactions between cord Pb, Mn, and organochlorines. Cord blood Pb was positively associated with BASC anxiety score at age 15 (β = 1.78 [95% CI: 0.58, 2.99] BASC-2 SRP anxiety score increase per doubling Pb) but not with Conners' anxious-shy score at age 8 years. Additionally, a positive association of cord blood Pb with depression score at age 15 was observed (β = 0.79 [95% CI: −0.39, 1.97]). The Connor's psychosomatic score was positively associated with cord Pb, and this association was stronger in boys (β = 2.08 [95% CI: 0.07, 4.10]) than in girls (β = 0.48 [95% CI: −1.00, 1.97]). A total of 528 of the original 788 (67%) mother-infant pairs participated in the 15-year follow-up. The models were adjusted for SES, maternal age, smoking, seafood, alcohol intake during pregnancy, maternal IQ, quality of parental caregiving, and child characteristics (sex, race/ethnicity, age at assessment).

Several additional studies used the BASC-2 to assess associations with Pb exposure. Rasnick et al. (2021) designed a study to identify sensitive time windows of exposure to Pb in air. These authors

controlled for concurrent BLL (age 12 years) in their analysis of the Cincinnati Study of Allergy and Air Pollution study data. Air Pb exposure was estimated using validated land use regression models, and behavioral outcomes, including depression and anxiety, were assessed using the BASC-2 administered at age 12. Models were adjusted for community deprivation, residential greenspace, and ECAT, in addition to concurrent BLL. Distributed lag models that predicted outcome responses based on current and past (i.e., lagged) predicted air Pb exposures identified a sensitive window in late childhood for anxiety but not depression (Figure 3-12). The sensitive time window is indicated by months when the estimated 95% CI did not include the null value.



BASC-2 = Behavior Assessment System for Children; edf =effective degrees of freedom.
The solid lines show the predicted change in score and the gray shading indicates the 95% CIs.
Source: Rasnick et al. (2021).

Figure 3-12 Associations of monthly airborne Pb exposure levels from birth to age 12 with scores for anxiety and depression behaviors on the Behavior Assessment System for Children.

Ruebner et al. (2019) evaluated the association between BLLs and attention among children with CKD. Internalizing behavior symptoms were assessed using the parental rating scales of the BASC-2, which includes a composite score for internalizing problems. Associations between BLL and behavioral symptoms on BASC-2 did not persist in models that were controlled for potential confounders including race, poverty, maternal education, and clinical factors related to CKD. The median BLL in this study was 1.2 µg/dL.

Two additional prospective studies examined the association Pb concentration in teeth and toenails with internalizing behavior on the BASC; these studies relied on a low proportion of the original cohort, however. Horton et al. (2018) analyzed data from the ELEMENT Project birth cohort in Mexico City to determine the association of weekly tooth Pb concentration (prenatal through 1 year postnatal) with BASC-2 scores assessed between 8 and 11 years old. Approximately 12% of the original cohort was enrolled in this study. Participants differed with respect to child birth weight and maternal IQ. A 0.4-unit

increase in anxiety score was associated with a log-transformed unit increase in tooth Pb concentration at 12 months, while no consistent pattern of association was observed with increased internalizing behavior symptoms overall. Doherty et al. (2020) followed children enrolled in the New Hampshire Birth Cohort Study (NHBCS) to examine the association of toenail Pb concentration with parent-rated internalizing behaviors on the BASC-2. Data were available for approximately 300 of the 2000 women enrolled in the study. No consistent pattern of association between pre- or postnatal toenail Pb concentration was observed with internalizing behaviors after adjustment for confounders, including parent education and parent perception of the parent-child relationship.

3.5.4.1.1 Summary

The 2013 Pb ISA included several prospective studies with moderate to high participation rates that controlled for potential confounders including SES, parental education, and quality of parental caregiving. These studies found associations of higher lifetime average blood (mean: ~14 μg/dL) or childhood tooth Pb levels with higher parent and teacher ratings of internalizing behavior on the CBCL in children aged 8–13 years. Several recent longitudinal epidemiologic studies with high to moderate participation rates, which relied on an expanded array of instruments to assess internalizing behaviors (i.e., CBCL, SDQ, CPRS, CTRS, and BASC-2), reported associations with blood Pb concentration (childhood average, prenatal, and postnatal BLLs <7 μg/dL). Several studies in children evaluated sex (Rokoff et al., 2022; Fruh et al., 2019; Joo et al., 2018) as an effect modifier. The majority of analyses controlled for important potential confounders including the quality of parental caregiving (Rokoff et al., 2022; Fruh et al., 2019) maternal education and SES (Rokoff et al., 2022; Fruh et al., 2019; Winter and Sampson, 2017; Liu et al., 2014b). No association with internalizing behaviors was observed for the blood Pb of children with CKD or in prospective studies of Pb concentration in blood (Sioen et al., 2013), teeth (Horton et al., 2018), or toenails (Doherty et al., 2020), which reported relatively low participation rates. The limited number of studies that aimed to distinguish types of internalizing behaviors indicated associations with the anxiety component (Rokoff et al., 2022; Rasnick et al., 2021).

3.5.4.2 Toxicological Studies of Anxiety and Depression

Evidence in the 2013 Pb ISA consistently supported increases in emotionality in Pb-treated animals. Postnatal exposure to Pb in female Long-Evans rats, resulting in mean BLLs between 13 and 31 μg/dL, increased disruption and frustration in response to errors and reward omission in discrimination task trials (Beaudin et al., 2007; Stangle et al., 2007). Pb-exposed female Rhesus macaques displayed increased negative responses to repeated tactile stimuli (i.e., tactile defensiveness) during adolescence (mean BLLs of 31 μg/dL) (Moore et al., 2008). Furthermore, decreased exploratory behaviors in the open-field test were also reported in male Wistar rats following Pb exposure from gestation through weaning (Souza Lisboa et al., 2005). Additional evidence for increased anxiety-like behavior, evaluated

via the elevated plus maze, was found in one study of postnatally exposed rats (mean BLLs 35 µg/dL at weaning) (Fox et al., 2010); however, no significant effects were found in another study of postnatal Pb exposure (Molina et al., 2011). Inconsistent evidence for depression-like behaviors measured in the forced swim test was also reported (Souza Lisboa et al., 2005; Stewart et al., 1996).

Tests of anxiety-like behavior (i.e., emotionality) in rodents are often designed to exploit the approach-avoidance conflict. Rodents must balance their motivation to explore novel environments (to gather food and resources) with the need to evade predators and other threats. The open-field test (OFT) allows for observation of rodent behavior within a bare, brightly lit, open area. Decreases in measures of exploration (e.g., rearing, sniffing) indicate a shift towards an anxiety-like phenotype, although some metrics may also be affected by other factors such as decreased motor function, to varying degrees. Basha et al. (2014) found that postnatal Pb exposure in male rats decreased rearing and sniffing in the OFT between PND 45 and 18 months, well after exposure was terminated. Grooming was also decreased at PND 45, 4 months, and 12 months, which may indicate an altered response to stress in comparison to controls. The same study also utilized the hole board test as another method to evaluate rodents' interest in exploration of a novel environment. Animals displayed anxiety-like behavior (i.e., decreases in head dip count and head dip duration) between PND 45 and 18 months. A follow-up study evaluated male Wistar rats using a prenatal Pb exposure paradigm that resulted in BLLs of 11 µg/dL at PND 21 and found decreased exploratory behaviors in both the OFT and hole board test between PND 21 and 4 months (Basha and Reddy, 2015). Decreases in head dipping behavior were also reported by Flores-Montoya and Sobin (2015), who evaluated male and female C57BL/6 mice following exposure to Pb from PND 0 to PND 28 that resulted in low BLLs (mean between 3 and 12 µg/dL). Further analysis of individual BLLs and head dipping behavior suggested a negative association (i.e., head dipping behaviors decreased as BLLs increased).

Enhanced thigmotaxis (i.e., tendency to remain close to the walls of the arena) within the OFT is also associated with an anxiety-like phenotype. Betharia and Maher (2012) reported that low dose Pb treatment had no significant effects on the latency of rodents to enter the center of the arena at PND 24 or PND 59. The Sprague Dawley rats used in this study were exposed to Pb through their mothers from gestation until PND 20 and had a mean BLL of 9 µg/dL at PND 2, which decreased to <1 µg/dL when behavior was assessed. Another recent study found that adolescent Pb exposure (between PND 24 and PND 56) in male Sprague Dawley rats, resulting in mean BLLs of 13 µg/dL, significantly decreased the time spent exploring the center of the arena compared with controls shortly after exposure was terminated (Wang et al., 2016). However, Shvachiy et al. (2018) found no significant effect of developmental Pb exposure on adult Wistar rats using the same measure, despite employing a longer exposure paradigm that resulted in higher BLLs than Wang et al. (2016). Interestingly, Abazyan et al. (2014) reported OFT findings suggestive of an anxiolytic effect of Pb exposure (i.e., increased central activity and increased rearing) in male transgenic mice that were heterozygous for mDISC1 (associated with increased risk for psychiatric disorders including schizophrenia) but phenotypically normal.

Six recent studies have evaluated the potential anxiogenic effects of Pb using the elevated plus maze (EPM). The EPM is comprised of four arms—two closed and two open (i.e., with or without walls)—and anxious behavior is indicated by an increase in the preference for the closed arms (or inversely, decreased preference for the open arms). Despite not finding conclusive results indicative of increased anxiety in the OFT, Shvachiy et al. (2018) found that Pb-treated Wistar rats (male and female adults exposed consistently or intermittently since gestation) spent significantly less time in the open arms of the EPM. This finding was corroborated in a subsequent study by the same research group, which investigated lifetime Pb exposure in Wistar rats and found that the percent of time animals spent in the open arms significantly decreased at 12, 20, and 28 weeks of age (Shvachiy et al., 2020). Interestingly, the greatest decrease in open arm presence was observed at 20 weeks. Abazyan et al. (2014) also demonstrated an anxiety-like phenotype using the EPM in 6-month-old male and female mice following lifetime exposure to Pb. Tartaglione et al. (2020) found that exposure to Pb from gestation to weaning significantly decreased entries into the open arms, decreased head dipping behavior and stretch-attend postures in female Wistar rats at PND 60 (mean BLLs of 25 µg/dL); however, only the decreases in stretch-attend postures were observed in males. One study, Neuwirth et al. (2019a), found no significant behavioral differences in the EPM in adolescent Long-Evans rats following gestational and developmental exposure in either dosing group (peak BLLs 3–11 µg/dL for lower dose group and 9–18 µg/dL for higher dose group).

Sobolewski et al. (2020) investigated the potential for transgenerational effects of Pb on this endpoint by exposing female C57BL/6J mice (F0) prior to mating and during gestation, resulting in offspring (F1) with BLLs of 10–15 µg/dL at PND 6–7. The developmentally exposed F1 generation was paired with unexposed mice at PND 60 to produce the F2 generation, and the process was repeated to produce the F3 generation which had no direct Pb exposure. F3 females spent significantly more time in the open arms of the EPM. This effect could be further traced to descendants of the F1 sire line instead of the F1 dam line. No significant effects were detected in F3 males.

The influence of Pb exposure on rodent behavior in the forced swim test (FST) and tail suspension test (TST) has also been evaluated in recent studies. These tests are classically considered models of emotional despair, with animals exhibiting both escape-directed behaviors and periods of immobility (e.g., floating or hanging). Originally used to screen for antidepressant drugs, decreases in immobility in the FST or TST following chemical exposure are interpreted as an antidepressant effect; however, it was recently suggested that immobility is instead an adaptive response to the acute stress of the FST or TST, and decreased immobility may be reflective of a maladaptive coping strategy or, potentially, an anxiety-like phenotype (Anyan and Amir, 2018; Molendijk and de Kloet, 2015). Cory-Slechta et al. (2013) reported that C57BL/6 mice which had been exposed to Pb from gestation to adulthood had significantly decreased immobile bouts in the FST compared with control animals. In another recent study, postnatal exposure to Pb in male and female CD1 mice significantly increased their time spent resisting in the TST (Duan et al., 2017). These recent results indicate that, at least under some experimental testing paradigms (producing mean BLLs as low as roughly 6 µg/dL), Pb exposure results in

what has classically been considered an antidepressant effect but may be more aptly attributed to an altered response to stress.

3.5.4.2.1 Summary

Studies in the previous ISA consistently supported increases in emotionality in rodents and nonhuman primates following developmental Pb exposure that produced mean BLLs as low as 13 μg/dL. Recent studies largely support and expand on this conclusion. Consistent decreases in rodent exploratory behaviors in the OFT and hole board test (e.g., rearing, sniffing, head dipping) were found in Pb-exposed rodents with peak BLLs from 3 to greater than 30 μg/dL, lower than previously demonstrated. An anxiety-like phenotype was also demonstrated in the EPM by multiple studies, with only one study reporting null effects. Sobolewski et al. (2020) also demonstrated potential sex-specific transgenerational effects of Pb exposure on this endpoint. Inconsistent effects of Pb on thigmotactic behavior were reported by a few studies, which was not an endpoint discussed in the previous ISA. Two studies demonstrated decreased immobility in classical tests of depression-like behavior, suggestive of an antidepressant effect, but the relevance of these tests to human depression is unclear. While limited studies reported null results, they were not stronger with respect to design or methodology and did not significantly weaken the larger body of evidence.

3.5.4.3 Relevant Issues for Interpreting the Evidence Base

3.5.4.3.1 Concentration-Response Function

Bayesian kernel machine regression (BKMR) and five-chemical linear regression models were used to examine covariate adjusted associations between Pb exposure and CPRS Anxious-Shy T-score at age 8 and BASC-second revision Anxiety T-score at age 15 Rokoff et al. (2022). BKMR analysis indicated linear associations between Pb exposure and these outcomes, and no interactions between cord Pb, Mn, and organochlorines.

3.5.4.3.2 Potentially At-Risk Populations

The 2013 Pb ISA did not describe populations of children potentially at higher risk of Pb-associated internalizing behaviors. Recent epidemiologic studies presented sex-stratified results or examined interactions between Pb exposure and other chemicals.

Sex

Fruh et al. (2019) studied mother-child pairs participating in Project Viva, a longitudinal birth cohort in eastern Massachusetts. This study found a stronger association of maternal BLL with the emotional component of the SDQ measured in mid-childhood for girls compared with boys (β = 0.52 [0.18, 0.86] for girls v. β = 0.17 [95% CI: −0.17, 0.50] for boys). Note that higher scores on the emotional problem scale indicate worse performance. In another study, Joo et al. (2018) found that late pregnancy and cord BLL was associated with increasing internalizing behavior ratings on the CBCL in boys (β = 2.55 [95% CI: 0.22, 4.88] and β = 2.44 [95% CI: −0.74, 5.63], respectively), while postnatal (age 2 and 5) BLL was associated with increasing internalizing behavior ratings on the CBCL in girls (β = 2.94 [95% CI: 0.36, 5.52] and β = 5.65 [95% CI: 0.5, 10.8]). In a study that used Conners' rating scale to ascertain internalizing behaviors, Rokoff et al. (2022) found the psychosomatic score was positively associated with cord Pb and this association was stronger in boys than in girls (β = 2.08 [95% CI: 0.07, 4.10] versus β = 0.48 [95% CI: −1.00, 1.97]). Of the experimental animal studies that evaluated both sexes, a small number identified behavioral changes in Pb-exposed females while detecting minimal or no changes in their male counterparts on the EPM, which could indicate that females are more sensitive to changes in anxiety-like behavior after exposure to Pb (Sobolewski et al., 2020; Tartaglione et al., 2020). Overall, no consistent pattern was observed across the limited number of epidemiologic and toxicologic studies that presented sex-stratified results. Each study used a different instrument to ascertain the outcomes.

Other Metals

A recent study examined the interaction effect between prenatal Pb exposure and other metals on internalizing behavior scores on the BASC and the CPRS. BKMR analysis indicated no interactions between cord blood Pb, Mn, and organochlorines that would indicate a deviation from additivity in a study by Rokoff et al. (2022).

3.5.4.3.3 Lifestages

Epidemiologic studies consistently show that BLLs measured during various lifestages and time periods, including the prenatal period, early childhood, and later childhood, and averaged over multiple years, are associated with increases in internalizing behaviors. The identification of critical lifestages and time periods of Pb exposure is complicated further by the fact that BLLs in older children, although affected by recent exposure, are also influenced by Pb stored in bone due to rapid growth-related bone turnover in children relative to adults. Thus, associations of neurodevelopmental effects with concurrent BLL in children may reflect the effects of past and recent Pb exposures. Recent prospective studies add to the evidence from the strongest studies in the 2013 Pb ISA that found associations with childhood average blood and tooth Pb levels in children. These recent studies found associations between internalizing behaviors and early childhood, maternal, and cord BLLs. Toxicological studies also provide

support that the sensitive exposure window is not limited to a single phase of development. Rather, effects of Pb exposure on anxiety or depression-like behavior in animals have been found following gestational and postnatal exposure, exposure starting in adolescence, and lifetime exposure.

3.5.4.4 Summary and Causality Determination of Internalizing Behaviors in Children

The 2013 Pb ISA concluded that a causal relationship was likely to exist between Pb exposure in children and internalizing behaviors based on the available evidence (U.S. EPA, 2013). Prospective studies demonstrated associations between higher average blood (roughly 14 μg/dL) or tooth Pb (i.e., reflective of prenatal or early postnatal Pb exposure depending on the tooth layer analyzed) levels and higher parent and teacher ratings of internalizing behaviors, including withdrawn behavior and symptoms of depression, fearfulness, and anxiety in children (aged 8–13). These associations were present after adjustment for SES, birth outcomes, and parental education, but some uncertainty regarding potential confounding by parental caregiving quality remained. Results from cross-sectional studies evaluating lower concurrent BLLs (5 μg/dL) were inconsistent. Increased emotionality in rodents and monkeys was demonstrated at BLLs as low as 13 μg/dL after exposure to Pb during development, and biological plausibility was supported by findings of alterations in the HPA axis and dopaminergic and GABAergic systems.

Several recent longitudinal epidemiologic studies with high to moderate participation rates relied on an expanded array of instruments to assess internalizing behaviors (i.e., CBCL, SDQ, PRS, CTRS, and BASC-2) compared with the studies in the 2013 Pb ISA. These studies observed associations with blood Pb exposure (early childhood and prenatal BLLs <7 μg/dL). A limited number of studies evaluated child sex (Rokoff et al., 2022; Fruh et al., 2019; Joo et al., 2018) as an effect modifier but were not consistent with regard to sex-specific effects. The majority of analyses controlled for important potential confounders including the quality of parental caregiving (Rokoff et al., 2022; Fruh et al., 2019), maternal education, and SES (Rokoff et al., 2022; Fruh et al., 2019; Winter and Sampson, 2017; Liu et al., 2014b); however, each potential confounder was not uniformly considered across studies. No association between blood Pb and internalizing behaviors was observed among children with CKD or in prospective studies of Pb concentration in blood (Sioen et al., 2013), teeth (Horton et al., 2018) or toenails (Doherty et al., 2020), which reported relatively low participation rates. The limited number of studies that aimed to distinguish types of internalizing behaviors indicated associations with the anxiety component (Rokoff et al., 2022; Rasnick et al., 2021). Recent studies that found associations with prenatal or cord BLLs add to the evidence. Uncertainty remains, however, regarding the exposure patterns associated BLLs in older children and adults.

Recent experimental animal studies provide coherence with the previous findings that moderate to high peak BLLs (12 to >30 μg/dL) increase anxiety-like behaviors on the EPM, hole board test, and OFT following Pb exposure during a single developmental window (including prenatal (Basha and

Reddy, 2015), postnatal (Basha et al., 2014), or adolescent periods (Wang et al., 2016)) or throughout development and beyond (Shvachiy et al., 2020; Tartaglione et al., 2020; Shvachiy et al., 2018; Abazyan et al., 2014). Overall, experimental animal studies provide more extensive support for anxiety-like behaviors than for depression-like behaviors. However, two recent studies reported that Pb exposure decreased immobility in classical tests of emotional despair following postnatal or lifetime Pb exposure (Duan et al., 2017; Cory-Slechta et al., 2013). In addition to the well demonstrated effects at moderate to high BLLs, two recent studies found altered behaviors in a nose poke task and FST following Pb exposures resulting in low BLLs (3.2–10 μg/dL); moreover, one study was able to demonstrate exposure-response relationships (i.e., higher BLLs were associated with greater behavioral changes) (Flores-Montoya and Sobin, 2015).

Overall, the evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and internalizing behaviors in children. This determination is based on consistent evidence from both recent and past prospective epidemiologic studies, which demonstrate positive associations between average blood Pb (prenatal, early childhood, lifetime) or childhood tooth Pb levels (generally reflecting prenatal or early postnatal exposure) and multiple measures of internalizing behaviors in children (aged 4–17) after adjustment for multiple confounding factors (e.g., SES, birth outcomes, parental education). Recent toxicological studies provide further support for anxiety-like behaviors following developmental and cumulative exposures that result in BLLs that are relevant to humans. Despite these findings, some uncertainties have not been addressed in the epidemiologic literature, including full consideration of certain confounding factors (e.g., parental caregiving quality) and uncertainty regarding the exposure patterns associated with observed BLLs. Furthermore, inconsistencies remain in the limited number of cross-sectional studies available in populations with BLLs below 5 μg/dL.

Table 3-5 Summary of evidence for a likely to be causal relationship between Pb exposure and internalizing behaviors in children

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent results from prospective epidemiologic studies with relevant exposures	Evidence from prospective studies for higher ratings of internalizing behaviors in children ages 8–13 yr in Boston and Port Pirie cohorts in association with tooth or lifetime average BLLs.	Section 4.3.4.1, (U.S. EPA, 2013) Burns et al. (1999) Bellinger et al. (1994b)	Blood Pb lifetime (to age 11–13 yr) average mean: ~14 µg/dL Tooth Pb (age 6 yr) mean: 3.4 µg/g
	Evidence from prospective studies for higher rating of internalizing behaviors in children 6–17 yr (cohorts in eastern MA, Chicago, Cincinnati, and China) in association with early childhood and prenatal BLLs.	Winter and Sampson (2017) Liu et al. (2014b) Fruh et al. (2019) Rokoff et al. (2022)	Early childhood <7 µg/dL (median/mean) Maternal and cord blood Pb, <2 µg/dL (median)
	Associations also found in children aged 4–5 yr in former Yugoslavia in association with lifetime average BLL Prospective studies had population-based recruitment with moderate follow-up participation. Participation not conditional on tooth/BLLs and behavior	Wasserman et al. (2001)	Blood Pb lifetime (to age 4–5 yr) average mean: 7.2 µg/dL
	Inconsistent results in cross-sectional studies with mean BLLs < 5	Section 4.3.4.1, (U.S. EPA, 2013)	
Uncertainty regarding potential confounding	Epidemiologic associations found with adjustment for SES, birth outcomes, parental education. Studies did not uniformly adjust for parental caregiving quality.	Section 3.7, Table 3-10E	
Uncertainty regarding the exposure patterns associated with observed BLLs.	Uncertainty in regarding past exposure in older children.		

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
And, supporting animal evidence with relevant exposures from multiple studies	Gestational, lactational, and adolescent exposures increasing anxiety-like behaviors and altered stress coping response.	Cory-Slechta et al. (2013) Flores-Montoya and Sobin (2015) Shvachiy et al. (2020)	Peak BLLs: 3–27 µg/dL

BLL = blood lead level; Pb = lead; yr = year(s); SES = socioeconomic status.
[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.

3.5.5 Motor Function in Children

The evidence assessed in the 2013 Pb ISA is sufficient to conclude that a "causal relationship is likely to exist" between Pb exposure and decrements in motor function in children. Evidence from prospective studies of Cincinnati and Yugoslavia birth cohorts indicated associations of decrements in fine and gross motor function with higher neonatal, concurrent, and lifetime average BLLs in children aged 4.5–6 years and with higher earlier childhood (ages 0–5 years on average, age 78 months) BLLs in children aged 15–17 years (Bhattacharya et al., 2006; Ris et al., 2004; Bhattacharya et al., 1995; Dietrich et al., 1993). The means for these blood Pb metrics ranged from 4.8 to 12 μg/dL. These associations were found with adjustment for several potential confounding factors, including SES, parental caregiving quality, and child health with no indication of substantial selection bias. Evidence from cross-sectional studies was less consistent, however (see Section 4.3.8 of (U.S. EPA, 2013)). The biological plausibility for associations observed in children was supported by a study that found poorer balance in male mice with relevant gestational to early postnatal (PND 10) Pb exposures. Overall, the strongest evidence was from a small number of prospective cohort studies of children with limited support from studies in mice with relevant exposures.

Measures of central tendency for Pb biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 3-11E (Epidemiologic Studies) and Table 3-11T (Toxicological Studies). An overview of the recent evidence is provided below. Overall, recent epidemiologic studies support findings from the 2013 Pb ISA and a limited number of recent experimental animal studies provide coherence for their observations demonstrating effects at relevant exposure concentrations.

3.5.5.1 Epidemiologic Studies of Motor Function

Evidence from prospective studies of Pb exposure and decrements in motor function in the 2013 Pb ISA indicated associations between higher neonatal, concurrent and lifetime average BLLs and motor function decrements. Several recent epidemiologic studies examined the association between Pb exposure and decrements in motor function in children. The findings generally support an association between Pb exposure and decrements in motor function; however, they varied by the specific measure of motor function as well as the timing of exposure measurement. Most studies were cohort studies and assessed motor function using a comprehensive motor score, such as the Psychomotor Developmental Index (PDI) score, from a version of the BSID (Jiang et al., 2022; Kao et al., 2021; Rygiel et al., 2021; Shekhawat et al., 2021; Kim et al., 2018b; Y Ortiz et al., 2017; Parajuli et al., 2015b; Parajuli et al., 2015a; Liu et al., 2014c; Kim et al., 2013c; Henn et al., 2012). A few studies used a motor score from the Chinese version of the GDS (Liu et al., 2022a; Zhou et al., 2017). The remaining studies assessed specific tasks, such as

balance, manual dexterity, coordination, and fine motor speed (Taylor et al., 2018; Boucher et al., 2016; Taylor et al., 2015).

Studies using the Bayley scales to measure motor function in infants and toddlers (i.e., through age 3) generally found associations between some Pb exposure metrics and decreased motor score. Kim et al. (2013c), Kim et al. (2018b), Y Ortiz et al. (2017), Liu et al. (2014c), Rygiel et al. (2021), and Shekhawat et al. (2021) observed a decrease in motor score using maternal or cord BLLs, as well as other blood Pb metrics, in several birth cohorts in multiple countries. Associations between BLLs and PDI are presented in Figure 3-13.

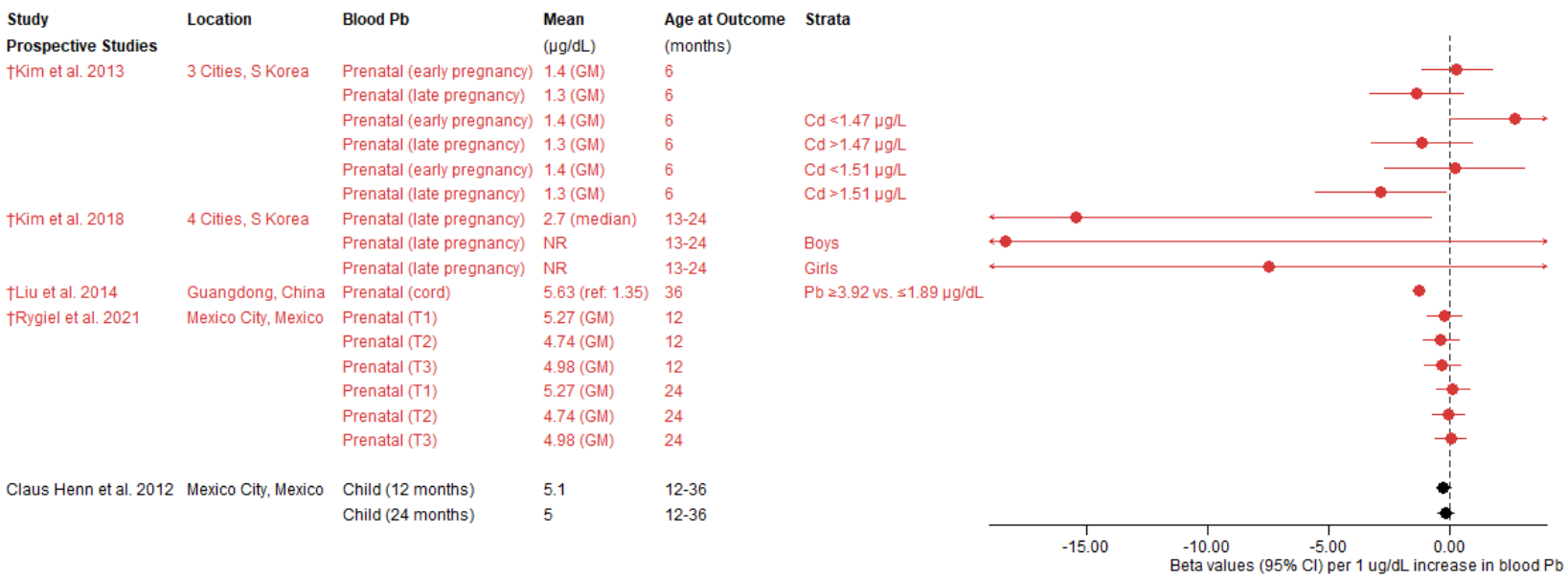


Figure 3-13 Associations between biomarkers of Pb exposure and Bayley Score of Infant Development Psychomotor Developmental Index.

Note: Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10th −90th percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized. Associations that could not be standardized are not included on the plot.
†Studies published since the 2013 Integrated Science Assessment for Lead.

Kim et al. (2013c) found that PDI score at 6 months of age decreased with increasing BLLs measured in the third trimester (median = 39th week) (β = −1.38 [95% CI: −3.31, 0.55] per 1 μg/dL increase in BLL) in the Korean MOCEH study. Another Korean study using the CHECK cohort (Kim et al., 2018b) also observed decrements in PDI among 13−24 month old infants in association with perinatal maternal BLLs (β per 1-μg/dL blood Pb = −15.45 [95% CI: –30.12, −0.79]). Sex-stratified results were slightly negative but not significant. In China, Liu et al. (2014c) observed an association between increasing prenatal (umbilical cord blood) Pb levels and worse PDI score at 36 months of age. Compared with low prenatal Pb (<1.89 μg/dL), children exposed to high prenatal Pb (>3.92 μg/dL) were more likely to have a lower PDI score (β = −1.30 [95% CI: −1.57, −1.03]), after adjusting for potential confounders.

Several studies in Mexico also examined the association of BLL with PDI assessed in infants. Rygiel et al. (2021) found a small negative association between prenatal (trimester-specific) BLLs and PDI scores at 12 months in the ELEMENT Project study (β per 1 μg/dL increase in 1st trimester Pb = −0.24 [95% CI: -0.95, 0.48]; β per 1 μg/dL increase in 2nd trimester Pb = −0.38 [95% CI: -1.10, 0.35]; β per 1 μg/dL increase in 3rd trimester Pb = −0.33 [95% CI: -1.06, 0.40]). At 24 months, the negative association persisted but with a smaller magnitude of effect. Rygiel et al. (2021) also examined whether DNA methylation mediated the association and found that DNA methylation of cg18515027 located within glucosaminyl (N-acetyl) transferase 1 (GCNT1) had a suppressive (positive indirect) effect on the inverse relationship between second trimester BLLs (ln-transformed) and PDI scores at 12 months ($\beta_{Indirect}$ = 1.25 (95% CI: −0.11, 3.32]). In the Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS) birth cohort in Mexico, Y Ortiz et al. (2017) found a negative association between motor score at 24 months of age and log-transformed BLLs measured during the third trimester (β = −11.01 [95% CI: −17.55, −4.48]), but not for BLLs measured during the second trimester (β = 1.97 [95% CI: −2.46, 6.40]). In a study using childhood BLLs, Henn et al. (2012) found a small negative association with repeated measures of PDI scores in another cohort of children in Mexico. From adjusted mixed-effects models with repeated measures of PDI scores at 12, 18, 24, 30, and 36 months, there was a negative association between 12-month blood Pb and PDI scores (β per 1-μg/dL blood Pb = −0.27 [95% CI: −0.56, 0.02]). Similarly, from adjusted mixed-effects models with repeated measures of PDI scores at 24, 30, and 36 months, there was a negative association between 24-month blood Pb and PDI scores (β per 1-μg/dL blood Pb = −0.18 [95% CI: −0.53, 0.17]).

Several studies are not pictured in Figure 3-13. Shekhawat et al. (2021) found that children with cord blood Pb concentrations of 5–10 μg/dL had reduced gross motor skills on the BSID at an average age of 6.5 months (β = −0.29 [95% CI: −5.00, 0.11]) for each 1 μg/dL increase in cord BLL. Additionally, in a birth cohort of mother-child pairs recruited from Bharatpur General Hospital in Nepal, Parajuli et al. (2015a) and Parajuli et al. (2015b) assessed the association of cord BLLs with PDI at 24 months old and 36 months of age, respectively. Negative but non-significant associations were observed between log-transformed cord BLLs and 24-month PDI (β = −4.83 [95% CI: −16.53, 6.86]) nor 36-month PDI (β = −2.56 [95% CI: −9.71, 4.59]). Notably, two additional studies that used biomarkers other than blood did not find associations, i.e., Jiang et al. (2022) measured Pb in meconium (at birth) and in hair and

fingernails (at 3 years of age) in Taiwan and did not find an association with any motor score (total, fine motor, or gross motor) at 3 years of age. Another study in Taiwan (Kao et al., 2021) that used hair and fingernail biomarkers of Pb concentrations similarly did not report significant associations with motor development among infants less than 3 years old.

Several other instruments were used to assess motor function in infants and toddlers. Parajuli et al. (2013) measured Pb, As, and Zn levels in cord blood and used the third edition of the Brazelton Neonatal Behavioral Assessment Scales (NBAS III) to assess neurodevelopment in one-day-old newborns in Chitwan, Nepal. The NBAS III contains 27 behavioral and 18 reflex items and is used for infants up to 2 months old. The multivariate model was adjusted for parity, family income, mother's age, education, BMI, birth weight, gestational age, and age in hours at NBAS assessment. The NBAS motor cluster score was inversely associated with the log-transformed cord BLLs (β = −2.15 [95% CI: −4.27, −0.03]). Liu et al. (2014d) used the Neonatal Behavioral Neurological Assessment (NBNA), which is based on the NBAS and has five clusters of behavior: passive tone, active tone, primary reflexes, and general assessment. Newborns in this study were assessed at 3 days old, and the NBNA has been validated among Chinese newborns between 2 and 28 days old. Associations between maternal BLL in the first trimester and the NBNA scores were observed (β = −4.86 [95% CI: −8.83, −0.89] per unit of log-transformed Pb). Less precise associations of second trimester, third trimester, and cord BLLs with decreased motor function were also observed. Among toddlers (2–3 years old) Zhou et al. (2017) and Liu et al. (2022a) both used the Chinese version of the GDS to calculate a motor score. For every log10 (μg/dL) increase in maternal blood Pb (measured at 28–36 weeks of gestation), Zhou et al. (2017) observed a positive association for gross motor development (β = 3.31 [95% CI: −6.11, 12.73] per log−10 transformed unit of BLL) as well as fine motor development (β = 0.49 [95% CI: −11.27, 12.24] per log−10 transformed unit of BLL); however, the effect estimates were extremely imprecise. On the other hand, for each ln (μg/L) increase in maternal Pb, Liu et al. (2022a) observed a negative association for gross motor development (β = −2.32 [95% CI: −3.61, −1.03] per ln-transformed unit of BLL). Furthermore, Nyanza et al. (2021) did not find associations between high Pb exposure and fine or gross motor impairment assessed by the MDAT.

Several additional studies were conducted using assessment instruments that measure children's (7 years or older) ability to perform certain tasks. In the ALSPAC, Taylor et al. (2015) conducted a heel-to-toe test in children at age 7 years, beam walking test (to measure dynamic balance) at age 10 years, and balancing test with eyes closed (to measure static balance) also at age 10 years. Pb levels measured in maternal blood (<18 weeks of gestation) and Pb levels measured in child blood (30 months old) were not associated with any measure of motor function in this study (Taylor et al., 2015). In another analysis of ALSPAC data, Taylor et al. (2018) examined the association between first trimester BLLs and different measures of coordination. Compared with prenatal blood Pb <5 μg/dL, children exposed to higher levels (≥5 μg/dL) of prenatal Pb were more likely to fail the tests of manual dexterity (threading lace, peg board using preferred hand, and peg board using non-preferred hand). When comparing the highest blood Pb quartile to the lowest blood Pb quartile, the only association remaining was for failing the peg board using

the preferred hand (OR for quartile 4 versus quartile 1 = 1.23 [95% CI: 0.92, 1.66]). Prenatal Pb exposure was not associated with tests of balance and the results were inconsistent for ball skills (inverse association for ≥5 µg/dL versus <5 µg/dL; positive association for quartile 4 versus quartile 1). In the Nunavik Child Development Study in Canada, Boucher et al. (2016) measured manual dexterity, fine motor speed, and visuomotor integration in children (ages 8.5–13.3 years). BLLs (log-transformed) measured at birth (cord blood) and at age 11 years were negatively associated with manual dexterity (β for cord blood Pb = −0.08 [p > 0.10]; β for child blood Pb = −0.17 [95% CI: −0.34, 0.00]) and fine motor speed (β for cord blood Pb = −0.19 [95% CI: −0.33, −0.05]; β for child blood Pb = −0.21 [95% CI: −0.37, −0.05]). For visuomotor integration, there was no association with cord blood Pb (β for cord blood Pb = −0.01 [p > 0.10]) and a positive association with child blood Pb (β for child blood Pb = 0.10 [p > 0.10]). The magnitude of effect was greater for child BLLs. Nozadi et al. (2021) collected blood samples from pregnant mothers at the 36-week visit or at the time of delivery and administered the ASQ:I at 10–13 months of age to evaluate communication, gross motor, fine motor, problem-solving, and personal-social development. A 1-µg/dL increase in prenatal blood Pb was associated with a decrease in fine motor (β = −0.63 [95% CI: −1.19, −0.08]) scores. Palaniappan et al. (2011) observed decrements of WRAVMA scores in association with 1-µg/dL increase in concurrent BLLs (Drawing: β = −0.29 [95% CI: −0.51, −0.07]; Matching: β = −0.14 [95% CI: −0.31, 0.02]; Pegboard: β = −0.19 [95% CI: −0.38, 0.01]; Composite: β = −0.26 [95% CI: −0.45, −0.07]).

3.5.5.1.1 Summary

Evidence from prospective studies of Cincinnati and Yugoslavia birth cohorts indicated associations of decrements in fine and gross motor function with higher neonatal, concurrent, and lifetime average BLLs in young children with higher earlier childhood BLLs. Several recent birth cohort studies observed lower scores on the Bayley PDI in association with maternal Pb exposure (no clear pattern by trimester of pregnancy), cord BLL, and postnatal concurrent blood Pb (Rygiel et al., 2021; Y Ortiz et al., 2017; Liu et al., 2014c; Kim et al., 2013c; Henn et al., 2012). Pb-associated decrements in motor function were observed in neonates (Liu et al., 2014d; Parajuli et al., 2013) and in some but not all studies of toddlers that assessed motor function using GDS (Liu et al., 2022a; Zhou et al., 2017) or children's (greater than 7 years old) abilities to perform certain tasks indicative of gross motor function (i.e., balance) (Taylor et al., 2015), although associations with fine motor function were observed (Taylor et al., 2018; Boucher et al., 2016).

3.5.5.2 Toxicological Studies of Motor Function

As described above and in previous reviews (U.S. EPA, 2013, 2006), epidemiologic studies provide evidence of associations between Pb exposures and fine and gross motor decrements, mainly in children. Evaluating performance in neurobehavioral toxicological studies with Pb exposure in rodents

can substantiate observed Pb exposure effects on motor function seen in humans. In past assessments, evidence in animal toxicological studies has been limited due to a lack of investigations with relevant Pb exposures. The purpose of this section is to update the collection of evidence available concerning Pb exposure-induced effects on motor function in animal models. Studies that examined various indices of locomotor activity are evaluated above in the Toxicological Studies of Hyperactivity section (Section 3.5.2.3.2).

Previous ISAs (U.S. EPA, 2013, 2006) highlighted rotarod and air righting reflex experiments with rodents to discuss the effects of Pb on development of motor coordination and balance. Typical rotarod tests compare the latency to fall for subjects placed on a rotating rod. Falling off more quickly indicates decreased coordination and/or balance. There are two rotarod studies discussed in previous U.S. EPA reviews that describe effects of developmental Pb exposure on rotarod performance that resulted in relevant BLLs less than 30 μg/dL. Interestingly, Moreira et al. (2001) saw no effect of Pb exposure, from the beginning of gestation through lactation, on Wistar rat rotarod performance at PND 70 with PND 23 mean BLLs of 21 μg/dL. In contrast, Leasure et al. (2008) observed substandard performance in pregestational through lactation Pb-exposed male, but not female, mice with peak BLLs of less than 10 μg/dL. Since Leasure et al. (2008), no other PECOS-relevant studies have assessed rotarod performance in rodents exposed to Pb throughout the entire developmental period. Two recent rotarod studies with mice, by Flores-Montoya and Sobin (2015) and Zou et al. (2015), showed no decrements in performance in rotarod tests after postnatal-only exposure to Pb in drinking water for PND 0–28 and 37–58 for respective studies.

While the outcomes of these two latest rotarod studies were mostly negative, additional investigations evaluating the effects of developmental Pb exposure on coordination and balance in neonatal rats using surface righting reflex, negative geotaxis reflex, and ascending wire mesh tests yielded mixed results. Surface righting reflex tests are run by placing pups in a supine position and then recording the time it takes to flip onto their feet. Slower times to flip indicate postural imbalances. For negative geotaxis reflex, or slant-board tests, pups are placed on a slanted board and the time it takes for the pup to face upward is recorded. Slower times to turn upward indicate that the vestibular response to gravity cues or motor coordination required for turning are underdeveloped. Success in ascending wire mesh tests also requires coordination, as the animals are required to climb to the top of a mesh out of a water bath in a predetermined period. In a study comparing the developmental effects on male Wistar rats with pregestational, gestational, or lactational Pb exposure, pups exposed during gestation achieved negative geotaxis significantly faster than unexposed counterparts when tested on PND 8, 10, and 12 (Rao Barkur and Bairy, 2016). In contrast, in the same study, Rao Barkur and Bairy (2016) observed no difference in negative geotaxis times between control, pregestation alone, and lactation alone Pb-exposed pups. No effects on surface righting reflex on PND 3 through 5 were observed for pups belonging to the previously mentioned exposure groups. The day of achievement in ascending wire mesh tests (PND 14–18) was delayed for animals in both gestation and lactation Pb-exposed groups but not for those in the pregestational group (Rao Barkur and Bairy, 2016). Betharia and Maher (2012) exposed pregnant

Sprague Dawley rats to Pb (II) acetate trihydrate via drinking water from the beginning of gestation through lactation and until weaning. Development of the surface righting reflex of control and exposed offspring was tested from PND 1 to 10. Slower righting times were observed for Pb-exposed offspring on PND 1; however, from PND 2 through 10, there were no differences between Pb-exposed and control groups. Basha and Reddy (2015) observed a significant increase in righting time in righting reflex tests done on PND 6 and 7 and an increase in latency to turn in negative geotaxis tests for male Wistar rats tested on PND 8, 9, and 10 after in utero exposure to Pb. Tartaglione et al. (2020) saw no decrements in righting reflex time or negative geotaxis achievement on PND 4, 7, 10, and 12 from Pb exposure in the offspring of dams exposed to Pb from 1 month pre-mating to offspring weaning.

Additional motor function experiments with early postnatal weaning in Wistar rats were carried out in studies with developmental Pb exposures. Tartaglione et al. (2020) recorded on PND 4, 7, 10, and 12 the duration of neonatal motor patterns of rat pups from dams exposed to Pb before mating until offspring weaning. On PND 10, Pb-exposed pups spent less time in locomotion compared with controls, in favor of head rising and wall climbing movements, demonstrating a stereotyped/preservative profile. Basha and Reddy (2015) observed a prenatal Pb-induced strength deficit when rats were subject to forelimb hang tests on PND 13, 14, 15, and 16 but not on day 12. This indicated Pb-induced underdevelopment of fine motor ability. Rao Barkur and Bairy (2016) tested rats on PND 6, 8, 10, and 12 for Pb-induced effects on swimming development. They observed no difference in swimming body angle or limb movements for ISA-relevant pregestation, gestation, or lactation-exposed groups compared with control. These novel studies warrant further investigation into the effects of Pb exposure at different concentrations and stages of development on neonatal movement patterns and forelimb hang tests.

3.5.5.2.1 Summary

The evidence supporting the link between developmental Pb exposure and deficits in motor function in animal models has expanded on account of recent studies utilizing Pb-exposed rodents with mean BLLs ≤30 µg/dL. These new studies illustrate the effects of Pb exposure on both gross and fine motor development in novel paradigms. In addition to the effect on rotarod performance (Leasure et al., 2008) described in the previous ISA, developmental Pb-induced decrements in righting reflex, negative geotaxis reflex (Basha and Reddy, 2015), ascending wire mesh (Rao Barkur and Bairy, 2016), and forelimb hang tests (Basha and Reddy, 2015) were observed. Interestingly, gestational Pb exposure was present among each type of study that yielded decrements in these measurements of motor function; therefore, it may be a more sensitive window compared with lactation or postnatal exposures. In terms of design or methodology, studies that found weak or null relationships were not stronger and did not weaken the overall body of corroborating data. Key aspects such as exposure levels and timing, ages of animals at testing, and slant-board angles were variable between the few relevant studies. Altogether, the results from these recent studies support the conclusions from the previous ISA. However, due to the limited number of reproduced experiments, these recent studies do not enhance the consistency of the

evidence. In addition to the fine motor, motor reflex, and coordination, and balance studies described in this section, effects of developmental Pb exposure on locomotor activity are evaluated separately in the Toxicological Studies of Hyperactivity section (Section 3.5.2.3.2) above. Briefly, due to heterogeneity in study design, the evidence for effects of developmental Pb on locomotor activity is mixed; however, a set of four independent studies with analogous conditions showed hyperactivity in rodents when tested within a PND 14 to 23 window after lactational Pb exposure (Duan et al., 2017; De Marco et al., 2005; Moreira et al., 2001; Rodrigues et al., 1996).

3.5.5.3 Relevant Issues for Interpreting the Evidence Base

3.5.5.3.1 Potentially At-Risk Populations

Sex

A limited number of toxicological studies have reported sex differences in Pb-related effects on motor function. Among studies in the 2013 Pb ISA, sex-specific differences in mice were observed for gross motor skills, with balance and coordination most affected among males at the lowest Pb exposures (Leasure et al., 2008).

Recent epidemiologic studies that evaluated sex as a potential modifier of the association between Pb exposure and motor function add to the evidence (Liu et al., 2022a; Y Ortiz et al., 2017). Y Ortiz et al. (2017) found that the observed association between maternal blood Pb during the third trimester and lower PDI scores was not different between boys and girls. Liu et al. (2022a) found that the association of maternal blood Pb exposure with gross motor development quotient on the GDS was modified by sex (−3.43 [95% CI: −6.16, −0.69] in boys and −1.18 [95% CI: −2.81, 0.44] in girls per ln-transformed unit).

Maternal Self-esteem

Maternal self-esteem has been shown to modify associations between BLLs and health effects in children. In one study, high maternal self-esteem appeared to attenuate the negative effects of the child's increased BLLs on PDI scores (Surkan et al., 2008). In this study, larger decreases in PDI scores were associated with increased BLLs among children whose mothers were in the lower quartiles of self-esteem (Surkan et al., 2008). Maternal self-esteem was not evaluated as an effect modifier in recent studies of Pb exposure and motor function among children.

Maternal Stress

In a recent epidemiologic study, Y Ortiz et al. (2017) found that the observed association of maternal blood Pb during the third trimester with lower PDI scores differed depending on maternal stress. Contrary to expectations, higher PDI scores were observed with higher maternal stress.

3.5.5.3.2 Lifestages

Multiple lifestages during childhood are implicated in the effects of Pb exposure on motor function in children. Analyses of children enrolled in the Cincinnati cohort at age 6 years indicated associations of concurrent, lifetime average, and neonatal Pb exposure with poorer upper limb dexterity and fine motor composite score. Studies conducted in the Cincinnati cohort found that prenatal or neonatal BLLs were not consistently associated with motor function decrements at ages 4–10 years (Bhattacharya et al., 1995; Dietrich et al., 1993). Several recent birth cohort studies support findings from the 2013 Pb ISA with observations of lower scores on the Bayley PDI in association with maternal Pb exposure (no clear pattern by trimester of pregnancy), cord BLL, and postnatal concurrent blood Pb (Rygiel et al., 2021; Y Ortiz et al., 2017; Liu et al., 2014c; Kim et al., 2013c; Henn et al., 2012). Animal toxicological studies mentioned above and in previous ISAs indicate the potential for delays in gross motor development with gestational and/or early postnatal Pb exposure (Rao Barkur and Bairy, 2016; Basha and Reddy, 2015; Leasure et al., 2008) and for fine motor decrements with gestational Pb exposure (Basha and Reddy, 2015). Apart from the study by Leasure et al. (2008), which tested balance in adults, these studies measured and found diminished motor development in early postnatal rodents (Rao Barkur and Bairy, 2016; Basha and Reddy, 2015).

3.5.5.4 Summary and Causality Determination: Motor Function in Children

The evidence assessed in the 2013 Pb ISA is sufficient to conclude that a "causal relationship is likely to exist" between Pb exposure and decrements in motor function in children. Key evidence came from prospective analyses of the CLS and Yugoslavia cohorts demonstrating associations of BLLs with poorer motor function with consideration of potential confounders including SES, parental caregiving quality and education, smoking birth outcomes, sex, and child health. Among children that participated in the Cincinnati cohort, higher earlier childhood BLLs (age 0–5 year average [median: 11.7 µg/dL] or age 78 month) were associated with poorer fine (i.e., grooved pegboard and finger tapping) (Ris et al., 2004) and gross motor function (i.e., postural balance) (Bhattacharya et al., 2006) assessed in adolescence (ages 12, 15–17 years). In addition, assessments of children enrolled in the Cincinnati cohort at age 6 years indicated associations of concurrent (mean: 10.1 µg/dL), lifetime average (mean: 12.3 µg/dL), and neonatal (mean: 4.8 µg/dL) but not prenatal maternal (mean: 8.4 µg/dL) BLLs with poorer upper limb dexterity, fine motor composite score (Dietrich et al., 1993), and poorer postural balance (Bhattacharya et

al., 1995). Wasserman et al. (2000) also examined the association of Pb exposure with motor function. In this prospective analysis of the Yugoslavian cohort, an association of lifetime average BLL (exact levels not reported) with decrements in fine but not gross motor function at age 4.5 years was observed (Wasserman et al., 2000). Evidence from cross-sectional studies for associations between motor function and concurrent BLL was mixed in populations with mean BLLs of 2–5 μg/dL (Min et al., 2007; Surkan et al., 2007; Després et al., 2005). Recent epidemiologic and toxicologic studies generally support findings from the 2013 Pb ISA. The key evidence, as it relates to the causal framework, is summarized in Table 3-6.

Several recent birth cohort studies report lower scores on the Bayley PDI in association with maternal Pb exposure (no clear pattern by trimester of pregnancy), cord BLL, and postnatal concurrent blood Pb (Rygiel et al., 2021; Y Ortiz et al., 2017; Liu et al., 2014c; Kim et al., 2013c; Henn et al., 2012). Pb-associated decrements in motor function were also observed in neonates (Liu et al., 2014d; Parajuli et al., 2013). A limited number of studies of children greater than 7 years old were conducted. Taylor et al. (2015) did not report associations with certain tasks indicative of gross motor function (i.e., balance), although associations with decreased fine motor function were observed (Taylor et al., 2018; Boucher et al., 2016).

Recent toxicological studies provide limited biological plausibility by showing effects on motor function in rodent models from developmental Pb exposure resulting in BLLs ≤30 μg/dL within one order of magnitude of recent concentrations observed in humans. Epidemiologic evidence of developmental Pb-induced impairment of balance and coordination is supported by observations of poorer rotarod performance in male mice exposed to Pb during gestation (Leasure et al., 2008). In addition, evidence from epidemiologic studies indicating Pb-induced delayed gross motor development in children is reinforced by toxicological studies that display slower times to achievement by postnatal rats gestationally exposed to Pb in surface righting reflex (gestational Pb), negative geotaxis reflex (gestational Pb) (Basha and Reddy, 2015), and ascending wire mesh tests (gestational Pb; lactational Pb) (Rao Barkur and Bairy, 2016). Epidemiologic studies revealing Pb-induced decrements in children's fine motor skills are supported by the observed grip strength deficits for gestational Pb-exposed early postnatal rats in forelimb hang tests (Basha and Reddy, 2015). Additional studies on Pb-induced changes on several neurochemical endpoints that factor into impaired motor function have been reported and are described in Section 3.3

Overall, the evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and motor function in children. This determination is based on consistent evidence from prospective epidemiologic studies, which demonstrate an association between higher childhood BLLs (neonatal, earlier childhood, concurrent and lifetime average) and poorer fine and gross motor function in children (aged 4.5–17) with adjustment for maternal IQ, parental education, SES, and HOME score. Additional prospective studies have also demonstrated consistent evidence in infants and toddlers using the Bayley PDI, but evidence supporting neonatal effects is more limited. Epidemiologic

evidence is supported by limited experimental animal studies that demonstrate impairments in balance, coordination, and grip strength, as well as delayed reflex development. There is some remaining uncertainty arising from cross-sectional studies using concurrent BLLs that have reported mixed results.

Table 3-6 Summary of evidence indicating a likely to be causal relationship between Pb exposure and motor function in children

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent findings from a few prospective epidemiologic studies with relevant BLLs	Evidence from prospective studies for fine and gross motor function decrements in children ages 4.5–17 yr in Cincinnati, Yugoslavia in association with neonatal, earlier childhood, concurrent, lifetime avg BLLs.	Ris et al. (2004) Dietrich et al. (1993) Bhattacharya et al. (1995)	Blood Pb means Cincinnati: neonatal (10 day) 4.8 µg/dL, concurrent (age 6 yr) 11.6 µg/dL, lifetime (to age 15–17 yr) avg 12.3 µg/dL, age 0–5 yr avg 11.7 µg/dL
	High follow-up participation, no selective attrition in Cincinnati cohort, higher loss-to-follow-up in Yugoslavia cohort with lower maternal IQ, HOME.	Wasserman et al. (2000)	Former Yugoslavia: NR
	Both studies adjusted for maternal IQ, parental education, SES, HOME score		
	Studies used various, widely used tests to assess outcomes.	Section 4.3.7, (U.S. EPA, 2013)	
	Mixed evidence for lower (concurrent) BLLs from cross-sectional studies that considered several potential confounding factors.	Section 4.3.7, (U.S. EPA, 2013)	
Consistent findings from prospective studies of infants and toddlers	Lower scores on the Bayley PDI in association with maternal Pb exposure (no clear pattern by trimester of pregnancy), cord BLL and postnatal concurrent blood Pb	Kim et al. (2013c) Y Ortiz et al. (2017) Liu et al. (2014c) Rygiel et al. (2021) Henn et al. (2012)	
Limited evidence in neonates	Pb-associated decrements in motor function (e.g., reflexes) observed	Parajuli et al. (2013) Liu et al. (2014d)	
Limited experimental animal evidence at relevant exposures	Deficient gross motor coordination and balance in rodents with developmental Pb exposure (less time on rotarod, slower righting and negative geotaxis reflexes, delayed day of achievement for ascending wire mesh test)	Leasure et al. (2008) Basha and Reddy (2015) Rao Barkur and Bairy (2016)	Blood Pb: ~10 µg/dL in mice after pregestational through lactation exposure, 5–11 µg/dL in rats after gestational exposure, 27 µg/dL in rats after lactational exposure

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
	Fine motor (grip strength) deficits in early postnatal rats with gestational Pb exposure	Basha and Reddy (2015)	Blood Pb: 11.2 µg/dL after gestational exposure
Limited experimental animal evidence at relevant exposures provide coherence for epidemiologic observations of effect modification by sex	Poorer balance (fell off rotarod more quickly) in adult male but not female mice with pregestational through lactation dietary Pb exposure	Leasure et al. (2008)	Blood Pb: ~10 µg/dL in mice after pregestational through lactation exposure
Biological plausibility demonstrated	Pathways involving oxidative stress, inflammation and Ca^{2+} signaling result in impaired neuron development, synaptic changes, and neurotransmitter changes.	U.S. EPA (2013) Section 3.3	
	Recent studies support and extend findings related to overt nervous system effects	Section 3.4.2	

avg = average; BLL = blood lead level; Ca^{2+} = calcium ion; HOME = Health Outcomes and Measures of the Environment; IQ = intelligence quotient; NR = not reported; Pb = lead; PDI = Psychomotor Developmental Index; SES = socioeconomic status; yr = year(s).
[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.

3.5.6 Sensory Organ Function in Children

The 2013 Pb ISA included separate causality conclusions for auditory and visual function. This ISA combines these categories and makes one causality determination for Sensory Organ Function because there are relatively few studies within this outcome grouping.

3.5.6.1 Auditory Function in Children

The evidence assessed in the 2013 Pb ISA was sufficient to conclude that "a causal relationship is likely to exist" between Pb exposure and decrements in auditory function in children (U.S. EPA, 2013). Evidence from a prospective study (Dietrich et al., 1992) and small number of cross-sectional studies of U.S. children, including NHANES and Hispanic Health and Nutrition Examination Survey (HHANES) analyses (Schwartz and Otto, 1991, 1987) indicated associations of higher BLLs with increases in hearing thresholds as well as decreases in auditory processing or auditory evoked potentials, with adjustment for potential confounding by SES in most studies and by child health and nutritional factors in some studies. The high participation rates in a prospective birth cohort study (Dietrich et al., 1992) reduced the likelihood of biased participation by children with higher BLLs. Across studies, associations were found with BLLs measured at various time periods, including prenatal maternal, neonatal (10 days, mean 4.8 μg/dL), lifetime average (to age 5 years), and concurrent (ages 4–19 years) BLLs (median 8 μg/dL). Evidence for Pb-associated increases in hearing thresholds or latencies of auditory evoked potentials was also found in adult monkeys with lifetime dietary Pb exposure. However, these effects in adult animals were demonstrated at higher peak or concurrent BLLs (i.e., 33–150 μg/dL) than those relevant to this ISA; thus, the biological plausibility for epidemiologic observations was unclear.

In the current ISA, several recent cross-sectional studies support the conclusion in the 2013 Pb ISA regarding the association of Pb exposure with hearing loss; however, results were inconsistent for other audiometric parameters. Recent toxicological studies provide additional evidence for hearing loss and auditory processing deficits in rodents at relevant BLLs. Measures of central tendency for Pb biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 3-12E (Epidemiologic Studies) and Table 3-16T (Toxicological Studies). An overview of the recent evidence is provided below.

3.5.6.1.1 Epidemiologic Studies of Auditory Function

Several recent epidemiologic studies examined the association between Pb exposure and decrements in auditory function in children. The findings generally support a positive association between Pb exposure and hearing loss. For other audiometric parameters, however, the results were inconsistent.

Most studies of auditory function were cross-sectional. In a meta-analysis of studies from Iran, Korea, China, and the United States, Yin et al. (2021) observed a positive association between Pb exposure and hearing loss indicated by pure-tone average (PTA) >25 dB in children and adolescents (3–19 years) (combined OR per unit increase in Pb = 1.53 [95% CI: 1.24, 1.87]). The pooled OR was based on only two studies (Xu et al., 2020; Choi and Park, 2017). Xu et al. (2020) conducted a case-control analysis of preschool-aged children (3 to 7 years of age) who resided in an area contaminated with Pb and Cd and in an uncontaminated reference area. This study found associations of exposures with hearing loss, potentially affected by epigenetic changes. The OR for Pb-associated hearing loss in both ears was 1.40 (95% CI: 1.06, 1.84 per unit change log-transformed BLL) after adjustment for characteristics of the child, parental education, SES, and noise exposure. Choi and Park (2017) measured speech- and high-frequency hearing loss in adolescents (12–19 years) and adults (20–87 years) in the Korea National Health and Nutrition Examination Survey (KNHANES). Hearing loss was defined as PTA >15 dB in adolescents. For each doubling of blood Pb, there was a positive association with speech-frequency hearing loss (OR = 1.2 [95% CI: 0.48, 3.05]) and high-frequency hearing loss (>25 dB) (OR = 1.26 [95% CI: 0.73, 2.16]) among adolescents.

In addition to the aforementioned studies, among adolescent NHANES participants (ages 12 to 19 years), Shargorodsky et al. (2011) found a positive association between blood Pb and hearing loss. Hearing loss was defined as low or high-frequency PTA >15 dB in either ear. Compared with study participants with low BLLs (<1 µg/dL), those with the highest level (≥2 µg/dL) were more likely to have any hearing loss (OR = 1.95 [95% CI: 1.24–3.07]), particularly high-frequency hearing loss (OR = 2.22 [95% CI: 1.39–3.56]). The direction of effect for low-frequency hearing loss was the same but at a smaller magnitude (OR = 1.13 [95% CI: 0.61–2.07]). Among younger children (3–7 years with median BLL <5 µg/dL) in China, a positive association between blood Pb and hearing loss was also observed (Liu et al., 2018c). For each µg/dL increase in blood Pb, the odds of any hearing loss increased by 1.24 times (OR = 1.24 [95% CI: 1.03, 1.49]). This association was not as evident for high-frequency hearing loss (OR = 1.08 [95% CI: 0.84, 1.38]) and low-frequency hearing loss (OR = 1.02 [95% CI: 0.87, 1.19]).

Auditory function in children was also measured according to the auditory brainstem response (ABR) (Silver et al., 2016; Alvarenga et al., 2015; Pawlas et al., 2015). In an unadjusted descriptive analysis of children (4–13 years) in Poland, BLLs were positively correlated with brainstem auditory evoked potentials (BAEP) and pure-tone audiometry and negatively correlated with acoustic otoemission (Pawlas et al., 2015). In multivariable analyses stratified by polymorphisms in the ALAD and vitamin D receptor (VDR) genes, the associations for BAEP per µg/dL increase in blood Pb were generally null (Pawlas et al., 2015). Silver et al. (2016) measured ABR in newborns (average 2 days old) in China. Compared with a low (<2 µg/dL) BLL measured during late pregnancy, infants exposed to medium (2–3.8 µg/dL) and high (>3.8 µg/dL) Pb levels were more likely to have a higher ABR central-to-peripheral (C-P ratio) (Silver et al., 2016). When using Pb levels measured in cord blood and during mid-pregnancy, however, the association for ABR C-P ratio moved toward the null (Silver et al., 2016). Although

quantitative results were not provided for a study of children (18 months–14 years) in Brazil, Alvarenga et al. (2015) observed no association between cumulative BLLs and BAEP.

Summary

A prospective study in the 2013 Pb ISA (Dietrich et al., 1992) found an association of Pb exposure with decreased auditory processing. In addition, cross-sectional studies found increased hearing thresholds in children aged 4–19 years that participated in NHANES and HHANES in association with higher concurrent BLLs. Recent cross-sectional and case-control studies of young children and adolescents generally support a positive association between Pb exposure and hearing loss (Xu et al., 2020; Choi and Park, 2017; Shargorodsky et al., 2011), whereas the results were inconsistent for ABR (Silver et al., 2016; Alvarenga et al., 2015; Pawlas et al., 2015).

3.5.6.1.2 Toxicological Studies of Auditory Function

Toxicological evidence for effects on auditory function in the 2013 Pb ISA was limited to one study (U.S. EPA, 2013). This study evaluated auditory thresholds using a behavioral task in 13-year-old monkeys (*Macaca mulatta*) who had previously been exposed to Pb either gestationally or postnatally (Laughlin et al., 2009). Potentially due to limitations noted within the study, small but nonsignificant increases in the auditory threshold were reported in Pb-exposed animals compared with controls. Stronger associations between Pb exposure, auditory threshold shifts, and latency in BAEP were reviewed in the 2006 Pb AQCD (U.S. EPA, 2006). Importantly, the associations demonstrated in the 2013 Pb ISA and 2006 Pb AQCD occurred at higher BLLs (>30 μg/dL) that would not be considered PECOS-relevant for this ISA.

Changes in auditory thresholds using BAEP have been further assessed in three recent rodent studies (Table 3-16T). Jamesdaniel et al. (2018) exposed male C57Bl/6 mice from PND 33 to PND 61 to Pb and subsequently detected 8–12-dB upward shifts in hearing thresholds (indicative of hearing loss) between 4 and 32 kHz. In contrast, another recent study using similarly aged male CBA/CaJ mice and a longer exposure paradigm (11 weeks) found no significant effect of Pb on hearing thresholds at 8, 16, and 32 kHz (Carlson et al., 2018). The final study, which exposed male and female Sprague Dawley rats postnatally to Pb did not detect significant differences in hearing thresholds between 4 and 28 kHz at PND 60 (Zhu et al., 2016). Animals in the two studies that did not detect an effect had lower BLLs than those in the study that did (3–8 μg/dL versus 29 μg/dL). However, due to the small number of studies, the existence of an exposure threshold for this effect remains uncertain.

Recent studies have also investigated the effect of Pb exposures on auditory processing, which was not discussed in previous ISAs. Zhu et al. (2016) exposed rat pups to Pb through their dams' drinking water until weaning, when they began drinking Pb-free water. BLLs of the pups were roughly 8 μg/dL

during exposure and had returned to baseline levels by PND 40. At PND 60, the Pb-exposed rats were found to have a decreased ability to discriminate between target and nontarget sound bursts. Additionally, these rats were found to have a reduced spike rate-following ability and decreased cortical response synchronization, indicative of a deficit in auditory cortical temporal processing. The same research group published a follow-up study using a similar exposure paradigm to investigate another aspect of auditory processing (i.e., sound localization) (Liu et al., 2019). In a sound-azimuth discrimination task, Pb-exposed animals took significantly longer to reach target accuracy and had significantly greater deviations (i.e., difference between the location of the desired response versus the location of incorrect response) compared with control animals. These behavioral impairments were accompanied by a degraded sound-azimuth selectivity in the primary auditory cortex neurons.

Summary

Earlier experimental animal studies have found decreased auditory function in adult monkeys and rodents after lifetime exposure to Pb in animals with peak BLLs greater than 30 μg/dL, but the persistence of these effects at lower BLLs and in juvenile animals was uncertain. Three recent studies evaluated auditory thresholds using BAEP in rodents exposed to Pb starting in the postnatal or juvenile period. Jamesdaniel et al. (2018) found 8–12-dB upward shifts in hearing thresholds between 4 and 32 kHz in young adult mice (peak BLLs of 29 μg/dL). Studies evaluating lower mean BLLs from 3 to 8 μg/dL did not report differences in BAEP thresholds. However, mice with mean peak BLLs of 8 μg/dL had significant deficits in auditory processing, including decreased sound discrimination and sound localization ability paired with dysfunction in the auditory cortical neurons (Liu et al., 2019; Zhu et al., 2016).

3.5.6.2 Visual Function

The evidence reviewed in the 2013 Pb ISA was inadequate to determine whether a causal relationship exists between Pb exposure and visual function in children (U.S. EPA, 2013). A study in children and a few studies in animals showed Pb-associated increases in supernormal electroretinograms; however, the biological plausibility of the observations was unclear. Overall, the available epidemiologic and toxicological evidence was of insufficient quantity, quality, and consistency to support a causality conclusion.

3.5.6.2.1 Epidemiologic Studies of Visual Function

Only a few epidemiologic studies examined the association between Pb exposure and decrements in visual function in children (Silver et al., 2016; Fillion et al., 2013). Since the measures of visual function differed between studies, it is difficult to draw any conclusions about Pb exposure and visual

function in children. Silver et al. (2016) measured grating visual acuity (VA) in 6-week-old infants in China. Compared with low (<2 µg/dL) BLLs measured during late pregnancy, infants exposed to medium (2–3.8 µg/dL) and high (>3.8 µg/dL) Pb levels were more likely to have lower grating VA (Silver et al., 2016). When using Pb levels measured in cord blood and during mid-pregnancy, however, the association for grating VA was attenuated and moved closer toward the null (Silver et al., 2016). In Brazil, Fillion et al. (2013) measured contrast sensitivity (cycles per degree [cpd]) and acquired color vision loss (color confusion index, CCI) in study volunteers that included adolescents (age range: 15–66 years). Based on the entire study population, blood Pb exposure was negatively associated with the intermediate spatial frequency of contrast sensitivity (12 cycles/degree); however, results varied by spatial frequency (Fillion et al., 2013). For CCI, there was a small positive association with blood Pb (Fillion et al., 2013).

Summary

Overall, the available epidemiologic and toxicological evidence assessed in the 2013 Pb ISA was of insufficient quantity, quality, and consistency to support a causality conclusion. A limited number of recent epidemiologic studies are available for consideration; however, measures of visual function differed between studies limiting observations regarding the consistency of the evidence overall.

3.5.6.2.2 Toxicological Studies of Visual Function

The evidence base pertaining to effects on visual function in the 2013 Pb ISA was largely supported by seminal literature reviewed previously in the 1986 and 2006 Pb AQCDs showing reduced VA, retinal alterations, and changes in CNS visual processing areas and subcortical neurons involved in vision (U.S. EPA, 2013, 2006, 1986). Electroretinography (ERG), which measures the bioelectrical response of the retina to a light stimulus, is used to detect abnormalities in retinal functioning. Fox et al. (2008) found that Pb exposure in female Long-Evans rats (gestation through PND 10, measured at PND 90) induced supernormal ERGs (i.e., increases in the response amplitude) at low and moderate exposure levels (BLLs of 12 and 24 µg/dL) and subnormal ERGs (i.e., decreases in the response amplitude) in the high exposure group (BLL of 46 µg/dL). Earlier studies have also found Pb-related aberrations in ERGs, but the direction of this effect is inconsistent (i.e., both subnormal and supernormal responses have been detected) (Fox et al., 1997; Lilienthal et al., 1988). As discussed in Giddabasappa et al. (2011), the effect direction may be related to both the lifestage during exposure (gestational versus postnatal) and the Pb dose. This study also demonstrated that low to moderate gestational Pb exposure (BLLs: 10 and 27 µg/dL) increased and prolonged retinal progenitor cell proliferation, resulting in selectively increased rod photoreceptor and bipolar cell neurogenesis in C57BL/6 mice at PND 60 (Giddabasappa et al., 2011). Adult monkeys (*Macaca fascicularis*) with lifetime Pb exposure, producing BLLs from 50–115 µg/dL, had temporal vision dysfunction but no change in spatial function (Rice, 1998). In contrast to these effects, Laughlin et al. (2008) found that Pb exposure in Rhesus monkeys (exposed from PND 8–26 weeks; BLLs of 35–40 µg/dL) did not significantly affect the development of photopic spatial acuity

assessed using a modified Teller preferential looking paradigm. Recent PECOS-relevant studies have not further examined the effects of Pb on visual function.

3.5.6.3 Relevant Issues for Interpreting the Evidence Base

3.5.6.3.1 Potentially At-Risk Populations

Genes

Pawlas et al. (2015) conducted multivariable analyses stratified by polymorphisms in the ALAD and VDR genes and found that the associations for BAEP and pure-tone audiometry per μg/L increase in blood Pb were generally null (Pawlas et al., 2015).

3.5.6.4 Summary and Causality Determination: Sensory Organ Function

The 2013 Pb ISA presented two causality determinations related to sensory function in children: auditory function and visual function (U.S. EPA, 2013). At the time, the evidence was sufficient to conclude that a causal relationship was likely to exist between Pb exposure and auditory function decrements in children. For visual function, the evidence was inadequate to determine if a causal relationship exists. In 2015, the Preamble to the ISA introduced minor changes to the language used in the causality framework descriptors (U.S. EPA, 2015). This change has affected the causality determination for this section. Importantly, the new determination is not intended to be interpreted as a weakening of the evidence base, as recent evidence has remained consistent with previously reviewed studies.

Auditory processing decrements were previously demonstrated in a prospective study by Dietrich et al. (1992). In 5-year-old children, elevated BLLs during infancy (mean BLLs of 4.8 μg/dL at 10 days old) were associated with poorer performance on a test for auditory processing disorders after adjusting for confounding factors including SES, HOME score, a variety of birth outcomes, maternal alcohol consumption, maternal smoking, and overall child health. Recently, experimental animal studies demonstrated that postnatal Pb exposure resulting in mean peak BLLs of 8 μg/dL also caused significant deficits in auditory processing, including decreased sound discrimination and sound localization ability paired with dysfunction in the auditory cortical neurons (Liu et al., 2019; Zhu et al., 2016).

Multiple large cross-sectional NHANES and HHANES studies have shown that higher BLLs (children aged 4–19; BLLs 8 μg/dL) are associated with increased hearing thresholds (Schwartz and Otto, 1991, 1987). These associations remained after adjustment for age, sex, race, family income, parental education, and nutritional factors. Recent cross-sectional and case-control studies continued to demonstrate associations with 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 (Xu et al., 2020; Liu et al., 2018c; Choi and Park, 2017; Shargorodsky et al., 2011). Furthermore, hearing threshold increases were previously demonstrated in adult nonhuman primates after developmental or lifetime Pb exposure, although BLLs in these studies were greater than 30 µg/dL (Laughlin et al., 2009; Rice, 1997). Recent experimental animal studies have not further evaluated hearing thresholds in nonhuman primates and instead have focused on BAEPs in rodents. Jamesdaniel et al. (2018) found 8–12-dB upward shifts in auditory thresholds between 4 and 32 kHz in young adult mice exposed during adolescence (peak BLLs 29 µg/dL). Similar studies did not detect differences in BAEPs in rodents with lower peak BLLs (3 to 8 µg/dL). Likewise, a few recent epidemiologic studies also evaluated BAEP with inconsistent results.

Although Pb-induced alterations in subcortical visual neurons, visual processing areas, and retinal development have been demonstrated, supporting the biological plausibility of Pb-associated effects on vision (U.S. EPA, 2013), evidence relating to visual function in epidemiological and toxicological studies remains limited and inconsistent. Silver et al. (2016) found that decreased visual acuity in infants was associated with maternal BLLs higher than 2 µg/dL in late pregnancy, but this association was weaker with BLLs in both mid-pregnancy and cord blood. Studies in nonhuman primates failed to detect changes in visual acuity at BLLs above 35 µg/dL, although one reported decrements in temporal acuity as a result of Pb exposure (Laughlin et al., 2008; Rice, 1998). Another recent study found associations with blood Pb and decrements in contrast sensitivity and color vision, an endpoint that has not been previously studied, in a study population that included adolescents (15–66 years old) (Fillion et al., 2013). Studies in both humans and animals have found significant but inconsistent changes in ERGs (Fox et al., 2008; Rothenberg et al., 2002; Fox et al., 1997), though it is unclear if these findings translate to functional visual changes.

In conclusion, the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and sensory function in children. This determination is based primarily on the strongest line of evidence within the sensory function grouping (*i.e.,* auditory function). No recent epidemiologic studies have further investigated the auditory processing decrements shown in Dietrich et al. (1992), but recent experimental animal studies have demonstrated Pb-induced effects on auditory processing. Cross-sectional and case-control studies focusing on the impact of Pb exposure on hearing loss generally support an association but are not entirely consistent. Experimental animal studies evaluating hearing loss at human relevant BLLs in young animals are not available. Limited epidemiologic studies have evaluated Pb exposure and visual function in children with inconsistent findings, but evidence for biological plausibility has been demonstrated.

Table 3-7 Evidence that is suggestive of, but not sufficient to infer, a causal relationship between Pb exposure and sensory organ function in children

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Auditory Function			
Consistent findings from a few epidemiologic studies with relevant BLLs	Prospective study found associations of prenatal (maternal), neonatal, yearly age 1 to 5 yr, lifetime avg BLLs with poorer auditory processing in children at age 5 yr in Cincinnati.	Dietrich et al. (1992)	Blood Pb means: neonatal (10 d) 4.8 µg/dL, yearly age 1 to 5 yr 10.6–17.2 µg/dL, lifetime (to age 5 yr) avg NR
	Cross-sectional and case-control studies for increased hearing thresholds in children ages 3–19 yr, including analyses of NHANES, HHANES and KNHANES in association with higher concurrent BLLs.	Section 4.3.6.1, (U.S. EPA, 2013)	Blood Pb median: HHANES: 8 µg/dL; NHANES: NR
		Xu et al. (2020) Liu et al. (2018c)	Means 3.63–5.69 µg/dL (3–7 yr)
		Shargorodsky et al. (2011)	NHANES (2005–2008): med ~1 µg/dL (12–19 yr)
		Choi and Park (2017)	KNHANES: GM: 1.26 µg/dL (15.6 yr)
Epidemiologic evidence helps to rule out chance, bias and confounding with reasonable confidence	Prospective study adjusted for SES, HOME score, birth outcomes, obstetrical complications, maternal smoking. Several other factors considered.	Dietrich et al. (1992)	
	Cross-sectional and case-control studies considered potential confounding by age, sex, race, income, parental education, nutritional factors.	Xu et al. (2020) Liu et al. (2018c) Shargorodsky et al. (2011) Choi and Park (2017)	

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Uncertainty due to lack of animal evidence in juveniles and limited evidence at relevant exposure levels	Hearing loss in adult monkeys and decreased BAEP in young adult rodents at higher exposure levels.	Rice (1997) Laughlin et al. (2009) Jamesdaniel et al. (2018)	Peak BLLs >29 µg/dL
	Decrements in sound discrimination and localization in young adult rodents.	Zhu et al. (2016) Liu et al. (2019)	Peak BLLs 8.2 µg/dL
Visual Function			
Limited evidence from epidemiologic studies	Associations with some tests of grating VA and contrast sensitivity observed.	Silver et al. (2016) Fillion et al. (2013)	
Uncertainty due to limited animal evidence in juveniles and at relevant exposures	Higher than relevant postnatal Pb exposure did not cause changes in VA in infant nonhuman primates in infants but did decrease temporal acuity in adults.	Laughlin et al. (2008) Rice (1998)	BLLs >35 µg/dL
Biological plausibility demonstrated	Pb-induced alterations in ERGs, subcortical visual neurons, visual processing areas, and retinal development demonstrated.	(U.S. EPA, 2013)	

avg = average; BAEP = brainstem auditory evoked potentials; BLL = blood lead level; d = day; ERG = electroretinography; GM = geometric mean; HHANES = Hispanic Health and Nutrition Examination Survey; HOME = Health Outcomes and Measures of the Environment; KNHANES = Korea National Health and Nutrition Examination Survey; NHANES = National Health and Nutrition Examination Survey; NR = not reported; Pb = lead; SES = socioeconomic status; VA = visual acuity; yr = year(s).

[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015). Note that the change from "likely to be causal" for auditory effects in children in the 2013 Lead ISA, to "suggestive of, but not sufficient to infer, a causal relationship" for sensory organ function in children reflects minor changes to the causal framework, rather than a weakening of the evidence base pertaining to auditory effects in children.

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

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

3.5.7 Social Cognition and Behavior in Children

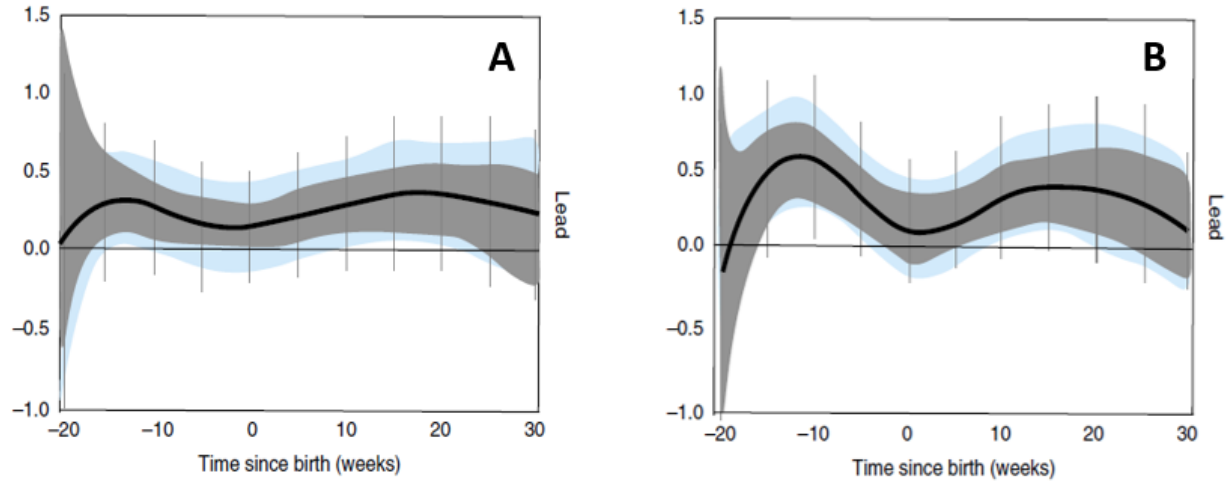
In addition to neurodevelopmental disorders covered in previous sections—including ADHD, intellectual and developmental disabilities, and motor disorders—there is an emerging body of research on autism spectrum disorder (ASD) and other conditions related to social cognition and behavior. The 2013 Pb ISA (U.S. EPA, 2013) did not evaluate any epidemiologic studies examining associations between Pb exposure and autism. ASD is generally characterized by restricted interests and behaviors, including stereotyped patterns of behavior and sensory sensitivities. To meet the DSM criteria for ASD, a child must have persistent deficits in social communication and demonstrate repetitive behaviors (APA, 2013). Social cognition, which is often impaired among individuals with ASD, involves the ability to interpret and respond to social cues, communication, and interaction. These traits (or behaviors) can be measured on a continuum in the general population with scores exhibiting a fairly normal distribution, with scores at the extreme impaired end indicating a higher risk for ASD (Constantino, 2011). Deficits in social cognition have been associated with lifelong educational, vocational, adaptive functioning, and mental health challenges among individuals with and without a clinically diagnosed disorder. Autism diagnosis (e.g., via the ICD code), the CBCL, Social Responsiveness Scale (SRS), BASC-2, BSID-II and III, CDIIT, ASQ:I, GDS, Social Maturity Scale (SMS), MDAT, and ECDI have been used in studies examining the association of Pb exposure with social cognition and behavior.

3.5.7.1 Epidemiologic Studies of Social Cognition and Behavior

There have been a number of recent studies of ASD and deficits in social cognition and related behaviors. Many of these recent studies did not control for potential confounders and/or did not include robust statistical methods to estimate C-R relationships between Pb exposure and outcome, and are not considered further in this section (Fiłon et al., 2020; Qin et al., 2018; Skalny et al., 2017; Macedoni-Lukšič et al., 2015; Alabdali et al., 2014; Yassa, 2014; De Palma et al., 2012; Blaurock-Busch et al., 2011; Tian et al., 2011). Instead, the ensuing discussion focuses on a number of autism and social cognition studies that include more comprehensive control for potential confounders. The relevant studies provide some evidence of a positive association between Pb exposure and ASD, along with generally consistent supporting evidence of an association with decrements in social cognition. Measures of central tendency for BLLs used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 3-13E of Section 3.7. An overview of the recent evidence is provided below.

Two recent studies used robust modeling approaches to assess the C-R relationship between exposure to Pb and ASD (Arora et al., 2017; Kim et al., 2016). While each study examined different biomarkers of exposure and exposure windows, both indicated associations between Pb exposure and ASD. Arora et al. (2017) conducted a difference-in-differences analysis of a small case-control study of

8- to 12-year-old twins with discordant or concordant ASD status. Pb was measured in shed deciduous teeth using a method that provided temporal estimates of tooth Pb levels ranging from 20 weeks before birth to 30 weeks after birth. To estimate the relationship between tooth Pb and ASD across this exposure window, the authors used distributed lag models to estimate the smoothed mean differences in tooth Pb levels in discordant pairs minus the mean differences in concordant twins at each time point. In this case, concordant twins served as the control group to account for natural variations in Pb exposure within a dyad. One analysis used concordant twins without ASD and the other used concordant twins with ASD as the control groups. In both cases, the difference in tooth Pb levels between discordant twins was greater than the difference in concordant twins across the entire exposure window, though there appeared to be bimodal peaks in tooth Pb differences from about 10 to 15 weeks before birth and 10 to 20 weeks after birth (see Figure 3-14).



ASD = autism spectrum disorder.
Black line represents the difference in mean differences in tooth Pb levels between discordant ASD twins and: A) control twins; or B) concordant ASD twins. Gray bands are unadjusted 95% CIs, while blue bands are adjusted for intra-twin correlations. Values above zero represent increased levels in ASD cases compared with the non-ASD sibling after taking into account average difference in control twins.
Source: Arora et al. (2017).

Figure 3-14 Differences in mean difference tooth Pb levels for autism spectrum disorder in discordant twin pairs versus (A) non-autism spectrum disorder twin pairs or (B) autism spectrum disorder concordant twin pairs.

In a large cohort study of children in South Korea, Kim et al. (2016) analyzed blood Pb in relation to autistic behaviors measured by parental response to the Autism Spectrum Screening Questionnaire (ASSQ) and the SRS at ages 11–12 years old. BLLs at study enrollment (7–8 years old) were associated with higher scores on the ASSQ (number of autistic behaviors) and SRS (severity across domains of social awareness, cognition, communication, motivation, and mannerisms). There were null associations

with blood Pb measured at 9–10 years and attenuated, but still positive, associations with concurrent BLLs (11–12 years old). Nonparametric generalized additive models indicated an approximately linear relationship between BLLs at enrollment and scores on the SRS. In addition to continuous models, the authors also dichotomized ASSQ scores and reported 45% higher odds (95% CI: 10%, 93%) of a positive screen for autism (ASSQ score ≥17) per 1 μg/dL higher BLL at enrollment. Notably, symptoms of ASD manifest as early as infancy and although BLLs in this study were measured prior to assessment of autistic behaviors, the relevant exposure window likely preceded exposure measurement.

In contrast to the results from Kim et al. (2016) and Arora et al. (2017), recent case-control studies did not observe an association between adjusted mean childhood BLLs and ASD cases (Rahbar et al., 2021; Rahbar et al., 2015). In addition to matching cases and controls on age and sex, the authors estimated mean differences using a linear model controlling for a variety of demographic and SES factors, including maternal age. Similarly, a recent case-control study reported a null association between tertiles of maternal BLLs and ASD in children, though there was some evidence of a nonlinear association in a cubic spline model (Skogheim et al., 2021). The study populations for these analyses included children and mothers with lower (<2 μg/dL; (Skogheim et al., 2021; Rahbar et al., 2015)) and higher (>7 μg/dL; (Rahbar et al., 2021)) mean or median BLLs.

One additional large retrospective study in Northeast China (Dong et al., 2022) compared current BLLs in children with moderate/severe versus mild autism, as determined by CARS scores. Mean BLLs for the mild and moderate/severe groups were 2.58 (SD: 1.08) μg/dL and 3.25 (SD: 1.89) μg/dL, respectively. After adjusting for age, residence, parental caregiving, parental education, and gastrointestinal conditions, autism severity was positively associated with BLL (β = 0.03 [95% CI: 0.01, 0.05]).

Additional supporting evidence was provided by several cohort studies that investigated associations between Pb exposure and social cognition in children without autism. Most of these studies reported inverse relationships between prenatal Pb exposure and social cognition measures. Several studies additionally investigated effect modification by various other factors.

Rygiel et al. (2021) assessed the relationship between maternal blood Pb and infant behavioral development at 12 to 24 months of age in a small analysis of three birth cohorts from the ELEMENT study in Mexico City. The authors used the behavioral rating scale (BRS) of the BSID-II to examine attention, social engagement, orientation, motivation, and emotional response, giving rise to two social cognition outcomes: orientation/engagement (ORIEN) and emotional regulation (EMOCI). The authors reported that children had lower 24-month EMOCI and ORIEN percentile ranks with higher maternal BLLs. Associations were observed in relation to maternal BLLs measured during each trimester, but greatest for the second trimester, with 1.13% (95% CI: −2.63%, 0.37%) and 0.98% (95% CI: −2.83%, 0.88%) lower 24-month EMOCI and ORIEN percentiles, respectively, for 1 μg/dL higher second trimester BLLs. In an examination of the mediation of trimester-specific Pb exposure by DNA methylation at several previously identified CpG sites, the authors observed both enhancing and

suppressive effects of DNA methylation on the association between blood Pb and neurocognitive outcomes, depending on the gene locus, with methylation at the majority of loci playing a suppressive role. Shekhawat et al. (2021) similarly reported null but slightly inverse associations between cord blood Pb and social-emotional scores from the BSID-III in a study of mother-child pairs in western Rajasthan, India. Neurocognitive assessments were conducted at the average age of 6.5 months. Additionally, in an analysis of the Navajo Birth Cohort Study, Nozadi et al. (2021) reported imprecise inverse associations between maternal BLLs and communication (β = −0.15 [95% CI: −0.58, 0.28]) and personal-social (β = −0.11 [95% CI: −0.72, 0.50]) domain scores on the ASQ:I at 10 months.

Some cohort studies examined interactions between Pb levels and the levels of other trace elements (Nyanza et al., 2021; Doherty et al., 2020; Lin et al., 2013). Lin et al. (2013) measured maternal blood Pb and assessed child development (including social and self-care skills) in the TBPS with the CDIIT, as described in Section 3.5.1.2. The authors observed that children with high Pb exposure (≥75th percentile: 1.65 μg/dL) had lower social DQs (β = −5.89 [95% CI: −10.81, −0.97]) compared with those with low prenatal Pb exposure. In addition, the authors reported lower social or self-help DQs among those with higher Pb and Mn concentrations in an interaction analysis. Nyanza et al. (2021) measured Pb, Hg, Cd, and As concentrations using dried blood spots from pregnant mothers at 16–27 weeks of gestation in Northern Tanzania. Adjusting for maternal age, maternal education, maternal and parental occupation, number of under-five siblings at home, family socioeconomic wealth quintile, infant sex, infant age, birth weight, and height and weight at neurocognitive testing, the authors did not observe an association between high Pb exposure (>3.5 μg/dL) and social impairment on the MDAT, which is described in Section 3.5.1.2. However, an interaction analysis with maternal blood Hg levels showed that children highly exposed to both Hg (≥0.08 μg/dL) and Pb were more likely to have global neurodevelopmental impairment (PR = 1.40 [95% CI: 0.90, 2.10]). Doherty et al. (2020) measured concentrations of Pb and other metals (As, Cu, Mn, Se, and Zn) in maternal prenatal and postnatal toenails and infant toenails at 6 weeks of life from mother-infant pairs in the New Hampshire Birth Cohort. The three exposure assessments estimated exposures that occurred during periconception and early pregnancy, mid-pregnancy, and late pregnancy and early neonatal life, respectively. The authors observed mostly negative but imprecise associations between prenatal and child toenail Pb levels and total SRS−2 scores. They also observed mostly positive but imprecise associations between postnatal maternal and child toenail Pb levels and the adaptive skills composite on the BASC-2 (see Section 3.7, Table 3-13E). Pb concentrations did not appear to interact with other metals on the total SRS−2 score or the BASC-2 adaptive skills composite, and sex-stratified analyses revealed inconsistent associations among girls.

An additional study assessed effect modification by maternal psychosocial measures. Zhou et al. (2017) investigated the interactions of maternal BLL in whole blood and maternal prenatal stress levels with child development (including adaptive behavior and social domains) using the GDS. Among those with high maternal stress levels (GSI: P75–P100), adaptive behavior DQs were 17.93 points lower (95% CI: −35.83, −0.03) per log10-transformed μg/dL higher maternal BLL. Social behavior DQs were also

inversely associated with maternal BLL in children of mothers with high stress levels (β = −41.00 [95% CI: −63.11, −18.89] per log−10 transformed unit of BLL).

One cross-sectional study (Ruebner et al., 2019) evaluated the association between concurrent BLL and neurocognitive outcomes including adaptive skills among children with CKD, using parent ratings on the BASC-2. This study is discussed in more detail in Section 3.5.2.1.1. Higher BLL was associated with worse adaptive skills composite scores (β = −3.1) in univariable analyses; however, this association did not remain after adjusting for key sociodemographic and clinical confounders.

One additional prospective study (Vigeh et al., 2014) measured domains of social and self-help skills but presented only associations with composite neurodevelopment test scores (described in Section 3.5.1.2), which impedes parsing of specific social cognition effects of Pb exposure. In addition, Kim et al. (2018b) evaluated concentrations of Pb in maternal serum, cord blood, urine, and breast milk in association with neurodevelopmental and behavioral outcomes, including social quotient (SQ) measures from the SMS among 13–24-month-old children. However, they reported only statistically significant results in the paper, precluding quantitative results for blood Pb and SQ.

Recent epidemiologic studies utilized a wide range of outcome measures, including diagnostic tests of autism (e.g., ICD code, DSM classification, ASSQ, and the Autism Diagnostic Observation Schedule [ADOS]), behavior rating systems (e.g., CBCL, SRS−2, BASC-2, and SMS), and neurodevelopmental assessments with social behavioral subtests (e.g., BSID-II and III, CDIIT, ASQ:I, GDS, MDAT, and ECDI). Psychometric tests of social cognition often add valuable dimensional information regarding the severity and type of social deficit among children with autistic traits, and the wide variety of tests used in the evaluated studies provided insight into diverse aspects of problems with social cognition, including communication, adaptive and self-help skills, social engagement, and emotional behavior. One limitation, however, is that this variety complicates a straightforward interpretation of results due to the lack of consistency of measures. Many behavioral tests provide outcomes that overlap with domains discussed in other sections such as externalizing behavior (Section 3.5.3) and internalizing behavior (Section 3.5.4), which can limit parsing of effects. Vigeh et al. (2014) examined social and adaptive skills but reported quantitative results using only the global neurodevelopmental composite score from the ECDI. Other studies (Nyanza et al., 2021; Rygiel et al., 2021) used rating subscale measures (i.e., EMOCI and ORIEN from the BRS; social development score from the MDAT) that are not widely used in the literature, making it difficult to compare results across studies.

3.5.7.1.1 Summary

Two recent high-quality studies of Pb exposure and ASD reported positive associations between increased Pb exposure and higher risk of ASD diagnosis or symptomatology (Arora et al., 2017; Kim et al., 2016). One retrospective study also observed a positive association between greater autism severity

and current BLL (Dong et al., 2022). However, some case-control studies did not find evidence of a positive association (Rahbar et al., 2021; Skogheim et al., 2021; Rahbar et al., 2015). Although most autism studies except one (Kim et al., 2016) were case-control studies, two of the case-control studies accounted for temporality of exposure and outcome by analyzing prenatal maternal blood (Skogheim et al., 2021) or using tooth Pb measurement methods that allow ascertainment of perinatal Pb exposure levels (Arora et al., 2017). Several cohort studies observed null or slight impairments of social dimensions scores. Recent studies of social cognition in children without ASD used a wide variety of psychosocial and neurodevelopmental instruments, such as BASC-2, BSID-II and III, CDIIT, ASQ:I, GDS, SRS, SMS, MDAT, and ECDI, to obtain scores of social, emotional, and adaptive abilities. These studies were mostly prospective in design and accounted for some key potential confounders, including maternal age, parental education, SES, and caregiving.

3.5.7.2 Toxicological Studies of Social Cognition and Behavior

The previous ISA incorporated evidence of the effects of Pb exposure on social cognition and behavior. Donald et al. (1986) reported sex-specific effects of Pb exposure on social investigatory behavior in mice, wherein males and females exposed to Pb displayed enhanced social interaction but at different times after exposure. In a subsequent publication, Donald et al. (1987) reported that Pb exposure increased non-social behavior in males while females displayed decreased non-social behavior. The previous evidence suggests that Pb may influence social behavior in rodents in a sex-specific manner, but the direction of the effect was not clear.

There is limited recent toxicological evidence available on the effects of Pb exposure on social cognition and behavior. A single study by Tartaglione et al. (2020) examined homing test and ultrasonic vocalizations (USV). USV are calls emitted by pups when separated from their mother and siblings and are markers of early emotional and communication development. Pups prenatally and lactationally exposed to Pb exhibited reduced numbers of calls at PND 4 and 12, with no significant differences at PND 7 and 10 from control animals. The same study also performed a homing test, which assesses discriminative performance and maternal preference behavior by separating the pup from the dam and recording the time taken to return to the nest from a maze. The time spent is a measure of both olfactory discrimination and social preference. The authors reported no difference in homing test performance between control and Pb-exposed pups at PND 12 (Tartaglione et al., 2020). In summary, there is limited evidence from the toxicological literature examining potential relationships between developmental Pb exposure and social behavior, which represents an area of uncertainty.

3.5.7.3 Relevant Issues for Interpreting the Evidence Base

3.5.7.3.1 Concentration-Response Function

Evaluation of the shape of the C-R function in recent studies of social cognition is limited, making it challenging to draw conclusions. Across studies, associations between Pb exposure and social cognition and behavior were observed at median or geometric mean maternal and cord BLLs ranging from 3.3 to 5.5 μg/dL, and BLLs measured in children ranging from 1.6 to 3.9 μg/dL (Table 3-8). Kim et al. (2016) used penalized regression splines to examine the C-R relationship between BLLs at 7–8 years old and SRS scores at 11–12 years old. The C-R relationship was approximately linear across the range of the BLL distribution, though there is more confidence in the shape of the C-R relationship (i.e., more narrow confidence limits) closer to the mean, where there is a higher density of observations. Spline models for most of the SRS subscales are also approximately linear, except for social cognition, which has a sublinear relationship with BLLs (i.e., a smaller slope below the mean).

3.5.7.3.2 Potentially At-Risk Populations

Maternal Stress

There is limited evidence that maternal stress modifies the association between Pb exposure and social cognition. Stratifying by maternal stress, Zhou et al. (2017) found that social behavior (β = −41.00, 95% CI: −63.11, −18.89 per log−10 transformed unit of BLL) and adaptive behavior (β = −17.93, 95% CI: −35.83, −0.03 per log−10 transformed unit of BLL) in toddlers were inversely associated with BLLs among children of mothers with high prenatal stress. In contrast, adaptive behavior appeared to have a positive but imprecise relationship (β = 7.57, 95% CI: −0.12, 15.27 per log−10 transformed unit of BLL) with BLLs among children of mothers with low prenatal stress, while the association with social behavior was null in the same population.

Co-exposure to Other Metals or Chemicals

A limited number of studies examined co-exposures to other metals as potential modifiers of the relationship between Pb and social cognition. Lin et al. (2013) observed slight impairments to social and self-help DQs among those with high concentrations of both Pb (≥1.65 μg/dL) and Mn (≥5.93 μg/dL). Nyanza et al. (2021) conducted interaction analyses of Pb and various neurodevelopmental outcomes with Hg, Cd, and As, but did not report results for social skills.

Gene-Environment Interactions

A single study evaluated the role of DNA methylation as a mediator of the relationship between Pb exposure and social cognition and behavior. Rygiel et al. (2021) found both enhancing and suppressing effects of DNA methylation at several CpG sites in mediation analyses. Methylation of cg23280166 within CCSER1, a gene which has been associated with ADHD, suppressed the association between second trimester Pb levels and ORIEN and EMOCI scores at 24 months old, while methylation at cg18515027 (GCNT1), positively mediated the association between first and second trimester BLLs and 24-month EMOCI scores. Likewise, DNA methylation of cg23280166 (VPS11) also positively mediated the relationship between third trimester BLLs and 24-month EMOCI scores.

Pre-existing Conditions

Although no recent studies evaluated pre-existing conditions as potential effect modifiers, one study evaluated the relationship between Pb exposure and adaptive behavior among children with CKD. After adjusting for sociodemographic and CKD-related variables, they did not report quantitative results because they did not observe a statistically significant association (Ruebner et al., 2019).

Sex

There is limited evidence on sex as a modifier of the association between Pb exposure and social cognition and behavior. Doherty et al. (2020) observed inconsistent associations between Pb and SRS−2 total and BASC-2 adaptive skills composite scores in sex-stratified analyses. Female infant toenail Pb concentration was positively associated with adaptive skills (β = 0.26 [95% CI: 0.07, 0.45] per log−2 transformed unit of BLL) and maternal prenatal toenail Pb was negatively associated with adaptive skills in female infants (β = −0.19 [95% CI: −0.34, −0.04] per log−2 transformed unit of BLL), but associations in male infants were null. Sample size limited statistical precision in sex-stratified analyses, which may help explain these inconsistencies.

3.5.7.3.3 Confounding

Several sociodemographic characteristics were considered as potential confounders in recent epidemiologic studies. Child age at outcome measurement was included in all but three studies (Shekhawat et al., 2021; Kim et al., 2018b; Vigeh et al., 2014) and child sex was included in all studies but two (Nozadi et al., 2021; Vigeh et al., 2014). Parental education, which was consistently associated with BLLs and measures of social cognition and/or autism status, was adjusted for or considered in all studies except Rygiel et al. (2021). However, Rygiel et al. (2021) was the only study to include maternal IQ as a potential confounder. Many studies also included SES among their modeled covariates (Nyanza et

al., 2021; Rygiel et al., 2021; Ruebner et al., 2019; Zhou et al., 2017; Vigeh et al., 2014). Quality of parental caregiving (e.g., HOME score) was included in only one study (Lin et al., 2013).

Various pregnancy and birth factors are also relevant for consideration as potential confounders. Maternal age is strongly associated with autism risk (Sandin et al., 2012) and is correlated with Pb exposure (Ettinger et al., 2020); hence, lack of inclusion in models may introduce bias. Additionally, autism, like many developmental disorders, is more prevalent as delivery diverges in both directions from 40 weeks of gestation. As such, gestational age, birth weight, and maternal age were consistently included as a potential confounder in most analyses. Breastfeeding, parity, maternal smoking and alcohol intake, and food consumption during pregnancy were also included in multiple studies.

Genetics may also play a large role in the association between Pb exposure and social cognition abilities. Arora et al. (2017) used a case-control design with twin pairs, which allowed for matching on genetic factors to some extent. Rahbar et al. (2021) evaluated interaction effects of glutathione S-transferase (GST) genes (GSTP1, GSTM1, and GSTT1), which have been linked to detoxification of environmental pollutants and to autism status. Rygiel et al. (2021) examined mediation by DNA methylation at various CpG sites linked to prenatal Pb levels.

Co-exposures and mixtures with other trace metals were considered in several studies. Nozadi et al. (2021) found positive correlations of BLLs with Mn and Cd. The authors used an algorithm to identify the control variables for each metal they analyzed, including all co-occurring metals and demographics; however, none met the inclusion criteria of being significantly associated with both the exposure and outcome, and the final model did not include any covariates. Additionally, Lin et al. (2013) and Nyanza et al. (2021) reported that Pb was positively correlated with Mn and As, and Cd and Pb, respectively. However, neither study adjusted for metals in their analyses. Kim et al. (2016) adjusted for Hg and was the only study to adjust for a co-occurring metal in its final model.

3.5.7.3.4 Lifestages

No epidemiologic studies examining the relationship between Pb exposure and social cognition and behavior in children were included in the 2013 Pb ISA (U.S. EPA, 2013). Recent studies demonstrated that BLLs measured during various lifestages and time periods (i.e., prenatal, early childhood, later childhood, and concurrent with outcome assessment) are associated with ASD and decrements in social cognition. Due to differences in study designs and the variety of psychometric tests used to assess aspects of social cognition, it is difficult to compare the magnitude of associations across studies to characterize important lifestages and time periods of Pb exposure. There is some examination of different exposure measurement windows within studies. In the case-control study of twins described previously, Arora et al. (2017) used laser ablation-inductively coupled plasma-mass spectrometry (ICP-MS) to estimate pre- and postnatal Pb exposure from shed deciduous teeth. Differences in tooth Pb levels were consistently higher in discordant ASD twins across the exposure period (20 weeks prenatal to 30

weeks postnatal) compared with concordant and control twins, with bimodal peaks around 10 to 15 weeks before birth and 10 to 20 weeks after birth (see Figure 3-14). This is consistent with results from a birth cohort study that reported negative associations between maternal BLLs and social cognition in infants (Rygiel et al., 2021). The observed associations were strongest in magnitude with maternal BLLs measured in the second trimester compared with BLLs in the first and third trimesters. Although the limited number of studies that evaluate different exposure windows makes it difficult to draw firm conclusions on critical lifestages, the nature of ASD as a developmental disorder suggests that prenatal and early infant exposures may be of particular importance.

It should be noted that children with ASD have a high prevalence of pica, a compulsive eating behavior of non-food items (Fields et al., 2021). Thus, children with ASD may have elevated BLLs due to their higher likelihood of ingesting soil or other materials contaminated with Pb, rather than Pb exposure causing ASD. As there is potential for reverse causation, accurately ascertaining the time of exposure measurement is crucial in order to determine whether a causal effect of Pb on ASD exists, and studies with exposure metrics that precede pica behavior would mitigate this concern. Such metrics include bone Pb, tooth Pb (Arora et al., 2017), and cord or maternal blood Pb (Nozadi et al., 2021; Nyanza et al., 2021; Rygiel et al., 2021; Shekhawat et al., 2021; Skogheim et al., 2021; Kim et al., 2018b; Zhou et al., 2017; Vigeh et al., 2014; Lin et al., 2013).

3.5.7.4 Summary and Causality Determination: Social Cognition and Behavior

The 2013 Pb ISA (U.S. EPA, 2013) did not include a causality determination for social cognition and behavior in children. There were no epidemiologic studies on social cognition and behavior in children in the previous ISA, and only a few toxicological studies that examined social behavior in mice. The number of studies examining autism and social cognition in relation to Pb exposure has increased substantially since the 2013 Pb ISA (U.S. EPA, 2013), highlighted by recent epidemiologic studies that provide some evidence that Pb exposure is associated with increased ASD incidence and symptomology, as well as decrements in social, emotional, and adaptive abilities. Recent toxicological evidence, along with studies reviewed in the 2013 Pb ISA, provide some evidence of Pb-induced changes in social behavior in mice, but the direction of the observed changes was inconsistent.

A recent novel epidemiologic analysis of twins provides strong evidence of an association between Pb exposure and ASD. Arora et al. (2017) examined tooth Pb levels with respect to ASD status among discordant and concordant twin pairs and observed higher Pb levels in the affected twin among discordant monozygotic and dizygotic pairs. In contrast, concordant twins demonstrated similar levels of exposure. This study also provided some insight into potentially sensitive time windows of exposure in which the association between tooth Pb levels and autistic status was highest between 10–15 weeks before birth and 10–20 weeks after birth. Additional support was provided by a prospective cohort study, which reported that the number and severity of autistic behaviors in young children was positively

associated with low BLLs (geometric mean: 1.58–1.64 µg/dL) at several points prior to outcome assessment (Kim et al., 2016). There is some uncertainty about the relevance of the exposure window in this study given that the earliest Pb measurements occurred at 7–8 years old, which is close to the outcome assessment age (11–12 years old) and later than autistic behaviors typically manifest. Additionally, covariates examined in this study did not include maternal age, which is an important potential confounder for developmental disorders like autism; therefore, lack of adjustment for this variable weakens the conclusions that can be drawn from the analysis. Dong et al. (2022) provides support for the positive association between autism severity and BLLs among children 2 to 13 years old at low levels of current blood Pb (mild group mean: 2.58 µg/dL; moderate/severe group mean: 3.25 µg/dL); however, the study's retrospective design and the wide range of the ages of assessed children introduce uncertainty regarding potential reverse causality.

Several prospective studies among children without autism provide some additional support for associations between Pb exposure and measures of social impairment in children (Nozadi et al., 2021; Nyanza et al., 2021; Rygiel et al., 2021; Shekhawat et al., 2021; Zhou et al., 2017; Lin et al., 2013). Median or geometric mean maternal and cord BLLs in these studies ranged from 3.3 to 5.5 µg/dL, and BLLs measured in children ranged from 2.7 to 3.9 µg/dL. These studies had moderate to good follow-up participation rates, and follow-up durations ranged from 6.5 months to 3 years. Furthermore, they demonstrated good confounder control, adjusting for maternal age and some measure of SES or parental education. Notably, the use of non-specific composite test scores (Vigeh et al., 2014) and lesser-used subscales (Nyanza et al., 2021; Rygiel et al., 2021) limits the specificity and generalizability of some studies. Additionally, results from recent studies were not entirely consistent, as some analyses did not observe associations (Rahbar et al., 2021; Skogheim et al., 2021; Doherty et al., 2020; Ruebner et al., 2019; Rahbar et al., 2015). These included mostly case-control studies, one prospective cohort study, and one cross-sectional study. Although all three case-control studies adjusted for maternal age and various relevant covariates among matched pairs, Ruebner et al. (2019) did not.

Two toxicological studies in the 2013 Pb ISA reported a potential sex-based effect modification of the effect of Pb exposure on social behavior (Donald et al., 1987, 1986). Female and male mice exhibited social interaction and non-social behavior at different timings and in different directions. One recent study observed that rats exposed to Pb made fewer ultrasonic vocalizations than did control rats at PND 4 and 12 but not at PND 7 and 10 (Tartaglione et al., 2020). The authors additionally did not observe differences between exposed and control rats on the homing test, which evaluates olfactory discrimination and social preference.

In summary, the body of evidence is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and social cognition and behavior in children. The strongest evidence supporting this causality determination comes from a novel case-control study in twins that provides strong support for a positive association between dentine Pb levels and autism risk. There are a number of recent prospective epidemiologic studies that provide supporting evidence of a positive

association of increases in BLLs with reduced social cognition and increased autistic behaviors in children, but the evidence is not entirely consistent and is limited by the potential for unmeasured confounding by maternal age or the potential for reverse causality due to the timing of exposure in studies examining blood Pb levels. Furthermore, the wide range of social cognition measures used in the evaluated studies simultaneously adds dimensionality and complicates interpretation of the results. Only one recent experimental animal study on Pb exposure and social cognition was available. This study, combined with the toxicological evidence reviewed in the previous ISA suggests that Pb exposure may influence social cognition and communication, though the direction of these effects is inconsistent. Thus, while the limited experimental animal evidence provides some coherence with the epidemiologic evidence, a number of uncertainties remain. The key evidence, as it relates to the causal framework, is summarized in Table 3-8.

Table 3-8 Evidence that is suggestive of, but not sufficient to infer, a causal relationship between Pb exposure and social cognition and behavior in children

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent evidence from a few high-quality epidemiologic studies with relevant blood, bone, and tooth Pb levels	Greater difference in tooth Pb levels among twins discordant for ASD status than among concordant twins.	Arora et al. (2017)	Deciduous tooth Pb NR (early and postnatal Pb levels)
	Lower scores on test of social cognition in a prospective study in South Korea in association with earlier childhood and concurrent mean BLLs.	Kim et al. (2016)	Child blood Pb GM: 7–8 yr: 1.64 µg/dL 9–10 yr: 1.58 µg/dL 11–12 yr: 1.58 µg/dL
	Evidence from multiple prospective cohort studies for small decrements in scores on tests of social cognition among children without autism ages 6.5 mo–3 yr at low levels of exposure.	Shekhawat et al. (2021)	Cord blood Pb GM: 4.14 µg/dL
		Rygiel et al. (2021)	Mat. blood Pb GM (SD): 1st tri.: 5.27 (1.93) µg/dL 2nd tri.: 4.74 (1.96) µg/dL 3rd tri.: 4.98 (1.93) µg/dL Infant blood GM (SD): 12 mo: 3.92 (1.80) µg/dL 24 mo: 3.49 (1.93) µg/dL
		Zhou et al. (2017)	Mat. blood Pb GM (95% CI): 3.30 (3.05, 3.57) µg/dL
		Section 3.5.7.1	

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Epidemiologic studies help rule out chance, bias, and confounding with reasonable confidence	Prospective studies had population-based recruitment with moderate to good follow-up participation not conditional on bone Pb/BLLs and social cognition scores.	Section 3.5.7.1	
	All studies controlled for maternal age, education and/or SES. Some controlled for HOME score, maternal IQ, and exposures to other pollutants.	Table 3-13E	
Limited supporting evidence from case-control and cross-sectional studies	Null findings from case-control studies conducting adjusted mean comparisons of ASD cases and typically developing controls with lower and higher mean or median BLLs, adjusting for maternal age, various demographic and lifestyle factors and dietary consumption.	Skogheim et al. (2021)	Mat. blood Pb GM cases: 0.83 µg/dL controls: 0.88 µg/dL
		Rahbar et al. (2015)	Child blood Pb GM (SD) cases: 2.25 (2.23) µg/dL controls: 2.73 (1.85) µg/dL
		Rahbar et al. (2021)	Child Blood Pb GM cases: 7.11 µg/dL controls: 8.48 µg/dL
	Greater BLLs among children 2–13 years old with moderate/severe vs. mild autism in a retrospective study.	Dong et al. (2022)	Child blood Pb mean (SD) Mild: 2.58 (1.08) µg/dL Moderate/severe: 3.25 (1.89) µg/dL
	Null finding from cross-sectional study. Lacked control for maternal age at delivery.	Ruebner et al. (2019)	Child blood Pb med: 1.2 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Limited experimental animal evidence at relevant exposures	Mixed evidence of enhanced or reduced social interaction behavior among Pb-exposed mice. Some suggestion of sex-specific effect modification.	Donald et al. (1986) Donald et al. (1987)	
	Reduced ultrasonic vocalizations among Pb-exposed rats. No evidence of a difference on homing tests of olfactory discrimination and social preference.	Tartaglione et al. (2020)	Med blood Pb after exposure during pregnancy and lactation: 0.26 µg/mL PND 23

ASD = autism spectrum disorder; BLL = blood lead level; CI = confidence interval; GM = geometric mean; HOME = Health Outcomes and Measures of the Environment; IQ = intelligence quotient; Mat = maternal; med = median; mo = month(s); NR = not reported; Pb = lead; PND = postnatal day; SD = standard deviation; SES = socioeconomic status; tri = trimester; yr = year(s).
[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.

3.6 Nervous System Effects Ascertained during Adult Lifestages

The strongest evidence of Pb-associated nervous system effects in adults without occupational exposure pertained to cumulative exposure and cognitive effects (U.S. EPA, 2013). Prospective studies 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 years) over 2- to 4-year periods. 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 was provided by cross-sectional studies, 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. The multiple exposures and health outcomes examined in many studies reduced the likelihood of biased participation specifically by adults with higher Pb exposure and lower cognitive function. Uncertainties remained due to residual confounding by age and lack of information on the patterns of exposure associated with the BLLs observed in the epidemiologic studies.

3.6.1 Cognitive Function in Adults

The evidence reviewed in the 2013 Pb ISA was sufficient to conclude that "a causal relationship is likely to exist" between long-term cumulative Pb exposure and cognitive function decrements in adults

(U.S. EPA, 2013). Prospective studies of the Normative Aging Study (NAS) and Baltimore Memory Study (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 years) over 2- to 4-year periods among adults without occupational exposure (see Table 4-10 (U.S. EPA, 2013)). 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 was provided by cross-sectional analyses of the NAS, BMS, and the Nurses' Health Study (NHS), which found stronger associations with bone Pb level than concurrent BLL indicating the relative importance of long-term Pb exposure. Cross-sectional analyses considered more potential confounding factors, including dietary factors, physical activity, medication use, and comorbid conditions. The multiple exposures and health outcomes examined in many studies reduced the likelihood of biased participation specifically by adults with higher Pb exposure and lower cognitive function. The effects of recent Pb exposures on cognitive function decrements in adults were indicated in Pb-exposed workers by associations found with BLLs, although these studies did not consider potential confounding by other workplace exposures. The biological plausibility for the effects of Pb exposure on cognitive function decrements in adults was 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 the hippocampus, prefrontal cortex, and nucleus accumbens (U.S. EPA, 2013).

Recent epidemiologic studies provide consistent evidence that higher cumulative exposure indicated by bone Pb levels or childhood BLLs are associated with decrements in cognitive function during young-, mid- or older-adulthood periods (Table 3-14E). Across populations, higher Pb levels were associated with decrements in FSIQ, global cognitive function, executive function, visuospatial and visuomotor skills, language, and memory. Much of this evidence was provided by extended analyses (about 15 years of follow-up data) of the NAS and NHS cohorts considered in the 2013 Pb ISA, and prospective cohort studies from Sweden and New Zealand that explored the effects of early childhood Pb exposure (7–12 years) on IQ and various cognitive domains during young adulthood (18–19 years). Findings from these recent prospective cohort studies, emphasize the important role of early childhood Pb exposure and persistent effects on adult cognition after adjustments of various sociodemographic factors and maternal and childhood IQ. Overall, the longitudinal design with longer follow-up periods, multiple and repeatedly measured cognitive outcomes, and multiple risk factors and confounders accounted for in the studies reduce the bias and strengthen the study findings related to the effects of Pb exposure on adult IQ and cognitive function. Recent evidence from animal studies provide support that postnatal exposure to Pb (either during adolescence or continuing into adulthood) negatively affects learning and memory in rodents. Additionally, adult rodents exposed during early developmental periods displayed impairments in tests of learning and memory conducted in adulthood (reviewed in Section 3.4). This suggests that early life Pb exposure contributes to cognitive dysfunction that persists into adulthood, which is new evidence in this review. Additionally, animals exposed to Pb during adulthood display similar cognitive impairment, though there is still uncertainty regarding the influence of age on Pb exposures during

adulthood. These studies add to the current evidence base suggesting a potential role of both early and later life Pb exposures and biological plausibility for the effects of Pb exposure on cognitive function decrements in adults.

A summary of the recent evidence, which is interpreted in the context of the entire body of evidence, is provided in the subsequent sections. Measures of central tendency for Pb biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Section 3.7, Table 3-14E (Epidemiology) and Table 3-4T (Toxicology).

3.6.1.1 Epidemiologic Studies of Cognitive Function in Adults

Studies in the 2013 Pb ISA (U.S. EPA, 2013) found that higher bone Pb levels, indicating long-term exposure to Pb, were associated with decrements in cognitive function in adults without occupational Pb exposure. There was variability in associations across the various domains of cognitive function tested within studies; however, higher bone Pb levels were associated with poorer performance in most of the tests conducted. Further, discordant Pb associations across domains of cognitive function are likely to reflect biologic variability or differences in the outcome pathophysiology. Across populations, higher bone Pb levels were associated with decrements in executive function, visuospatial skills, learning, and memory. Much of this evidence was provided by analyses of the BMS and NAS, with additional findings reported in the NHS and smaller populations. The strongest evidence for bone Pb-associated cognitive decrements demonstrated that higher tibia (means: 19, 20 μg/g) and patella (mean: 25 μg/g) bone Pb levels measured at baseline were associated with subsequent declines in cognitive function over 2- to 4-year periods (Bandeen-Roche et al., 2009; Weisskopf et al., 2007). These findings indicated that long-term Pb exposure may contribute to ongoing declines in cognitive function in adults. These associations were found with adjustment for potential confounding by age, education, smoking, and alcohol use in the NAS and age, sex, race, household wealth, and education in the BMS. While the NAS and Nurses' Health Study included primarily white men and white women, respectively, the BMS examined a more diverse population of men and women of various races and ethnicities.

In a recent analysis of the NAS cohort, Farooqui et al. (2017) examined the associations between long-term Pb exposure quantified using bone biomarkers (mean patella Pb: 30.6 μg/g and tibia Pb: 21.6 μg/g) and longitudinal changes in cognition (repeatedly measured up to five visits over the 15 years follow-up period) adjusted for age at the first cognitive test, education level, baseline smoking status, and alcohol intake. The study found that higher patella bone Pb concentration (IQR: 21 μg/g) was associated with a 0.062 point lower baseline Mini Mental State Examination (MMSE) score (95% CI: -0.012, 0.003), 0.008 units/year MMSE decline (95% CI: −0.015, 0) over 15 years, and an increased risk of having an MMSE score below 25 (threshold considered to represent cognitively not normal or at risk for dementia) (hazard ratio [HR] = 1.10 (95% CI: 0.99, 1.21)). Similar but weaker and less precise

associations were observed when tibia Pb and MMSE outcomes were assessed. The study also used "global cognition" as a separate proxy for worsening cognitive impairment, and combined seven test scores assessed in NES2, CERAD, and WAIS-R. Weaker associations were observed between both patella and tibia Pb and global cognition (both baseline and longitudinal change). When separate cognitive domains were assessed, patella Pb was associated with faster longitudinal decline in language and memory domains, whereas similar but weaker associations were observed with tibia Pb.

A longitudinal study of women aged 45-74 enrolled in the NHS cohort (Power et al., 2014) added to the evidence provided by previous analyses. The authors examined the associations between Pb exposures using bone and blood biomarkers (mean patella Pb: 12.6 μg/g and tibia Pb: 10.5 μg/g; mean blood Pb: 2.9 μg/dL) and cognitive decline (repeatedly measured using a telephone battery of cognitive tests assessing learning, memory, executive function, and attention during 2–4 waves over the 13-year follow-up period). Results were adjusted for alcohol consumption, smoking status, education, husband's education, menopausal status and hormone therapy use, physical activity, ibuprofen use, aspirin use, vitamin E supplementation, percentage of residential census tract of white race or ethnicity, and median income of residential census track. A weak and imprecise association was observed for an excess annual decline in the overall cognitive test Z-score per SD increase in tibia bone Pb concentration (−0.002 standard units; 95% CI: −0.005, 0.000). When individual cognitive tests were considered, a decline on the East Boston Memory Test as well as immediate (a measure of episodic memory) and category fluency (a measure of executive function and memory) was observed in relation to increased tibia Pb concentration (Power et al., 2014). There was little evidence for associations between patella Pb or blood Pb and the decline in overall cognition, verbal memory, or individual cognitive tests.

Associations between either tibia or patella Pb concentration and cognitive function decline observed in these longitudinal studies are supported by (Weuve et al., 2013), a cross-sectional study that assessed bone Pb and cognitive function (assessed using telephone cognitive assessment battery) among participants from an existing case-control study of Parkinson's disease. The Pb concentration observed in this study is similar to that reported in the NHS cohort. Separate analyses were performed for the group of participants with PD and for all participants including both PD and control groups. Analysis of the PD group showed that higher tibia Pb was significantly associated with worse overall performance (as shown by the global cognitive score) and worse performance on the majority of telephone cognitive tests (in the model adjusted for age at cognitive assessment, sex, race, education, smoking history). Patella Pb concentration, however, was not consistently associated with cognitive performance. In the model with both PD and control groups, interactions were observed for the association between tibia Pb and global cognition by case-control status. Among the participants, a 10 μg/g increase in tibia Pb corresponded to a decrease in the global cognitive score by 0.12 standard units (95% CI: −0.22, −0.01), but the association among controls was weak (0.06 standard units, 95% CI: −0.09, 0.20).

Evidence of the cognitive effects of cumulative Pb exposure observed in the NAS and NHS studies is strengthened and extended further by the findings from cohort studies that examined the

associations of childhood Pb exposure and continued long-term exposures with cognitive impairments in young adults (18–19 years) (Skerfving et al., 2015) or in mid-adulthood (38 or 45 years of age) (Reuben et al., 2020; Reuben et al., 2017). Skerfving et al. (2015) included samples of 7–12 year-old school children in southern Sweden and followed them over time to examine the association between childhood BLL (age 7–12 years old, mean blood Pb: 3.4 μg/dL) and cognitive performance (IQ) assessed for military conscription at 18–19 years of age using generalized linear models. The study found an IQ loss of 0.127 (95% CI: -0.209, -0.045) points per μg/dL increase in childhood BLL for all participants and an IQ loss of 0.204 (95% CI: -0.392, -0.016) points per μg/dL increase in childhood BLL among those with childhood BLLs ≤50 μg/L, even in multivariable models adjusted for parent's income, education, and father's IQ. Reuben et al. (2017) and Reuben et al. (2020) examined a New Zealand birth cohort with participants born in 1972–1973 (a time when Pb exposure in New Zealand cities were higher than international standards) who were part of the Dunedin Multidisciplinary Health and Development Study. Infants were followed from birth through adulthood. Blood collection at 11 years of age provided blood biomarker data for Pb (mean blood Pb: 10.99 μg/dL). Cognitive performance was assessed using objective tests of cognitive performance such as the WISC-R during childhood at ages 7 and 9 years. Cognitive performance was also assessed using the WAIS-IV when participants were 38 years old (Reuben et al., 2017) and again when they were 45 years old (Reuben et al., 2020). Reuben et al. (2020), in addition to the objective tests, also included subjective reports of everyday cognitive functioning (memory or attention problems) at age 45 years as provided by study participants and their nominated informants. The studies examined the association between childhood blood Pb and adult cognitive outcomes or cognitive decline (change in IQ score between childhood and mid-adulthood), using OLS multiple regression models. Reuben et al. (2017) found that each 1 μg/dL higher level of blood Pb in childhood was associated with a 0.39-point lower score in adult FSIQ (95% CI: −0.67, −0.12), and a 0.32-point decline (95% CI: −0.50, −0.15) after adjusting for sex, childhood IQ, maternal IQ, and childhood SES. Similarly, with additional years of data (Reuben et al., 2020) continued to show significant associations between childhood BLL and IQ at 45 years of age. Each 1 μg/dL higher childhood BLL was associated with a −0.41 (95% CI: −0.68, −0.15) point decline in full-scale IQ from baseline. When using a residualized change model to adjust for autocorrelation between baseline and follow-up IQ, the decline in IQ was similar (−0.39 [95% CI: −0.58, −0.21]). The study also found that the relationship between childhood blood Pb and adult IQ persisted and remained significant even after adjustment for brain structure measures. Results pertaining to brain structure are discussed in Section 3.4.1.

Several recent cross-sectional studies also examined the associations of Pb exposure and decrements in cognitive function. The majority used concurrent blood biomarkers (Sasaki and Carpenter, 2022; Xiao et al., 2021; Przybyla et al., 2017; Souza-Talarico et al., 2017; Khalil et al., 2014; van Wijngaarden et al., 2011). A few studies used other biomarkers such as toenails (Meramat et al., 2017), bone (Weuve et al., 2013), or urine (Sasaki and Carpenter, 2022). As described further below, results were not entirely consistent across studies.

Three of the cross-sectional studies examining the blood Pb-cognitive function association used data from various NHANES cycles including participants aged 60–84 years (Sasaki and Carpenter, 2022; Przybyla et al., 2017; van Wijngaarden et al., 2011). van Wijngaarden et al. (2011) examined the associations of blood Pb (mean blood Pb: 2.46 μg/dL) with self-reported confusion and memory problems using data from NHANES (1999–2008). Data from the 1999–2002 NHANES cycle were used to estimate the association between BLL and performance on the Digit Symbol Substitution Test (DSST) scores. After adjustment for age, sex, education level, ethnicity, poverty-income ratio (PIR), self-reported health status, and comorbid conditions, no association of BLLs with self-reported confusion or memory problems or DSST performance was observed (van Wijngaarden et al., 2011). Two other studies, Przybyla et al. (2017) and Sasaki and Carpenter (2022), included the NHANES participants from 1999–2002 and 2011–2014 cycles, respectively. These studies explored the cross-sectional associations of blood and urine biomarkers of multiple metals and metalloids (separately and jointly) on cognitive function. (Przybyla et al., 2017) used a path analysis approach to model multiple exposures of 14 chemicals simultaneously while adjusting for multiple comparisons. The study found that the association of BLL (Geometric mean: 2.17 μg/dL) with lower cognition scores was attenuated when the model controlled for smoking status. Specifically, a 1-SD increase in BLL was weakly associated with a slightly lower Digit Symbol Coding (DSC) test score from WAIS-III (β = −0.10, 95% CI: −0.20, −0.00) after controlling for co-exposure and sociodemographic covariates. The study also performed stratified analysis by sex and age (above and below median age) and found a greater magnitude of associations for female and higher age categories (>10%), despite a lack of statistical evidence of an interaction. (Sasaki and Carpenter, 2022) used two stage linear regression models. First, they performed single metal analyses separately for each of seven metals or metalloids followed by a second analysis including multiple metals or metalloids from the stage 1 analysis to examine the associations with immediate, delayed, and working memory quantified using CERAD and DSST. When single metals were assessed, increased blood Pb concentration was associated with decrements in performance on all three cognitive tests after adjusting for sociodemographic, behavior, and clinical characteristics (immediate recall: β = −0.58, 95% CI: −0.91, −0.24; delayed recall: β = −0.19, 95% CI: −0.35, −0.02; Digital Symbol Substitution: β = −1.08, 95% CI: −2.12, −0.05). Multi-metal analysis stratified by age group (60–70 and >70 years old) suggested greater declines in immediate recall among participants over the age of 70. Khalil et al. (2014) examined the association between concurrent blood Pb concentration (mean blood Pb: 2.25 μg/dL) and cognitive function among a subset of non-institutionalized community dwelling non-Hispanic Caucasian men 65 years and older who participated in the Osteoporotic Fractures in Men Study (MrOS) cohort study. Cognitive function was assessed using the Modified MMSE (3MS) and the Trail Making Test Part B. Higher scores on the 3MS and faster time on the Trail Making Test Part B both represent better performance. Multivariable analysis found no association between blood Pb concentration and cognitive function (Khalil et al., 2014).

Souza-Talarico et al. (2017) examined the association between blood Pb (and interactions between blood Pb and Cd) and working memory capacity (WMC) in a population of 125 older adults aged 50–82 years, in the metropolitan area of Sao Paulo, Brazil. The study also explored the mediating

role of antioxidant capacity (using various oxidative stress biomarkers) in the heavy metals-memory associations. Using regression models accounting for age, sex, income, and hemoglobin, the study did not find an association between blood Pb (mean 2.1 μg/dL) and WMC (β = 0.106, 95% CI:-0.208, 0.417); however, an interaction between blood Pb and blood Cd level was observed as well as a significant inverse association between the blood Cd × blood Pb interaction term and WMC was observed (Souza-Talarico et al., 2017). The Monte Carlo Method for Assessing Mediation test for mediation revealed that the association between the blood Cd × blood Pb interaction term and WMC was significantly mediated by total antioxidant capacity.

(Xiao et al., 2021) examined the association between multiple metals (22 metals including Pb; mean blood Pb: 5.15 μg/dL) and cognitive function measured using MMSE in participants aged ≥60 years from Guangxi, Southern China. The study used least absolute shrinkage and selection operator (LASSO) penalized regression to identify main metals associated with cognitive function. Twelve metals (including Pb) selected from LASSO were then explored in a multi-metal generalized linear regression model adjusted for age, gender, education attainment, annual income, BMI, smoking, alcohol, insomnia, and physical activity. No association was observed for blood Pb and cognitive function after adjustment for other metals.

Notably, a limitation of cross-sectional studies of concurrent BLLs is that the relative contribution of the recent versus past Pb exposure is not well characterized. A recent prospective study was designed to address the uncertainties related to the exposure patterns associated with BLLs observed in studies of adults (Yu et al., 2021). Yu et al. (2021) examined the association of BLLs and neurocognitive performance among newly hired employees at battery manufacturing and Pb recycling plants with no previous occupational Pb exposure, a subset of participants in the Study for Promotion of Health in Recycling Lead (SPHERL) cohort study. Baseline blood Pb concentration was measured, and the participants were followed annually over a 2-year period to measure blood Pb biomarkers and assess if higher recent occupational exposure to Pb was associated with neurocognitive dysfunction. The participants completed the DSST and SCWT at baseline and annual follow-up visits. The geometric mean blood Pb at baseline and first and second follow-up visits were 3.97 μg/dL, 13.4 μg/dL, and 12.8 μg/dL, respectively, showing an almost three-fold increase in blood Pb over the 2 years of occupational exposure. The study used a linear mixed model to examine the changes in DSST and SCWT corresponding to changes in blood Pb separately for the 1- and 2-year visits. Despite the three-fold increase in blood Pb concentration, the study found no association between blood Pb and cognitive function. The change in latency time and error rate based on the DSST test showed an increase from baseline to follow-up, with an increase in the follow-up-to-baseline blood Pb concentration ratio, but the association was weak and imprecise in the fully adjusted models (change in latency: 0.55%, 95% CI: −0.33, 1.42; error rate: OR: 1.01, 95% CI:1.00, 1.03)

3.6.1.1.1 Summary

Longitudinal cohort studies evaluated in the 2013 Pb ISA found consistent evidence of an association between increased long-term exposure to lead indicated by bone Pb levels and decreased cognition in adults. Recent prospective cohort studies add to the body of evidence informing the relationship between Pb exposure and cognitive performance in adults without occupational Pb exposure. More specifically, recent cohort studies indicated that higher adult bone Pb levels, which indicate cumulative Pb exposure (tibia mean range: 10.5, 21.6 μg/g, patella mean range: 12.6, 30.6 μg/g) or childhood BLLs (mean range: 3.4 μg/dL, 10.99 μg/dL at 7–12 years of age), were associated with decrements in cognitive function or IQ during young-, mid-, or older-adulthood periods (Table 3-14E). There was some variability in the associations with various domains of cognitive function tested within studies; however, variability in the associations observed across domains of cognitive function generally reflects biologic variability or differences in the outcome pathophysiology rather than inconsistent study results. Across studies, higher Pb levels were associated with decrements in FSIQ, global cognitive function, executive function, visuospatial and visuomotor skills, language, and memory. Extended analyses of the NAS and NHS cohorts with 13 to 15 years of follow-up add to the evidence base (Farooqui et al., 2017; Power et al., 2014). These studies found associations of cumulative Pb exposure with decrements in cognitive function in adults after adjustment for potential confounding by combinations of factors including demographic, socioeconomic, behavioral, clinical, and neighborhood-level factors. In addition, findings from recent prospective cohort studies in Sweden and New Zealand that explored the effects of Pb exposure during childhood lifestages (7–12 years) on IQ and cognitive effects during young adulthood (18–19 years) (Skerfving et al., 2015) and mid-adulthood (38–45 years) (Reuben et al., 2020; Reuben et al., 2017). These studies found that higher childhood BLLs were associated with declines in IQ ascertained in adulthood 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. Overall, the longitudinal design with longer follow-up periods, multiple and repeatedly measured cognitive outcomes, and multiple risk factors and confounders accounted for in epidemiologic studies investigating long-term cumulative exposure and early childhood exposure reduce uncertainties and strengthen the evidence related to the association of Pb exposure with cognitive function in adulthood. Sex (male versus female, premenopause versus postmenopause) and age (young versus mid-aged versus old-aged adults) differences in bone kinetics and turnover, as well as disease comorbidity, particularly at middle- and older-adulthood lifestages may potentially lead to differences in bone Pb and blood Pb levels and add complexity when modeling the associations since inclusion of only age or sex in the model may not fully account for these differences.

3.6.1.2 Toxicological Studies of Cognitive Function in Adults

3.6.1.2.1 Learning and Memory – Morris Water Maze

This section specifically reviews studies that exposed animals to Pb during either adulthood or late adolescence. Studies that exposed animals during development (i.e., pregestation, gestation, lactation) are reviewed in Section 3.5.1.3.2. Animals exposed to Pb via drinking water in adulthood displayed impaired learning and memory. Using the Morris water maze, Mansouri et al. (2012) found that short-term Pb exposure (50 mg/L Pb in drinking water, PND 70 to 100), which produced mean BLLs of 8 µg/dL, significantly impaired both learning and memory, though the magnitude of the effect on memory was smaller compared with the effect observed in other studies of developmental exposure (Section 3.5.1.3.2). Also using the Morris water maze, Mansouri et al. (2013) reported that long-term Pb exposure (50 ppm in drinking water, PND 60 to 240), which produced peak BLLs of 11–19 µg/dL, significantly impaired learning and memory performance in both sexes. Cognitive impairment was also observed in studies that utilized daily administration of Pb via gavage. Singh et al. (2019) reported significantly increased escape latencies and path lengths (i.e., distance traveled to reach the platform, another measure of learning) in exposed rats following long-term Pb exposure via gavage (2.5 mg/kg, PND 90 to 180), which produced peak BLLs of 28 µg/dL. No probe phase was conducted in this study. Additionally, Su et al. (2016) found that male rats gavaged with Pb solutions daily (200 ppm, PND 20 to 76) displayed significant impairments in both the learning and memory components of the Morris water maze.

In two recent studies, Zou et al. (2015) and Han et al. (2014) reported significant learning and memory deficits following short-term exposure of juvenile animals. Zou et al. (2015) exposed mice from PND 35 to 56 with mean BLLs of 22 µg/dL, while Han et al. (2014) exposed rats from PND 21 to 42 and reported mean BLLs of 15 µg/dL. Other studies examined the effects of long-term Pb exposure on juvenile rodents and found similar effects. For example, (An et al., 2014) exposed groups of juvenile rats to multiple doses of Pb for 56 days (PND 28 to 84). All examined doses (100, 200, and 300 ppm in drinking water) produced BLLs relevant to this ISA. At the time of Morris water maze assessment (PND 84), the mean BLL ranged from 11 to 23 µg/dL. All exposed animals displayed impaired memory during the probe trial relative to controls. Only animals in the two highest dose groups were reported to show learning deficits during training, suggesting that, with juvenile exposures, Pb may have a greater effect on memory than learning processes. Another study that exposed juvenile mice to Pb in drinking water (0.2%) for 90 days (PND 28 to 112) assessed Morris water maze performance in the same animals at multiple time points during and immediately following exposure (Wu et al., 2020b). This long-term exposure produced relatively high mean BLLs of 28 µg/dL, and all exposed animals showed signs of impaired learning and memory in the maze. Interestingly, both measures of cognition improved in the exposed animals over time, which may reflect either increasing familiarity with the task or clearance of Pb over time. In contrast to all other studies in young and juvenile animals, Li et al. (2013) reported that rats given Pb in drinking water for 84 days (from PND 28 to 112) with peak BLLs of 16 µg/dL showed no

indication of learning or memory impairment in the Morris water maze. Despite this one discrepant study, recent evidence supports the notion that postnatal exposure to Pb (either during adolescence or continuing into adulthood) negatively affects learning and memory in rodents, which contrasts with several of the key studies reviewed in the previous ISA.

3.6.1.2.2 Summary

Four recent studies of rodents with exposure resulting in mean BLLs ≤30 μg/dL add to the evidence informing the association of both short- and long-term Pb exposure during adulthood with measures of learning and memory in rodents. While these studies are consistent with one another, toxicological evidence for the effects of Pb on cognitive function in adults remains limited. Additionally, a few recent studies in juvenile rodents also provide some support for the association between postnatal Pb exposure either during adolescence or continuing into adulthood and cognitive impairment, specifically learning and memory.

3.6.1.3 Relevant Issues for Interpreting the Evidence Base

3.6.1.3.1 Concentration-Response Function

The 2013 Pb ISA reviewed a small number of studies that examined the shape of the C-R relationship between blood or bone Pb levels and cognitive function. Studies using BMS and NAS cohorts assessed nonlinearity using quadratic terms, penalized splines, or visual inspection of bivariate plots. Prospective analyses of the NAS cohorts provided some evidence of nonlinearity (Wang et al., 2007; Weisskopf et al., 2007) Figures 4-7 and 4-8 from 2013 Pb ISA). Weisskopf et al. (2007) found that a 20 μg/g difference in patella Pb level was associated with a 0.07-ms increase in response latency (95% CI: 0.04, 0.12; larger values mean slower reaction times in the pattern comparison test) among all men and a 0.15-ms increase among men with patella Pb level <60 μg/g. These results suggest that Pb-associated latency worsens with increasing Pb up to 60 μg/g and levels off at higher values. Wang et al. (2007) found that among NAS men with an HFE gene variant, there was a larger decline in MMSE score (a global examination of cognitive function with low scores indicating poor cognitive performance) per unit increase in tibia Pb level at higher tibia Pb levels.

In the current review, the shape of the C-R function was not assessed in studies that examined the associations of Pb biomarkers with cognitive function in adults. The majority of studies selected analytical models that assumed linear associations in the Pb-cognitive function associations. A few studies in the recent review examining the influence of childhood Pb exposure on cognitive impairments at the young- (18–19 years) (Skerfving et al., 2015) or mid-adulthood periods (38 or 45 years of age). Reuben et al. (2017) and Reuben et al. (2020) performed separate analyses for the subsets of the

population exposed to higher and lower Pb levels to examine possible nonlinear relationships or threshold effects. Reuben et al. (2017) found a 1.97-IQ-point reduction in adulthood (95% CI: −3.34, −0.59) for the overall sample, a 4.25-IQ-point reduction for individuals above the level of concern, and a 2.73-IQ-point reduction for individuals below the level of concern for each 5-µg/dL increase in the childhood blood Pb. Similarly, IQ decline from childhood to adulthood suggested a mean decline of a 1.61 IQ points (95% CI: −2.48, −0.74) in adulthood for the overall sample, a mean decline of 1.68 IQ points for participants above the level of concern, and a mean increase of 1.22 IQ points for participants below the level of concern for each 5-µg/dL increase in the childhood blood Pb. Similar results were observed by (Reuben et al., 2020) in the same population studied in (Reuben et al., 2017) and followed till 45 years of age. Skerfving et al. (2015) examined the influence of early childhood Pb exposure on long-term cognitive impairments at young adulthood (18–19 years) using generalized linear models. The study found an IQ loss of 0.127 (95% CI: -0.209, -0.045) points per µg/dL increase in childhood BLLs for all participants, and a slightly larger IQ loss (i.e., 0.204 [95% CI: -0.392, -0.016] point per µg/dL increase in childhood BLL) for the populations with childhood BLLs ≤50 µg/L. Reuben et al. (2017) and Reuben et al. (2020) examined the association of childhood blood Pb (11 years) with cognitive performance during mid-adulthood and cognitive decline (change in IQ score between childhood and mid-adulthood) for the overall sample as well as separately for participants above or below the historic level of concern (i.e., >10 µg/dL). Overall, these childhood exposure studies suggested persistence and continued cognitive effects of childhood Pb exposure through mid-adulthood, and the strength of associations were higher in magnitude for the participants with childhood exposure above the historic level of concern (>10 µg/dL).

The limited recent toxicological evidence generally supports the dose-dependent effects of Pb on cognitive function at relevant BLLs in adult animals. Only one study examined juvenile animals exposed to multiple concentrations of Pb and reported greater decrements in learning and memory at higher doses (An et al., 2014).

3.6.1.3.2 Potentially At-Risk Populations

Age and Sex:

In the 2013 Pb ISA, an analysis using the NAS cohort reported an interaction between Pb and age (Wright et al., 2003). The study reported that the inverse association between age and cognitive function was greater among those with high blood or patella Pb levels. Specifically, in the highest quartile of patella Pb, each year increase in age led to a four-fold steeper decline in the MMSE score relative to the effect of age in the lowest quartile of patella Pb. Effect estimates were in the same direction for tibia Pb, but the interaction was not statistically significant.

Two recent epidemiologic studies using NHANES data from the 1999–2002 and 2011–2014 cycles explored the cross-sectional associations of blood and urine biomarkers of multiple metals and

metalloids (separately and jointly) with cognitive function and provided some insights into potential effect modifications of Pb-associated decrements in cognitive function (Sasaki and Carpenter, 2022; Przybyla et al., 2017). Stratified analysis by sex and/or age groups (above and below median age groups) performed in these studies suggested a greater magnitude of Pb-cognitive function associations (beta estimates >10%) for females and for older age categories, however, the statistical test for the interactions suggested no difference between the sex and age categories.

Toxicological studies investigating potential sex differences in Pb-induced cognitive impairment are limited. A study by Mansouri et al. (2013) reported that Pb produced similar decrements in learning and memory in both male and female animals. Given the lack of toxicological evidence available, the possible influence of sex on Pb-induced cognitive impairment in adult animals remains unclear.

Pre-existing conditions:

One study evaluated the association of bone Pb (mean ranges for various age groups: tibia Pb: 4.4–9.2 μg/g; patella Pb: 5.9–15.2 μg/g) with cognitive function among individuals with PD and controls participating in a case-control study (Weuve et al., 2013). The patella Pb and tibia Pb concentrations reported in this study for all study participants increased with increasing age. The highest Pb concentrations were found in study participants in the 75–81 years old category, and the lowest concentrations were found in participants in the 54–65 years old category. When the data were analyzed separately for participants with PD, higher tibia Pb concentration was significantly associated with lower scores on all of the telephone cognitive tests (adjusted difference in scores per 10 μg/g increase in bone Pb: Telephone Interview for Cognitive status (TICS) test: −0.20 [−0.4, −0.00]; digit span forward: −0.23 [−0.43, −0.03]; digit span backward: −0.19 [−0.37, −0.00]) and global cognitive score (adjusted difference in scores per 10 μg/g increase in bone Pb: −0.13 [−0.25, −0.01]). When the overall (cases and control) data were analyzed, significant interactions were observed for the association between tibia Pb and global cognition by case-control status. Participants with PD showed worse scores compared with controls (1 SD increase in tibia Pb led to worsening of the global cognitive score by 0.12 units [95% CI: −0.22, −0.01] among cases; controls: 0.06 [95% CI: −0.09, 0.20]).

Genetics:

Studies investigating the association between Pb levels and cognitive function in 2013 Pb ISA extensively evaluated the effect modification by ALAD and HFE gene variants. The evidence was provided by an NHANES analysis (Krieg et al., 2009) as well as multiple analyses from the NAS cohort examining different tests of cognitive function (Rajan et al., 2008; Weuve et al., 2006). In the study using a cohort from NHANES III, associations with concurrent BLLs were more pronounced in groups with CC and CG ALAD genotypes (i.e., ALAD2 carriers) for several indices of cognitive function (Krieg et al., 2009). In the NAS cohort of men, Weuve et al. (2006) found that higher concurrent BLL but not bone Pb level was associated with a larger decrease in a test of general cognitive function among ALAD2 carriers.

Another NAS study examined the function of specific cognitive domains (e.g., vocabulary, memory, visuospatial skills) and found variable evidence for effect modification by ALAD genotype across tests (Rajan et al., 2008). For example, among ALAD2 carriers, concurrent BLL was associated with a more pronounced decrease in vocabulary score but less pronounced decrease in a memory index and no difference in the associations with other cognitive tests. For tibia and patella Pb levels, ALAD genotype was found to modify associations with different tests, for example, executive function and perceptual speed. It is not clear why the direction of effect modification would vary among different cognitive domains. The limited number of populations examined, and the different cognitive tests performed in each study, make it difficult to conclusively summarize findings for effect modification by ALAD variants. However, in the limited available body of evidence, blood and bone Pb levels were generally associated with lower cognitive function in ALAD2 carriers.

Longitudinal analysis of the NAS cohort also indicated that HFE gene variants modified the blood Pb-cognition association (Wang et al., 2007). Wang et al. (2007) found an IQR higher tibia Pb level (15 μg/g) was associated with a 0.22 point steeper annual decline (95% CI: −0.39, −0.05) in the MMSE, which assesses cognitive impairment in a number of domains, among the men with at least one HFE variant allele (H63D or C282Y variant). The association was found to be nonlinear, with larger Pb-associated declines observed at higher tibia Pb levels. Tibia Pb level was not associated with a decline in MMSE score in men with the HFE wildtype genotype. Moreover, the deleterious association between tibia Pb and cognitive decline appeared progressively worse in participants with increasingly more copies of HFE variant alleles (p-trend = 0.008). These findings suggest that HFE polymorphisms greatly enhance susceptibility to Pb-related cognitive impairment in a pattern consistent with allelic dose.

None of the studies in the current review examined the effect modification by genetic variants.

Other Metal Exposure:

Various studies that examined other metals either evaluated the relationship of each metal separately with the outcomes of interest or included multiple metals jointly in the model (Sasaki and Carpenter, 2022; Xiao et al., 2021; Przybyla et al., 2017). In a study of adults 50 to 82 years old in Sao Paulo, Brazil, Souza-Talarico et al. (2017) examined the associations of heavy metals (Cd and Pb) in blood and WMC separately as well as together in a model for metal interactions. The study found no significant association between blood Pb and WMC in the model including Pb only, but significant interactions were observed between blood Cd and blood Pb and the inverse association with WMC ($\beta = -0.38$, $p \leq 0.001$).

3.6.1.3.3 Lifestages

The identification of critical lifestages and time periods of Pb exposure is complicated by the fact that the majority of adult cognitive studies used concurrent adult BLLs. Although possibly affected by

recent exposure, BLLs are also influenced by Pb stored in bone. Thus, associations in adult studies using concurrent BLL may reflect the effects of past and recent Pb exposures on cognitive outcomes. Some cohort studies in the 2013 Pb ISA and the current review using bone Pb suggested the effects of cumulative long-term Pb exposure on cognitive impairment during adulthood. However, it is still difficult to specifically identify exposures at particular lifestages (prenatal, infancy, early and late childhood, early adulthood, etc.) that could have led to the long-term cognitive impairment observed in these studies. Few recent prospective studies evaluating early childhood exposures at 7–12 years of age and long-term cognitive impairment and decline at young- (18–19 years) (Skerfving et al., 2015) and mid-adulthood (38 or 45 years of age) (Reuben et al., 2020; Reuben et al., 2017) provided an insight into critical lifestages (i.e., early childhood and persistence of the cognitive effects through adulthood). Skerfving et al. (2015) examined the association of childhood BLL in children from southern Sweden (age 7–12 years old, mean blood Pb: 3.4 μg/dL) with cognitive performance (IQ) at the age of 18–19 years. They found an IQ loss of 0.127 (−0.209, −0.045) points per μg/dL increase in childhood BLL for all participants and an IQ loss of 0.204 (−0.392, −0.016) points per μg/dL increase in childhood BLL among those with childhood BLLs ≤50 μg/L even in multivariable models adjusted for parent's income, education, and father's IQ. Reuben et al. (2017) and Reuben et al. (2020) followed a New Zealand birth cohort to examine the association of childhood Pb level (age 11 years, mean blood Pb: 10.99 μg/dL) with cognitive performance and decline at 38 years (Reuben et al., 2017) and 45 years (Reuben et al., 2020). Reuben et al. (2017) found that each 5-μg/dL higher level of blood Pb in childhood was associated with a 1.97-point decrease in IQ score (95% CI: −3.34, −0.59) and a 1.61-point decline (95% CI: −2.48, −0.74) in adult FSIQ after adjusting for sex, childhood IQ, maternal IQ, and childhood SES. With additional years of data, Reuben et al. (2020) also showed a significant association between childhood BLL and IQ at 45 years of age. Each 5-μg/dL higher level of blood Pb in childhood was associated with a 2.07-point decrease in the full-IQ score (95% CI: −3.39, −0.74), and a 1.97-point decline (95% CI: −2.92, −1.03) after adjusting for covariates. These study findings suggest that Pb exposure during childhood lifestages can influence cognition in adulthood.

Overall, recent rodent studies of learning and memory evaluating Pb exposure at various lifestages suggest cognitive impairment. However, the magnitude of the effect at different lifestages has been shown to differ. Adult animals may be less sensitive than juvenile animals, and juvenile animals may be less sensitive than animals exposed during development (reviewed in Section 3.5.1). This general pattern is consistent with evidence describing critical windows for brain development (Section 3.3). Additionally, critical evidence for the association of Pb with cognitive impairment across lifestages comes from a series of studies describing the effects of lifetime Pb exposure on nonhuman primates (Rice, 1992; Rice and Gilbert, 1990a; Rice, 1990; Rice and Karpinski, 1988). Cynomolgus monkeys (*Macaca fascicularis*) were dosed continuously from birth and tested repeatedly throughout their lifetime. While these exposures yielded BLLs beyond values considered relevant for the current assessment (>30 μg/dL), they provide key evidence of Pb-induced cognitive impairments that persisted into adulthood in a translationally relevant species. However, given the limited number of studies conducted in juvenile and adult animals, and the lack of studies examining the same endpoint across multiple age groups, the precise role of exposures at various stages on the cognitive effects in adult animals remains unclear.

3.6.1.4 Summary and Causality Determination: Cognitive Function in Adults

The 2013 Pb ISA (U.S. EPA, 2013) concluded that the available evidence was sufficient to conclude "a causal relationship is likely to exist" between long-term cumulative Pb exposure and cognitive function decrements in adults. This causality determination was based on a small body of prospective studies that indicated strong 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 years) over 2- to 4-year periods among adults without occupational exposure (i.e., NAS and BMS cohorts). Supporting evidence was provided by analyses of the NAS, BMS, and NHS cohorts, that found stronger associations with cognitive impairment for cumulative exposure (i.e., bone Pb level) than for concurrent BLL, which reflects recent Pb exposure and Pb that has been mobilized from the bone. The timing, frequency, duration, and magnitude of Pb exposures that contributed to the associations observed with blood Pb levels were not discernable from cross-sectional associations reported in these studies. The biological plausibility for the effects of Pb exposure on cognitive function decrements in adults was 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 the hippocampus, prefrontal cortex, and nucleus accumbens.

Results from recent epidemiologic and animal studies add to the evidence base reviewed in the 2013 Pb ISA. Recent epidemiologic studies consistently report that higher cumulative Pb exposure (i.e., bone Pb levels) or childhood BLLs, were associated with poor cognitive performance or decrements in cognitive function during young-, mid-, or older-adulthood periods (Table 3-14E). Across populations, higher Pb levels were associated with decrements in FSIQ, global cognitive function, executive function, visuospatial and visuomotor skills, language, and memory. Discordant Pb associations across domains of cognitive function are likely to reflect inherent biologic variability or differences in the outcome pathophysiology as opposed to inconsistency in the evidence. Much of this evidence on adult cognitive outcomes was obtained from analyses of the NAS and NHS cohorts, including recent analyses that extended follow-up periods beyond the analyses evaluated in the 2013 Pb ISA. Recent evidence also comes from early childhood exposure cohort studies conducted in Sweden and New Zealand. These studies strengthen findings that childhood Pb exposures are associated with decrements in IQ and cognitive function during young- and mid-adulthood. Longitudinal study designs with longer follow-up periods, multiple and repeatedly measured cognitive outcomes, and multiple risk factors and confounders accounted for in the studies reduce the bias and strengthen the study findings related to Pb exposure and adult cognitive function. Further, significant findings from new studies specifically investigating the influence of early childhood Pb exposure on adult IQ and cognitive outcomes, even after adjustments for various confounders including childhood IQ, provide evidence for the role of early childhood Pb exposures on decrements in cognitive function in adulthood.

Strong evidence for cognitive function declines associated with cumulative Pb exposures was provided by prospective cohort studies that demonstrated increased bone Pb levels (tibia mean: 10.5, 21.6

μg/g, patella mean: 12.6, 30.6 μg/g) measured at baseline were associated with cognitive decline over the follow-up period of 13–15 years (Farooqui et al., 2017; Power et al., 2014). Findings from these studies suggest that long-term Pb exposure may contribute to ongoing declines in cognitive function in adults. These associations remained significant even after adjustment for potential confounding by combinations of factors including demographic, socioeconomic, behavioral, clinical, and neighborhood level factors. Increased bone Pb level (tibia mean range: 4.4–9.2 μg/g) was associated with cognitive function outcomes among cases of PD (Weuve et al., 2013). Additional support for the effects of cumulative or past Pb exposure is provided by an analysis of past blood Pb exposures during childhood (either low or high Pb exposure scenarios; blood Pb mean: 3.4 μg/dL at 7–12 years, 10.99 μg/dL at 11 years) and studies that followed study participants through young or mid-adulthood (Reuben et al., 2020; Reuben et al., 2017; Skerfving et al., 2015). These studies indicated that higher childhood BLL was associated with declines in IQ at 18 to 19 years old and at 38 years or 45 years old.

Findings from cross-sectional studies that assessed the relationships of concurrent blood (2.1 μg/dL to 5.1 μg/dL) and cognitive function outcomes were more mixed. Concurrent blood Pb level does not clearly indicate recent Pb exposure in adults because Pb is mobilized from the bone in various adult lifestages complicating the interpretation of these studies. Two studies including NHANES data found inverse association between concurrent BLLs and cognitive outcomes (Sasaki and Carpenter, 2022; Przybyla et al., 2017), while others suggested null associations (Xiao et al., 2021; Souza-Talarico et al., 2017; Khalil et al., 2014; van Wijngaarden et al., 2011). The NHANES studies demonstrating significant associations considered multiple metals in their analytical models including Pb, used advanced model approaches to handle multiple exposures and issues around multiple comparison and multi-collinearity, and adjusted for sociodemographic, behavioral, and clinical characteristics. These approaches reduced the bias and uncertainty in the study findings. A recent study using a prospective design addressed some of the concern around the health effects of recent Pb exposure (Yu et al., 2021). The study included a group of individuals with no prior occupational exposure and recently hired young workers at battery manufacturing and Pb recycling plants. The association between neurocognitive performance and blood Pb was examined prior to and up to 2 years after the first occupational exposure (geometric mean baseline: 3.97 μg/dL; 13.4 μg/dL, and 12.8 μg/dL at the first and second follow-up visits). The study did not observe significant associations of changes in neurocognitive function in the workers with an over three-fold increase in blood Pb concentration over the 2-year follow-up period, though the follow-up time in this study may not have been adequate to detect the long-term effects of Pb on cognitive function.

Sex and age differences in bone kinetics and turnover could have contributed to differences in the magnitude of associations observed for different bone Pb biomarkers and cognitive function in the NHS and NAS cohorts. Specifically, the role of specific bone biomarkers (i.e., tibia or patella Pb) as indicators of Pb exposure for specific age and sex groups in relation to individual cognitive domains is yet to be fully understood. For instance, the findings from the NHS cohort with shorter follow-up, Weuve et al. (2009), suggested that higher tibia Pb in women was inversely associated with the overall cognitive score. The associations with the majority of the domain-specific cognitive scores were also negative (except for

letter fluency, which was positive) but the estimates were imprecise. The recent extended analysis of the NHS cohort Power et al. (2014), on the other hand, suggested that higher tibia Pb in women was inversely associated with individual cognitive scores representing executive function and memory domains, and was unexpectedly positively associated with immediate verbal memory domain. Associations with other cognitive domains or the overall cognitive score were imprecise. Similarly, analyses from the NAS men cohort with shorter versus extended follow-up periods indicated heterogeneous associations with global and domain scores as well. Results from the analysis with shorter follow-up (Weisskopf et al., 2007) suggested stronger inverse association between higher patella Pb and declines in the visuospatial and visuomotor domains over time, but weaker and imprecise associations were observed for other domains. In contrast, results from the extended analysis Farooqui et al. (2017) observed that higher patella Pb was associated with faster longitudinal decline in MMSE (a measure of global cognition) and declines in the language and memory domains, whereas associations with other cognitive scores or domains were imprecise.

Recent studies of rodents with exposure resulting in mean BLLs ≤30 μg/dL add to the evidence informing the association of both short- and long-term Pb exposure during adulthood with measures of learning and memory in rodents. While these studies are consistent with one another, toxicological evidence for effects of Pb on cognitive function in adults remains limited., A few recent studies in juvenile rodents also provide some support for the association between postnatal Pb exposure either during adolescence or continuing into adulthood and cognitive impairment, specifically learning and memory. Previous studies in nonhuman primates demonstrated that early life exposure to Pb may produce cognitive impairment in adulthood. Hence, these findings add to the current evidence base suggesting potential roles of both early and later life Pb exposures to produce cognitive function decrements in adults. Additionally, animal, and in vitro studies lend biological plausibility to the association between adult Pb exposure and adult cognitive impairment, showing that Pb has negative effects on neuronal function and integrity, neurotransmission, and synaptic plasticity in regions of the brain associated with learning and memory (Section 3.6).

Overall, the collective evidence is sufficient to conclude that there is *a causal relationship* between Pb exposure and cognitive effects in adults. Recent prospective epidemiologic studies expand and strengthen the previous body of evidence. These recent prospective studies include extended analyses with longer follow-up periods, repeated measurements of cognitive outcomes, and adjustment for an array of important potential confounders. Together, they provide compelling evidence for an association between Pb exposure during various lifestages including childhood and decreased cognitive function in adulthood. Discordant Pb associations across domains of cognitive function likely reflect differences in the outcome pathophysiology rather than inconsistent results, and they do not detract from the strength of the evidence overall. Recent evidence from animal studies supports the biological plausibility for the effects of Pb exposure on cognitive function in adults and demonstrates that postnatal exposure to Pb (either during adolescence or continuing into adulthood) may also negatively affect learning and memory.

Table 3-9 Summary of evidence for a causal relationship between Pb exposure and cognitive effects in adults

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Consistent findings from prospective epidemiologic studies with relevant adult bone Pb levels or early childhood BLLs suggesting significant association of long-term and early childhood Pb exposure with cognitive impairment and decline	Prospective analyses in NAS cohort of white men and NHS cohort of white women found cognitive function decrements over the 13 to 15 yr follow-up in association with patella or tibia Pb levels.	Power et al. (2014)	Mean patella Pb: 12.6 µg/g Mean tibia Pb: 10.5 µg/g
		Farooqui et al. (2017)	Mean patella Pb: 30.6 µg/g Mean tibia Pb: 21.6 µg/g
	Prospective analyses of childhood Pb exposure and long-term cognitive impairments suggested persistent effects on cognition during adulthood by showing lower IQ at young- and mid-adulthood periods, and significant decline in IQ between childhood and adulthood periods due to exposure to higher childhood Pb levels.	Skerfving et al. (2015)	Mean childhood (7–12 yr) blood Pb: 3.4 µg/dL
		Reuben et al. (2017) Reuben et al. (2020)	Mean childhood (11 yr) blood Pb: 10.99 µg/dL
	Models adjusted for various confounding factors including baseline individual-level, socioeconomic, demographics, behavioral, and clinical factors, as well as various neighborhood level variables. The early childhood Pb exposure studies also adjusted for parental education, HOME scores, parent IQ and childhood IQ.		
Supporting epidemiologic studies	Analysis of bone Pb and cognitive function among cases and controls of PD found lower cognitive performance score with increased tibia Pb among cases.	Weuve et al. (2013)	Mean tibia Pb: 4.4–9.2 µg/g (for age groups) Mean patella Pb: 5.9–15.2 µg/g (for age groups)

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
	Cross-sectional analysis of concurrent blood Pb (along with multi-metals) and cognitive function using NHANES data and advanced modeling approach suggested significant inverse association between concurrent BLL and cognitive outcomes. Models adjusted for socioeconomic and demographic factors, education, health status, comorbidities, and co-exposure to other metals.	Przybyla et al. (2017) Sasaki and Carpenter (2022)	Geometric mean blood Pb: 2.17 µg/dL Mean blood Pb: 1.9 µg/dL
Consistent evidence in animals with relevant exposures	Recent evidence from animal studies supports the notion that postnatal exposure to Pb (either during adolescence or continuing into adulthood) negatively affects learning and memory in rodents.	Mansouri et al. (2012) Mansouri et al. (2013) Singh et al. (2019) Su et al. (2016)	Mean BLL: 8 µg/dL Peak BLL: 11–19 µg/dL Peak BLL: 28 µg/dL Mean BLL: 8.4 µg/dL
Some uncertainty remains	Sex and age differences in bone kinetics and turnover may contribute differences in biomarker Pb levels.		

BLL = blood lead level; HOME = Health Outcomes and Measures of the Environment; IQ = intelligence quotient; NAS = Normative Aging Study; NHANES = National Health and Nutrition Examination Survey; NHS = Nurses' Health Study; Pb = lead; PD = Parkinson's disease, yr = year.
[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.

3.6.2 Psychopathological Effects in Adults

The evidence assessed in the 2013 Pb ISA was sufficient to conclude that "a causal relationship is likely to exist" between Pb exposure and psychopathological effects in adults. Cross-sectional studies in a small number of distinct U.S. populations demonstrated associations of higher concurrent blood or tibia Pb levels with self-reported symptoms of depression and anxiety in adults (Bouchard et al., 2009; Rajan et al., 2007; U.S. EPA, 2006). The examination of multiple exposures and outcomes in the available studies does not provide a strong indication of biased reporting of psychopathological effects specifically by adults with higher Pb exposures. In adults, Pb-associated increases in depression and anxiety were found with adjustments for age, SES, and in the NAS, daily alcohol intake. The biological plausibility for epidemiologic evidence was provided by observations of depression-like behavior in animals with dietary lactational Pb exposure, with some evidence at relevant BLLs. In addition, Pb-induced changes in the HPA axis and dopaminergic and GABAergic systems were demonstrated in animals. Overall, the strongest evidence was from epidemiologic studies of adults without occupational Pb exposure, with additional support from a few experimental animal studies; however, uncertainties related to residual confounding of bone Pb associations by age in epidemiologic studies remained. Overall, recent studies add to the evidence and generally support the findings from the 2013 Pb ISA.

3.6.2.1 Epidemiologic Studies of Psychopathological Effects in Adults

A limited number of epidemiologic studies evaluated in the 2006 Pb AQCD (U.S. EPA, 2006) and 2013 Pb ISA (U.S. EPA, 2013) examined the relationship between blood or bone Pb levels and psychopathological effects in adults. All of these studies were cross-sectional and most examined occupationally exposed populations. In addition to the occupational studies, which provided consistent evidence of positive associations between BLLs (mean levels >15 μg/dL) and the prevalence of self-reported symptoms of depression, anxiety, and tension, a prospective analysis of the NAS cohort (Rajan et al., 2007) and a cross-sectional analysis of NHANES participants (Bouchard et al., 2009) reported positive associations between much lower concentrations of concurrent blood (NHANES; mean ~ 6 μg/dL) or bone (NAS) Pb levels and symptoms of depression and anxiety or prevalent major depressive disorder, respectively. The findings from the NAS cohort are notable because tibia and patella Pb reflect cumulative exposures that occur over several years to decades and thus serve as a retrospective assessment of Pb exposure despite the cross-sectional study design.

Recent evidence includes several prospective cohort studies and cross-sectional analyses of Pb exposure and general psychopathological effects or internalizing symptoms, as well as a case-control study of schizophrenia. In general, recent prospective studies provide evidence of an association between blood or bone Pb levels and psychopathological effects in adults. Results from cross-sectional studies are inconsistent. Additionally, with blood or bone Pb levels, it is difficult to characterize the specific timing,

duration, frequency, and level of Pb exposure that contributed to associations observed with cognitive function. This uncertainty may apply particularly to assessments of BLLs, which in nonoccupationally exposed adults reflect both current exposures and cumulative Pb stores in bone that are mobilized during bone remodeling. Measures of central tendency for blood and bone Pb levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Table 3-15E. An overview of the recent evidence is provided below.

A few recent prospective cohort studies report generally consistent evidence of associations between blood or bone Pb levels and psychopathological effects in adults, although the results for specific endpoints are not entirely consistent. In a recent prospective cohort study examining a subset of the NAS cohort, Peters et al. (2011) used structural equation models to examine the interrelations of childhood and adult SES, bone Pb levels, pessimism, and depression in older adults. After controlling for childhood and adult SES through a combination of latent variables—including parental and participant education, occupation, and home ownership—10 μg/g higher tibia Pb levels measured prior to psychological measurement were independently associated with a 0.3-unit (95% CI: 0.0, 0.6) higher score for pessimism level on the Life Orientation Test. An independent association between bone Pb levels and depression was not observed when controlling for pessimism (quantitative results not reported), but pessimism was strongly associated with increased odds of depression (OR = 1.04 [95% CI: 1.02, 1.05] per 1 unit higher pessimism level), indicating a potential mediating effect of pessimism on the relationship between bone Pb levels and depression. Other recent prospective cohort studies examined the relationship between childhood BLLs and a wider range of psychopathological effects (Reuben et al., 2019; McFarlane et al., 2013). In an analysis of the Dunedin cohort in New Zealand, Reuben et al. (2019) reported that each 1-μg/dL higher BLL at age 11 was associated with 0.27-point (95% CI: 0.02, 0.51) higher standardized general psychopathology scores (mean [SD]: 100 [15]) in early adulthood. In more specific analyses of psychopathology components, the association with general psychopathology appeared to be driven by positive associations with symptoms of internalizing behavior and thought disorder. These results are somewhat consistent with a follow-up analysis of the Port Pirie cohort, a birth cohort from a South Australian Pb-smelting town (McFarlane et al., 2013). In this study, BLLs averaged over the first 7 years of life were not associated with depressive symptoms measured during follow-up at ages 25 through 29. However, the authors did report positive associations between BLLs and some internalizing behaviors in women (e.g., social phobia, specific phobia, and anxiety problems). There were generally null associations for the same outcomes in men. A notable limitation of this study is that attrition in the original cohort led to a small sample size that was even further reduced in sex-stratified models, resulting in limited power to detect an association. Additionally, due to high community exposure to Pb, the participants in the Reuben et al. (2019) and McFarlane et al. (2013) studies had a high mean childhood BLL (11.08 and 17.2 μg/dL, respectively). The mean BLLs in these studies are not directly comparable to other studies in this section, which used concurrent BLLs in adult populations that likely had higher past exposures.

Associations between BLLs and mood states were inconsistently observed in cross-sectional studies of pregnant women in China (Li et al., 2017) and Japan (Ishitsuka et al., 2020). In a small study of pregnant women in Shanghai, Li et al. (2017) observed nonlinear associations between BLLs and depression, anxiety, and psychological distress in nonparametric models. Based on visual inspection of the spline curves, the authors ran separate piecewise linear regression models for each outcome with a knot at 2.57 μg/dL. In the piecewise models, BLLs were associated with higher prevalence of depression, anxiety, and psychological stress at levels below 2.57 μg/dL, whereas smaller inverse associations were observed above the knot. In contrast, a much larger cross-sectional study of pregnant women across Japan noted that BLLs measured during middle or late pregnancy were not associated with increased odds of Kessler Psychological Distress Scale (K6) scores greater than or equal to 5 or 13 (Ishitsuka et al., 2020). The authors used different cut points to account for potential differences in the optimal sensitivity-specificity tradeoff for assessing depression in their study population. The contrasting results in these studies are not readily explained by variations in BLLs, as Li et al. (2017) observed positive associations at low BLLs in linear spline models, and the population analyzed by Ishitsuka et al. (2020) had a geometric mean BLL <1 μg/dL.

Other recent cross-sectional studies assessed the relationship between blood or bone Pb levels and mood states measured by validated questionnaires or self-reported physician's diagnosis in a range of study populations, including a population-based analyses of NHANES (Berk et al., 2014) and KNHANES participants (Nguyen et al., 2022), older women participating in subcohorts of the NHS (Eum et al., 2012), and older adults from two communities selected using cluster-based sampling of communities in Luan, China (Fan et al., 2020). Similar to previously discussed studies, results from these analyses were inconsistent. Fan et al. (2020) reported monotonic increases in odds of depression associated with increasing blood Pb exposure quartiles. In this study, older adults in the highest quartile of exposure (BLLs ≤3.06 μg/dL) had just over twice the odds of depression as those with BLLs <2.03 μg/dL (OR = 2.03 [95% CI: 1.23, 3.35]). In contrast, Eum et al. (2012), Berk et al. (2014), and Nguyen et al. (2022) reported null associations between bone or blood Pb levels and anxiety or depression. However, in a subgroup analysis restricting the study population to pre- and postmenopausal women taking hormone replacement therapy (HRT), Eum et al. (2012) reported that increasing tibia Pb tertiles were associated with monotonically increasing odds of phobic anxiety and lower scores on the Mental Health Index 5-item (MHI−5; indicating worse depressive symptoms). The authors restricted the analysis by HRT status to account for potential exposure measurement error in the non-HRT population, resulting from higher variability in bone turnover. Notably, patella Pb was not associated with depressive symptoms in this population and was inversely associated with phobic anxiety. Since tibia Pb has a longer half-life than patella Pb, the results could be indicative of a long-term exposure window contributing to changes in anxiety and depression. However, the subgroup analyses also had small sample sizes and thus a lack of precision and higher probability of chance findings.

While most recent studies of psychopathological effects in adults examined internalizing behaviors or general psychopathological effects, a small case-control study in China evaluated serum

heavy metal levels in association with the risk of schizophrenia (Ma et al., 2019). The authors reported that higher serum Pb levels were associated with higher odds of schizophrenia, but the association was imprecise (OR = 3.15 [95% CI: 1.24, 7.99] per ng/mL higher BLL). Although the cases and controls were matched on age and sex, it is unclear what, if any, other potential confounders were included in the adjusted models. This finding was ostensibly consistent with a pooled analysis of two small cohorts evaluated in the 2013 Pb ISA that observed an association between higher δ-ALAD levels and increased odds of schizophrenia spectrum disorder in adolescents and adults (Opler et al., 2008). However, this pooled analysis had a number of limitations that precluded any conclusions regarding a relationship between Pb exposure and schizophrenia, including the lack of direct measurements of Pb biomarker levels and limited consideration for potential confounding. As noted previously, Reuben et al. (2019) reported a positive association between childhood BLLs and symptoms of thought disorder in early adulthood. However, the metric for thought disorders included factor loadings for obsessive compulsive disorder and mania in addition to schizophrenia, making it difficult to distinguish an independent relationship between BLLs and schizophrenia.

3.6.2.1.1 Summary

A limited number of cross-sectional studies evaluated in the 2013 Pb ISA (U.S. EPA, 2013) provided consistent evidence of positive associations between blood and bone Pb levels and the prevalence of self-reported symptoms of depression, anxiety, and tension. 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.

3.6.2.2 Toxicological Studies of Psychopathological Effects in Adults

No studies in the 2013 Pb ISA evaluated the effect of adult-only exposure on anxiety and depression-like behaviors in animals. Nevertheless, developmental studies consistently supported an effect of Pb exposure on these endpoints in adult animals (U.S. EPA, 2013). Of particular importance, the increased reactivity to errors and reward omission reported by Beaudin et al. (2007) and Stangle et al. (2007) extended to adulthood, well after postnatal exposure was terminated. Furthermore, Pb exposure during adolescence reduced immobility on the FST in adult rats (Stewart et al., 1996).

A few recent studies have investigated adult-only exposure and anxiety-like outcomes using the OFT and EPM. Similar to developmental exposures, adult male mice displayed anxiety-like behavior (i.e., increased time spent in closed arms) in the EPM following 6 weeks of Pb exposure given via oral gavage (mean BLLs 7.1 μg/dL) (Al-Qahtani et al., 2022). Singh et al. (2019) also found that oral gavage of Pb for 90 days decreased the amount of time rodents spent in the open arms of the EPM compared with control animals. Another study of long-term adult exposure (126 days) to Pb in Wistar rats found increased rearing and grooming, but not sniffing, in males, and no significant effects in females in the OFT

(Mansouri et al., 2013). The same research group found that Pb did not affect these endpoints (i.e., rearing, sniffing) following shorter-term exposure (30 days) in adult animals (Mansouri et al., 2012).

Studies that employed developmental exposure paradigms are discussed in more detail in Section 3.5.4.2. However, they provide consistent evidence to support the notion that the effects of developmental exposures may persist into adulthood. In one study of gestational exposure, there were significant decreases in exploratory behaviors in the OFT and hole board test in Wistar rats at 4 months old (BLLs peaked at 12 µg/dL and decreased to 6 µg/dL by 4 months) (Basha and Reddy, 2015). A similar study utilizing postnatally exposed rats found that some measures of decreased exploratory behavior in the OFT and hole board test persisted until 18 months, when the study was terminated (Basha et al., 2014). The mean BLL at PND 45 in this study was high (50 µg/dL) but had decreased to 11 µg/dL by 18 months. Several additional studies investigated lifetime Pb exposure (gestation through 6–12 months), and all found significant treatment effects on EPM or FST behavior during adulthood (Shvachiy et al., 2020, 2018; Abazyan et al., 2014; Cory-Slechta et al., 2013).

Toxicological studies also provide biological plausibility to support a connection between exposure to Pb and schizophrenia. As discussed in the 2013 Pb ISA, antagonists of NMDAR's glycine site have been shown to exacerbate schizophrenia symptoms in affected individuals and induce a schizophrenic phenotype in unaffected subjects (Coyle and Tsai, 2004). Previous studies have shown that Pb is a potent allosteric inhibitor at NMDARs (Hashemzadeh-Gargari and Guilarte, 1999; Guilarte, 1997). A recent study found that developmental Pb exposure (BLLs of 22 µg/dL at PND 50) reduced the number of parvalbumin-positive GABAergic interneurons in the median prefrontal cortex and hippocampus and induced subcortical dopaminergic hyperactivity, consistent with studies of schizophrenic patients (Stansfield et al., 2015; Volman et al., 2011). Pb exposure may also affect DISC1, a gene-protein pair associated with increased susceptibility to schizophrenia and other mental disorders. You et al. (2012) found that expression of the DISC1 protein was increased in the hippocampus of rats exposed to Pb during gestation and lactation. Abazyan et al. (2014) utilized a transgenic mouse model expressing mutant DISC1 (mDISC1) to evaluate a potential gene-environment interaction using lifetime Pb exposure. Pb-exposed mDISC1 mice exhibited behavioral and structural abnormalities consistent with schizophrenia, which were not found in unexposed mDISC1 mice or Pb exposure regular mice (i.e., heterozygous for mDISC1 but phenotypically normal).

3.6.2.2.1 Summary

Toxicologic studies providing support for adult psychopathological effects in the previous ISA used developmental exposure paradigms. Recent developmental exposure studies were consistent with the previous evidence and were predominantly focused on anxiety-like behaviors. Multiple studies demonstrated the persistence of these effects into adulthood (up to 1.5 years), in some cases long after termination of Pb exposure. A few recent studies focused on adult-only exposures found some associations with anxiety-like behavior after 42–126 days of exposure but not following a 30-day

exposure; additional studies are needed to strengthen this line of evidence. Two recent studies also provided further biological plausibility support for an NMDAR-mediated association between Pb exposure and schizophrenia.

3.6.2.3 Relevant Issues for Interpreting the Evidence Base

3.6.2.3.1 Concentration-Response Function

One recent study used a nonparametric model to assess the C-R relationship between BLLs and depressive symptoms in pregnant women (Li et al., 2017). The authors observed nonlinear associations between BLLs and depression, anxiety, and psychological distress scores and used the nonparametric models to determine knots for a piecewise linear regression model. The subsequent models indicated positive associations between BLLs and depression, anxiety, and psychological stress at levels below 2.57 µg/dL, whereas smaller inverse associations were observed for BLLs above 2.57 µg/dL. Other cross-sectional studies reported inconsistent evidence of associations despite evaluating populations with low mean BLLs. However, in studies analyzing BLLs in adult populations with higher past exposures, it is a challenge to ascertain the level, timing, frequency, and duration of Pb exposure that contributed to observed associations.

3.6.2.3.2 Potentially At-Risk Populations

A few of the recent epidemiologic studies detailed in this section evaluated populations that are potentially at-risk for Pb-related health effects. The conclusions that can be drawn from these analyses are limited. A prospective analysis of young adults reported sex-specific associations between childhood BLLs and internalizing symptoms in early adulthood (McFarlane et al., 2013). The observed associations, which were only present in stratified models including women, were extremely imprecise due to a small sample size that was even further reduced by stratification. The small sample size in this study reduced the statistical power to detect an association and the likelihood that an observed result reflects a true effect, making it difficult to draw firm conclusions on these sex-specific comparisons. Additionally, two cross-sectional studies examining depressive symptoms in pregnant women observed inconsistent evidence of an association with BLLs (Ishitsuka et al., 2020; Li et al., 2017).

3.6.2.3.2.1 Lifestages

Toxicological studies provide consistent evidence that developmental and lifetime exposures to Pb can lead to increases in anxiety-like behaviors. Comparatively fewer studies have investigated the effects of adult-only exposure, but some effects have been demonstrated. Epidemiologic studies provide

some supporting evidence for the importance of developmental and cumulative exposures. In a recent prospective cohort study, Peters et al. (2011) reported that increased depressive symptoms in older adults were associated with tibia Pb levels, a measure of cumulative exposure. Other recent prospective analyses observed associations between childhood BLLs and increased internalizing symptoms in young adults (Reuben et al., 2019; McFarlane et al., 2013). Additionally, (Reuben et al., 2019) also observed positive associations between childhood BLLs and internalizing symptoms at the time of BLL testing, which is coherent with toxicological evidence that suggests the persistence of developmental effects into adulthood. Given the uncertainties regarding potentially higher historical exposures in adults, the cross-sectional epidemiologic studies evaluated in this section are less suited to address the importance of concurrent exposures.

3.6.2.3.3 Confounding

The studies evaluated in this section controlled for a range of potential confounding variables that may be associated with both Pb exposure and psychopathological effects, including age, sex, SES factors, and marital status (see Table 3-15E).

3.6.2.4 Summary and Causality Determination: Psychopathological Effects in Adults

The 2013 Pb ISA (U.S. EPA, 2013) concluded that the available evidence was sufficient to conclude that "a causal relationship is likely to exist" between Pb exposure 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). 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 post-lactational exposure. 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 since it is an indicator of cumulative Pb exposure. Nonetheless, because these studies included adults with likely higher past Pb exposures, uncertainties exist regarding the Pb exposure level, timing, frequency, and duration contributing to the associations observed with blood or bone Pb levels. An uncertainty in the toxicological evidence base was the limited number of studies that administered exposures resulting in BLLs that are not relevant to humans. Recent epidemiologic and toxicological evidence continues to link Pb exposure to psychopathological effects in adults, though some uncertainties still remain. The key evidence, as it relates to the causality determination, is presented in Table 3-10 and Table 3-11 and summarized below.

Recent evidence from prospective epidemiologic studies provides further support for positive associations between Pb exposures and pathological effects, including increased internalizing symptoms. Specifically, a study of older men in the NAS cohort provides evidence of an (indirect) association between Pb exposure and depression in adults (Peters et al., 2011), and an analysis of a cohort in New Zealand similarly reported that increased childhood BLLs were associated with increased internalizing symptoms in young adults (Reuben et al., 2019). Together, these studies address an uncertainty from the previous ISA regarding the temporality of the exposure and outcome. Another recent prospective study of young adults from the Port Pirie cohort reported null associations between childhood BLLs and depression in adults but noted several sex-specific associations between BLLs and other internalizing symptoms in young women (McFarlane et al., 2013). The small analytic sample of the stratified models used in this analysis reduces the likelihood of detecting a true effect. Notably, supporting evidence from recent cross-sectional epidemiologic studies conducted in diverse populations is largely inconsistent. However, these studies are less informative given the limitations of the study design.

The epidemiologic evidence is supported by coherence with results from an expanded number of toxicological studies conducted at BLLs relevant to humans. Recent toxicological studies examine multiple exposure windows and provide strong support for Pb-induced anxiety-like behaviors following developmental and cumulative exposures. Multiple studies demonstrate the persistence of these effects into adulthood (up to 1.5 years), in some cases long after termination of Pb exposure. The evidence for effects resulting from adult-only exposures is more limited, though there is some evidence for an increase in anxiety-like behavior following 42–126 days of exposure but not following a 30-day exposure. The 2013 Pb ISA also highlighted Pb-induced changes in the dopaminergic and GABAergic systems and the HPA axis, which underlie biological plausibility for the changes in mood and emotional state that have been observed in epidemiologic and toxicological studies (U.S. EPA, 2013). Recent studies continue to demonstrate changes in corticosterone and glucocorticoid receptors (i.e., HPA axis changes (Cory-Slechta et al., 2012)) and the dopaminergic system (Section 3.4.2.2).

In addition to studies of depression, anxiety, and mood-related disorders, some recent studies examined the relationship between Pb exposure and schizophrenia. A recent case-control study in China reported a positive, but imprecise association between serum Pb levels and schizophrenia prevalence in adults (Ma et al., 2019). Because serum Pb was measured after schizophrenia was diagnosed, the results do not establish temporality between exposure and outcome. Additionally, the reported analytic methodology does clarify the confounding variables considered outside of the age- and sex-based matching of cases and controls. Recent toxicological studies provide biological plausibility to support a connection between exposure to Pb and schizophrenia. Consistent with evidence from the 2013 Pb ISA, two recent studies support Pb-induced pathophysiological features in rodents consistent with schizophrenia, likely through inhibition of NMDAR activity. Although the toxicological evidence presents a biologically plausible pathway through which exposure to Pb could lead to schizophrenia, the limited quantity and quality of the epidemiologic evidence precludes meaningful consideration of this endpoint in the causality determination for Pb exposure and psychopathological effects.

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. The strongest evidence comes from a limited number of recent prospective epidemiologic studies that add to previous evidence of a positive association between bone or BLLs and psychopathological effects in older adults and addresses prior uncertainties regarding the temporality of exposure and outcome. Recent toxicological studies strengthen the overall evidence base, providing further support for anxiety-like behaviors following developmental and cumulative exposures that result in BLLs that are relevant to humans. Despite generally consistent evidence from prospective epidemiologic studies that Pb is associated with general internalizing behavior scores or some components of internalizing behavior, the evidence from these limited number of studies is not consistent for any single component. Although these inconsistencies may reflect differences in outcome pathophysiology rather than inconsistent results, there is remaining uncertainty given the limited body of evidence. The key evidence, as it relates to the causal framework, is summarized in Table 3-10.

Table 3-10 Summary of evidence for a likely to be causal relationship between Pb exposure and psychopathological effects in adults

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Limited epidemiologic evidence from high-quality prospective cohort studies with relevant bone Pb levels	Prospective analyses reported positive associations between tibia Pb levels and depressive symptoms in older men, mediated by pessimism; and childhood BLLs and psychopathology scores in early adulthood.	Peters et al. (2011)	Mean: 20.6 µg/g
		Reuben et al. (2019)	Mean: 11.08 µg/dL
	Some supporting evidence from a prospective analysis reported imprecise positive associations between childhood BLLs and prevalence of social phobia, specific phobia, PTSD, anxiety problems, somatic problems, and antisocial personality problems in young adult women.	McFarlane et al. (2013)	Mean: 17.2 µg/dL
Consistent evidence in animals with relevant exposures	Increased anxiety-like behaviors in adulthood (up to 18 mo) following developmental or lifetime Pb exposure provides coherence with epidemiologic evidence.	Section 3.5.4.2	Peak blood Pb after lifetime exposure: 7–24 µg/dL Peak blood Pb after developmental exposure: 12–50 µg/dL
Inconsistent supporting evidence from cross-sectional epidemiologic studies with relevant blood and bone Pb levels	A limited body of cross-sectional studies provides inconsistent evidence of associations between generally lower blood and bone Pb levels and depression and anxiety.	Section 3.6.2.1	Mean/median range across studies: Bone: 10.3–12.5 µg/dL Blood: 0.58–3.97 µg/dL
Uncertainty regarding potential confounding	Most studies included adjustment for age, sex, SES factors, and marital status, Table 3-15E but did not consider use of antidepressants		

BLL = blood lead level; mo = months; Pb = lead; PTSD = post-traumatic stress disorder; SES = socioeconomic status.
[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.

3.6.3 Sensory Organ Function in Adults

The 2013 Pb ISA included separate causality conclusions for auditory and visual function. This ISA combines these categories and makes one causality determination for Sensory Organ Function (see Section 3.6.3.5). Recent studies are summarized in Table 3-16E and Table 3-16T. An overview of the recent evidence is provided below.

3.6.3.1 Auditory Function

The evidence assessed in the 2013 Pb ISA was "suggestive of a causal relationship" between Pb exposure and auditory function decrements in adults (U.S. EPA, 2013). The strongest evidence was provided by the analysis of NAS men, which revealed associations between higher tibia Pb levels and a higher rate of elevations in hearing threshold over 20 years (Park et al., 2010). Findings demonstrating decreased auditory evoked potentials in animals provided biological plausibility for the observations in this epidemiologic study, but uncertainties related to effects on auditory function in adult animals with relevant Pb exposures remained.

3.6.3.1.1 Epidemiologic Studies of Auditory Function

Several recent epidemiologic studies examined the association between Pb exposure and decrements in auditory function in adults (Tu et al., 2021; Yin et al., 2021; Wang et al., 2020; Kang et al., 2018; Choi and Park, 2017; Shiue, 2013; Choi et al., 2012). The findings generally supported an association between Pb exposure and hearing loss in adults. These studies are described below.

Most studies were cross-sectional, using data from NHANES (Tu et al., 2021; Shiue, 2013; Choi et al., 2012) and KNHANES (Kang et al., 2018; Choi and Park, 2017). Choi et al. (2012) and Tu et al. (2021) measured blood Pb in adult NHANES participants (20–69 years) in 1999–2004 and 2011–2012, respectively. Choi et al. (2012) observed an increased likelihood of hearing loss per doubling of blood Pb (OR = 1.09 [95% CI: 0.95, 1.26]) as well as an increased percent change in hearing threshold (% change = 5.41 [95% CI: 2.12, 8.81]). Similar findings were noted in quintile analyses, with higher blood Pb quintiles having a greater magnitude of effect when compared with the lowest quintile (0.20–0.80 μg/dL) (Choi et al., 2012). Tu et al. (2021) measured hearing loss at speech frequency and at high frequency. In quartile analyses, the magnitude of effect increased with each blood Pb quartile for each type of hearing loss (Tu et al., 2021). Compared with the lowest quartile (<0.07 μg/dL), the highest blood Pb quartile (>0.16 μg/dL) was positively associated with speech-frequency hearing loss (OR = 1.46 [95% CI: 0.81, 2.64]) and high-frequency hearing loss (OR = 1.98 [95% CI: 1.27, 3.10]). In sex-stratified analyses, the direction of effect remained but the magnitude of effect was greater among males. In age-stratified

analyses, a positive association remained for ages <35 years and 35–52 years for both types of hearing loss; however, ORs were generally imprecise for the younger age group (<35 years). On the contrary, there appeared to be an inverse association between BLLs and hearing loss in the oldest age group (>52 years) (Tu et al., 2021). Also using NHANES data, Shiue (2013) measured Pb exposure in urine and did not find an adverse association with self-reported hearing among older adults (≥50 years). For self-reported ear ringing, urinary Pb had a slightly positive association (Shiue, 2013). In KNHANES, Choi and Park (2017) measured speech- and high-frequency hearing loss in adolescents (12–19 years) and adults (20–87 years). Hearing loss was defined as pure-tone average >25 dB in adults. For each doubling of blood Pb, there was an increased likelihood of speech-frequency hearing loss (OR = 1.15 [95% CI: 0.94, 1.41]) and high-frequency hearing loss (OR = 1.30 [95% CI: 1.08, 1.57]). In quartile analyses, the magnitude of effect increased with each blood Pb quartile when compared with the lowest quartile (Choi and Park, 2017). In another analysis conducted in the KNHANES population, Kang et al. (2018) observed an association between BLLs and hearing impairment in adults (20–87 years). In quartile analyses, the magnitude of effect for high-level frequency hearing impairment was greatest in the highest blood Pb quartile compared with the lowest blood Pb quartile in males (OR = 1.63 [95% CI: 1.16, 2.29]) as well as in females (OR = 1.50 [1.03–2.20]). For low-frequency hearing impairment, the associations were less consistent by quartile and more attenuated (Kang et al., 2018).

In a meta-analysis of studies from Iran, Korea, China, and the United States, Yin et al. (2021) observed consistent positive associations between Pb exposure and any hearing loss (combined OR per unit increase in Pb = 1.42 [95% CI: 1.22, 1.67]), low-frequency hearing loss (combined OR = 1.31 [95% CI: 1.17, 1.47]), and high-frequency hearing loss (combined OR = 1.96 [95% CI: 1.48, 2.60]). When stratified by age group, the association persisted in adults (≥20 years; combined OR per unit increase in Pb = 1.34 [95% CI: 1.18, 1.52]) (Yin et al., 2021). Despite these results, there are still some inconsistencies in the recent literature. In a case-control study of adults in China who participated in a survey of hearing loss, Wang et al. (2020) did not observe an association with blood Pb before and after adjusting for workplace noise exposure.

Summary

The strongest evidence described in the 2013 Pb ISA was provided by the analysis of NAS men for associations of higher tibia Pb level with a higher rate of elevations in hearing threshold over 20 years (Park et al., 2010). Several recent cross-sectional analyses of NHANES and KNHANES generally support an association of Pb exposure (i.e., concurrent BLLs) with hearing loss; however, recent studies are not entirely consistent.

3.6.3.1.2 Toxicological Studies of Auditory Function

Recent animal studies on the auditory effects of Pb exposures have investigated exposures beginning during development (postnatal or adolescent), discussed in Section 3.5.6.1.2. In particular, Carlson et al. (2018) did not detect any significant changes in BAEP in 4-month-old adult mice with very low BLLs (3 μg/dL). The strongest evidence for adult effects of Pb exposure was presented in the previous ISA (U.S. EPA, 2013). Lifetime Pb exposure was found to increase hearing thresholds and latencies in BAEP in adult monkeys (aged 8–13 years) (Rice, 1997; Lilienthal and Winneke, 1996). Moreover, Laughlin et al. (2009) detected small nonsignificant shifts in auditory threshold in 13-year-old Rhesus monkeys following gestational or postnatal Pb exposure. However, these effects were demonstrated at higher BLLs than are relevant to this ISA (33–150 μg/dL).

3.6.3.2 Visual Function

The evidence pertaining to visual function assessed in the 2013 Pb ISA was limited. A case-control study found higher Pb in retinal tissue from macular degeneration cases but lacked rigorous statistical analysis and examination of potential confounding. Studies in adult animals showed differential effects on ERGs, depending on the timing and concentration of exposure. Because the available epidemiologic and toxicological evidence was of insufficient quantity, quality, and consistency, the 2013 Pb ISA concluded the "evidence is inadequate to determine that a causal relationship exists between Pb exposure and visual function decrements in adults."

3.6.3.2.1 Epidemiologic Studies of Visual Function

Only a few epidemiologic studies examined the association between Pb exposure and decrements in visual function in adults (Paulsen et al., 2018; Fillion et al., 2013; Shiue, 2013). Fillion et al. (2013) measured contrast sensitivity (cpd) and acquired color vision loss (CCI) in adolescents and adults (15–66 years) in Brazil. Blood Pb exposure was negatively associated with the intermediate spatial frequency of contrast sensitivity (12 cycles/degree); however, results varied by spatial frequency. For CCI, there was a slightly positive association with blood Pb, but the effect estimate was imprecise (Fillion et al., 2013). In another study of contrast sensitivity, Paulsen et al. (2018) used the Pelli-Robson letter sensitivity chart and did not observe an association with blood Pb in a U.S.-based cohort (HR for blood Pb ≥2.06 μg/L versus. <2.06 μg/L = 0.91 [95% CI: 0.69, 1.18]). Visual function has also been measured using self-reported eyesight. Using NHANES data, Shiue (2013) measured Pb exposure in urine and did not find an association with self-reported visual impairment among older adults (≥50 years).

Summary

The epidemiologic evidence pertaining to the association of Pb exposure with visual function in adults remains limited. A small number of recent studies examining contrast sensitivity or acquired color vision loss found inconsistent results for associations with blood or urine Pb level (Paulsen et al., 2018; Fillion et al., 2013; Shiue, 2013).

3.6.3.2.2 Toxicological Studies of Visual Function

No recent PECOS-relevant studies have evaluated the effects of Pb exposure on visual function. Section 3.5.6.2.2 summarizes the literature discussed in the 2013 Pb ISA (U.S. EPA, 2013).

3.6.3.3 Olfactory Function

The 2013 Pb ISA did not assess any evidence on the relationship between Pb exposure and olfactory function in adults (U.S. EPA, 2013).

3.6.3.3.1 Epidemiologic Studies of Olfactory Function

In the Heinz Nixdorf Recall Study (HNRS) in Germany, male participants were recruited in 2000–2003 and followed up in 2011–2014 (Casjens et al., 2018). Casjens et al. (2018) examined the effect of Pb exposure on odor identification using the Sniffin' sticks odor identification test of 12 odors. Participants were classified as normosmic (identified >9 odors), hyposmic (identified 7–9 odors), and functionally anosmic (identified <7 odors). Compared with the lowest BLL at baseline (<5 μg/dL), the highest BLL (≥9 μg/dL) was associated with impaired odor identification (proportional OR = 1.96 [95% CI: 0.94, 4.11]). Similar results were observed using BLLs measured at follow-up (proportional OR = 1.57 [95% CI: 0.47, 5.19]).

3.6.3.4 Relevant Issues for Interpreting the Evidence Base

3.6.3.4.1 Potentially At-Risk Populations

Sex

Tu et al. (2021) measured hearing loss at speech frequency and at high frequency. In quartile analyses, the magnitude of effect increased with each blood Pb quartile for each type of hearing loss (Tu et al., 2021). In sex-stratified analyses, the direction of effect remained but the magnitude of effect was

greater among males. Kang et al. (2018) also observed an association between BLLs and hearing impairment in adults. In quartile analyses, the magnitude of effect for high-level frequency hearing impairment was greatest in the highest blood Pb quartile compared with the lowest blood Pb quartile, with similar associations observed in males (OR = 1.63 [95% CI: 1.16, 2.29]) and females (OR = 1.50 [1.03–2.20]).

3.6.3.5 Summary and Causality Determination: Sensory Organ Function in Adults

In the 2013 Pb ISA, causality determinations were separately determined for auditory and visual function in adults, while no studies of olfactory function were evaluated (U.S. EPA, 2013). For auditory function in adults, the evidence was suggestive of, but not sufficient to infer, a causal relationship, based primarily on findings from a few epidemiologic studies. Similar to the conclusion for children, the evidence relating to visual function in adults was inadequate to determine if a causal relationship exists. In the current ISA, the evidence for auditory, visual, and olfactory function are evaluated together, forming a single causality determination for sensory organ function.

The strongest evidence described in the 2013 Pb ISA was provided by the analysis of NAS men for associations between higher tibia Pb levels and a higher rate of elevations in hearing threshold over 20 years (Park et al., 2010). Several recent cross-sectional analyses of NHANES and KNHANES generally support an association of Pb exposure (i.e., concurrent BLLs) with hearing loss (Tu et al., 2021; Kang et al., 2018); Choi and Park (2017); (Choi et al., 2012); however, recent studies are not entirely consistent (Wang et al., 2020). Hearing loss and altered responses on BAEPs in adult nonhuman primates and rodents following lifetime or developmental Pb exposure have been demonstrated at BLLs as low as 29 µg/dL (Jamesdaniel et al., 2018; Laughlin et al., 2009; Rice, 1997). The few studies that investigated BLLs from 3–8 µg/dL did not report altered BAEP in rodents, though effects on auditory processing may occur at these lower exposure levels (Liu et al., 2019; Carlson et al., 2018; Zhu et al., 2016).

The epidemiologic and experimental animal evidence pertaining to the association of Pb exposure with visual function in adults remains limited. Toxicological studies have demonstrated biological plausibility for Pb-induced effects on vision, including dysfunction of subcortical visual neurons, visual processing areas, and retinal development (U.S. EPA, 2013). A small number of recent studies examining contrast sensitivity or acquired color vision loss in humans found inconsistent results for associations with blood or urine Pb level (Paulsen et al., 2018; Fillion et al., 2013; Shiue, 2013). Deficits in visual temporal acuity have been demonstrated in adult nonhuman primates, although peak exposure levels are higher than considered relevant for this assessment (Rice, 1998). Altered responses to ERGs have been detected at a wide range of BLLs, but the direction of this effect (i.e., supernormal or subnormal responses) is overall inconsistent (Fox et al., 2008; Rothenberg et al., 2002; Fox et al., 1997).

Olfactory function was not discussed in the 2013 Pb ISA. Recently, baseline BLL was associated with reduced odor identification in a prospective analysis of the German HNRS (Casjens et al., 2018).

Overall, the evidence is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and sensory function in adults. This determination is supported by generally consistent prospective and cross-sectional analyses demonstrating Pb-associated hearing loss in adults. The few experimental animal studies available provide coherence for this endpoint when BLLs are greater than 29 μg/dL, but not at BLLs more relevant to current human exposures. Human and experimental animal studies investigating the effect of Pb on visual and olfactory function are limited and inconsistent.

Table 3-11 Summary of the evidence that is suggestive of, but not sufficient to infer, a causal relationship between sensory function in adults

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Auditory Function			
Generally consistent associations observed in multiple epidemiologic studies.	Prospective study found association between tibia Pb level and higher rate of increase in hearing threshold over 23 yr in males enrolled in the NAS.	Park et al. (2010)	Tibia Pb mean: 22.5 µg/g, measured near end of follow-up
	Cross-sectional analyses of NHANES and KNHANES find Pb-associated effects on hearing loss	Shiue (2013) Choi et al. (2012) Tu et al. (2021) Kang et al. (2018) Choi and Park (2017)	
Uncertainty at relevant exposure levels in experimental animal studies	Hearing loss and altered responses on BAEPs in adult nonhuman primates and rodents demonstrated	Rice (1997) Laughlin et al. (2009) Jamesdaniel et al. (2018).	Lifetime or developmental Pb exposure >29 µg/dL
	No altered BAEP in rodents, though effects on auditory processing may occur	Carlson et al. (2018) Zhu et al. (2016) Liu et al. (2019)	3–8 µg/dL
Visual Function			
Inconsistent results across limited epidemiologic studies	Associations of blood or urine Pb level with contrast sensitivity or acquired color vision loss were inconsistent	Shiue (2013) Paulsen et al. (2018) Fillion et al. (2013)	
Limited evidence from experimental animal studies	Deficits in visual temporal acuity demonstrated in adult nonhuman primates	Rice (1998)	>30 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Biological plausibility demonstrated	Dysfunction of subcortical visual neurons, visual processing areas, and retinal development	(U.S. EPA, 2013)	
Olfactory Function			
Single study indicates association	Impaired odor identification associated with BLL in a single study	Casjens et al. (2018)	>9 vs. ≤5 μg/dL

BAEP = brainstem auditory evoked potentials; BLL = blood lead level; KNHANES = Korea National Health and Nutrition Examination Survey; NAS = Normative Aging Study; NHANES = National Health and Nutrition Examination Survey; Pb = lead; yr = year(s).
[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.

3.6.4 Neurodegenerative Diseases

The 2013 Pb ISA concluded that the evidence was "inadequate to determine that a causal relationship exists" between Pb exposure and neurodegenerative diseases (U.S. EPA, 2013). Evidence was inconclusive for amyotrophic lateral sclerosis (ALS) (see Section 4.3.9.2 of (U.S. EPA, 2013)) and Alzheimer's disease (AD; see Section 4.3.9.1 of (U.S. EPA, 2013)); however, a few case-control studies each found higher BLLs in adults with essential tremor and higher bone Pb levels in adults with PD (Weisskopf et al., 2010; U.S. EPA, 2006).The evidence was considered inconclusive overall due to a limited number of studies, the potential for reverse causation (specifically for case-control studies in which the reduced physical activity among cases could result in greater bone turnover and greater release of Pb from bones into blood as compared with controls), and limited consideration for potential confounding factors.

Recent epidemiologic studies indicated potential relationships between Pb exposure and some neurodegenerative disease endpoints among non-occupational cohorts. The strongest evidence in the current review includes well-designed studies of ALS and PD outcomes. Findings for AD, tremor, and motor function were inconclusive. Measures of central tendency for Pb biomarker levels used in each study, along with other study-specific details, including study population characteristics and select effect estimates, are highlighted in Section 3.7, Table 3-17E. A large number of toxicological studies adds to the evidence suggesting that developmental exposure to Pb increases the expression of pathophysiological markers of AD, including amyloid beta (Aβ) peptides, tau, and phosphorylated tau (p-tau), at lower BLLs than were investigated in the previous ISA (<10 μg/dL). Toxicological studies investigating potential associations between Pb exposure and PD, ALS, and essential tremor remain limited in this review. However, toxicological evidence for PD and ALS are supported by some studies in the 2013 review that provided pathophysiological evidence for Pb-induced decreases in dopaminergic cell activity in the substantia nigra, which can contribute to PD development, and Pb exposure affecting neurophysiologic changes associated with ALS.

3.6.4.1 Epidemiologic Studies of Neurodegenerative Diseases

3.6.4.1.1 Alzheimer's Disease

MMSE is a widely used screening tool for AD and other types of dementia. Lower scores on MMSE were consistently associated with higher bone Pb levels, which indicated long-term or cumulative exposure to Pb, in the NAS studies assessed in the 2013 Pb ISA (Wang et al., 2007; Weisskopf et al., 2004; Wright et al., 2003). There was heterogeneity in the results of studies that examined associations between MMSE scores and BLLs in adults (Weuve et al., 2006; Nordberg et al., 2000). Blood Pb is

generally considered a marker of recent exposure; however, in studies of adults, blood Pb level also reflects Pb that is mobilized from the bone introducing uncertainty and complicating the interpretation of cross-sectional studies that assess exposure using concurrent blood Pb level. Evidence regarding the association of Pb exposure with clinical diagnosis of AD was limited to studies which did not find associations with higher occupational exposure to Pb (Graves et al., 1991) or higher Pb concentration in the brains (Haraguchi et al., 2001) in AD cases compared with unaffected controls. The latter studies were limited because of their case-control designs, which may be subject to reverse causation where AD leads to higher Pb levels, limited consideration for potential confounding, and because of the potential misalignment with relevant exposure window.

Recent studies add to the evidence base, including an analysis of the NAS cohort that examined the association of bone Pb biomarkers with cognitive impairment, including MMSE score, Farooqui et al. (2017), and two studies that examined the association of blood Pb biomarkers with the clinical endpoints of AD risk or AD mortality (Horton et al., 2019; Yang et al., 2018) in non-occupational cohorts (Table 3-16T). Among the older male participants in the NAS, higher patella Pb concentration (IQR: 21 μg/g) was associated with increased risk (HR: 1.10, 95% CI: 0.99, 1.21) of having an MMSE score below 25 (threshold that represent cognitively not normal or at risk for dementia), while less support was observed for an association with tibia Pb concentration (HR: 1.03, 95% CI: 0.88, 1.22) (Farooqui et al., 2017). Studies that specifically assessed clinically diagnosed AD or mortality did not provide strong evidence of an association. A case-control study by Yang et al. (2018) included participants from clinical settings in Taiwan and used standard case-control as well as propensity score-matched approaches to assess the relationship between the heavy metals (Pb, Cd, Se, Hg) and AD risk. Findings from the multivariable analysis showed the association between BLL and AD risk in tertiles, either in the full population tertile 2 (OR 1.00, 95% CI 0.56–1.79) and tertile 3 (OR 0.87, 95% CI 0.49–1.55) or propensity score-matched population (tertile 2: OR 1.16, 95% CI 0.55–2.47; and tertile 3: OR 1.12, 95% CI 0.53–2.39), was imprecise. A cohort study by Horton et al. (2019) used national data from five NHANES cycles (1999–2008) and followed a large cohort of 8,080 participants from 1999 till December 2014 for AD-related mortality to examine the longitudinal association between blood Pb and AD mortality. Results from Cox proportional hazard models adjusted for various confounders and competing risks for AD mortality (death due to cancer, cardiovascular disease (CVD), cerebrovascular accident [CVA], nephritis, and respiratory disease) indicated that BLLs of 1.5 and 5 μg/dL had 1.2 (95% CI = 0.70, 2.1) and 1.4 (95% CI = 0.54, 3.8) times the rate of AD mortality compared with those with a BLL of 0.3 μg/dL, respectively. The associations observed for various BLL categories with respect to the reference category of BLL 0.3 μg/dL were in a positive direction with increased AD risk for increasing BLL categories; however, the associations were imprecise. The imprecise effect estimates are likely due to the small number of AD mortality cases (n = 81), which resulted from AD mortality being determined from the listing of the immediate cause of death rather than the underlying cause of death. This means the study may be underpowered, potentially resulting in an unstable effect estimate.

3.6.4.1.2 Amyotrophic Lateral Sclerosis

Case-control and cohort studies examining the association of BLL and ALS risk or ALS survival that were included in the 2006 AQCD for Pb or the 2013 Pb ISA produced inconsistent results (Fang et al., 2010; Kamel et al., 2008; Kamel et al., 2002; Vinceti et al., 1997). Recent case-control and cohort studies that assessed biomarkers of Pb before disease development addressed uncertainties related to temporality and reverse causality identified in previous reviews, thus expanding the support for an association of BLL with ALS risk and survival.

Strong evidence for the association of Pb and ALS is provided by a recent prospective cohort study that used data from the National Registry of Veterans in the United States with ALS cases ascertained between April 2003 and September 2007 (with blood samples collected from January to September 2007) and followed through the date of death or July 2013 (April 2003–Sep 2007) Fang et al. (2017). The study was novel in that it assessed ALS mortality and survival and its association with blood Pb level, and also bone turnover (formation and resorption) biomarkers. The association of ALS survival time with blood Pb indicated that increased blood Pb was significantly associated with the increased mortality and thus shorter survival after ALS diagnosis (HR: 1.23 [95% CI:1.02, 1.49]) in the model mutually adjusted for bone resorption and formation and other confounding variables. The observation of the association between BLL and ALS after adjustment for biomarkers of bone turnover reduced uncertainties related to assessing exposure using Pb concentration in the blood. In another study, Peters et al. (2020) conducted a nested case-control study within the prospective European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study. ALS cases were defined to include subjects with motor neuron disease (ICD10 G12.2) as the underlying cause of death. Pb concentration was measured in erythrocytes as a marker of ongoing exposure. The associations of Pb in erythrocytes comparing categories of >56.8 to ≤ 89.0 ng/g and >89.0 ng/g to the reference category (≤56.8 ng/g) with ALS mortality were 1.83 (95% CI: 0.99, 3.35) and 1.89 (95% CI: 0.97, 3.67), respectively.

Additional studies indicating associations of Pb concentration in cerebrospinal fluid (CSF) and Pb in air also provide some support for an association between Pb exposure and ALS. A case-control study in Italy used CSF biomarkers for heavy metals including Pb Vinceti et al. (2017). The odds of ALS were greater in the highest tertile of CSF Pb concentration than in the lowest tertile; however, the effect estimate was imprecise (OR: 1.39, 95% CI 0.48–4.25). Another case-control study of a large nationally representative U.S. sample (cases: 26,199 and controls: 78,597) used the U.S. healthcare claims database from the Symphony Health's Integrated Dataverse (Andrew et al., 2022). Participants with the first ALS diagnosis after 6 months of enrollment in the database were included (diagnosis years 2013–2019). Controls were matched based on age and sex, selected from the Symphony Health network, and also required to have a minimum of 6 months enrollment in the database. The study did not use the Pb biomarkers but rather used the airborne contaminants level data for 268 contaminants (including Pb) obtained from the U.S. EPA National Emissions Inventory (NEI) for 2008 to estimate the past exposure prior to the ALS onset (2013–2019) at the participants' location of residence. The study used a three-

phase approach to assess ALS risk nationwide: discovery, validation, and confirmation. First, in the discovery phase, the study identified major contaminants (out of 268 contaminants) that were significantly associated with the ALS risk. Second, in the validation phase, the study evaluated various combinations of contaminants associated with the ALS risk. In the final confirmatory phase, the study used cohorts only from NH, VT, and OH, incorporating their detailed residential history information to capture changes in exposure due to residential move prior to ALS diagnosis. The discovery phase identified 49 airborne contaminants (including Pb) associated with ALS risk. The relationship between these 49 contaminants and the risk of ALS was further analyzed in the validation cohort, and airborne Pb and five PCBs were identified associated with an increased risk for ALS (Pb: OR: 1.02, 95% CI: 1.01–1.03). The confirmatory analysis using NH/VT and OH based cohorts with detailed residential history to calculate 5-, 10-, and 15-year past exposure prior to diagnosis suggested significant increased risk for ALS associated with 10-year Pb exposure history when the >75th percentile group was compared with the <50th percentile group (NH/VT: OR: 2.03, 95% CI: 1.46–2.80, and OH: OR: 1.60, 95% CI: 1.28–1.98) in a multivariable model. Despite the strong design and larger sample size of the study, the inference regarding the Pb-ALS risk for this study should be interpreted with caution given the uncertainty regarding the relationship between the estimated concentration of Pb in the air and Pb concentration in biomarkers as well as the influence of potential unmeasured confounders.

3.6.4.1.3 Parkinson's Disease

A limited number of case-control studies assessed in the 2013 Pb ISA found positive associations between bone Pb concentration and PD. A recent study by Paul et al. (2021) examined participants from two large and independent population-based case-control studies (total n > 2,600)—the System Genomics of Parkinson's Disease (SGPD), a consortium of three studies from across Australia and New Zealand; and the Parkinson's Environment and Genes (PEG) study, a population-based study from three agricultural counties of Central California—to explore the association of cumulative Pb exposure on the PD risk. The study used novel epigenetic biomarkers of cumulative Pb exposure (i.e., DNA methylation [DNAm] Pb data in the patella and tibia developed in the NAS cohort). The study analyzed the relationship between DNAm Pb and PD separately for two cohorts and meta-analyzed the results. The findings from the multivariable adjusted model suggested that PD risk was strongly associated with the DNAm biomarker for tibia Pb levels in both cohorts (SGPD cohort: OR: 2.06, 95% CI: 1.66–2.56; PEG cohort: OR: 1.60, 95% CI: 1.20, 2.15; meta-analyzed results [meta-OR: 1.89, 95% CI: 1.59–2.24]).

3.6.4.1.4 Tremor

A limited number of studies examined the association between BLLs and tremor. The studies were potentially influenced by reverse causation because inactivity due to disease condition and subsequent bone resorption can lead to increased BLLs. A recent study used a cohort of men in the NAS

and assessed the longitudinal relationship of tremor score with bone Pb in the tibia (n = 670, mean: 21.23 μg/g) and patella (n = 672, mean: 27.98 μg/g), in addition to BLL (n = 807, mean: 5.01 μg/dL). Ji et al. (2015) found that over 8 years of follow-up, neither blood Pb nor bone Pb was associated with the tremor score. However, among men younger than the median age (68.9 years), the tremor score increased as the quintile of blood Pb increased (p = 0.03), with men in the highest quintile scoring 0.35 (95% CI: 0.03, 0.67) points higher on the tremor scale than those in the lowest quintile. This pattern was not evident for bone Pb. The tremor score in the study was based on assessments of drawing capability and not the clinical diagnosis.

3.6.4.1.5 Motor Function

Several epidemiologic studies examined the association between Pb exposure and decrements in motor function in adults (Casjens et al., 2018; Khalil et al., 2014; Grashow et al., 2013; Ji et al., 2013; Shiue, 2013; Min et al., 2012). Motor function was assessed using measures of balance, walking speed, coordination, and strength. Inconsistencies in the results made it difficult to draw conclusions about the association between Pb exposure and motor function in adults.

Most studies were cross-sectional in design. Results from studies that measured balance were inconsistent. Among older adults (≥50 years) in NHANES 2003–2004, Shiue (2013) observed an inverse association between urinary Pb and balance disorders defined as self-reported dizziness, difficulty with balance, or difficulty with falling in the past 12 months. For every log unit increase in urinary Pb (unit not specified), the likelihood of having a balance disorder decreased (OR = 0.56 (95% CI: 0.38, 0.84]) (Shiue, 2013). Among adults (≥40 years) who participated in the NHANES Balance Component, Min et al. (2012) found that higher levels of blood Pb were generally associated with an increased likelihood of failing a balance test. Balance dysfunction was evaluated using the Romberg Test of Standing Balance on Firm and Compliant Support Surfaces, which measured a participant's ability to maintain balance under various test conditions. Compared with the lowest quintile of blood Pb (<1.2 μg/dL), the likelihood of any balance dysfunction (failing any balance test) increased in the fourth quintile (2.3–3.2 μg/dL; OR = 5.23 [95% CI: 0.59, 46.43]) and fifth quintile (3.3–48 μg/dL; OR = 33.33 [95% CI: 1.94, 573.16]) (Min et al., 2012).

Among older adults (50–85 years) in NHANES, Ji et al. (2013) assessed the relationship between blood Pb and walking speed. Walking speed was measured by timing a participant's walk for 20 feet at their usual walking pace. Compared with the lowest quintile of blood Pb (0.2 to ≤1.2 μg/dL), walking speed decreased with increasing quintiles of blood Pb in women (p-trend = 0.005). In the highest quintile of blood Pb (3.0 to ≤53.0 μg/dL), the estimated mean walking speed in women was 0.11 feet/second slower (β = −0.11 [95% CI: −0.19, −0.04]). On the contrary, BLL did not appear to be associated with walking speed in men (Ji et al., 2013). In MrOS, Khalil et al. (2014) examined the association between blood Pb and walking speed and strength among older non-Hispanic Caucasian men (≥65 years). In this cross-sectional analysis, blood Pb did not appear to be associated with grip strength, walking speed, or

narrow-walk pace. Leg extension power (watts) measured with the Nottingham power rig had a negative association for every log-μg/dL increase in blood Pb (β = −0.03 [95% CI: −1.97, 2.03]). In addition, blood Pb had a negative association with the participants' ability to stand from a chair without using their arms (OR per log-μg/dL increase in blood Pb = 0.97 [95% CI: 0.88, 1.07]) (Khalil et al., 2014). The reported associations were very imprecise.

A few cohort studies measured fine motor abilities and hand-eye coordination in adults. In the HNRS in Germany, Casjens et al. (2018) examined the effect of Pb exposure on fine motor abilities among male participants who were recruited in 2000–2003 and followed up in 2011–2014. Fine motor abilities were measured at follow-up (at ages 55–86 years) and included four tasks (tapping, aiming, line tracing, and steadiness) carried out separately with each hand. Compared with the lowest BLL at baseline (<5 μg/dL), the highest BLL (≥9 μg/dL) was positively associated with tapping hits (OR = 1.35 [95% CI: 0.49, 3.70]) and steadiness errors (OR = 1.36 [95% CI: 0.50, 3.66]) but negatively associated with aiming errors (OR = 0.56 [95% CI: 0.22, 1.42]) and line tracing errors (OR = 0.93 [95% CI: 0.32, 2.74]). The magnitude of each association increased when using BLLs measured at follow-up, except for tapping hits, which changed to a negative association (OR = 0.98 [95% CI: 0.82, 1.16]). In general, the ORs were imprecise (Casjens et al., 2018). In the Department of Veterans Affairs NAS, Grashow et al. (2013) examined the association between bone Pb and a coordination task which involved inserting metal pegs into a grooved pegboard. Bone Pb was measured at the patella and the midtibial shaft and was positively associated with the grooved pegboard completion time. In other words, the pegboard test took longer to complete for every 10 μg/g increase in patella Pb (β = 1.97 [95% CI: 0.55, 3.38]) and 10 μg/g increase in tibia bone Pb (β = 3.11 [95% CI: 1.16, 5.06]) (Grashow et al., 2013).

3.6.4.1.6 Summary

In summary, recent epidemiologic studies found relationships between Pb exposure and some neurodegenerative disease endpoints among non-occupational cohorts. Similar to the conclusion of the 2013 Pb ISA, the direction and strength of the association is stronger for some endpoints than for others. In the 2013 Pb ISA, evidence was inconclusive for ALS and AD while a limited number of case-control studies indicated relationships between higher BLLs in adults and essential tremor, and between higher bone Pb levels in adults and PD. In the current review, the epidemiologic evidence pertaining to ALS and PD has strengthened due to the availability of better designed case-control and cohort studies. Recent studies of Pb exposure and clinically diagnosed AD were also conducted. These studies added to the previous evidence which generally relied on assessing AD using screening instruments; however, studies that specifically assessed clinically diagnosed AD or mortality did not provide strong evidence of an association.

Studies for ALS in this review included one cohort study that examined the relationship between BLLs and ALS survival among U.S. veterans (Fang et al., 2017) and a large case-control study of participants from a healthcare claims dataset examining associations between past airborne Pb exposures

and ALS risk (Andrew et al., 2022). The findings from the cohort study by (Fang et al., 2017) indicate that increased levels of baseline blood Pb are associated with shorter ALS survival even after mutually accounting for bone resorption and formation. This finding is in agreement with the results of a study included in the previous review that suggested positive associations between Pb in blood or bone with ALS risk (Fang et al., 2010; Kamel et al., 2002). An important uncertainty in these studies is the potential for reverse causality because increased bone turnover in ALS patients could cause higher blood Pb levels, potentially explaining the observed associations. Fang et al. (2017) addressed this uncertainty by demonstrating that the association of blood Pb level with ALS survival persisted after adjustment for a biomarker of bone turnover. Another study investigating ALS risk using a case-control design with a large sample from a healthcare database and well characterized exposure and outcomes examined whether previous airborne Pb exposures were related to ALS development. The study found significant positive associations between Pb exposure and increased ALS risk (Andrew et al., 2022), specifically for residential Pb exposure over the past 10 years. The use of estimated airborne exposure without corresponding measurement of Pb exposure biomarkers is a potential limitation of this study.

In a study of PD, Paul et al. (2021) conducted a case-control analysis using a novel, epigenetic biomarker to estimate cumulative Pb exposure measured in tibia and patella bone. The study found an association between DNA methylation (DNAm), as a biomarker of tibia Pb levels, and PD risk. This empirically-derived DNA methylation signature is potentially a more sensitive predictor of the effect of Pb exposure on PD than bone Pb concentration (Paul et al., 2021). With regard to tremor outcomes, no association with blood and bone Pb biomarkers was observed (Ji et al., 2015). However, the results indicated an association of blood Pb and tremor score, particularly in younger men, when analysis was stratified by age categories. Studies reviewed for Pb exposure and motor function in adults yielded inconsistent findings.

Studies of the association of Pb exposure with AD in the previous ISA examined cognitive impairment (e.g., as indicated by MMSE scores, which are used to screen for dementia and AD) rather than the clinical diagnosis of AD. Recent studies add to the evidence through their examination of clinical diagnosis of AD and AD mortality in non-occupational cohorts. In a case-control study, Yang et al. (2018) reported an imprecise positive association between BLL and AD risk. The inability to establish temporal relationships with this case-control study, given the inclusion of prevalent cases of AD, leads to uncertainty about potential reverse causality. A recent prospective study that investigated the relationships between BLLs and AD mortality addressed the temporality of the association (Horton et al., 2019). The study calculated HRRs for selected BLLs (i.e., 0.5, 1, 1.5, 2, 3, 5 µg/dL) compared a reference category of 0.3 µg/dL. In addition to considering confounders in their model, the authors specified model to consider the design effect (i.e., accounting for the NHANES survey design utilized by incorporating survey weights) and competing risks. The study observed a positive association between blood Pb and AD mortality risk, but the association was imprecise (Horton et al., 2019). For example, HRR for participants with BLL of 1.5 1.5 (95% CI = 0.81, 2.9) compared to those with BLL of 0.3 µg/dl, respectively, after accounting for design effect.

3.6.4.2 Toxicological Studies of Neurodegenerative Diseases

Although the evidence was inconclusive overall, a few toxicological studies in the 2013 Pb ISA suggested that Pb exposure in early life could influence AD-like pathologies (U.S. EPA, 2013). AD exhibits several neuropathologic hallmarks, such as senile plaques and neurofibrillary tangles (comprised of Aβ and hyperphosphorylated tau aggregates, respectively), as well as synaptic loss and neuronal death. Developmental exposure to Pb in rodents, resulting in BLLs >40 μg/dL, increased Aβ peptides, hyperphosphorylated tau, and other related endpoints (Li et al., 2010; Basha et al., 2005). Importantly, these effects were not found following adult-only exposure. Wu et al. (2008) also demonstrated that 23-year-old monkeys (*Macaca fascicularis*) given Pb from birth to PND 400 had elevated Aβ and amyloid plaques in their frontal cortex compared with unexposed age-matched controls. BLLs in these animals ranged from 19 to 26 μg/dL at PND 400 but had returned to baseline by adulthood. One previous study performed in transgenic superoxide dismutase 1 (SOD1) mice (a model of ALS) found that adolescent exposure to Pb reduced astrocyte reactivity and extended the survival time but had no significant effects on the onset of disease in this model (Barbeito et al., 2010). Tavakoli-Nezhad et al. (2001), reviewed in the 2006 AQCD, demonstrated Pb-induced decreases in dopaminergic cell activity in the substantia nigra, which is associated with PD. No recent PECOS-relevant studies have investigated the effects of Pb exposure on ALS-relevant endpoint or endpoints related to essential tremor.

The potential relationship between Pb exposure and AD has been further explored in recent literature (Table 3-17T). Of the two major Aβ isoforms (Aβ40 and Aβ42), the less predominant isoform, Aβ42, is typically considered more prone to aggregation (Xiao et al., 2015). A low Aβ42/Aβ40 ratio in plasma and CSF has also been shown to indicate an increased risk for AD (Graff-Radford et al., 2007). (Zhou et al., 2018) found increased expression of Aβ42 in the cerebral cortex and hippocampus of Sprague Dawley rats following Pb exposure during adolescence. Gestational and lactational Pb exposure resulting in lower BLLs, between 4–10 μg/dL, also significantly increased Aβ40 in the cerebral cortex of Kunming mice (Li et al., 2016c). Utilizing a transgenic mouse model (Tg-SwDI), Gu et al. (2012) reported that adolescent Pb exposure significantly increased both Aβ40 and Aβ42 in the cerebral cortex, hippocampus, and CSF; however, the ratio of Aβ42/Aβ40 was not significantly different. Pb-treated animals in this study also had increased amyloid plaque formation, which was co-localized with brain Pb deposits. Increases in the expression of amyloid precursor protein (APP) and beta-secretase 1 (BACE1; the enzyme that cleaves APP into Aβ) have been demonstrated in some recent studies (Wu et al., 2020b; Zhou et al., 2018; Sun et al., 2014), but not all (Gu et al., 2012).

Changes in the expression of both total tau (t-tau) and p-tau are considered biomarkers of AD in humans. One recent study demonstrated that developmental Pb exposure (GD 0–PND 21; resulting in BLLs of 7 μg/dL) increased t-tau and p-tau in the cerebral cortex and cerebellum but not the hippocampus of juvenile Wistar rats (Gąssowska et al., 2016b). These changes coincided with some evidence of enhanced activity of two tau kinases (glycogen synthase kinase−3β and cyclin-dependent kinase 5 [CDK5]) in relevant brain regions. Another study found that postnatal Pb exposure in Wistar rats caused

significant changes in t-tau, p-tau, and related phosphatases in the hippocampus, but these effects were transient and inconsistent at the time points tested (PND 21 and PND 30) (Rahman et al., 2012b). Wu et al. (2020b) also found no significant increases in hippocampal p-tau in Pb-exposed C57Bl/6 mice at 4 months old; however, increases in hippocampal p-tau became apparent at 13 months old and persisted until 16 months old. In the prefrontal cortex, p-tau was significantly elevated above age-matched control values at 4 month and 13 months, but not 16 months. Importantly, BLLs in these rodents at 4 months (when exposure was terminated) were nearly 60 μg/dL and did not decrease to PECOS-relevant values until 16 months (28 μg/dL). One additional study Zhang et al. (2012) reported that 8 weeks of Pb exposure increased p-tau in the hippocampus at BLLs as low as 10 μg/dL. Notably, this study also reported increased alpha-synuclein in the hippocampus. Alpha-synuclein is a major constituent of Lewy bodies, which are a neuropathologic hallmark of PD (Baba et al., 1998).

In the 1980s, Rice (1990) established a cohort of monkeys (*Macaca fascicularis*) exposed to Pb in the first 400 days of life (resulting in BLLs between 19–26 μg/dL) and terminated at 23 years old. At the time of termination, BLLs had returned to control levels. Using tissues from these animals, Wu et al. (2008) found increases in the protein expression of Aβ and APP, as well as increases in the gene expression of APP and specificity protein 1 (Sp1, a transcriptional regulator of APP and tau), reported in the previous ISA. Recently, Bihaqi and Zawia (2013) extended these findings by analyzing the cerebral cortex tissue for changes in tau-related endpoints. Compared with age-matched controls, Pb-exposed animals had significantly increased expression of t-tau, p-tau, and CDK5 (a tau kinase). These findings were further supported by neuropathological changes (i.e., increases in p-tau immunoreactivity and deposits). This study also found that mRNA levels of tau, CDK5, Sp1, and Sp3 were significantly increased.

Recent studies have also measured endpoints outside of those related to Aβ and tau. Dysregulation of lipid pathways has been implicated in AD and neurodegenerative disorders (Di Paolo and Kim, 2011). Zhou et al. (2018) found that Pb exposure decreased total and free cholesterol levels via dysregulation of cholesterol metabolism in the cerebral cortex and hippocampus. Feng et al. (2019) found that lifetime exposure to Pb significantly decreased neuronal density in the cerebral cortex at PNW 70. This change was accompanied by a decrease in overall brain volume. In addition, several studies that reported on AD-related neuromolecular changes also reported significant impairment of learning and memory assessed via the Morris water maze (Wu et al., 2020b; Li et al., 2016c; Gu et al., 2012; Rahman et al., 2012b). However, these results cannot be definitively attributed to AD-related neurobehavioral changes due to the well-known effects of Pb on cognitive function, which are unrelated to AD.

Deficiencies in balance, walking speed, coordination, and strength can also arise from insults to the motor system in adulthood. Recent toxicological studies exposed mature rodents to Pb and investigated the effects on motor function. Typical rotarod tests compare the latency to fall for subjects placed on a rotating rod. Falling off more quickly indicates decreased coordination or balance. Locomotor activity tests (e.g., measurements of distance traveled, counts of square crossings) can detect gross motor

problems as well; however other influences on behavior may factor into differences in the amount of movement. Fine motor forelimb grip strength can be determined in rodents by pulling subjects holding onto a measurement-taking tension bar. Mansouri et al. (2012) subjected Wistar rats to Pb acetate for 30 days and observed hyperactivity in open-field tests in males but not females on the final day (PND 100). They also observed no effect on rotarod performance in both males and females on PND 100. However, in a subsequent study, Mansouri et al. (2013) found that long-term exposure to Pb acetate in drinking water (155–159 days starting at PND 55–60) resulted in substandard rotarod performance (7.5 months old) for male Wistar rats, whereas the exposure had no effect on performance of female rats. Similarly, in a long-term exposure study by Singh et al. (2019), male Wistar rats exposed daily to Pb acetate by oral gavage from 3 months to 6 months of age performed worse in rotarod and grip strength tests compared with their saline-treated counterparts. Singh et al. (2019) also found decreased activity in 6-month-old Pb-treated rats. Al-Qahtani et al. (2022) observed a decrease in locomotor activity in 15-week-old male mice after a 6-week Pb treatment period.

Summary

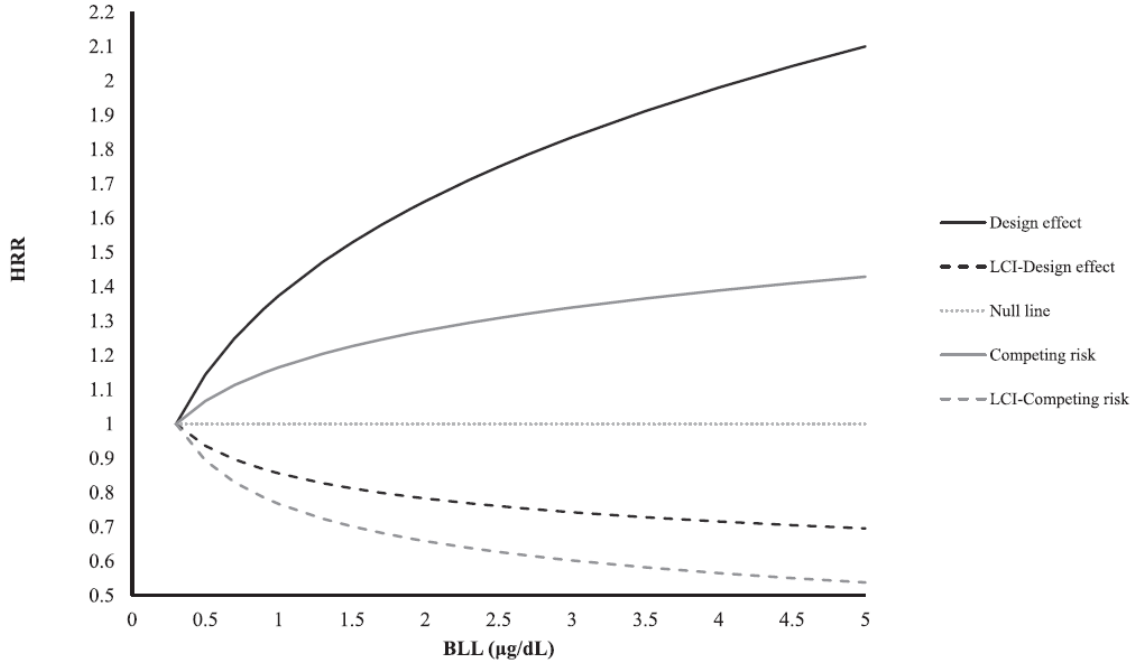
In summary, recent studies have significantly expanded the toxicological literature base established in the last Pb ISA for AD. Significant increases in Aβ40 and Aβ42 following Pb exposure were consistently detected in the cerebral cortex, hippocampus, and CSF in multiple studies at BLLs of 4–30 μg/dL. Pb-induced amyloid plaque formation was also reported in a transgenic mouse model of AD (Tg-SwDI) (Gu et al., 2012). Aged cynomolgus monkeys (23 years old), exposed to Pb during infancy, had both amyloid plaques and tau deposits in their cerebral cortex; however, these findings are limited somewhat by the small sample size (Bihaqi and Zawia, 2013; Wu et al., 2008). In rodents, mean BLLs <10 μg/dL were shown to increase the expression and phosphorylation of tau in multiple brain regions, but this effect was not entirely consistent between studies. Overall, recent studies have primarily focused on exposure paradigms beginning during development, but one study demonstrated effects from an exposure beginning in early adulthood (8 weeks) (Gu et al., 2012). One study reported that the PD-related protein, alpha-synuclein, was increased in the hippocampus in Pb-treated male rats (Zhang et al., 2012). Recent studies have not expanded on previous findings on ALS-related endpoints or contributed evidence related to essential tremor.

3.6.4.3 Relevant Issues for Interpreting the Evidence Base

3.6.4.3.1 Concentration-Response Function

The shape of the C-R function was not examined in the studies of the association of Pb biomarkers with neurodegenerative diseases in adults in the past review. The majority of studies in the current review also did not explore the shape of the C-R function in the Pb-neurodegenerative disease

associations. Horton et al. (2019) explored the relationship between BLL and AD mortality using Cox regression models that incorporated design effect or competing risks. The study found an increase in the hazard rate ratio (HRR) by 14%–30% with each unit increase in BLL (see Figure 3-15 below). Given the small number of AD mortality events in the study population, the effect estimates were imprecise and had larger CIs. The authors also performed categorical analysis to explore blood Pb-AD mortality association. Results from Cox proportional hazard models adjusted for various confounders and competing risks for AD mortality (death due to cancer, CVD, CVA, nephritis, and respiratory disease) indicated that participants in the 1.5 and 5 µg/dL BLL categories had 1.2 (95% CI = 0.70, 2.1) and 1.4 (95% CI = 0.54, 3.8) times the rate of AD mortality compared with those with a blood Pb reference of 0.3 µg/dL, respectively. The associations observed for various BLL categories with respect to the reference category of BLL 0.3 µg/dL were imprecise.



BLL = blood lead level; HRR = hazard rate ratio; LCI = lower confidence interval.
Source: Reproduced with permission from Horton et al. (2019).

Figure 3-15 Hazard rate ratios for Alzheimer's disease mortality by blood Pb level including the lower 95% confidence interval.

3.6.4.3.2 Potentially At-Risk Populations

Genetics

Several studies in the 2013 Pb review evaluating the association between Pb and MMSE (a marker for AD) and effect modification by genetic variants provided support for effect modification of the association by the ALAD genotype (details on Potentially At-Risk Populations in the Cognitive Function Section: 3.6.1.3.2). A study by (Fang et al., 2010) examining the association of BLL and ALS risk and effect modification by the ALAD genotype suggested a significant Pb-ALS association among ALAD1−1 carriers but a weaker and imprecise association among ALAD2 carriers. Tests to identify an interaction between Pb and the ALAD genotype in the Pb-ALS association suggested no significant difference in association between ALAD1−1 versus ALAD2 carriers, however ($p = 0.32$).

In the current Pb review, (Ji et al., 2015) considered both bone and blood Pb biomarkers among the NAS cohort and performed stratified analysis by ALAD gene (ALAD−2 carriers or non-carriers). They found no effect modification by the ALAD genotype for the association between Pb biomarkers and elevated tremor.

Age and Sex

A few studies in the current review explored the effect modification of the Pb-neurodegenerative disease associations by age or sex. (Ji et al., 2015) examined the associations of bone and blood Pb biomarkers with tremor among the NAS cohort. The results suggested that among younger cohorts (i.e., below the median age of 68.9 years), the tremor score increased significantly with increasing quintile of blood Pb ($p = 0.03$), and those in the highest quintile scored 0.35 (95% CI: 0.03, 0.67) points higher than those in the lowest quintile. This pattern was not apparent when bone Pb biomarkers were used. Similarly, (Paul et al., 2021) performed stratified analysis of the DNAm estimated tibia and patella Pb concentrations and PD risk by sex and found a significant association when tibia Pb concentration was used. The magnitude of risk was higher for men in the SGPD cohort (OR and 95% CI: men: 2.48 [1.86, 3.34]; women: 1.67 [1.21, 2.33]), and the risk was higher for women in the PEG cohort (OR and 95% CI: men: 1.49 [1.02, 2.20]; women: 1.81 [1.17, 2.85]).

3.6.4.4 Summary and Causality Determination: Neurodegenerative Diseases

The 2013 Pb ISA (U.S. EPA, 2013) concluded that the available evidence was "inadequate to determine that a causal relationship exists between Pb exposure and neurodegenerative diseases in adults." This conclusion was based on a limited number of studies that examined the association of blood Pb or bone Pb levels with essential tremor, PD, ALS, and AD. These studies were not sufficient to reach a conclusion regarding the presence or absence of an effect due largely to the potential for reverse causation

(i.e., reduced physical activity among cases resulting in greater bone turnover and higher BLLs), and limited consideration for potential confounding factors. Limited studies in monkeys and rodents found that developmental Pb exposure induced pathologies that underlie AD, and rodent studies suggested neurophysiologic characteristics and changes related to ALS and PD. Recent epidemiologic studies expanded the evidence base indicating associations between Pb exposure and some neurodegenerative diseases among non-occupational cohorts. The strongest evidence in the current review includes well-designed case-control and cohort studies of ALS and PD, whereas findings from recent epidemiologic studies of clinically diagnosed AD or AD mortality did not provide strong evidence to address uncertainties in the body of evidence. Findings from recent toxicological studies, however, add to the evidence suggesting that developmental exposure to Pb increases the expression of proteins related to AD, including Aβ, tau and p-tau at lower BLLs than the values investigated in the previous ISA (<10 μg/dL). Alterations in neuropathologic hallmarks of AD in older monkeys were also demonstrated following developmental Pb exposure.

Studies for ALS in this review included a well-designed cohort study that examined the relationship of the blood Pb biomarker and ALS survival after ALS diagnosis among U.S. veterans (Fang et al., 2017) and a large case-control study that examined associations between past airborne Pb exposures and ALS risk in participants from a healthcare claims dataset (Andrew et al., 2022). The findings from the cohort study by (Fang et al., 2017) suggested that increased levels of past blood Pb prior to mortality follow-up were associated with shorter ALS survival even after mutually accounting for bone resorption and bone formation, thus reducing the uncertainty due to reverse causality. (Andrew et al., 2022) found significant positive associations between airborne Pb exposure and increased ALS risk, specifically for residential Pb exposure over the past 10 years. For PD outcomes, only one case-control study investigated the relationship between the risk of PD and epigenetic biomarkers by quantifying DNAm tibia and patella Pb concentrations as cumulative Pb exposure. The authors found an association between DNAm tibia Pb levels and PD risk (Paul et al., 2021). This empirically-derived DNA methylation signature is potentially a more sensitive predictor of the effect of Pb exposure on PD than bone Pb concentration.

Toxicological studies investigating potential associations between Pb exposure and ALS or PD remain limited. In one study reviewed in the previous ISA, Pb exposure was found to induce neurophysiologic changes in a rodent model of ALS. Neurophysiologic characteristics of PD, such as decreased activity of dopaminergic neurons in the substantia nigra and increased expression of hippocampal alpha-synuclein, have also been demonstrated following Pb exposure.

The bulk of the epidemiologic evidence in the 2013 Pb ISA drawn upon to evaluate the association of Pb exposure AD focused on cognitive impairment identified using dementia screening instruments such as the MMSE. Recent studies that examined the association of blood Pb biomarkers with clinical endpoints of AD risk (Yang et al., 2018) or AD mortality (Horton et al., 2019) in non-occupational cohorts add to the evidence. The association between blood Pb exposure and AD risk observed in Yang et al. (2018) was imprecise. Uncertainties related to potential reverse causality and

timing of exposure were not addressed in this study. (Horton et al., 2019) addressed concerns raised for the case-control study design used in Yang et al. (2018) but also observed imprecise relationships between blood Pb and AD mortality risk, (Horton et al., 2019). For tremor outcomes, no significant association was observed between blood Pb and the tremor score when all study participants were analyzed; however, an increase in the tremor score was observed for increasing BLL among younger participants (Ji et al., 2015). Studies reviewed for Pb exposure and motor function in adults also provided inconsistent findings. Overall, the relationships of Pb biomarkers with AD risk, tremor, or motor function are inconclusive. In contrast to the inconclusive epidemiologic study findings on AD, a large number of recent toxicological studies add to the evidence which suggests that developmental exposure to Pb increases the expression of proteins related to AD, including Aβ, tau, and p-tau, at lower BLLs than the values investigated in the previous ISA (<10 μg/dL). In older monkeys (23 years), the neuropathologic hallmarks of AD (i.e., amyloid plaques and tau deposits) were also demonstrated following developmental Pb exposure.

In summary, **the evidence from epidemiologic and experimental animal studies is *suggestive of, but not sufficient to infer, a causal relationship* between Pb exposure and neurodegenerative diseases.** This determination reflects a strengthening of the evidence since the 2013 Pb ISA, which found that the evidence was "inadequate." Recent epidemiologic studies of varying quality strengthen the evidence for the association of Pb exposure with ALS and PD, and reduce uncertainty related to the potential for reverse causality by better establishing the temporal association between Pb exposure and these clinical endpoints. Although recent epidemiologic studies of clinically diagnosed AD and AD mortality add to the evidence, findings from these studies do not substantially strengthen the evidence overall. In contrast to the epidemiologic evidence, multiple recent toxicological studies add to the evidence indicating that developmental exposure to Pb increases the expression of proteins related to AD, including Aβ, tau, and p-tau at lower BLLs than the values investigated in the previous ISA (<10 μg/dL). Alterations in neuropathologic hallmarks of AD in older monkeys were also demonstrated following developmental Pb exposure. However, toxicological studies investigating potential associations between Pb exposure and ALS or PD remain limited.

Table 3-12 Summary of evidence that is suggestive of, but not sufficient to infer, a causal relationship between Pb exposure and neurodegenerative diseases in adults

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
ALS and Parkinson's Disease			
At least one high-quality prospective cohort or case-control study finds associations with ALS and PD.	A prospective analysis of U.S. veterans found that higher baseline BLL was associated with increased mortality / shorter survival after ALS diagnosis. The association persisted after controlling for confounders including a biomarker of bone turnover (formation and reabsorption), thus addressing the issue of reverse causality.	Fang et al. (2017)	
	Support from recent case-control studies using novel exposure metrics that found associations between higher estimated air Pb exposure and ALS risk and between a DNAm biomarker of tibia Pb and PD.	Paul et al. (2021)	
Limited number of studies address uncertainty due to temporality and reverse causation.	Well-designed case-control studies and prospective studies of ALS and PD assessed exposure prior to disease development and accounted for increased bone turnover resulting from the disease state.		
Alzheimer's Disease			
Coherence for AD provided by consistent evidence in animals with relevant exposures.	Amyloid plaques and/or tau deposits in transgenic rodents and aged monkeys following Pb exposure.	Bihaqi and Zawia (2013)	Peak BLLs: 19–30 µg/dL
	Increased expression of Aβ, tau, and other AD-related proteins across multiple brain regions in rodents.	Wu et al. (2008) Gu et al. (2012) Section 3.6.4.2	Peak BLLs: 4–58 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	References[b]	Pb Biomarker Levels Associated with Effects[c]
Evidence describes biologically plausible pathways.	Evidence suggests that exposure to Pb results in neuronal cell death associated with oxidative stress, neuroinflammation and altered energy metabolism, all of which may underlie general neurodegenerative processes.	Section 3.3	

AD = Alzheimer's disease; ALS = amyotrophic lateral sclerosis; BLL = blood lead level; DNAm = DNA methylation; Pb = lead; PD =Parkinson's disease.
[a]Based on aspects considered in judgments of causality and weight of evidence in causal framework in Table I and Table II of the Preamble to the ISAs (U.S. EPA, 2015).
[b]Describes the key evidence and references, supporting or contradicting, contributing most heavily to causality determination and, where applicable, to uncertainties or inconsistencies. References to earlier sections indicate where the full body of evidence is described.
[c]Describes the Pb biomarker levels at which the evidence is substantiated.

3.7 Evidence Inventories – Data Tables to Summarize Study Details

Table 3-1E Epidemiologic studies of Pb exposure and overt nervous system toxicity

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Yuan et al. (2006) Cincinnati, OH	CLS n: 24	Blood Age at measurement: BLL from 3 to 78 mo averaged Mean:14.18 Range: 4.77−31.06 µg/dL	MRI (subject asked to generate verbs to activate language with bilateral finger tapping)	birth weight and marijuana use; consideration of IQ, sex, SES, gestational age	Increasing BLL associated with decreased brain activation in the left frontal gyrus and left middle temporal gyrus, regions (semantic language function)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Reuben et al. (2020) Dunedin New Zealand 1972–2019 Cohort	Dunedin Study n: 512	Whole blood Pb (µg/dL) was measured via GFAAS Age at measurement: 11 yr Mean (SD): 10.99 (4.63) µg/dL Max: 31 µg/dL	Cortical thickness, cortical surface area, hippocampal volume, WMH volumFe, BrainAGE index High resolution images showing cortical thickness, cortical surface area, bilateral hippocampal volume, WMH, and FA were produced using T1-weighted, fluid-attenuated inversion recovery and diffusion-weighted sequences with a Siemens Skyra 3T scanner with 64-channel head and neck coil. BrainAGE index was calculated as a composite measure of all measured indices. Outcomes were assessed at 45 yr of age. Age at outcome:	Sex, maternal IQ, childhood SES.	**Betas** BrainAGE Index: 0.03 (0.00, 0.06) Hippocampal Volume: 0.00 (−0.01, 0.00)) Cortical Surface Area: −0.05 (−0.09, 0.00) Cortical Thickness (mm): 0.00 (0.00, 0.00) WMH: 0.00 (0.00, 0.01)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cecil (2011) Cincinnati, Ohio, Cincinnati Children's Hospital Medical Center United States Enrollment(mothers): 1979–1984. Follow-up: Birth to 24 y Cohort	CLS n: 159	Whole blood Pb measured using anodic stripping voltammetry Age at measurement: 3-78 mo old Pb prenatally and at intervals to age 17 yr; imaging 19–24 yr Mean (SD) mcg/dL: prenatal 8.3 (3.7), 3–12 mo 10.6 (5.1). (Reported in Dietrich et al. 1993)	MRI brain assessments of 4 types: volumetric (morphology), spectroscopy (chemical concentrations), diffusivity (organization), and functionality (activation related to tasks). Brain MRI/fMRI measures of four types. (1) Volume of gray matter. (2) Spectroscopy – metabolites linked to neuronal function and myelin architecture: N-acetyl aspartate, creatine and phosphocreatine, phosphocholines and glycerolphosphocholine, myo-inositol, glutamate and glutamine. (3) Diffusivity in white matter regions reflecting axonal and myelin effects: FA; mean, axial and radial diffusivity. (4) Functionality: activation related to task performance. Age at outcome: 19−24 yr	Varied by outcome; included age at imaging and birth weight.	Reported a negative association between childhood BLL and gray matter volume in several regions: medial and superior frontal gyri, inferior parietal lobule, cerebellar hemispheres Reported an association between higher childhood BLL and lower metabolite concentrations in several regions: white matter, left basal ganglia, left cerebellar hemisphere, vermis

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Beckwith et al. (2021) Cincinnati, OH United States in utero to up to 33 yr of age Cohort	CLS n: 123	Pb was measured in whole blood at 10 d, on a quarterly basis up to 60 mo, and monthly at 66, 72, and 78 mo. Samples were collected mainly by venipuncture, but occasionally by heel or finger stick. Pb concentrations were quantified using anodic stripping voltammetry Age at measurement: 0-78 mo 10 days, on a quarterly basis up to 60 mo, and monthly at 66, 72, and 78 mo Mean (SD) blood Pb at 78 mo: 7.82 µg/dL (4.2) Max: 24.75 µg/dL	MRI brain volumetrics of white and gray matter, focusing on regions involved in cognitive and emotional function. MRI scans (Voxel based morphometry) were used to examine spatial differences in regional gray and white matter volumes in adulthood (mean age 26.8 yr) associated with childhood blood Pb concentrations at 78 mo. Age at outcome: 18−33 yr	Age at time of imaging, birth weight, total intracranial volume.	BLLs were associated with MRI-derived decreases in white and gray matter volumes in the frontal, parietal, and temporal lobes. Decreased gray matter volume in brain regions responsible for cognition and emotional regulation associated with criminal arrests

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Lamoureux-Tremblay et al. (2021) Nunavik, Northern Quebec Canada Cohort	NCDS n: 71	Blood Cord and concurrent blood; GFAAS with Zeeman background correction Age at measurement: 16–22 Cord blood: median 3.73 µg/dL, mean 4.56 µg/dL. Adolescent blood: median 1.52 µg/dL, mean 1.78 µg/dL Max: 17.81 µg/dL	Activation of the human neural fear circuitry fMRI analysis of brain activation in response to a validated fear conditioning and extinction stimulus test Age at outcome: 16−22 yr	Sex, age, SES, and alcohol/drug consumption.	Higher differential activation in the right dorsolateral prefrontal cortex in association with higher postnatal BLL.
†Ethier et al. (2012) Nunavik, Quebec Canada 11 yr Cohort	Prospective 11 yr study of Inuit children from Nunavik n: 149	Blood, Maternal Blood Concurrent venous blood; GFAAS with Zeeman background correction (Perkin Elmer model ZL 4100). Age at measurement: Pre-natal and 11 yr At birth mean: 4.6 µg/dL, SD: 3.1; At 11 yr mean: 2.6 µg/dL; SD: 2.3	Neurological Achromatic pattern-reversal VEPs with different visual contrast levels were administered, using generated vertical sinusoidal gratings with a spatial frequency of 2.5 cycles per degree. Children viewed stimuli binocularly and were instructed to fixate on a small red dot. Pattern-reversal VEPs were recorded from the scalp over the visual cortex at 0z derivation according to the International 10–20 system Age at outcome: 10−13 yr	Analysis of variance models controlled for current Se, cord Se, and gender.	**Betas** *N150 Latency* 95% Contrast Level: 0.056 (0.099, 0.014) *Note- 95% CIs were converted from author reported p-values

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Kim et al. (2018a) Seoul Korea Enrollment 2010–2015 Case-Control	n: 150	Blood Blood Pb was measured using atomic absorption spectrometer graphite furnace Age at measurement: 6–17 years Mean (SD) – Cases: 1.3 (0.6) µg/dL; Controls: 1.5 (0.7) µg/dL	Cortical Thickness Cortical thickness of brain regions was ascertained via whole-brain structural MRI. Age at outcome: 6−17 yr	Age, intracranial volume, gender.	An interaction between DRD2 and BLL on the cortical thickness of the frontal lobe in the ADHD group, and a brain–behavior correlation between cortical thickness and the ADHD-RS inattention score was observed.

BLL = blood lead level; BrainAGE = Brain Age Gap Estimation; CI = confidence interval; CLS = Cincinnati lead study; d = day(s); FA = fractional anisotropy; fMRI = functional magnetic resonance imaging; GFAAS = graphite furnace atomic absorption spectrometry; IQ = intelligence quotient; mo = month(s); MRI = magnetic resonance imaging; Pb = lead; SD = standard deviation; Se = selenium; SES = socioeconomic status; VEP = visual evoked potential; WMH = white matter hyperintensities; yr = year(s).
[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.
[b]Results are not standardized (e.g., BLL distribution data needed to calculate the standardized estimate was not reported or categorical data was analyzed).
†Studies published since the 2013 Integrated Science Assessment for Lead.

Table 3-1T Animal toxicological studies of Pb exposure and brain function

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Graham et al. (2011)	**Rat (Sprague Dawley)** Control (vehicle), M/F, n = 4–8 1 mg/kg, M/F, n = 4–8 10 mg/kg, M/F, n = 4–8	PND 4 to PND 28, every other day	Oral, gavage	PND 29: 0.289 µg/dL for Control 3.27 µg/dL for 1 mg/kg 12.6 µg/dL for 10 mg/kg	PND 11, 19, 29: Neurotransmitter

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Liu et al. (2012)	**Rat (Sprague Dawley)** Control (tap water), M, n = 20 100 ppm, M, n = 20	PND 24 to PND 80	Oral, drinking water	PND 21: 15 µg/L (1.5 µg/dL) for Control 45 µg/L (4.5 µg/dL) for 100 ppm PND 28: 14 µg/L (1.4 µg/dL) for Control 94 µg/L (9.4 µg/dL) for 100 ppm PND 35: 16 µg/L (1.6 µg/dL) for Control 103 µg/L (10.3 µg/dL) for 100 ppm PND 42: 13 µg/L (1.3 µg/dL) for Control 94 µg/L (9.4 µg/dL) for 100 ppm PND 49: 14 µg/L (1.4 µg/dL) for Control 98 µg/L (9.8 µg/dL) for 100 ppm	PND 56: Electrophysiology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Cory-Slechta et al. (2012)	**Rat (Long-Evans)** Control (tap water), M, n = 12 50 ppm Pb, M, n = 12	GD −60 to 10 mo	Oral, drinking water Oral, lactation In utero	PND 5–6: <5 µg/dL for Control 12.5 µg/dL for 50 ppm 2.5 mo: <5 µg/dL for Control 6.43 µg/dL for 50 ppm 10 mo: <5 µg/dL for Control 8.98 µg/dL for 50 ppm	10–11 mo: Neurotransmitter
Weston et al. (2014)	**Rat (Long-Evans)** Control (tap water), M/F, n = 18–22 (9–11/9–11) 50 ppm, M/F, n = 18–22 (9–11/9–11)	GD −60 to PND 21	Oral, lactation In utero	PND 5–6 – Males: 0.76 µg/dL for Control 15.7 µg/dL for 50 ppm PND 5–6 Females: 0.82 µg/dL for Control 14.7 µg/dL for 50 ppm	PND 60: Neurotransmitter

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Han et al. (2014)	**Rat (Wistar)** Control (tap water), M, n = 8 2 mM – postweaning (PW), M, n = 8 2 mM – ME, M, n = 8	PW group: PND 21 to PND 42 ME group: GD −21 to PND 20	Oral, drinking water Oral, lactation In utero	PND 21: 7.36 µg/L (0.74 µg/dL) for Control NR for 2 mM – PW 146.6 µg/L (14.7 µg/dL) for 2 mM – ME PND 63: 9.22 µg/L (0.92 µg/dL) for Control 147.9 µg/L (14.8 µg/dL) for 2 mM – PW 46.13 µg/L (4.6 µg/dL) for 2 mM – ME	PND 68: Histopathology
Barkur and Bairy (2015a)	**Rat (Wistar)** Control (untreated), M/F, n = 9 0.2% solution – Pregestation, M/F, n = 9 0.2% solution – Lactation, M/F, n = 9 0.2% solution – Gestation, M/F, n = 9 0.2% solution – Gestation and Lactation, M/F, n = 9	Pregestation exposure – GD −30 to GD 0 Lactation only exposure – PND 0 to PND 22 Gestational exposure – GD 0 to GD 20 Gestation and Lactation exposure – GD 0 to PND 22	In utero	PND 22: 0.19 µg/dL for Control 3.04 µg/dL for 0.2% Pregestation 5.26 µg/dL for 0.2% Gestation 26.8 µg/dL for 0.2% Lactation 31.9 µg/dL for 0.2% Gestation and Lactation	PND 30: Brain Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Basha et al. (2014)	**Rat (Not Specified)** Control (deionized water), M, n = 6 0.2% solution, M, n = 6	PND 1 to PND 21	Oral, lactation	PND 45: 0.42 µg/dL for Control 49.5 µg/dL for 0.2% solution 4 mo: 0.56 µg/dL for Control 14.4 µg/dL for 0.2% solution 12 mo: 0.46 µg/dL for Control 6.96 µg/dL for 0.2% solution 18 mo: 0.12 µg/dL for Control 11.2 µg/dL for 0.2% solution	PND 45, 4 mo, 12 mo, 18 mo: Neurotransmitter Analysis
Rahman et al. (2012b)	**Rat (Wistar)** Control (tap water), M/F, n = 4–10 0.2% solution, M/F, n = 4–10	PND 1 to PND 30	Oral, drinking water Oral, lactation	PND 21: 1.4 µg/dL for Control 12.1 µg/dL for 0.2% solution PND 30: 1.2 µg/dL for Control 12.8 µg/dL for 0.2% solution	PND 21, 30: Brain Weight, Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Nam et al. (2019b)	**Rat (Sprague Dawley)** Control (not specified), M/F, n = 12 0.2 % Solution, M/F, n = 12	GD 0 to 22	In utero	PND 21: 0.64 µg/dL for Control 17.30 µg/dL for 0.2% solution	PND 21: Histopathology
Saleh et al. (2018)	**Rat (Sprague Dawley)** Control (deionized water), M/F, n = 8 litters 160 ppm, M/F, n = 8 litters	GD 1 to GD 20	In utero	Maternal Blood Pb GD 20: 5.1 µg/dL for Control 27.7 µg/dL for 160 ppm	GD 20: Brain Weight, Histopathology
Meng et al. (2016)	**Rat (Sprague Dawley)** Control (deionized water), M/F, n = 7 300 ppm, M/F, n = 7	PND 0 to PND 21	Oral, lactation	PND 35: 7.61 µg/L (0.76 µg/dL) for Control 84.3 µg/L (8.43 µg/dL) for 300 ppm	NR: Histopathology
Amos-Kroohs et al. (2016)	**Rat (Sprague Dawley)** Control (sodium acetate), M/F, n = 16 (8/8) per time point 1 mg/kg Pb, M/F, n = 16 (8/8) per time point 10 mg/kg Pb, M/F, n = 16 (8/8) per time point	PND 4 to PND 28	Oral, gavage	PND 29: 1.27 µg/dL for Control 2.76 µg/dL for 1 mg/kg 9.07 µg/dL for 10 mg/kg	PND 29: Neurotransmitter

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Rahman et al. (2018)	**Rat (Wistar)** Control (tap water), M/F, n = 20 0.2% solution, M/F, n = 20	PND 1 to PND 21	Oral, drinking water Oral, lactation	PND 21: 2.2 µg/dL for Control 12.4 µg/dL for 0.2% solution PND 30: 3.3 µg/dL for Control 22.7 µg/dL for 0.2% solution	PND 21, 30: Brain Weight
Baranowska-Bosiacka et al. (2017)	**Rat (Wistar)** Control (distilled water), M/F, n = 8 0.1% solution, M/F, n = 8	GD 0 to PND 21	Oral, lactation In utero	PND 28: 0.05 µg/dL for Control 6.90 µg/dL for 0.1% solution	PND 28: Histopathology
Baranowska-Bosiacka et al. (2013)	**Rat (Wistar)** Control (distilled water), M/F, n = 36 (17/19) 0.1% solution, M/F, n = 36 (18/18)	GD 0 to PND 21	Oral, lactation In utero	PND 28: 0.93 µg/dL for Control 6.86 µg/dL for 0.1% solution	PND 28: Histopathology
Wang et al. (2013)	**Rat (Sprague Dawley)** Control (untreated), M/F, n = 6 0.2% Pb (w/v), M/F, n = 6 – Gestational Exposure 0.2% Pb (w/v), M/F, n = 6 – Lactational Exposure 0.2% Pb (w/v), M/F, n = 6 – Ablactational Exposure	GD 0 to PND 1, PND 1 to PND 21, PND 21 to 42	Oral, drinking water Oral, lactation In utero	PND 72: 34.99 µg/L (3.5 µg/dL) for Control 35.78 µg/L (3.58 µg/dL) for 0.2 % solution Gestational 65.97 µg/L (6.60 µg/dL) for 0.2% solution Lactational 110.67 µg/L (11.07 µg/dL) for 0.2% solution Ablactational	PND 72: Brain Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Wang et al. (2016)	**Rat (Sprague Dawley)** Control (tap water), M, n = 7 100 ppm, M, n = 9	PND 24 to PND 56	Oral, drinking water	PND 56: 11 µg/L (1.1 µg/dL) for Control 133 µg/L (13.3 µg/dL) for 100 ppm	PND 60–66: LTP, Neuronal Morphology
Li et al. (2016b)	**Mouse (Kunming)** Control (deionized water), M/F, n = 10 0.1% (1000 ppm), M/F, n = 10 0.2% (2000 ppm), M/F, n = 10 0.5% (5000 ppm), M/F, n = 10	GD 0 to PND 21	Oral, lactation In utero	PND 21: 8.27 µg/L (0.827 µg/dL) for Control 41.05 µg/L (4.11 µg/dL) for 0.1% solution 82.93 µg/L (8.29 µg/dL) for 0.2% solution 105.33 µg/L (10.53 µg/dL) for 0.5% solution	PND 21: Histopathology
Sobolewski et al. (2018)	**Mouse (C57BL/6)** Control (deionized water), M/F, n = 6–12 100 ppm, M/F, n = 6–12	GD −60 to PND 21	Oral, lactation In utero	PND 6–7: 0.37 µg/dL for Control 10.2 µg/dL for 100 ppm	PND 60: Epigenetics

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Barkur and Bairy (2016)	**Rat (Wistar)** Control (tap water with acetic acid), M/F, n = 8 0.2% solution, pregestation only (PG), M/F, n = 8 0.2% solution, gestation only, M/F, n = 8 0.2% solution, lactation, M/F, n = 8 0.2% solution, gestation and lactation, M/F, n = 8	GD −30 to PND 21	Oral, lactation In utero	PND 22: 0.5 µg/dL for Control 9.4 µg/dL for 0.2% solution, pregestation only (PG) 16.6 µg/dL for 0.2% solution, gestation only 30.1 µg/dL for 0.2% solution, lactation 33.4 µg/dL for 0.2% solution, gestation and lactation	PND 30: Histopathology
Shvachiy et al. (2018)	**Rat (Wistar)** Control (tap water), M/F, n = 8 0.2% (p/v) solution (distilled water), M/F, n = 9 – Intermittent exposure 0.2% (p/v) solution, M/F, n = 9 – Continuous exposure	Intermittent Exposure: GD 7 to PND 84, PND 140 to PND 196 Continuous Exposure: GD 7 to PND 196	Oral, drinking water Oral, lactation In utero	PND 196: <0.1 µg/dL for Control 18.8 µg/dL for 0.2% (Intermittent) 24.4 µg/dL for 0.2% (Continuous)	PND 189: Brain Histopathology
Stansfield et al. (2015)	**Rat (Long-Evans)** Control (chow), M/F, n = 4–7 1500 ppm, M/F, n = 4–7	GD 0 to PND 50	Oral, diet Oral, lactation In utero	PND 50: 0.6 µg/dL for Control 22.2 µg/dL for 1500 ppm	PND 50: Neurotransmitter Analysis, Brain Histopathology
Listos et al. (2013)	**Rat (Wistar)** Control (tap water), M/F, n = 6–11 0.1% solution, M/F, n = 6–11	GD 0 to PND 28	Oral, drinking water Oral, lactation In utero	PND 60: 0.93 µg/dL for Control 20.45 µg/dL for 0.1% solution	PND 60: Neurotransmitter

Zhao et al. (2018)	**Rat (Sprague Dawley)** Control (tap water), M, n = 8 0.005% solution, M, n = 8 0.01% solution, M, n = 8 0.02% solution, M, n = 8	GD −14 to PND 10	Oral, lactation In utero	PND 0: 1.9 µg/dL for Control 17.9 µg/dL for 0.005% solution 23.2 µg/dL for 0.01% solution 48.8 µg/dL for 0.02% solution PND 3: 1.9 µg/dL for Control 6.7 µg/dL for 0.005% solution 11.5 µg/dL for 0.01% solution 23.1 µg/dL for 0.02% solution PND 7: 1.3 µg/dL for Control 8.1 µg/dL for 0.005% solution 12.3 µg/dL for 0.01 % solution 18.7 µg/dL for 0.02% solution PND 10: 1.2 µg/dL for Control 5.6 µg/dL for 0.005% solution 7.0 µg/dL for 0.01% solution 12.3 µg/dL for 0.02% solution PND 14: 0.7 µg/dL for Control	PND 30: Electrophysiology, Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				4.0 µg/dL for 0.005% solution 5.5 µg/dL for 0.01% solution 8.9 µg/dL for 0.02% solution PND 21: 1.1 µg/dL for Control 2.5 µg/dL for 0.005% solution 2.5 µg/dL for 0.01% solution 2.98 µg/dL for 0.02% solution PND 30: 1.5 µg/dL for Control 1.0 µg/dL for 0.005% solution 1.5 µg/dL for 0.01% solution 1.5 µg/dL for 0.02% solution	
Dominguez et al. (2019)	**Mouse (C57BL/6)** Control (tap water), M/F, n = 10 (7/3) 30 ppm, M/F, n = 10 (6/4) 330 ppm, M/F, n = 10 (4/6)	PND 0 to PND 28	Oral, lactation	PND 28 – Females: 0.02 µg/dL for Control 3.03 µg/dL for 30 ppm 12.79 µg/dL for 330 ppm PND 28 – Males: 0.03 µg/dL for Control 3.68 µg/dL for 30 ppm 15.42 µg/dL for 330 ppm	PND 28: Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Du et al. (2015)	**Rat (Sprague Dawley)** Control (distilled water), M/F, n = 8 250 ppm, M/F, n = 8	PND 0 to PND 90	Oral, drinking water Oral, lactation	PND 30: 13.9 µg/L (1.4 µg/dL) for Control 205.6 µg/L (20.6 µg/dL) for 250 ppm PND 60: 15.0 µg/L (1.5 µg/dL) for Control 321.9 µg/L (32.2 µg/dL) for 250 ppm PND 90: 11.8 µg/L (1.2 µg/dL) for Control 379.2 µg/L (37.9 µg/dL) for 250 ppm	PND 30, 60, 90: Histopathology
Mansouri et al. (2013)	**Rat (Wistar)** Control (tap water or water + NaAc), M/F, n = 16 (8/8) 50 ppm, M/F, n = 16 (8/8)	PND 55 to PND 181	Oral, drinking water	PND 178–181 – Females: NR for Control 10.6 µg/dL for 50 ppm PND 178–181 – Males: NR for Control 18.9 µg/dL for 50 ppm	PND 161–179: Neurotransmitter

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Zhou et al. (2018)	**Rat (Sprague Dawley)** Control (distilled water), M, n = 10 0.5% solution, M, n = 10 1.0% solution, M, n = 10 2.0% solution, M, n = 10	PND 24 to PND 52	Oral, drinking water	PND 52: 13.3 µg/L (1.3 µg/dL) for Control 148.9 µg/L (14.9 µg/dL) for 0.5% solution 231.3 µg/L (23.1 µg/dL) for 1.0% solution 293.4 µg/L (29.3 µg/dL) for 2.0% solution	PND 24, 31, 38, 45, 52: Brain Weight, Brain Histopathology
Dumková et al. (2017)	**Mouse (ICR)** Control, F, n = 10 10^6/cm^3 Pb0 nanoparticles, F, n = 10	NR (24 g) – 6 wk continuous exposure	Inhalation	After 6 wk treatment: 11 ng/g (1.16 µg/dL) for Control 132 ng/g (13.99 µg/dL) for 10^6/cm^3	After 6 wk treatment: Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Xiao et al. (2014)	**Rat (Wistar)** Control (tap water), M/F, n = 10 (5/5) Pre-weaning: 2 mM solution, M/F, n = 10 (5/5) Postweaning: 2 mM solution, M/F, n = 10 (5/5)	Pre-weaning: GD −21 to PND 21 Postweaning: PND 21 to PND 84	Oral, drinking water Oral, lactation In utero	PND 21 – Pre-weaning: 10.09 µg/L (1 µg/dL) for Control 103.8 µg/L (10.4 µg/dL) for 2 mM solution PND 21 – Postweaning: Not Reported PND 91 – Pre-weaning: 10.32 µg/L (1 µg/dL) for Control 39.27 µg/L (3.9 µg/dL) for 2 mM solution PND 91 – Postweaning: 10.32 µg/L (1 µg/dL) for Control 105.45 µg/L (10.5 µg/dL) for 2 mM solution	PND 84 and PND 91: Histopathology
Sobin et al. (2013)	**Mouse (C57BL/6)** Control (tap water), M/F, n = 30 30 ppm, M/F, n = 30 230 ppm, M/F, n = 30 330 ppm, M/F, n = 30	PND 1 to PND 28	Oral, lactation	PND 28: 0.22 µg/dL for Control 4.12 µg/dL for 30 ppm 10.31 µg/dL for 230 ppm 13.84 µg/dL for 330 ppm	PND 28: Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Sobolewski et al. (2020)	**Mouse (C57BL/6)** F0: Control (deionized water), F, n = 10 100 ppm, F, n = 10 F1: see Figure 1, n = 12 F2: see Figure 1, n = 12 F3: see Figure 1, n = 8–10	F1: GD −60 to PND 23–27	Oral, lactation In utero	F1 PND 6–7: 0 µg/dL for Control 12.5 µg/dL for 100 ppm (F0 dosing) F3 PND 6–7: 0 ng/dL for Control 0 µg/dL for 100 ppm (F0 dosing)	PND 60–120 (variable by endpoint): Neurotransmitter, Epigenetics
Ouyang et al. (2019)	**Rat (Sprague Dawley)** Control (tap water), M/F, n = 6–10 0.05/0.01% solution, M/F, n = 6–10	GD 0 to PND 679	Oral, drinking water Oral, lactation In utero	wk 97: 0 mg/L (0 µg/dL) for Control 0.216 mg/L (21.6 µg/dL) for 0.05/0.01% solution	PND 679: Histopathology
Saleh et al. (2019)	**Rat (Sprague Dawley)** Control (deionized water), F, n = 8 160 ppm, F, n = 8	NR (190–220g) – 20 d of treatment	Oral, drinking water	After 20 d treatment: 5.4 µg/dL for Control 23.8 µg/dL for 160 ppm	After 20 d treatment: Brain Weight Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Singh et al. (2019)	**Rat (Wistar)** Control (distilled water), M, n = 5 2.5 mg/kg, M, n = 5	3 mo to 6 mo	Oral, gavage	6 mo: 5.76 µg/dL for Control 28.4 µg/dL for 2.5 mg/kg	6 mo: Brain Weight Brain Histopathology
Xiao et al. (2020)	**Rat (Sprague Dawley)** Control (tap water), F, n = 10 125 ppm, F, n = 10	GD −7 to PND 68	Oral, drinking water Oral, lactation In utero	PND 68: 24.23 ng/mL (2.4 µg/dL) for Control 205 ng/mL (20.5 µg/dL) for 125 ppm	PND 22, 68: Histopathology
Sun et al. (2014)	**Rat (Sprague Dawley)** Control (tap water), NR, n = 20 580 ppm, NR, n = 20	NR (230–260 g) – 3 mo of treatment	Oral, drinking water	After 3 mo treatment: 3.0 µg/L (0.3 µg/dL) for Control 56.8 µg/L (5.7 µg/dL) for 580 ppm	After 3 mo treatment: Histopathology
Su et al. (2016)	**Rat (Sprague Dawley)** Control (deionized water with 0.9% saline), M, n = 4 200 ppm, M, n = 4	PND 20 to PND 76	Oral, gavage	PND 76: 7.99 µg/L (0.8 µg/dL) for Control 84.17 µg/L (8.4 µg/dL) for 200 ppm	PND 76: Histopathology
Song et al. (2014)	**Rat (Sprague Dawley)** Control (tap water), M, n = 9 100 µg/mL, M, n = 9 200 µg/mL, M, n = 9 300 µg/mL, M, n = 9	PND 20–22 to PND 76–78	Oral, drinking water	PND 76–78: 0.73 µg/dL for Control 4.7 µg/dL for 100 µg/mL 10.1 µg/dL for 200 µg/mL 12.3 µg/dL for 300 µg/mL	PND 76–78: Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Zhou et al. (2020a)	**Rat (Sprague Dawley)** Control (distilled water), M, n = 5–11 0.5 g/L solution, M, n = 5–11 2.0 g/L solution, M, n = 5–	GD 1 to PND 364	Oral, drinking water	PND 21: 0 mg/L (0 µg/dL) for Control 0.1 mg/L (10 µg/dL) for 0.5 g/L solution 0.36 mg/L (36 µg/dL) for 2.0 g/L solution PND 364: 0 mg/L (0 µg/dL) for Control 0.15 mg/L (15 µg/dL) for 0.5 g/L solution 0.51 mg/L (51 µg/dL) for 2.0 g/L solution	PND 21, 364: Histopathology, Electrophysiology
Liu et al. (2019)	**Rat (Sprague Dawley)** Control (tap water), F, n = 12 58 mg/L, F, n = 11	PND 1 to PND 21	Oral, lactation	PND 9: 0 µg/dL for Control 7.9 µg/dL for 58 mg/L PND 21: 0 µg/dL for Control, 8.2 µg/dL for 58 mg/L PND 40: 0 µg/dL for Control 0 µg/dL for 58 mg/L	PND 93: Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Nan et al. (2016)	**Mouse (C57BL/6)** Control (sterile water), NR, n = 30 9.6 mmol/L, NR, n = 30	PND 21 to PND 56	Oral, drinking water	PND 7: 0 µg/L (0 µg/dL) for Control 106.3 µg/L (10.6 µg/dL) for 9.6 mmol/L PND 14: 0 µg/L (0 µg/dL) for Control 293.2 µg/L (29.3 µg/dL) for 9.6 mmol/L PND 35: 0 µg/L (0 µg/dL) for Control 959.6 µg/L (96 µg/dL) for 9.6 mmol/L	PND 56: Histopathology
Singh et al. (2017)	**Rat (Wistar)** Control (distilled water), M, n = 3–6 7.5 mg/kg, M, n = 3–6	NR (160–200 g) – 14 days of treatment	Oral, gavage	12 hr after last treatment: 5.54 µg/dL for Control 30.28 µg/dL for 7.5 mg/kg	12 hr after last treatment: Brain Weight, Histopathology
Bijoor et al. (2012)	**Rat (Wistar)** Control (deionized water), M/F, n = 10 50 ppm, M/F, n = 10	GD 0 to PND 45	Oral, drinking water Oral, lactation In utero	PND 45: 4.06 µg/dL for Control 10.65 µg/dL for 50 ppm	PND 45: Neurotransmitter

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Wang et al. (2021a)	**Rat (Sprague Dawley)** Control (deionized water), M, n = 3 0.05% solution, M, n = 3 0.1% solution, M, n = 3	GD 0 to PND 21	Oral, lactation In utero	PND 21: 23.1 µg/L (2.31 µg/dL) for Control 248 µg/L (24.8 µg/dL) for 0.05% solution 302 µg/L (30.2 µg/dL) for 0.1% solution 361 µg/L (36.1 µg/dL) for 0.2% solution	PND 21: Histopathology
Liu et al. (2022c)	**Rat (Sprague Dawley)** Control (tap water), M, n = 10 0.2% solution, M, n = 10	PND 35 to PND 119	Oral, drinking water	PND 119: 10.9 µg/L (1.09 µg/dL) for Control 176 µg/L (17.6 µg/dL) for 0.2% solution	PND 119: Histopathology
Hsu et al. (2021)	**Rat (Sprague Dawley)** Control (deionized water), M, n = 6 250 ppm, M, n = 6	PND 42 to PND 77	Oral, drinking water	PND 84: 0.9 µg/L (0.09 µg/dL) for Control 15.3 µg/L (1.53 µg/dL) for 250 ppm	PND 78 to PND 84: Electrophysiology
Sadeghi et al. (2021)	**Rat (Wistar)** Control (untreated), M, n = 5 1500 ppm, M, n = 5	GD 0 to PND 50	Oral, drinking water Oral, lactation In utero	PND 50 : 0.58 µg/dL for Control 3.4 µg/dL for 1500 ppm	PND 50: Histopathology
Vigueras-Villaseñor et al. (2021)	**Rat (Wistar)** Control (tap water), M, n = 20 320 ppm, M, n = 20	GD 0 to PND 21	Oral, lactation In utero	PND 110: 2.04 µg/dL for Control 26.3 µg/dL for 320 ppm	PND 90 to PND 110: Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Long et al. (2022)	**Rat (Sprague Dawley)** Control (untreated), M, n = 12 200 mg/L solution, M, n = 12	6 wk to 18 wk	Oral, drinking water	18 wk: 2.14 µg/L (0.214 µg/dL) for Control 32.48 µg/L (3.25 µg/dL) for 200 mg/L solution	NR: Histopathology, Neurotransmitter
Abazyan et al. (2014)	**Mouse (CAMKII-tTA; heterozygous or homozygous for mDISC1)** Control (het), M/F, n = 5–10 Control (mutant), M/F, n = 5–10 1500 ppm (het), M/F, n = 5–10 1500 ppm (mutant), M/F, n = 5–10	GD 0 to PND 180	Oral, diet Oral, lactation, in utero	6 mo – Females: 0.6 µg/dL for Control (het) 0.8 µg/dL for Control (mutant) 34.9 µg/dL for 1500 ppm (het) 33.3 µg/dL for ppm (mutant) 6 mo – Males: 1.1 µg/dL for Control (het) 1.1 µg/dL for Control (mutant) 26.1 µg/dL for 1500 ppm (het) 25.0 µg/dL for 1500 ppm (mutant)	PND 180: Brain Volume, Brain MRI, Morphometric Measurements in several regions

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Zhu et al. (2013)	**Rat (Sprague Dawley)** Control (untreated), M, n = 11–13 510 mg/L, M, n = 11–13	GD 0 to PND 490	Oral, drinking water Oral, lactation, in utero	PND 21 0 µg/L for control 0.27 mg/L (27 µg/dL) for 510 mg/L PND 287 0 µg/L for control 0.24 mg/L (24 µg/dL) for 510 mg/L PND 490 0 µg/L for control 0.25 mg/L (25 µg/dL) for 510 mg/L	PND 21 to PND 490: Histopathology
Nam et al. (2018a)	**Rat (Sprague Dawley)** Control (distilled water), M/ F, n = 12 0.2% solution M/F, n = 12	GD 0 to PND 21	Oral, drinking water Oral lactation, in utero	PND 21 1.28 µg/dL for control 12.67 µg/dL for 0.2% solution	PND 21**:** Histopathology
Gąssowska et al. (2016a)	**Rat (Wistar)** Control (drinking water), M/F, n = 4–8 0.1% solution M/F, n = 4–8	GD 0 to PND 28	Oral, drinking water Oral lactation, in utero	PND 28 0.93 µg/dL for control 6.86 µg/dL for 0.1%	PND 28**:** Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Gąssowska et al. (2016b)	**Rat (Wistar)** Control (drinking water), M/F, n = 4–8 0.1% solution, M/F, n = 4–8	GD 0 to PND 28	Oral, drinking water Oral lactation, in utero	PND 28 0.93 µg/dL for control 6.86 µg/dL for 0.1%solution	PND 28: Histopathology
Sepehri and Ganji (2016)	**Rat (Wistar)** Control, M, n = 8 0.05% solution, M, n = 8	GD 5 to PND 25	Oral, drinking water Oral lactation, in utero	PND 25 0.78 µg/dL for control 28.3 µg/dL for 0.05%	PND 25: Histopathology
Zhu et al. (2019a)	**Rat (Sprague Dawley)** Control (distilled water), M, n = 10 0.5 g/L, M, n = 10	GD −10 to 12 mo	Oral, drinking water Oral lactation, in utero	12 mo 0 µg/dL for control 0.27 mg/L (27 µg/dL) for 0.5 g/L	12 mo: Electrophysiology
Zhang et al. (2015b)	**Rat (Long-Evans)** Control (0 ppm), M/F, n = 10 1500 ppm, M/F, n = 10	GD −10 to PND 50	Oral, diet Oral lactation, in utero	PND 50 0.8 µg/dL for control 21.1 µg/dL for 1500 ppm	PND 50: Histopathology, Electrophysiology
Wang, 2021, 10296633@@author-year	**Rat (Sprague Dawley)** Control (deionized water), M/F, n = 12 0.05% solution, M/F, n = 10	GD −28 to PND 21	Oral, lactation In utero	PND 21: 23.9 µg/L (2.39 µg/dL) for Control 206 µg/L (20.6 µg/dL) for 0.05% solution	

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Wu et al. (2020a)	**Mouse (C57BL/6J)** Control (ultra-pure water), F, n = 8 200 mg/L, F, n = 8 **Mouse (APP/PS1)** Control (ultra-pure water),F, n = 8 200 mg/L, F, n = 8	GD −7 to 7 mo	Oral, diet Oral lactation, in utero	PND 207–210 **Mouse (C57BL/6J)** 19.71 µg/L (1.97 µg/dL) for control 84.53 µg/L (8.45 µg/dL) for 200 mg/L **Mouse (APP/PS1)** 19.96 µg/L(1.99 µg/dL) for control 205.49 µg/L(20.54 µg/dL) for 200 mg/L	7 mo: Brain Weight, Histopathology
Mani et al. (2020)	**Rat (Wistar)** Control (distiller water), M, n = NR 10 mg/kg, M, n = NR 50 mg/kg, M, n = NR 100 mg/kg, M, n = NR	8 mo to 9 mo	Oral, gavage	NR 2.3 µg/dL for Control 8.5 µg/dL for 10 mg/kg 16.4 µg/dL for 50 mg/kg 16.3 µg/d for 100 mg/kg	NR: Histopathology, Brain Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Shvachiy et al. (2020)	**Rat (Wistar)** Control (tap water), M/F, n = 12 0.2% solution (3 mo), M/F, n = 12 0.2% solution (5 mo), M/F, n = 12 0.2% solution (7 mo), M/F, n = 12	GD 7 to 3 mo GD 7 to 5 mo GD 7 to 7 mo	Oral, drinking water Oral, lactation In utero	3 mo: <1 for Control 24.0 µg/dL for 0.2% solution 5 mo: <1 for Control 24.8 µg/dL for 0.2% solution 7 mo: <1 for Control 26.9 µg/dL for 0.2% solution	PND 189: Histopathology

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Zhao et al. (2021)	**Rat (Sprague Dawley)** Control, M, n = 6 109 ppm, M, n = 6	GD −14 to PND 10	Oral, drinking water Oral, lactation In utero	PND 10 0.6 µg/dL for control 11.4 µg/dL for 109 ppm PND 21 0.85 µg/dL for control 3.5 µg/dL for 109 ppm PND 30 0.98 µg/dL for control 1.8 µg/dL for 109 ppm	PND 30: Histopathology, Electrophysiology

APP = amyloid precursor protein; BLL = blood lead level; DI = deionized; F = female; F0 = gestating female; GD = gestational day; LTP = long-term potentiation; M = male; ME = maternal exposure; MRI = magnetic resonance imaging; mo = month(s); NaAc = sodium acetate; NR = not reported; Pb = lead; PG = pregestation; PND = postnatal day; PW = postweaning; wk = week(s); yr = year(s).

Table 3-2E Epidemiologic studies of Pb exposure and full-scale intelligence quotient

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Lanphear et al. (2005) Lanphear et al. (2019) International pooled analysis: Prospective cohorts from Boston, Cincinnati, Cleveland, Mexico City, Port Pirie, Rochester, and Yugoslavia. Followed from birth (1979–1995) up to age 10 yr	n = 1,333 children	Blood Median (5th–95th) Early childhood (6–24 mo): 12.7 (3.5–34.5) Peak: 18 (6.0–47.0) Lifetime avg (through outcome measurement at 4.8–10 yr): 11.9 (3.6–34.5) Concurrent: 9.7 (2.5–33.2)	FSIQ: WISC-III, WISC-R, WPPSI, WISC-S (depending on the cohort) Ages 4.8–10 yr	HOME score, birth weight, maternal IQ and education. Also considered potential confounding by child sex, birth order, marital status, maternal age, prenatal smoking status and alcohol use.	Early Childhood: −0.137 (−0.209, −0.064) Lifetime avg: −0.206 (−0.285, −0.126) Concurrent: −0.187 (−0.26, −0.114) Peak: −0.126 (−0.182, −0.071)
Lanphear et al. (2005) Lanphear et al. (2019), subset of with peak BLLs <7.5 µg/dL	n = 103 children	Same Concurrent Mean: 3.2	Same	Same	−2.53 (−4.48, −0.58)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Crump et al. (2013) Reanalysis of Lanphear et al. (2019, 2005)	N = 1355 children (note that the reanalysis included prenatal BLLs in lifetime avg and employed a different strategy including covariates that allowed a larger number of observations to be included in the analysis)	Blood BLL distribution reported by cohort not for the pooled dataset as a whole.	FSIQ: WISC-III, WISC-R, WPPSI, WISC-S	Same but defined to be cohort specific	Concurrent: β= −3.315 (−4.546, −2.084) Peak β= −2.484 (−3.825, −1.142) Early childhood β= −2.459 (−3.817, −1.102) Lifetime avg β= −3.246 (−4.659, −1.833) 24-month β= −1.955 (−3.193, −0.717) Note: the estimates are not standardized)
Van Landingham et al. (2020) Reanalysis of Lanphear et al. (2005) and Lanphear et al. (2019)	NR	NR	FSIQ: WISC-III, WISC-R, WPPSI, WISC-S	Defined highly likely confounders: HOME score, maternal education and maternal IQ and included interaction terms between BLL and each of these covariates	B=-4.945 Interaction terms: Maternal IQ x ln(BLL+1): -0.0003 Mother's education x ln(BLL+1): -0.0051 HOME x ln (BLL+1): 0.0437 Note: the estimates are not standardized)
Canfield et al. (2003a) Rochester, NY Prospective cohort Born 1994–1995 followed from age 6 mo to 5 yr	n = 101 Children recruited from dust control study	Blood Concurrent, children with peak <10 Mean: 3.3	FSIQ Stanford-Binet Age 5 yr	Child sex, Fe status, birth weight, maternal race, education, IQ, income, and prenatal smoking status, HOME score.	−1.8 (−3.0, −0.60)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Bellinger and Needleman (2003) Boston area, MA. Prospective Followed from birth (1979–1981) to age 10 yr.	n = 48 children Recruited at birth	Blood Early childhood (age 2 yr) Mean (SD) Peak <10: 3.8 (range: 1–9.3) Detection limit NR	FSIQ: WISC-R Age 10 yr	HOME score (age 10 and 5), child stress events, race, maternal IQ, age, marital status, SES, sex, birth order, # residence changes before age 5 yr. Also considered potential confounding by family stress, maternal age, psychiatric factors, child serum ferritin levels	−1.6 (−2.9, −0.2)
Surkan et al. (2007) Boston, MA and Farmington, ME Cross-sectional Sep 1997–Mar 2005	n = 389 Children recruited from trial of amalgam dental fillings.	Blood Concurrent Group1: 1–2 Group 2: 3–4 Group 3: 5–10 Mean (SD): 2.2 (1.6)	WISC-III Age 6–10 yr	Caregiver IQ, child age, SES, race, birth weight. Also considered site, sex, birth order, caregiver education and marital status, parenting stress, and maternal utilization of prenatal and annual health care (not parental caregiving quality.)	1.0 (reference) −0.12 (−3.3, 3.1) −6.0 (−11, −1.4)
Chiodo et al. (2007) Detroit, MI area Cross-sectional	495 children (born 1989–1991) age 7 yr,	Blood Concurrent Mean (SD): 5.0 (3.0)	WPPSI Age 7 yr	Maternal psychopathology, IQ, prenatal smoking, prenatal marijuana, SES, HOME score, caretaker education and marital status, # children in home, child sex. Also considered child age, maternal age, custody, cocaine use, prenatal alcohol use.	−0.19 (−0.30, −0.08) Note: standardized regression coefficient. 95% CI estimated using the reported p-value of 0.01

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Kim et al. (2009) Seoul, Seongnam, Ulsan, and Yeoncheon, South Korea Cross-sectional Children born 1996–1999	261 children School recruitment	Blood Concurrent Mean (SD): 1.7 (0.80) Age: 8–11 yr	KEDI-WISC Ages 8–11 yr	Maternal age, education and prenatal smoking status, paternal education, yearly income, smoking exposure status after birth, child age, sex, and birth weight (not parental caregiving quality or IQ)	Blood Mn <1.4 µg/dL −2.4 (−6.0, 1.1) Blood Mn >1.4 µg/dL −3.2 (−6.1, −0.24)
†Braun et al. (2018) Cincinnati, OH United States Mar 2003–Jan 2006 Followed for 8 yr Cohort	HOME study n: 355 (Intervention group: 174, Control group: 181) Clinical trial of pregnant women, mean gestation of 16 wk and residence in a house built in or before 1978 Intervention to reduce Pb exposure	Blood Maternal and child blood; ICP-MS Dust Pb loadings floor, interior windowsill and window at 20 wk gestation, child age 1 and 2 yr; GFAAS. Age at Measurement: 16, 26 wk of gestation, delivery (maternal); 1,2,3,4,5, 8 yr (child) Baseline GM (Intervention and control groups): maternal: 0.7 and 0.7 µg/dL, floor dust Pb: 1.5 and 1.9 µg/sq ft, windowsill dust Pb: 28 and 33 µg/sq ft, window trough dust Pb: 574 and 510 µg/sq ft.	WPPSI Age at outcome: 5–8 yr	NA	Mean FSIQ score difference[b]: 0.5 (−3.3, 24.2), comparing the treatment to the injury prevention control group.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
† Taylor et al. (2017) UK Cohort April 1, 1991–Dec 31, 1992 (followed until age 4–8 yr)	ALSPAC n: 4285 Mother-infant pairs.	Blood Maternal and child venous blood; ICP-MS Age at Measurement: Prenatal (mean gestational age 11 wk) and postnatal (30 mo) Prenatal: 3.67 µg/dL; Child BLL: 4.22 µg/dL.	FSIQ, VIQ, PIQ (WPPSI or WISC-III). Age at outcome: 4–8 yr	Family adversity index, housing tenure, household crowding, smoking in the first trimester, alcohol consumption in the first trimester, maternal age at index birth, parity, maternal education, length of time the mother lived in Avon, child sex, child age at testing, weighted life events score, and hemoglobin level.	WISC-Boys[b]: −0.29 (−1.02, 0.44) WISC-Girls[b]: 0.73 (0.13, 1.33) WPPSI-Girls[b]: −0.65 (−2.065, 0.765) WPSSI-Boys[b]: −0.54 (−2.015, 0.935)
†Tatsuta et al. (2020) Tohoku district, coastal area Japan 2002–2006 (enrollment) through 2015–2018 (12 yr followup) Cohort	TSCD coastal cohorts n: 289 mother-child pairs (singleton births); 148 boys and 141 girls	Blood Cord and child venous blood; ICP-MS Age at Measurement: Delivery (cord), 12 yr (child) Median: Cord = 0.8 µg/dL, 12-yr = 0.7 µg/dL 95th: Cord: 1.4 µg/dL, 12-yr: 1.1 µg/dL	FSIQ (Japanese version WISC-IV), age equivalent ranking and scores for verbal comprehension, perceptual reasoning, working memory, and processing speed composites; BNT (cues and no cues) Age at outcome: 12 yr	Birth weight, drinking or smoking during pregnancy, the Raven's score (parent assessment for child at 18 mo of age), passive smoking status at 12 yr old, family income, WISC/BNT tester, and cord blood total Hg	Cord-Boys: β=−3.683 (- Cord-Girls: β = 10.714, 3.349) Child-Boys: β = 1.463 (−2.905, 5.831) Child-Boys: β = −9.88 (−18.977, −0.782) Child-Girls: −4.406 (−15.94, 7.129)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Desrochers-Couture et al. (2018) 10 study sites Canada 2008–2011 Followed 3–4 yr from birth Cohort	MIREC Study n: 609 Birth cohort: Mother-infant pairs recruited during 1st trimester	Blood Maternal, cord, and postnatal child (venous) ICP-MS Age at Measurement: Maternal (6–13 wk, 32–34 wk), birth (cord); and 3–4 yr (postnatal child) GM: 1st trimester: 0.62 µg/dL; 3rd trimester: 0.59 µg/dL; cord blood: 0.76 µg/dL; child blood: 0.70 µg/dL Max: 1st trimester: 4.14 µg/dL; 3rd trimester: 3.93 µg/dL; cord blood: 3.52 µg/dL; child blood: 5.49 µg/dL.	FSIQ, VIQ, PIQ, General Language composite WPPSI–3rd Edition, short version. The age-standardized WPPSI-III Canadian norms were used to calculate the scores. Age at outcome: Between 2 yr 6 mo and 3 yr 11 mo	Cord blood model: child age, child sex, maternal education, evaluation site and cord blood Hg (log−2 scale). Child blood model: child age, child sex, evaluation site, marital status, familial income, HOME total score, Parenting Stress Index, and cord blood Pb (log−2 scale).	Cord: β=−0.123 (−0.251, 0.005) Child: β = 0.027 (−0.135, 0.188) Cord-Boys: β=−5.686 (−9.968, −1.405) Cord-Girls: β = 0.287 (−3.787, 4.361)
†Zhou et al. (2020b) Jiangsu Province China June 2009-Jan 2010 to June 2016-July 2017 Cohort	Sheyang Mini Birth Cohort Study n: 296 Birth cohort- mother-infant pairs from an agricultural region.	Blood, Urine Cord blood tested for Mn, Cd and Pb using GFAAS. Postnatal urine samples urine also tested for the elements. Age at Measurement: Cord; postnatal Urine NR GM: cord blood: 15.88 µg/L, urine: 1.43 µg/L, 75th: cord blood: 21.83 µg/L, urine: 2.27 µg/L, Max: cord blood: 1168.20 µg/L, urine: 62.47 µg/L,	FSIQ, VIQ, PIQ (Chinese version WISC-R). Age at outcome: 6–7 yr (school-aged children)	Sex, maternal age, maternal education, family annual income, family inhabitation area, and passive smoking; multiple effects were also assessed by entering all other metals in the model. Sex-stratified analysis conducted.	Cord-Girls: 0.615 (−0.909, 2.138) Cord-Boys: 0.835 (−1.164, 2.833) Cord-All: 0.67 (−0.514, 1.854)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Liu et al. (2015) Chongqing, China March 4, 2003-June 19, 2003 (enrollment) Followed 5 yr Cohort	Birth cohort with mother-infant pairs n: 149 Mothers gave birth in 4 hospitals in Tongliang county.	Blood Maternal and cord serum (Hg, Cd, Pb); Pb determined with AAS. Ratio of maternal to cord serum levels (i.e., placental transport ratio of metal) estimated. Age at Measurement: Delivery Mean: 3.45 µg/dL.	VIQ, PIQ, and FSIQ (Shanghai version WPPSI) Raw scores were converted to composite scores and age equivalent percentile ranks were estimated. Age at outcome: 5 yr	Maternal age, educational level, vitamins, placental transport ratios, maternal exposure to ETS. Pb, Hg and Cd were considered in multivariable models (covariates retained based on evaluation of VIFs).	Final predictive model did not include associations with Pb

†Wang et al. (2022) Wujiang China Birth cohort established from 2009–2010; follow-up from 2016–2017. Cohort	n: 148	Blood Blood Pb measured via AAS. Age at Measurement: Mean, SD (mo): 89.90, 3.77 Cord blood: GM = 28.26 µg/L, Median = 27.56 µg/L; Venous blood: GM = 22.99 µg/L, Median = 23.80 µg/L 75th: Cord blood: 38.42 µg/L; Venous blood: 33.00 µg/L Max: Cord blood: 249.00 µg/L; Venous blood: 71.40 µg/L.	Cognitive Effects in children – FSIQ Child health personnel conducted the WISC-CR for FSIQ, PIQ, and VIQ. Scores were age converted and standardized. Age at outcome:	General linear models adjusted for child sex, maternal age at delivery, age of children, maternal education level, paternal education level, monthly household income, parity, inhabitation area, passive smoking.	"Table 3, Beta (95% CI): VIQ, total population, cord blood: Q2 vs. Q1: −0.296 (−7.005, 6.413) Q3 vs. Q1: 4.468 (−2.840, 11.776) Q4 vs. Q1: −1.275 (−8.231, 5.682) VIQ, boys, cord blood: Q2 vs. Q1: −2.752 (−12.594, 7.091) Q3 vs. Q1: 5.681 (−6.288, 17.649) Q4 vs. Q1: 2.119 (−8.913, 13.150) VIQ, girls, cord blood: Q2 vs. Q1: 5.679 (−5.242, 16.600) Q3 vs. Q1: 6.510 (−4.501, 17.521) Q4 vs. Q1: −1.331 (−11.933, 9.271) VIQ, total population, venous blood: Q2 vs. Q1: 4.942 (−3.957, 13.841) Q3 vs. Q1: −0.536 (−9.560, 8.487)

	Q4 vs. Q1: −3.304 (−12.117, 5.509) VIQ, boys, venous blood: Q2 vs. Q1: 5.592 (−7.193, 18.378) Q3 vs. Q1: 8.858 (−4.271, 21.988) Q4 vs. Q1: 7.143 (−5.649, 19.935) VIQ, girls, venous blood: Q2 vs. Q1: 3.179 (−10.810, 17.169) Q3 vs. Q1: −13.548 (−27.506, 0.411) Q4 vs. Q1: −14.964 (−28.412, −1.517), p-value = 0.036 PIQ, total population, cord blood: Q2 vs. Q1: −5.584 (−14.011, 2.842) Q3 vs. Q1: −0.441 (−9.620, 8.738) Q4 vs. Q1: −9.365 (−18.103, −0.628), p-value = 0.038 PIQ, boys, cord blood: Q2 vs. Q1: −13.080 (−24.907, −1.254), p-

	value = 0.035 Q3 vs. Q1: −9.686 (−24.067, 4.695) Q4 vs. Q1: −7.592 (−20.848, 5.663) PIQ, girls, cord blood: Q2 vs. Q1: −0.002 (−14.192, 14.188) Q3 vs. Q1: 4.023 (−10.284, 18.331) Q4 vs. Q1: −13.293 (−27.069, 0.483) PIQ, total population, venous blood: Q2 vs. Q1: −7.293 (−17.605, 3.020) Q3 vs. Q1: −8.176 (−18.633, 2.281) Q4 vs. Q1: −4.507 (−14.720, 5.706) PIQ, boys, venous blood: Q2 vs. Q1: −8.218 (−22.276, 5.841) Q3 vs. Q1: −6.701 (−21.138, 7.737) Q4 vs. Q1: −4.294 (−18.360, 9.772) PIQ, girls, venous blood:

	Q2 vs. Q1: −10.417 (−29.104, 8.270) Q3 vs. Q1: −16.397 (−35.043, 2.248) Q4 vs. Q1: −6.994 (−24.957, 10.968) FSIQ, total population, cord blood: Q2 vs. Q1: −3.369 (−10.711, 3,974) Q3 vs. Q1: 2.396 (−5.603, 10.394) Q4 vs. Q1: −6.087 (−13.700, 1.527) FSIQ, boys, cord blood: Q2 vs. Q1: −8.599 (−19.015, 1.818) Q3 vs. Q1: −1.434 (−14.100, 11.232) Q4 vs. Q1: −2.552 (−14.227, 9.123) FSIQ, girls, cord blood: Q2 vs. Q1: 2.986 (−9.126, 15.098) Q3 vs. Q1: 5.743 (−6.469, 17.955) Q4 vs. Q1: −8.635 (−20.394, 3.123) FSIQ, total population,

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					venous blood: Q2 vs. Q1: −0.950 (−10.606, 8.706) Q3 vs. Q1: −4.930 (−14.722, 4.861) Q4 vs. Q1: −4.773 (−14.336, 4.790) FSIQ, boys, venous blood: Q2 vs. Q1: −1.367 (−14.675, 11.941) Q3 vs. Q1: 1.366 (−12.300, 15.033) Q4 vs. Q1: 1.929 (−11.386, 15.243) FSIQ, girls, venous blood: Q2 vs. Q1: −3.771 (−20.071, 12.529) Q3 vs. Q1: −17.326 (−33.590, −1.062), p-value = 0.044 Q4 vs. Q1: −13.625 (−29.293, 2.0”3)”

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Iglesias et al. (2011) Antofagasta, Northern Chile 1998–2005 Cohort	Sepulveda study n: 192 Children lived or attended school in area contaminated by Pb mineral concentrate stored in open sites at railroad terminal (closed in 1998).	Blood Child's venous blood; AAS. Age at Measurement: In 1998 at 0–7 yr old; in 2005 at 7–16 yr old Mean and Median: blood Pb 1998: 10.8 and 10 µg/dL; blood Pb 2005: 3.5 and 3.2 µg/dL 75th: blood Pb 1998: 14 µg/dL; blood Pb 2005: 4.3 µg/dL Max: Blood Pb 1998: 33 µg/dL; blood Pb 2005: 14 µg/dL.	FSIQ, VIQ, PIQ (Chilean version of WISC-R). Age at outcome: 7–16 yr	Sex, birth weight, birth order, # of siblings, milk type during the first six months of life, history of anemia, SES (household income, home ownership, and school type: public or private), parental education, maternal smoking during pregnancy, maternal IQ, children's stimulation at home, HOME score.	Concurrent: −0.94 (−1.77, −0.11) Early childhood: −0.14 (−0.445, 0.165)
†Ruebner et al. (2019) 46 centers U.S. Cohort 3 enrollment periods, 2005–2009, 2011–2014, 2016–2020 Followed up to 9 yr	CKiD Cohort study n: 412 Children with mild to moderate CKD	Blood Child venous blood; ICP-MS. The BLL measurement closest to the time of neurocognitive testing was used for analysis (concurrent). Age at measurement: NR; 2, 4, or 6 yr after study entry Median: 1.2 µg/dL 75th: 1.8 µg/dL Max: 5.1 µg/dL	FSIQ Mullen Scales of Early Learning (age 12–29 mo), WPPSI (30 mo–5 yr), and WASI (6–18 yr). The last available test results were to evaluate long-term effects. Mean time between BLL and neurocognitive testing was 2.3 yr. Age at outcome: 1–16 yr	Age, sex, race, poverty, and maternal education	Concurrent: β=−2.1 (−3.95, −0.25)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Lee et al. (2021) Seoul, Gyeonggi, and Incheon provinces South Korea 2008–2017 (Recruitment 2008–2010; follow-up from 2012–2017) Cohort	Environment and Development of Children n: 502	Blood Whole blood Pb from mothers during their second trimester of pregnancy and children at ages 4 yr and 6 yr were analyzed by atomic absorption spectrophotometry. Age at Measurement: Maternal mean age (SD) = 31.3 (3.5) yr. Children at 4 yr and 6 yr. Prenatal GM (SD) = 1.32 (1.32) µg/dL; children at 4 yr = 1.43 (1.38) µg/dL; children at 6 yr = 1.43 (1.35) µg/dL 75th: Prenatal = 1.56 µg/dL; children at 4 yr = 1.72 µg/dL; children at 6 yr = 1.70 µg/dL 95th: Prenatal = 2.11 µg/dL; children at 4 yr = 2.47 µg/dL; children at 6 yr = 2.28 µg/dL.	Cognitive Effects (FSIQ) Intelligence quotients of children assessed using 'KEDI-WISC. Age at outcome:	Multivariate models adjusted by maternal education level, exposure to ETS during the pregnancy, maternal age, and maternal IQ.	Table–3 – Estimated coefficients and 95% CI of associations between single metals and children's IQ at 6-years old (standardized) Prenatal period: −1.202 (−4.87, 2.467) At age 4: −1.829 (−4.664, 1.006) At age 6: −2.614 (−5.623, 0.396)
†Dantzer et al. (2020) Greater Cincinnati, Ohio Metro area U.S. Cross-sectional analysis of data collected at age 12	CCAAPS n: 344 Cohort recruited at birth Oct 2001–Jul 2003	Blood, nails Postnatal child venous blood, toenail; ICP-MS. Mean blood Pb: 0.57 µg/dL; toenail Pb: 0.66 µg/g; information also available by gender and race Age: 12 yr.	FSIQ (WISC-IV) Age at outcome: 12 yr	Caregiver IQ, community deprivation index, and BMI. Sex considered as a potential confound.	Concurrent (blood): B=−10.871 (−16.893, −4.848) B=−1.70 (−4.27, −0.862)

†Martin et al. (2021) East Liverpool, Ohio United States 2013–2014 Cross-Sectional	CARES n: 66	BLLs from the children were analyzed by ICP-MS. Age at Measurement: Mean (SD) = 8.4 (0.9) yr GM (SD) = 1.13 (1.96) µg/dL Max: 6.64 µg/dL.	Cognitive Effects Cognitive performance was assessed using the WISC-IV. Age at outcome:	Regression models were adjusted for sex, income, and ln (serum cotinine).	"Table 3 – Interaction effects between Ln Blood Pb-Ln Hair Mn, ß (95% CI) Blood Pb (per 1 ln µg/dL difference) FSIQ At ln hair Mn = 5 ng/g: 1.686 (−3.039, 6.412) At ln hair Mn = 6.25 ng/g: −4.447 (−8.333, −0.561) At ln hair Mn = 7 ng/g: −8.133 (−13.4, −2.867) At ln hair Mn = 7.5 ng/g: −10.596 (−17.172, −4.02) Perceptual Reasoning At ln hair Mn = 5 ng/g: 2.392 (−4.055, 8.839) At ln hair Mn = 6.25 ng/g: −4.612 (−9.918, 0.694) At ln hair Mn = 7 ng/g: −8.808 (−15.996, −1.62) At ln hair Mn = 7.5 ng/g: −11.616 (−20.592, −2.639) Processing Speed At ln hair Mn = 5 ng/g: −0.62 (−4.263, 3.024) At ln hair Mn = 6.25 ng/g: −2.565 (−5.565, 0.435)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					At ln hair Mn = 7 ng/g: −3.725 (−7.788, 0.337) At ln hair Mn = 7.5 ng/g: −4.502 (−9.576, 0.573) Verbal Comprehension At ln hair Mn = 5 ng/g: 1.208 (−3.451, 5.867) At ln hair Mn = 6.25 ng/g: −4.141 (−7.976, −0.306) At ln hair Mn = 7 ng/g: −7.349 (−12.549, −2.149) At ln hair Mn = 7.5 ng/g: −9.49 (−15.976, −3.004) Working Memory At ln hair Mn = 5 ng/g: 2.376 (−2.404, 7.157) At ln hair Mn = 6.25 ng/g: −2.133 (−6.067, 1.8) At ln hair Mn = 7 ng/g: −4.831 (−10.161, 0.498) At ln hair Mn = 7.5 ng/g: −6.635 (−13.286, 0.0”6)”

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Haynes et al. (2015) Marietta or Cambridge, Ohio, and surrounding communities U.S. Oct 2008-March 2013 Cross-sectional	CARES n: 404 Participants resided in study area throughout their life; not moving for at least 1 yr	Blood Child venous blood: ICP-MS Age at Measurement: 7–9 yr GM: 0.82 µg/dL Max: NR.	FSIQ (WISC-IV), 4 domains of intellectual functioning (reasoning, processing speed, working memory and verbal comprehension) Age at outcome: 7–9 yr	Sex, parent's IQ, parent education, parent confidence T-score, Mn or Pb, community residence (FSIQ models only); other sets of variables added depending on domain.	Processing speed: β = –3.53 [–6.95, –0.12) Association with FSIQ NR (Note: main effect is Mn)
†Hong et al. (2015) 5 administrative regions South Korea NR Cross-sectional	n: 1001 General population of children	Blood Venous blood; GFAAS Age at Measurement: 8–11 yr old Median: 1.81 µg/dL 75th: 2.25 µg/dL, 95th: 3.01 µg/dL Max: 6.16 µg/dL.	KEDI-WISC Age at outcome: 8–11 yr old	Age, sex, residential region, paternal education level, and yearly income log10-transformed blood Hg, Mn, urine concentrations of cotinine, phthalate metabolites	B=−1.948 (−3.608, −0.288), adjusted for other metals B=−2.113 (−3.73, −0.496), adjusted for ADHD and CPT B=−2.118 (−3.792, −0.445), adjusted for socio-demographic factors
†Menezes-Filho et al. (2018) Salvador, Bahia Brazil Cross-sectional Study years: NR	School-based cohort n: 225 Children from 4 elementary schools in industrial town.	Blood Child venous blood Pb, hair and toenails tested for Mn; GFAAS Age at Measurement: 7–12 yr Mean: 1.64 µg/dL, Median: 1.15 µg/dL, only about 2% of children above the Centers for Disease Control and Prevention ref value of 5 µg/dL 75th: 2.1 µg/dL Max: 15.6 µg/dL.	IQ estimated using vocabulary and matrix reasoning (WASI). Age at outcome: 7–12 yr	Age, Maternal IQ Effect modification by Mn assessed. Both Pb and Mn were log-transformed to include in the model. Interaction between Pb and Mn assessed.	Put results for Model B which is adjusted for Mn, age and maternal IQ

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Lucchini et al. (2012) Valcamonica and Garda Lake areas in Province of Brescia Italy Cross-sectional	Junior high school-age children from 20 local public schools n: 299	Blood Children's venous blood; GFAAS Age at Measurement: 11–14 yr 1.71 µg/dL, Median: 1.50 75th: 2.10 µg/dL Max: 10.2 µg/dL.	IQ tested using WISC-III (verbal IQ and performance IQ assessed). Age at outcome: 11–14 yr	Sex, age at testing, parental education, SES, family size, parity order, BMI	B=−2.248 (−4.111, −0.385)

AAS = atomic absorption spectrometry; ALSPAC = Avon Longitudinal Study of Parents and Children; avg = average; BLL = blood lead level; BNT = Boston Naming Test; CARES = Communities Actively Researching Exposure Study; CCAAPS = Cincinnati Childhood Allergy and Air Pollution Study; Cd = cadmium; CI = confidence interval; CKD = chronic kidney disease; CKiD = Chronic Kidney Disease in Children Study; ETS = environmental tobacco smoke; FSIQ = full-scale intelligence quotient; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; Hg = mercury; HOME = Health Outcomes and Measures of the Environment; ICP-MS = inductively coupled plasma mass spectrometry; IQ = intelligence quotient; KEDI = Korean Educational Development Institute; MIREC = Maternal-Infant Research on Environmental Chemical; Mn = manganese; mo = month(s); NA = not available; NR = not reported; Pb = lead; PC = primary caregiver; PIQ = performance IQ; Q = quartile; SD = standard deviation; SES = socioeconomic status; VIF = variance inflation factor; VIQ = verbal IQ; WASI = Wechsler Abbreviated Scale of Intelligence; WISC = Weschler Intelligence Scale for Children; wk = week(s); WPPSI = Wechsler Preschool and Primary Scale of Intelligence; yr = year(s).

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

[b]Results are not standardized (e.g., BLL distribution data needed to calculate the standardized estimate was not reported or categorical data was analyzed).

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

Table 3-3E Epidemiologic studies of Pb exposure and infant development

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Bellinger et al. (1987) Boston, MA U.S. Apr. 1979 – Apr. 1981 (enrollment) Followed through 2 yr Cohort	Birth cohort, n = 182 infants Recruitment from births at Brigham and Women's Hospital	Blood Cord blood; anodic stripping voltammetry (ASV) Age at measurement: Delivery Mean (SD): 6.6 (3.2) µg/dL Low: <3 µg/dL Medium: 6–7 µg/dL High: ≥10 µg/dL	MDI assessed using BSID-II Age-standardized scores (mean: 100, SD: 16) Age at outcome: 2 yr	Maternal age, race, IQ, education, years of smoking, and alcohol drinks/wk in 3rd trimester, SES, HOME score, child sex, birth weight, gestational age, birth order.	Beta: **Cord blood:** Low vs. high: −3.8 (−6.3, −1.3) Medium vs. high: −4.8 (−7.3, −2.3) Concurrent blood reported not to be associated with MDI, quantitative data not reported.
Jedrychowski et al. (2009b) Krakow, Poland 2001–2004 (enrollment) Followed through 3 yr Cohort	Birth cohort, n = 381–415 children Recruited pregnant mothers from prenatal clinics in Krakow inner city in 1st and 2nd trimesters.	Blood Cord blood; ICP-MS Age at measurement: Delivery GM (95% CI): 1.29 (1.24, 1.34) µg/dL Median: 1.23 µg/dL	MDI assessed using BSID-II (Polish version) Standardized scores Age at outcome: 12, 24, 36 mo	Maternal education and prenatal smoking, child sex and birth order	Beta Age 2 yr: −1.8 (−3.4, −0.14) Age 3 yr: −1.6 (−2.9, −0.21)
Henn et al. (2012) Mexico City Mexico 1997−2000 (enrollment) Followed through 24 mo	N: 455 Women recruited during pregnancy or at delivery	Blood Child venous blood; ICP-MS Age at measurement: 12, 24 mo Mean (SD):	MDI assessed using BSID-II (Spanish version) Age at Outcome: 12, 18, 24, 30, 36 mo	Sex, gestational age, hemoglobin, maternal IQ, maternal education, and visit	Beta 12-months: −0.07 (−0.39, 0.25) 24-months: –0.08 (–0.46, 0.30) 12 mo Pb * Mn <2 µg/dL: –0.31 (–1.25, 0.62)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cohort		12 mo: 5.1 (2.6) µg/dL 24 mo: 5.0 (2.9) µg/dL			24 mo Pb * Mn <2 µg/dL: –1.27 (–2.18, –0.37)
Hu et al. (2006) Mexico City Mexico 1997−2000 (enrollment) Followed through 24 mo Cohort	N: 83 (cord) – 146 (24-months child blood) Women recruited during pregnancy or at delivery	Blood Maternal blood, cord blood, and child venous blood; ICP-MS Age at measurement: T1, T2, T3 (maternal), delivery (cord), 12, 24 mo (child) Mean (SD): Maternal T1: 7.07 (5.10) µg/dL; T3: 6.86 (4.23) µg/dL Cord: 6.20 (3.88) µg/dL Child 24 mo: 4.79 (3.71) µg/dL	MDI assessed using BSID-II (Spanish version) Age at Outcome: 24 mo	Maternal age and IQ, child sex, current weight, height-for-age Z score, and concurrent blood Pb (in models examining prenatal blood Pb)	Maternal T1: −0.76 (−1.50, −0.03) Maternal T3: −0.43 (−1.10, 0.27) Cord: −0.06 (−0.87, 0.74) Child 24 mo: −0.23 (−0.92, 0.45)
† Y Ortiz et al. (2017) Mexico City Mexico Jul 2007-Feb 2011 Followed through 24 mo Cohort	PROGRESS birth cohort n: 536 Women <20 wk of gestation and planning to reside in Mexico City for the next 3 yr.	Blood Maternal blood; ICP-MS. Age at measurement: T2, T3 Mean: T2: 3.7 µg/dL T3: 3.9 µg/dL.	Cognitive and language development assessed using BSID-III. Standardized scores (mean: 100, SD: 15). Cognitive, language and motor scores were jointly considered for standardizing. Age at outcome: 24 mo	Infant sex, birth weight, gestational age, maternal age, maternal IQ (WAIS Spanish version), HOME score.	Beta **Cognitive Development:** T2: 0.76 (−3.35, 4.87)[b,c] T3: −6.60 (−13.49, 0.29)[b,c] Stress[2]: −0.23 (−0.45, −0.01)[b,c] T3*Stress: 1.02 (−0.78, 2.82)[b,c] **Language Development:** T2: 0.97 (−3.18, 5.12)[b,c] T3: −6.00 (−12.94, 0.94)[b,c]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Kim et al. (2013c) and Kim et al. (2013b) Seoul, Cheonan and Ulsan Korea 2006–2010 Followed through 6 mo Cohort	MOCEH study n: 884 Mothers recruited before 20th wk of pregnancy between and were in locations (Seoul, Cheonan and Ulsan).	Blood Maternal venous blood; GFAAS with Zeeman background correction, measured for Pb and Cd Age at measurement: Early (<20 wk) and late pregnancy (med = 39 wk) Early pregnancy: 1.4 (GM), 2.1 (90th), 9.8 (max) µg/dL Late pregnancy: 1.3 (GM); 2.1 (90th), 4.3 (max) µg/dL	MDI assessed using BSID-II (Korean version) Age-standardized scores (mean: 100, SD: 15). Age at outcome: 6 mo	Birth weight, infant sex, maternal age and education, family income, breastfeeding status, residential area.	Beta **Early**: Overall: 0.02 (−1.20, 1.24) Cd <1.47 µg/L: 2.44 (0.04, 4.83) Cd >1.47 µg/L: −0.87 (−2.52, 0.78) **Late**: Overall: −1.74 (−3.37, −0.12) Cd <1.51 µg/L: −0.29 (−2.88, 2.30) Cd >1.51 µg/L: −3.20 (−5.35, −1.06)
†Kim et al. (2018b) 4 cities: Seoul, Anyang, Ansan and Jeju Korea 2011–2012 (enrollment) Followed through 24 mo Cohort	CHECK cohort n: 140 birth cohort- pregnant women recruited from 4 cities in Korea before delivery.	Blood Maternal and cord blood; method NR Age at measurement: Delivery Median (IQR): Maternal: 2.7 (3.5, 5.7) µg/dL Cord: 1.2 (0.8, 1.7) µg/dL	MDI assessed using BSID-II (Korean version) Age at outcome: 13–24 mo	BPA, and phthalates, maternal age (continuous), birth delivery mode (categorical), monthly household income (categorical), child's sex, and BDI (continuous) of the mother, gestational age (continuous), primiparous (categorical), and pre-pregnancy BMI (categorical).	Associations of blood Pb concentrations and MDI were assessed but not reported because they lacked statistical significance.
†Valeri et al. (2017) Pabna and Sirajdikhan districts Bangladesh 2010–2013 (enrollment)	Birth cohort n: 825 (Pabna: 409, Sirajdikhan: 416) Mother-infant pairs,	Blood Cord blood; ICP-MS, measured for Pb, As, and Mn Age at measurement:	Cognitive and language development using BSID-III (Bengali version, adapted for rural Bangaldesh)	Child sex, age at testing, maternal age and education, maternal IQ, HOME score, ETS, protein intake.	Beta **Pabna** Cognitive: 0.012 (−0.05, 0.074)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Followed through 20–40 mo Cohort	pregnant women enrolled in the first trimester.	Delivery GM: Pabna: 1.8 µg/dL, Sirajdikhan: 6.0 µg/dL. 75th: Pabna: 2.4, Sirajdikhan: 9.7 Max: Pabna: 79.1 µg/dL, Sirajdikhan: 36.0 µg/dL.	Two primary outcomes derived by summing across raw scores of cognitive and language development. Z-scores were calculated. Age at outcome: 20–40 mo		Language: −0.014 (−0.076, 0.048) **Sirajdikhan** Cognitive: −0.011 (−0.024, 0.001) Language: −0.004 (−0.026, 0.017)
†Koshy et al. (2020) Old Town, Salavanpet and neighboring areas in Vellore, South India Mar 2010-Feb 2012 (enrollment) Followed through 5 yr Cohort	Etiology, Risk Factors and Interactions of Enteric Infections and Malnutrition and the Consequences for Child Health and Development (MAL-ED) Network n: 228 (followed 2 yr) and 212 children (followed 5 yr) Birth cohort of mother-infant pairs in eight adjacent urban slum dwelling areas	Blood Child venous blood; GFAAS. Mean BLL derived by averaging BLLs at 15 and 24 mo for analysis at 2 yr, and 15, 24 and 36 mo for analysis at 5 yr. Age at measurement: 7, 15, 24 and 36 mo Mean: 15 mo: 0.5 µmol/L, 24 mo: 0.6 µmol/L, 36 mo: 0.6 µmol/L	Cognitive and language development assessed using BSID-III (culturally adapted and translated) Raw scores of cognition and expressive and receptive language domains. Age at outcome: 24 mo	Child sex, maternal intelligence raw scores, SES, mean body Fe levels.	Beta **Cognitive:** −0.2 (−0.2, −0.03) Expressive language: −0.2 (−0.3, −0.1) Receptive language: −0.04 (−0.1, 0.02)
†Shekhawat et al. (2021) Western Rajasthan India 2018–2019 (enrollment) Followed through 6.5 mo (average)	n:117 Mother-child pairs in third trimester or at delivery	Blood Cord blood; ICP-OES Age at measurement: Delivery GM = 4.14 µg/dL; mean = 4.77 ± 3.3 µg/dL; median =	Cognitive and language development assessed using BSID-III Age at outcome: 6.5 mo (average)	Maternal age, gravida, gestational age, maternal education, child sex and weight, preterm birth, maternal food intake during pregnancy, smoking, alcohol consumption, maternal residential and	ß (95 % CI) (A) Umbilical cord Pb level <5 µg/dL (n = 70) Composite cognitive: 0.19 (−0.03, 0.34) Composite language: 0.21 (−0.23, 0.42) Subscale receptive language: 0.11 (−0.6, 1.66) Subscale expressive

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cohort		4.23 µg/dL 75th: 5.1 µg/dL.		occupational history, delivery type.	language: 0.22 (−0.03, 1.87) (B) Umbilical cord Pb level = 5.0–10.5 µg/dL (n = 47) Composite cognitive: −0.13 (−0.77, 0.28) Composite language: −0.05 (−0.7, 0.47) Subscale receptive language: −0.04 (−3.5, 2.5) Subscale expressive language: 0.04 (−3.8, 2.9)
†Parajuli et al. (2015a) Chitwan, Bharatpur District Nepal Sep-Oct 2008 (enrollment) Followed through 24 mo Cohort	Birth cohort from Bharatpur General Hospital n: 100 Resided in area for at least 2 yr delivered at term (i.e., >37 wk).	Blood Cord blood; ICP-MS, measured for Pb, As and Zn Age at measurement: Delivery Median: 2.06 µg/dL Max: 22.08 µg/dL.	MDI assessed using BSID-II Age at outcome: 24 mo	Maternal age and education, BMI, gestational age, family income, parity, birth weight, weight at 24 mo, child age assessment, As, Zn, HOME score (smoking and alcohol consumption not included given low prevalence).	Beta −4.21 (−13.62, 5.20)[c]
†Parajuli et al. (2015b) Chitwan, Bharatpur district Nepal Sep-Oct 2008 (enrollment) Followed through 36 mo Cohort	Birth cohort from Bharatpur General Hospital n: 100 Resided in area for at least 2 yr delivered at term (i.e., >37 wk).	Blood Cord blood; ICP-MS, measured for Pb, As and Zn Age at measurement: Delivery Median: 2.06 µg/dL Max: 22.08 µg/dL.	MDI assessed using BSID-II Age at outcome: 36 mo	Maternal age and education, BMI, gestational age, family income, parity, birth weight, weight at 24 mo, child age at assessment, As, Zn, HOME score (smoking and alcohol consumption not included given low given low prevalence).	Beta 4.05 (−3.21, 11.31)[c]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
† Zhou et al. (2017) Shanghai China 2010–2012 (enrollment) Followed through 24–36 mo Cohort	Shanghai Stress Birth Cohort Study n: 139 Women enrolled in prenatal clinics of maternity hospitals during mid-to-late pregnancy.	Blood Maternal blood; AAS Age at measurement: 28–36 wk of gestation GM (95% CI): 3.30 (3.05, 3.57) µg/dL.	Language development assessed using GDS (Chinese version) Age at outcome: 24–36 mo	Maternal age at enrollment, economic status, maternal education, gestational week, child sex, birth weight and age.	Beta per log−10 transformed BLL Language development Overall: −6.76 (−17.29, 3.77)[d] Low stress: −1.76 (−13.03, 9.51)[d] High stress: −33.82 (−60.04, −7.59)[d]
†Vigeh et al. (2014) Tehran Iran October 2006 – March 2011 Followed through 36 mo Cohort	Birth cohort n: 174 Mother-infant pairs recruited in first trimester (8–12 wk).	Blood Maternal blood, cord blood; ICP-MS Age at measurement: 3 trimesters during pregnancy and delivery Mean: Maternal T1: 4.15 µg/dL, T2: 3.44 µg/dL, T3: 3.78 µg/dL Cord: 2.86 µg/dL Max: Maternal T1: 20.5 µg/dL, T2: 7.5 µg/dL, T3: 8.0 µg/dL Cord: 6.9 µg/dL	Mental development composite assessed using the ECDI by Harold Ireton (language comprehension, expressive language, gross motor, self-help, social interaction). Cutoff point scores for development delay were score <20% of that expected for children's age. Age at outcome: 36 mo	Maternal educational, BMI, family income, gestational age, birth weight, birth order (first born).	OR Total ECDI: 1.74 (1.18, 2.5).
†Lin et al. (2013) Taipei, Taiwan April 2004-Jan 2005 (enrollment)	Birth cohort n: 230 Mother-infant pairs from medical center, local hospital, and obstetric clinics.	Blood Maternal blood, cord blood; ICP-MS, measured for Pb, Mn, As, and Hg.	Cognitive and language development assessed using CDIIT	Maternal age, education, infant gender, ETS during pregnancy and after delivery, fish intake, and HOME score.	Beta Cognitive High vs. Low Pb: −5.35 (−9.642, −1.058)[b] High Mn*low Pb: −4.15 (−9.618, 1.318)[b]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Followed through 2 yr Panel Study		Pb categories: Low: <16.45 µg/L High: ≥16.45 µg/L Mn categories: Low: <59.59 µg/L High: ≥59.59 µg/L Age at measurement: delivery Mean: 13 µg/L, GM: 10.61 µg/L 75th: 16.45 µg/L Max: 43.22 µg/L	Age at outcome: 2 yr		Low Mn*high Pb: −4.79 (−10.298, 0.718)[b] High Mn*high Pb: −8.19 (−14.403, −1.977)[b] Language High vs. Low Pb: −2.53 (−6.234, 1.174)[b] High Mn*low Pb: −1.56 (−6.264, 3.144)[b] Low Mn*high Pb: 0.22 (−4.523, 4.963)[b] High Mn*high Pb: −6.81 (−12.161, −1.459)[b]
†Nozadi et al. (2021) Navajo Nation United States February 2013–June 2018 (enrollment) Followed through 10–13 mo Cohort	Navajo Birth Cohort Study n: 327	Blood Maternal blood, child blood; ICP-DRC-MS. Age at measurement: Delivery or 36-wk visit (maternal); 10, 13 mo (child) GM = 0.410 µg/dL; median = 0.37 µg/dL 75th: 0.51 µg/dL 95th: 1.20 µg/dL	Problem-solving scores assessed using ASQ:I. Age-adjusted scores. Age at outcome: 10–13 mo	Urine strontium and arsenic.	Beta Problem-Solving: −0.67 (−1.54, 0.20)
†Nyanza et al. (2021) Northern Tanzania Tanzania 2015–2017 (enrollment) Followed through 6-12 mo	Mining and Health Prospective Longitudinal Study in Northern Tanzania n: 439 Birth cohort of mother-child pairs recruited in 2nd trimester	Maternal dried blood spots; ICP-MS, measured for Pb, Hg, and Cd Age at measurement: T2 Median: 2.72 µg/dL	Language and global neurodevelopment assessed using MDAT. Scores in each domain classified as normal (≥90th percentile on all items in that	Maternal age and education, maternal and paternal occupation, number siblings under 5 yr at home, and family SES, infant sex, age, birth weight, height, and weight as a proxy for nutritional status.	Prevalence ratio Language Development: 1.0 (1.0, 1.0) Global neurodevelopmental status: 1.0 (0.9, 1.0)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cohort		75th: 4.25 µg/dL Max: 14.5 µg/dL	domain or <90th percentile on one or two items in the domain) or impaired (<90th percentile on more than two items in a domain). Age at outcome: 6−12 mo	(Covariates with p < 0.20 retained in the final models.)	Hg ≥0.08 µg/dL * Pb≥ 3.5 µg/dL: 1.4 (0.9, 2.1)

AAS = atomic absorption spectrometry; As = arsenic; ASQ:I = Ages and Stages Questionnaires: Inventory; BDI = Beck Depression Inventory; BLL = blood lead level; BMI = body mass index; BPA = bisphenol A; BSID = Bayley Scales of Infant and Toddler Development; CARES = Communities Actively Researching Exposure Study; CCAAPS = Cincinnati Childhood Allergy and Air Pollution Study; Cd = cadmium; CDIIT = Comprehensive Developmental Inventory for Infants and Toddlers; CHECK = Children's Health and Environmental Chemicals in Korea; CI = confidence interval; CKD = chronic kidney disease; CKiD = Chronic Kidney Disease in Children Study; ECDI = Early Child Development Inventory; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; ETS = environmental tobacco smoke; FSIQ = full-scale IQ; GDS = Gesell Developmental Schedules; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; Hg = mercury; HOME = Health Outcomes and Measures of the Environment; ICP-DRC-MS = dynamic reaction cell for inductively coupled plasma mass spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; ICP-OES = inductively coupled plasma optical emission spectrometry; IQ = intelligence quotient; MDAT = Malawi Development Assessment Tool; MDI = Mental Developmental Index; Mn = manganese; mo = month(s); MOCEH = Mothers' and Children's Environmental Health; NBAS = Neonatal Behavioral Assessment Scale; NR = not reported; OR = odds ratio; Pb = lead; PDI = Psychomotor Developmental Index; PROGRESS = Programming Research in Obesity, Growth, Environment and Social Stressors; SD = standard deviation; SES = socioeconomic status; T1 = first trimester of pregnancy; T2 = second trimester of pregnancy; T3 = third trimester of pregnancy; WISC = Weschler Intelligence Scale for Children; wk = week(s); yr = year(s).
[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.
[b]The CI was calculated from a p-value and the true CI may be wider or narrower than calculated.
[c]Results are unstandardized because the log base used for exposure transformation was unspecified in the study.
[d]Results are unstandardized because the Pb level distribution data was not available.
†Studies published since the 2013 Integrated Science Assessment for Lead.

Table 3-4E Epidemiologic studies of Pb exposure and performance on neuropsychological tests of cognitive function, i.e., learning, memory, and executive function

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Lanphear et al. (2000) United States	U.S. NHANES n = 4,853 children ages 6–16 yr (born 1972–1988)	Blood Concurrent GM (SD): 1.9 (7.0)	Digit span WISC-R Age at outcome: 6–16 yr	Child sex, race/ethnicity, poverty index ratio, reference adult education, serum ferritin and cotinine levels. Did not consider potential confounding by	−0.05 (−0.09, −0.01)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
1988–1994 Cross-sectional	Large U.S. representative study of multiple risk factors and outcomes	63.5% <2.5 Detection limit = 0.5 Interval analyzed: 1–5	Linear regression	parental cognitive function or caregiving quality.	
Krieg et al. (2010) United States 1991–1994 Cross-sectional	U.S. NHANES n = 773 children ages 12–16 yr (born 1972–1982) Large U.S. representative study of multiple risk factors and outcomes	Concurrent GM (SD): 1.9 (7.0) 63.5% <2.5 Detection limit = 0.5 Interval analyzed: 1–5	Digit span WISC-R Age at outcome: 6–16 yr Log-linear regression	Child sex, caregiver education, family income, race/ethnicity, test language. Did not consider potential confounding by parental cognitive function or caregiving quality.	−0.34 (−0.59, −0.08)
Surkan et al. (2007) Boston, Massachusetts and Farmington, Maine United States Cross-sectional	n = 389 children 6–10 yr Recruitment from trial of amalgam fillings	Blood Concurrent Group 1: 1–2 Group 2: 3–4 Group 3: 5–10 Mean (SD): 2.2 (1.6)	General memory index, WRAML Age at outcome: 6–10 yr	Caregiver IQ, child age, SES, race, birth weight. Also considered potential confounding by site, sex, birth order, caregiver education and marital status, parenting stress, and maternal utilization of prenatal and annual health care but not parental caregiving quality.	−0.69 (−4.4, 3.0) −6.7 (−12, −1.2)
†Yorifuji et al. (2011) Faroese island Denmark 1986–1987 (enrollment) Followed through 7-14 yr Cohort	Birth cohort n: At age 7: 896, At age 14: 808 Birth cohort of mother-infant pairs	Blood, hair Cord blood; electrothermal AAS. Age at measurement: At birth GM of cord blood Pb: 1.57 µg/dL 75th: 2.2 µg/dL	Verbal and visuospatial reasoning, language, learning, and memory assessed using WISC-R similarities, WISC-R block designs, BNT, and CVLT-C. Age at outcome: 7, 14 yr	Age, sex, maternal Raven's score, paternal employment and education, maternal education, daycare at age 7, medical risk, and maternal alcohol use and smoking during pregnancy	**Beta** *WISC-R at 7 yr old with cord mercury* Block Design: −0.011 (−0.083, 0.062) Similarities: −0.122 (−0.38, 0.135) Digit Span Forward: −0.1 (−0.183, −0.016) *WISC-R at 7 yr old*

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Block Design: −0.004 (−0.013, 0.006) Similarities: 0.019 (−0.051, 0.088) Digit Span Forward: −0.028 (−0.049, −0.006) *CVLT-C at 14 yr old plus interaction with cord mercury* Recognition: −0.053 (−0.136, 0.031) Long-term Recall: −0.1 (−0.256, 0.057) Short-term Recall: −0.009 (−0.178, 0.16) Learning: −0.438 (−0.965, 0.089) *CVLT-C at 14 yr old* *Recognition:* −0.001 (−0.022, 0.021) Long-term Recall: 0.041 (0, 0.082) Short-term Recall: 0.013 (−0.031, 0.058)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Learning: 0.037 (−0.103, 0.177) *Boston Naming Test at 14 yr old plus interaction with cord mercury* With Cues: 0.002 (−0.337, 0.342) No Cues: −0.095 (−0.473, 0.283) *Boston Naming Test at 14 yr old* With Cues: 0.033 (−0.056, 0.122) No Cues: 0.003 (−0.096, 0.102) *WISC-R at 14 yr old plus interaction with cord mercury* Block Design: 0.241 (−0.575, 1.057) Similarities: −0.147 (−0.383, 0.089) Digit Span Backward: −0.16 (−0.253, −0.067) Digit Span Forward: −0.107 (−0.199, −0.016)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Digit Span: −0.267 (−0.423, −0.111) *WISC-R at 14 yr old* Block Design: −0.023 (−0.238, 0.191) Similarities: −0.007 (−0.069, 0.055) Digit Span Backward: −0.035 (−0.06, −0.009) Digit Span Forward: −0.024 (−0.048, 0) Digit Span: −0.059 (−0.1, −0.017) *CVLT-C at 7 yr old plus interaction with cord mercury* Recognition: −0.094 (−0.2, 0.011) Long-term Recall: 0.037 (−0.141, 0.215) Short-term Recall: −0.068 (−0.22, 0.084) Learning: −0.501 (−0.981, −0.02) *CVLT-C at 7 yr old*

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Recognition: −0.003 (−0.032, 0.026) Long-term Recall: 0.033 (−0.014, 0.081) Short-term Recall: 0.043 (0.003, 0.084) Learning: 0.073 (−0.057, 0.202) *Boston Naming Test at 7 yr old plus interaction with cord mercury* With Cues: −0.138 (−0.469, 0.193) No Cues: −0.046 (−0.376, 0.284) *Boston Naming Test at 7 yr old* With Cues: 0.042 (−0.045, 0.129) No Cues: 0.039 (−0.049, 0.127)
†Tatsuta et al. (2014) Sendai, Tohoku region Japan Study years NR Followed through 42 mo	TSCD birth cohort n: 387 Mother-infant pairs urban areas of the Tohoku district	Blood Cord blood; ICP-MS. Age at measurement: Delivery	Intelligence and achievement (K-ABC) Age at outcome: 42 mo	Child sex, birth order, alcohol and smoking habits, duration of breastfeeding, annual family income at 42 mo, and maternal IQ (Raven SPM)	**Beta** *Adjusted Model* Mental Processing Score: −3.319 (−12.41, 5.774)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cohort		Median: 1.0 µg/dL Max: 1.8 µg/dL			Sequential Processing Score: −2.136 (−12.80, 8.531)
†Oppenheimer et al. (2022) New Bedford Harbor, Massachusetts United States 1993–1998 (enrollment) Followed through 2008–2014 Cohort	New Bedford Cohort n: 373	Blood Cord blood; isotope dilution ICP-MS Age at measurement: Delivery Mean (SD): 1.4 (0.9) µg/dL Max: 9.4 µg/dL	Cognitive Effects Cognitive effects were assessed using four subtests of the Delis-Kaplan Executive Function System. These included Trail Making: Number-Letter Switching condition, Verbal Fluency: Category Switching condition, Design Fluency: Filled Dots and Empty Dots Switching condition, and Color-Word Interference: Inhibition/Switching condition. Age at Outcome: 14−18 yr	Multiple linear regression models adjusted for child race, sex, age at exam, year of birth, HOME score, maternal marital status at child's birth, maternal IQ, maternal seafood consumption during pregnancy, maternal smoking during pregnancy, maternal and paternal education, and annual household income at child's birth, and study examiner.	**Beta** *WRAML* Verbal Working Memory: 0.12 (−0.20, 0.45) Symbolic Working Memory: 0.09 (−0.246, 0.42) Working Memory Index Differences: 0.59 (−0.97, 2.15)
Cho et al. (2010) Seoul (metropolitan), Seongnam (suburban), Ulsan and Incheon (industrial), and Yeoncheon (rural) South Korea 2009 Cross-sectional	n = 639 children (8–11 yr) School-based recruitment	Blood Child blood; GFAAS with Zeeman background correction Age at measurement: 8-11 yr Mean (SD): 1.9 (0.67) µg/dL 10th–90th: 1.2–2.8 µg/dL	Color-Word score SCWT Age at outcome: 8–11 yr	Age, sex, paternal education, maternal IQ, child IQ, birth weight, urinary cotinine, residential area. Did not consider potential confounding by parental caregiving quality.	**Beta** 0 (−0.02, 0.02)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Fruh et al. (2019) Eastern Massachusetts U.S. 1999–2002 (enrollment) Followed through 7 yr Cohort	Project Viva n: 1006 Birth cohort of mother-child pairs	Blood Maternal venous erythrocyte blood specimens; ICP-MS Age at measurement: 2nd to 3rd trimester of pregnancy (median: 27.9 wk) Med (IQR): 1.1 (0.06) µg/dL	Executive Function (see also Section 3.5.1) Parent teacher ratings on BRIEF Age at outcome: 7 yr	Scores standardized for child age and sex; Additional adjustment for maternal 2nd trimester Hg and Mn levels, nulliparity, smoking during pregnancy, IQ, and education; Paternal education; HOME composite score and household income; and child race/ethnicity.	**Beta** **BRIEF Parent-Reported** *Behavioral Regulation Index* All: 1.15 (−0.217, 2.517) Girls: 1.717 (0.025, 3.408) Boys: 0.85 (−1.058, 2.758) *Metacognition Index* All: 0.95 (−0.25, 2.15) Girls: 1.483 (−0.108, 3.075) Boys: 0.6 (−1.05, 2.25) *General Executive Composite* All: 1.217 (−0.1, 2.533) Girls: 1.95 (0.1, 3.8) Boys: 0.783 (−0.958, 2.525) **BRIEF Teacher-Reported** *Behavioral Regulation Index* All: 0.767 (−0.567, 2.1)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Girls: 0.933 (−1.142, 3.008) Boys: 0.75 (−0.9, 2.4) *Metacognition Index* All: 0.683 (−0.717, 2.083) Girls: 0.9 (−1.308, 3.108) Boys: 0.683 (−1.142, 2.508) *General Executive Composite* All: 0.7 (−0.65, 2.05) Girls: 0.883 (−1.258, 3.025) Boys: 0.683 (−1.008, 2.375)
†Fruh et al. (2021) Eastern Massachusetts, U.S. 1999–2002 (enrollment), Followed through 6–11 yr Cohort	Project Viva n: 2128 Birth cohort of mother-child pairs	Blood Maternal venous erythrocyte blood specimens; ICP-MS Age at measurement: 2nd to 3rd trimester of pregnancy (median: 27.9 wk)	Global Executive Composite (GEC); Total Difficulties score BRIEF; SDQ Age at Outcome: 6–11 yr	Scores on BRIEF standardized for age, sex and model adjusted for child race/ethnicity, maternal parity, maternal smoking status, maternal IQ, maternal education, paternal; education, hemoglobin, HOME score, household income, and fish consumption. SDQ model adjusted for age, sex, and above covariates. Pb, Mn, Se	**Beta** SDQ Total Difficulties: 0.617 (−0.058, 1.292) BRIEF GEC: 1.11 (−0.12, 2.34)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Med (IQR): 1.1 (0.06) µg/dL		and MeHg included together in the models.	
†Ruebner et al. (2019) 46 centers U.S. Study Years: NR Followed through: 1–16 yr Cohort	CKiD Cohort study n: 412 Children with mild to moderate CKD	Blood Child venous blood; ICP-MS. The BLL measurement closest to the time of neurocognitive testing was used for analysis (concurrent). Age at measurement: NR; 2, 4, or 6 yr after study entry Median: 1.2 µg/dL 75th: 1.8 µg/dL Max: 5.1 µg/dL	Executive function (see also Section 3.5.1 [FSIQ], Section 3.5.2 [attention and hyperactivity]) Age-specific assessments administered at visit 3, 5, 7, or 9. Last available results used (mean time between BLL and outcome assessment = 2.3 yr). Delis-Kaplan Executive Function System Tower Subset (>6 yr), BRIEF-P (2–5 yr), BRIEF (6–18), BRIEF-A (≥18 yr) Age at outcome: 1 to >18 yr	Age, sex, race, poverty, maternal education.	Adjusted BRIEF results were not reported because they were not statistically significant.
†Merced-Nieves et al. (2022) Mexico City Mexico 2007-2011 (enrollment) Followed through 6-7 yr Cohort	PROGRESS Cohort n = 549 Birth cohort	Blood Maternal, cord, and child blood; Agilent 8800 ICP Triple Quad Age at measurement: Maternal: T2, T3, delivery Cord: delivery Postnatal: 4-6 yr Mean (SD) Maternal T2: 2.7 (2.7) µg/dL	Various measures from Condition Position Responding (CPR), Temporal Response Differentiation (TRD), Delayed Matching-to-Sample (DMTS), and Incremental Repeated Acquisition (IRA) from the OTB Age at Outcome: 6–7 yr	Child's age at testing, maternal education (<high school, High school, >high school), and SES. Modification by sex examined.	Betas for BLL at T3 CPR Observing response latency: 0.001s (−0.08, 0.08s) TRD Average latency: 0.14s (−0.001, 0.29s) DMTS Average observing response latency: 0.08s (−0.04, 0.20s)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Maternal T3: 3.9 (2.8) µg/dL Maternal at delivery: 4.3 (3.2) µg/dL Cord: 3.4 (2.6) µg/dL Child: 2.4 (2.6) µg/dL			IRA Effective response rate: −0.01s (−0.03, −0.002s)

AAS = atomic absorption spectrometry; BLL = blood lead level; BNT = Boston Naming Test; BRIEF = Behavior Rating Inventory of Executive Functions; CANTAB = Cambridge Neuropsychological Test Automated Battery; CI = confidence interval; CKD = chronic kidney disease; CKiD = Chronic Kidney Disease in Children Study; CVLT-C = California Verbal Learning Test-Children's version; ETS = environmental tobacco smoke; FSIQ = full-scale IQ; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; HOME = Health Outcomes and Measures of the Environment; ICP-MS = inductively coupled plasma mass spectrometry; K-ABC = Kaufman Assessment Battery for Children; MANAs = Metals, Arsenic and Nutrition in Adolescents Study; MeHg = methyl mercury; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OTB = Operant Test Battery; Pb = lead; SCWT = Stroop Color-Word test; SD = standard deviation; SDQ = Strengths and Difficulties Questionnaire; SES = socioeconomic status; SPM = Standard Progressive Matrices; T1 = first trimester of pregnancy; T2 = second trimester of pregnancy; T3 = third trimester of pregnancy; TSCD = Tohoku Study of Child Development; WISC = Weschler Intelligence Scale for Children; WRAML = Wide Range Assessment of Memory and Learning; WRAT = Wide Range Achievement Test; yr = year(s).
[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.
†Studies published since the 2013 Integrated Science Assessment for Lead.

Table 3-4T Animal toxicological studies of Pb exposure and cognitive function

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Cory-Slechta et al. (2012)	**Rat (Long-Evans)** Control (tap water), M, n = 12 50 ppm, M, n = 12	GD −60 to 10 mo	Oral, drinking water Oral, lactation In utero	PND 5–6: <5 µg/dL for Control 12.5 µg/dL for 50 ppm 2.5 mo: <5 µg/dL for Control 6.43 µg/dL for 50 ppm 10 mo: <5 µg/dL for Control 8.98 µg/dL for 50 ppm	2–3 mo to 10 mo: Operant Behavior

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Zou et al. (2015)	**Mouse (ICR)** Control (distilled water), M, n = 10 250 mg/L solution, M, n = 10	~5 wk to 8 wk	Oral, drinking water	8 wk: 1.8 µg/dL for Control 21.7 µg/dL for 250 mg/L	8 wk: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Cory-Slechta et al. (2013)	**Mouse (C57BL/6)** Control (distilled deionized water) – NS, M/F, n = 10–16 Control (distilled deionized water) – PS, M/F, n = 10–16 100 ppm (NS), M/F, n = 10–16 100 ppm (PS), M/F, n = 10–16	GD −60 to 12 mo	Oral, drinking water Oral, lactation In utero	PND 75 – Females: <LOD for Control (NS) <LOD for Control (PS) 8.42 µg/dL for 100 ppm (NS) 9.94 µg/dL for 100 ppm (PS) PND 75 – Males: <LOD for Control (NS) <LOD for Control (PS) 7.05 µg/dL for 100 ppm (NS) 7.16 µg/dL for 100 ppm (PS) 12 mo – Females: <LOD for Control (NS) <LOD for Control (PS) 9.38 µg/dL for 100 ppm (NS) 10.1 µg/dL for 100 ppm (PS) 12 mo – Males: <LOD for Control (NS) <LOD for Control (PS) 6.94 µg/dL for 100 ppm (NS) 8.03 µg/dL for 100 ppm (PS)	7–12 mo: Operant Behavior

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Weston et al. (2014)	**Rat (Long-Evans)** Control (tap water), M/F, n = 22 (11/11) 50 ppm, M/F, n = 22 (11/11)	GD −60 to PND 21	Oral, lactation In utero	PND 5–6 – Males: 0.76 µg/dL for Control 15.7 µg/dL for 50 ppm PND 5–6 – Females: 0.82 µg/dL for Control 14.7 µg/dL for 50 ppm	≥PND 60: Operant Behavior
Betharia and Maher (2012)	**Rat (Sprague Dawley)** PND 21–25: Control (RO DI water), M/F, n = 11–13 10 µg/mL, M/F, n = 11–13 PND 56–60: Control (RO DI water), M/F, n = 9–11 10 µg/mL, M/F, n = 9–11	GD 0 to PND 20	Oral, lactation In utero	PND 2: 1.77 ng/g (0.188 µg/dL) for Control 85.17 ng/g (9.02 µg/dL) for 10 µg/mL PND 25: 0.83 ng/g (0.088 µg/dL) for Control 9.21 ng/g (0.98 µg/dL) for 10 µg/mL PND 60: 0.23 ng/g (0.024 µg/dL) for Control 0.30 ng/g (0.032 µg/dL) for 10 µg/mL	PND 21–25, 56–60: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Han et al. (2014)	**Rat (Wistar)** Control (tap water), M, n = 8 2 mM – PW, M, n = 8 2 mM – ME, M, n = 8	PW group: PND 21 to PND 42 ME group: GD −21 to PND 20	Oral, drinking water Oral, lactation In utero	PND 21: 7.36 µg/L (0.74 µg/dL) for Control NR for 2 mM – PW 146.6 µg/L (14.7 µg/dL) for 2 mM – ME PND 63: 9.22 µg/L (0.92 µg/dL) for Control 147.9 µg/L (14.8 µg/dL) for 2 mM – PW 46.13 µg/L (4.6 µg/dL) for 2 mM – ME	PND 63 to PND 68: Morris water maze
Flores-Montoya et al. (2015)	**Mouse (C57BL/6)** Control (Sodium treated water), M/F, n = 10 (8/2) 30 ppm, M/F, n = 10 (5/5) 330 ppm, M/F, n = 13 (7/6)	GD 0 to PND 28	Oral, drinking water	PND 28 – Females: 0.02 µg/dL for Control 2.63 µg/dL for 30 ppm 12.92 µg/dL for 330 ppm PND 28 – Males: 0.31 µg/dL for Control 3.10 µg/dL for 30 ppm 15.21 µg/dL for 330 ppm	PND 28: Novel Odor Recognition
Rahman et al. (2012a)	**Rat (Wistar)** Control, M/F, n = 6 0.2% solution (0.002 g/mL), M/F, n = 10	PND 1 to PND 21	Oral, drinking water	PND 21: 1.35 µg/dL for Control 12.40 µg/dL for 0.2% solution	PND 21: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Rahman et al. (2012b)	**Rat (Wistar)** Control (tap water), M/F, n = 6 0.2% solution, M/F, n = 10	PND 1 to PND 30	Oral, drinking water Oral, lactation	PND 21: 1.4 µg/dL for Control 12.1 µg/dL for 0.2% solution PND 30: 1.2 µg/dL for Control 12.8 µg/dL for 0.2% solution	PND 21, 30: Morris water maze
Mansouri et al. (2012)	**Rat (Wistar)** Control (distilled water), M/F, n = 16 (8/8) 50 mg/L, M/F, n = 16 (8/8)	PND 70 to PND 100	Oral, drinking water	PND 100 – Males: 2.05 µg/dL for Control 8.8 µg/dL for 50 mg/L PND 100 – Females: 2.17 µg/dL for Control 6.8 µg/dL for 50 mg/L	PND 100: Morris water maze, Novel Object Recognition

Anderson et al. (2016)	**Rat (Long-Evans)** Control (untreated), M/F, n = 16 (8/8) 150 ppm, M/F, n = 16 (8/8) per duration 375 ppm, M/F, n = 16 (8/8) per duration 750 ppm, M/F, n = 16 (8/8) per duration	Perinatal exposure group: GD −10 to PND 21 Early postnatal exposure group: PND 0 to PND 21 Long-term postnatal exposure group: PND 0 to PND 55	Oral, diet Oral, lactation In utero	PND 65 – Perinatal exposure females: 0 µg/dL for Control 1.36 µg/dL for 150 ppm 2.13 µg/dL for 375 ppm 2.08 µg/dL for 750 ppm PND 65 – Early postnatal exposure females: 0 µg/dL for Control 2.11 µg/dL for 150 ppm 2.0 µg/dL for 375 ppm 3.09 µg/dL for 750 ppm PND 65 – Long-term exposure females: 0 µg/dL for Control 4.5 µg/dL for 150 ppm 5.75 µg/dL for 375 ppm 9.58 µg/dL for 750 ppm PND 65 – Perinatal exposure males: 0 µg/dL for Control 1.25 µg/dL for 150 ppm 2.42 µg/dL for 375 ppm 2.47 µg/dL for 750 ppm	PND 55, 56, 57, and 65: Trace Fear Conditioning

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				PND 65 – Early postnatal exposure males: 0 µg/dL for Control 1.64 µg/dL for 150 ppm 1.95 µg/dL for 375 ppm 2.83 µg/dL for 750 ppm PND 65 – Long-term exposure males: 0 µg/dL for Control 2.01 µg/dL for 150 ppm 8.0 µg/dL for 375 ppm 7.46 µg/dL for 750 ppm	
Meng et al. (2016)	**Rat (Sprague Dawley)** Control (deionized water), M/F, n = not specified 300 ppm Pb, M/F, n = not specified	PND 0 to PND 21	Oral, lactation	7.61 µg/L (0.76 µg/dL) for Control 84.3 µg/L (8.43 µg/dL) for 300 ppm	PND 35–40: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Li et al. (2016a)	**Mouse (Kunming)** Control (untreated), M/F, n = 10 0.1% solution (1000 ppm), M/F, n = 10 0.2% solution (2000 ppm), M/F, n = 10 0.5% solution (5000 ppm), M/F, n = 10	GD 1 to PND 21	Oral, drinking water	PND 21: 9.8 µg/L (0.98 µg/dL) for Control 42.5 µg/L (4.25 µg/dL) for 1,000 ppm 85.3 µg/L (8.53 µg/dL) for 2000 ppm 106.4 µg/L (10.64 µg/dL) for 5000 ppm	PND 21, 22, 23, 24, 25, 26: Morris water maze
Li et al. (2016c)	**Mouse (Kunming)** Control (distilled water), M/F, n = 10 0.1% solution (mass fraction), M/F. n = 10 0.2% solution (mass fraction), M/F, n = 10 0.5% solution (mass fraction), M/F, n = 10	GD 0 to PND 21	Oral, lactation In utero	PND 21: 10.62 µg/L (1.1 µg/dL) for Control 40.71 µg/L (4.1 µg/dL) for 0.1% solution 81.77 µg/L (8.2 µg/dL) for 0.2% solution 103.36 µg/L (10.3 µg/dL) for 0.5% solution	PND 21: Morris water maze
Meng et al. (2016)	**Rat (Sprague Dawley)** Control (deionized water), M/F, n = 7 300 ppm, M/F, n = 7	PND 1 to PND 21	Oral, lactation	PND 35: 5.6 µg/L (0.56 µg/dL) for Control 84.84 µg/L (8.48 µg/dL) for 300 ppm	NR: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Wang et al. (2013)	**Rat (Sprague Dawley)** Control (untreated), M/F, n = 6 0.2% solution (w/v), M/F, n = 6 – Gestational Exposure 0.2% solution (w/v), M/F, n = 6 – Lactational Exposure 0.2% solution (w/v), M/F, n = 6 – Ablactational Exposure	GD 0 to PND 1, PND 1 to PND 21, PND 21 to 42	Oral, drinking water Oral, lactation In utero	PND 72: 34.99 µg/L (3.5 µg/dL) for Control 35.78 µg/L (3.58 µg/dL) for 0.2 % solution Gestational 65.97 µg/L (6.60 µg/dL) for 0.2% solution Lactational 110.67 µg/L (11.07 µg/dL) for 0.2% solution Ablactational	PND 65 to PND 69: Morris water maze
Wang et al. (2016)	**Rat (Sprague Dawley)** Control (tap water), M, n = 7 100 ppm, M, n = 9	PND 24 to PND 56	Oral, drinking water	PND 56: 11 µg/L (1.1 µg/dL) for Control 133 µg/L (13.3 µg/dL) for 100 ppm	PND 60–66: Trace Fear Conditioning
Zhang et al. (2014)	**Mouse (Kunming)** Control (distilled water), M/F, n = 12 0.4% solution, M/F, n = 13	GD 0 to PND 21	Oral, lactation In utero	PND 36: 18.5 µg/L (1.9 µg/dL) for Control 136.7 µg/L (13.7 µg/dL) for 0.4% Solution	PND 29, 30: Passive Avoidance Test, PND 31–35: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Barkur and Bairy (2015b)	**Rat (Wistar)** Control (untreated), M, n = 6 0.2% solution – Gestational, M, n = 6 0.2% solution – Lactational, M, n = 6 0.2% solution – Gestation + Lactation, M, n = 6 0.2% solution – Pregestational, M, n = 6	GD −30 to PND 21	Oral, lactation In utero	PND 22: 0.18 µg/dL for Control 3.02 µg/dL for 0.2% solution – Pregestation 5.30 µg/dL for 0.2% solution – Gestational 26.65 µg/dL for 0.2% solution – Lactational 32.0 µg/dL for 0.2% solution – Gestation + Lactation	PND 30 to PND 36: Morris water maze, PND 26, 27, 28: Passive Avoidance Test
Barkur et al. (2011)	**Rat (Wistar)** Control (tap water), M, n = 9 0.2% solution (w/v), M, n = 9	GD 0 to PND 21	Oral, lactation In utero	PND 120: 0.24 µg/dL for control 0.47 µg/dL for 0.2% solution	PND 120: Passive Avoidance Test

Verma and Schneider (2017)	**Rat (Long-Evans)** Control, M/F, n = 32 (16/16) 150 ppm chow (PERI), M/F, n = 32 (16/16) 150 ppm chow (EPN), M/F, n = 32 (16/16)	PERI: GD −14 to PND 21 EPN: PND 0 to PND 21	Oral, lactation In utero	PND 14 – PERI Males: <LOD for Control 5.65 µg/dL for 150 ppm PND 14 – PERI Females: <LOD for Control 4.38 µg/dL for 150 ppm PND 14 – EPN Males: <LOD for Control 5.95 µg/dL for 150 ppm PND 14 – EPN Females: <LOD for Control 5.38 µg/dL for 150 ppm PND 65 – PERI Males: <LOD for Control <LOD for 150 ppm PND 65 – PERI Females: <LOD for Control <LOD for 150 ppm PND 65 – EPN Males: <LOD for Control <LOD for 150 ppm PND 65 – EPN Females:	PND 56, 57, 65: Trace Fear Conditioning

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				<LOD for Control <LOD for 150 ppm	

Verma and Schneider (2017)	**Rat (Sprague Dawley)** Control, M/F, n = 36 (18/18) 150 ppm Chow (PERI), M/F, n = 36 (18/18) 150 ppm Chow (EPN), M/F, n = 36 (18/18)	PERI: GD −14 to PND 21 EPN: PND 0 to PND 21	Oral, lactation In utero	PND 14 – PERI Males: <LOD for Control 5.425 µg/dL for 150 ppm PND 14 – PERI Females: <LOD for Control 4.521 µg/dL for 150 ppm PND 14 – EPN Males: <LOD for Control 5.45 µg/dL for 150 ppm PND 14 – EPN Females: <LOD for Control 5.06 µg/dL for 150 ppm PND 65 – PERI Males: <LOD for Control <LOD for 150 ppm PND 65 – PERI Females: <LOD for Control <LOD for 150 ppm PND 65 – EPN Males: <LOD for Control <LOD for 150 ppm PND 65 – EPN Females:	PND 56, 57, 65: Trace Fear Conditioning

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				<LOD for Control <LOD for 150 ppm	
Liu et al. (2013b)	**Rat (Sprague Dawley)** Control (tap water), M/F, n = 10 100 ppm, M/F, n = 9	PND 0 to PND 21	Oral, lactation	PND 22: 18.95 µg/L (1.9 µg/dL) for Control 121.44 µg/L (12.1 µg/dL) for 100 ppm	PND 42: Morris water maze

Anderson et al. (2012)	**Rat (Long-Evans)** Control (untreated chow), M/F, n = 28 (11/17) 250 ppm Chow, M/F, n = 15 (10/5) 750 ppm Chow, M/F, n = 25 (13/12) 1500 ppm Chow, M/F, n = 23 (12/11)	GD −10 to PND 21	Oral, lactation	PND 1 – Males: 0 µg/dL for Control 18.9 µg/dL for 250 ppm 52.5 µg/dL for 750 ppm 52.5 µg/dL for 1500 ppm PND 1 – Females: 0 µg/dL for Control 21.9 µg/dL for 250 ppm 47.2 µg/dL for 750 ppm 56.7 µg/dL for 1500 ppm PND 7 – Males: 0 µg/dL for Control 8.5 µg/dL for 250 ppm 29.1 µg/dL for 750 ppm 35.7 µg/dL for 1500 ppm PND 7 – Females: 0 µg/dL for Control 14.7 µg/dL for 250 ppm 26.9 µg/dL for 750 ppm 37.6 µg/dL for 1500 ppm PND 14 – Males: 0 µg/dL for Control	PND 55: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				10.5 µg/dL for 250 ppm	
				18.6 µg/dL for 750 ppm	
				24.8 µg/dL for 1500 ppm	
				PND 14 – Females:	
				0 µg/dL for Control	
				11.8 µg/dL for 250 ppm	
				20.2 µg/dL for 750 ppm	
				26.4 µg/dL for 1500 ppm	
				PND 21 – Males:	
				0 µg/dL for Control	
				18.6 µg/dL for 250 ppm	
				28.8 µg/dL for 750 ppm	
				28.7 µg/dL for 1500 ppm	
				PND 21 – Females:	
				0 µg/dL for Control	
				17.9 µg/dL for 250 ppm	
				27.4 µg/dL for 750 ppm	
				29.8 µg/dL for 1500 ppm	

Zhao et al. (2018)	**Rat (Sprague Dawley)** Control (tap water), M, n = 8 0.005% solution, M, n = 8 0.01% solution, M, n = 8 0.02% solution, M, n = 8	GD −14 to PND 10	Oral, lactation In utero	PND 0: 1.9 µg/dL for Control 17.9 µg/dL for 0.005% solution 23.2 µg/dL for 0.01% solution 48.8 µg/dL for 0.02% solution PND 3: 1.9 µg/dL for Control 6.7 µg/dL for 0.005% solution 11.5 µg/dL for 0.01% solution 23.1 µg/dL for 0.02% solution PND 7: 1.3 µg/dL for Control 8.1 µg/dL for 0.005% solution 12.3 µg/dL for 0.01 % solution 18.7 µg/dL for 0.02% solution PND 10: 1.2 µg/dL for Control 5.6 µg/dL for 0.005% solution 7.0 µg/dL for 0.01% solution 12.3 µg/dL for 0.02% solution PND 14: 0.7 µg/dL for Control	PND 30: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				4.0 µg/dL for 0.005% solution 5.5 µg/dL for 0.01% solution 8.9 µg/dL for 0.02% solution PND 21: 1.1 µg/dL for Control 2.5 µg/dL for 0.005% solution 2.5 µg/dL for 0.01% solution 2.98 µg/dL for 0.02% solution PND 30: 1.5 µg/dL for Control 1.0 µg/dL for 0.005% solution 1.5 µg/dL for 0.01% solution 1.5 µg/dL for 0.02% solution	
Neuwirth et al. (2019b)	**Rat (Long-Evans)** Control (tap water), M/F, n = 12 (6/6) 363.83 µM solution, M/F, n = 12 (6/6)	GD 0 to PND 22	Oral, lactation In utero	PND 22: NR for Control 5.3–15 µg/dL for 364 µM solution PND 56–90: ND for Control, ND for 364 µM	PND 56–90: Attention Set Shifting Test

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Neuwirth et al. (2019c)	**Rat (Long-Evans)** Control, M/F, n = 12 (6/6) 150 ppm Pb-chow (PERI), M/F, n = 12 (6/6) 150 ppm Pb-chow (EPN), M/F, n = 12 (6/6)	PERI: GD −14 to PND 22 EPN: PND 0 to PND 22	Oral, lactation In utero	PND 14 – Females: <LOD for Control 4.38 µg/dL for 150 ppm PERI 5.38 µg/dL for 150 ppm EPN PND 14 – Males: <LOD for Control 5.65 µg/dL for 150 ppm PERI 5.95 µg/dL for 150 ppm EPN	NR: Attention Set Shifting Test
Mansouri et al. (2013)	**Rat (Wistar)** Control (tap water or water + NaAc), M/F, n = 16 (8/8) 50 ppm, M/F, n = 16 (8/8)	PND 55 to PND 181	Oral, drinking water	PND 178–181 – Females: NR for Control 10.6 µg/dL for 50 ppm PND 178–181 – Males: NR for Control 18.9 µg/dL for 50 ppm	PND 163–167 or PND 169–173: Morris water maze
Wu et al. (2020b)	**Mouse (C57BL/6)** Control (distilled deionized water), M, n = 7–10 0.2% solution, M, n = 7–10	4 wk to 4 mo	Oral, drinking water	16 mo: 66.4 µg/L (6.6 µg/dL) for Control 278.9 µg/L (27.9 µg/dL) for 0.2% solution	16 mo: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Tartaglione et al. (2020)	**Rat (Wistar)** Control (tap water), M/F n = 16 (9/7) 50 mg/L, M/F, n = 16 (9/7)	GD −28 to PND 23	Oral, lactation In utero	PND 23: 0.007 µg/mL (0.7 µg/dL) for Control 0.255 µg/mL (25.5 µg/dL) for 50 mg/L	PND 35: Y Maze – Spontaneous Alternation, PND 63–65: Novel Object Recognition, PND 68–72: Morris water maze
Xiao et al. (2014)	**Rat (Wistar)** Control (tap water), M/F, n = 10 (5/5) Pre-weaning: 2 mM solution, M/F, n = 10 (5/5) Postweaning: 2 mM solution, M/F, n = 10 (5/5)	Pre-weaning: GD −21 to PND 21 Postweaning: PND 21 to PND 84	Oral, drinking water Oral, lactation In utero	PND 21 – Pre-weaning: 10.09 µg/L (1 µg/dL) for Control 103.8 µg/L (10.4 µg/dL) for 2 mM solution PND 21 – Postweaning: Not Reported PND 91 – Pre-weaning: 10.32 µg/L (1 µg/dL) for Control 39.27 µg/L (3.9 µg/dL) for 2 mM solution PND 91 – Postweaning: 10.32 µg/L (1 µg/dL) for Control 105.45 µg/L (10.5 µg/dL) for 2 mM solution	PND 85 to 90: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Sobolewski et al. (2020)	**Mouse (C57BL/6)** F0: Control (distilled DI water), F, n = 10 100 ppm, F, n = 10 F1: see Figure 1, n = 12 F2: see Figure 1, n = 12 F3: see Figure 1, n = 8–10	F1: GD −60 to PND 23–27	Oral, lactation In utero	F1 PND 6–7: 0 µg/dL for Control 12.5 µg/dL for 100 ppm (F0 dosing) F3 PND 6–7: 0 ng/dL for Control 0 µg/dL for 100 ppm (F0 dosing)	PND 60–120 (variable by endpoint): FI Training
Ouyang et al. (2019)	**Rat (Sprague Dawley)** Control (tap water), M/F, n = 6–10 0.05/0.01% solution, M/F, n = 6–10	GD 0 to PND 679	Oral, drinking water Oral, lactation In utero	wk 97: 0 mg/L (0 µg/dL) for Control 0.216 mg/L (21.6 µg/dL) for 0.05/0.01% solution	PND 674 to PND 679: Morris water maze
Singh et al. (2019)	**Rat (Wistar)** Control (distilled water), M, n = 5 2.5 mg/kg, M, n = 5	3 mo to 6 mo	Oral, gavage	6 mo: 5.76 µg/dL for Control 28.4 µg/dL for 2.5 mg/kg	6 mo: Morris water maze
Xiao et al. (2020)	**Rat (Sprague Dawley)** Control (tap water), F, n = 10 125 ppm, F, n = 10	GD −7 to PND 68	Oral, drinking water Oral, lactation In utero	PND 68: 24.23 ng/mL (2.4 µg/dL) for Control 205 ng/mL (20.5 µg/dL) for 125 ppm	PND 56 −61: Morris water maze, PND 55: Y Maze – Spontaneous Alternation

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Su et al. (2016)	**Rat (Sprague Dawley)** Control (deionized water with 0.9% saline), M, n = 15 200 ppm, M, n = 16	PND 20 to PND 76	Oral, gavage	PND 76: 7.99 µg/L (0.8 µg/dL) for Control 84.17 µg/L (8.4 µg/dL) for 200 ppm	PND 76: Morris water maze

An et al. (2014)	**Rat (Sprague Dawley)** Control (deionized water with NaAc), M, n = 12 100 ppm, M, n = 12 200 ppm, M, n = 12 300 ppm, M, n = 12	4 wk to 12 wk	Oral, drinking water	5 wk: 0.96 µg/dL for Control 7.07 µg/dL for 100 ppm 11.54 µg/dL for 200 ppm 14.76 µg/dL for 300 ppm 6 wk: 0.96 µg/dL for Control 8.13 µg/dL for 100 ppm 12.92 µg/dL for 200 ppm 16.65 µg/dL for 300 ppm 7 wk: 0.96 µg/dL for Control 9.68 µg/dL for 100 ppm 13.37 µg/dL for 200 ppm 19.48 µg/dL for 300 ppm 8 wk: 0.96 µg/dL for Control 9.64 µg/dL for 100 ppm 17.07 µg/dL for 200 ppm 22.02 µg/dL for 300 ppm 9 wk: 0.96 µg/dL for Control	12-wk: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				12.12 µg/dL for 100 ppm	
				20.7 µg/dL for 200 ppm	
				22.28 µg/dL for 300 ppm	
				10 wk:	
				0.96 µg/dL for Control	
				11.48 µg/dL for 100 ppm	
				17.75 µg/dL for 200 ppm	
				24.69 µg/dL for 300 ppm	
				11 wk:	
				0.96 µg/dL for Control	
				11.51 µg/dL for 100 ppm	
				17.52 µg/dL for 200 ppm	
				22.18 µg/dL for 300 ppm	
				12 wk:	
				0.96 µg/dL for Control	
				11.41 µg/dL for 100 ppm	
				17.23 µg/dL for 200 ppm	
				22.57 µg/dL for 300 ppm	

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Li et al. (2013)	**Rat (Wistar)** Control (tap water), M/F, n = 16 (8/8) 500 ppm, M/F, n = 16 (8/8)	4 wk to 16 wk	Oral, drinking water	4 mo: 29.99 µg/L (3 µg/dL) for Control 159.54 µg/L (16 µg/dL) for 500 ppm	4 mo: Morris water maze
Zhu et al. (2019b)	**Rat (Sprague Dawley)** Control (deionized water), M/F, n = 32 0.5 g/L solution, M/F, n = 32	GD 0 to 12 mo	Oral, drinking water Oral, lactation In utero	12 mo: <LOD for Control 29.1 µg/dL for 0.5 g/L solution	NR: Morris water maze
Zhou et al. (2020a)	**Rat (Sprague Dawley)** Control (distilled water), M, n = 18–27 0.5 g/L solution, M, n = 18–27 2.0 g/L solution, M, n = 18–27	GD 1 to PND 364	Oral, drinking water	PND 21: 0 mg/L (0 µg/dL) for Control 0.1 mg/L (10 µg/dL) for 0.5 g/L solution 0.36 mg/L (36 µg/dL) for 2.0 g/L solution PND 364: 0 mg/L (0 µg/dL) for Control 0.15 mg/L (15 µg/dL) for 0.5 g/L solution 0.51 mg/L (51 µg/dL) for 2.0 g/L solution	PND 21, 364: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Zhang et al. (2012)	**Rat (Sprague Dawley)** Control (deionized water), M, n = 10 100 ppm, M, n = 10 200 ppm, M, n = 10 300 ppm, M, n = 10	NR (40–60 g)	Oral, drinking water	+8 wk from start of exposure: 49.9 ng/mL (5 µg/dL) for Control 100.9 ng/mL (10.1 µg/dL) for 100 ppm 128.6 ng/mL (12.9 µg/dL) for 200 ppm 147.7 ng/mL (14.8 µg/dL) for 300 ppm	+8 wk from start of exposure: Morris water maze
Hong et al. (2021)	**Rat (Sprague Dawley)** Control (tap water), M/F, n = 50 1 g/L Pb solution, M/F, n = 50	GD 0 to PND 21	Oral, lactation In utero	0.009 mg/L for Control, 0.291 mg/L for 1 g/L Pb – PND 21	PND 21–27: Morris water maze
Bijoor et al. (2012)	**Rat (Wistar)** Control (deionized water), M/F, n = 10 50 ppm, M/F, n = 10	GD 0 to PND 45	Oral, drinking water Oral, lactation In utero	PND 45: 4.06 µg/dL for Control 10.65 µg/dL for 50 ppm	PND 45: Passive Avoidance Test
Wang et al. (2021a)	**Rat (Sprague Dawley)** Control (deionized water), M, n = 8 0.05% solution, M, n = 8 0.1% solution, M, n = 8	GD 0 to PND 21	Oral, lactation In utero	PND 21: 23.1 µg/L (2.31 µg/dL) for Control 248 µg/L (24.8 µg/dL) for 0.05% solution 302 µg/L (30.2 µg/dL) for 0.1% solution 361 µg/L (36.1 µg/dL) for 0.2% solution	PND 21: Morris water maze

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Liu et al. (2022c)	**Rat (Sprague Dawley)** Control (tap water), M, n = 10 0.2% solution, M, n = 10	PND 35 to PND 119	Oral, drinking water	PND 119: 10.9 µg/L (1.09 µg/dL) for Control 176 µg/L (17.6 µg/dL) for 0.2% solution	PND 119: Morris water maze
Wang et al. (2021b)	**Rat (Sprague Dawley)** Control (deionized water), M/F, n = 12 0.05% solution, M/F, n = 10	GD −28 to PND 21	Oral, lactation In utero	PND 21: 23.9 µg/L (2.39 µg/dL) for Control 206 µg/L (20.6 µg/dL) for 0.05% solution	PND 21: Morris water maze
Al-Qahtani et al. (2022)	**Mouse (Albino)** Control (distilled water), M, n = 10 0.2 mg/kg, M, n = 10	8–9 wk to 14–15 wk	Oral, gavage	14–15 wk: 1.2 µg/100 mL (1.2 µg/dL) for Control 7.1 µg/100 mL (7.1 µg/dL) for 0.2 mg/kg	NR: Active Avoidance Test
Long et al. (2022)	**Rat (Sprague Dawley)** Control (untreated), M, n = 12 200 mg/L solution, M, n = 12	6 wk to 18 wk	Oral, drinking water	18 wk: 2.14 µg/L (0.214 µg/dL) for Control 32.48 µg/L (3.25 µg/dL) for 200 mg/L solution	NR: Morris water maze, NR: Active Avoidance Test

BLL = blood lead level; CI = confidence interval; EPN = early postnatal; F = female; F1 = first filial generation; FI = fixed interval; GD = gestational day; LOD = limit of detection; M = male; ME = maternal exposure; mo = month(s); NaAc = sodium acetate; NR = not reported; NS = no stress; Pb = lead; PERI = perinatal; PND = postnatal day; PS = prenatal stress; PW = postweaning; RO DI = reverse osmosis deionized; SD = standard deviation; wk = week(s).

Table 3-5E Epidemiologic studies of Pb exposure, academic performance, and achievement

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIsa
Chandramouli et al. (2009) Avon U.K. Jul. – Dec. 1992 (birth) Followed 8 yr Cohort	10% random subsample of Avon Longitudinal Study of Parents and Children (ALSPAC) n = 488 School children	Blood Earlier childhood venous blood; AAS using micro sampling flame atomization Age at measurement: 30 mo Mean (SD): NR Group 1: 0–<2 µg/dL Group 2: 2–<5 µg/dL Group 3: 5–<10 µg/dL Group 4: >10 µg/dL	Academic achievement Standardized Achievement Test Age at outcome: 7 yr	Maternal education and smoking, home ownership, home facilities score, family adversity index, paternal SES, parenting attitudes at 6 mo, child sex. Also considered child IQ	Per doubling BLL[b] −0.3 (−0.5, −0.1)
Miranda et al. (2009) North Carolina U.S. 1995 through 1999 (screening) Cohort	School children, n= 57,568 Screened for Pb at age 9–36 mo in 100 NC counties	Blood Surveillance database Age at measurement: 9–36 mo	Academic achievement 4th grade EOG test score for reading (2001–2005)	Sex, age of blood Pb measurement, race, enrollment in free/reduced lunch program, parental education, charter school.	Score vs. blood Pb category 1 µg/dL 2 µg/dL: −0.30 (−0.58, −0.01) 3 µg/dL: −0.46 (−0.73, −0.19) 4 µg/dL: −0.52 (−0.79, −0.24) 5 µg/dL: −0.80 (−1.08, −0.51)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIsa
Min et al. (2009) Cleveland, OH 1994–1996 (birth) Followed to age 11 yr Cohort	Birth cohort, n = 267 86% African-American with high prevalence of prenatal drug and alcohol exposure	Blood Earlier childhood (age 4 yr) Mean (SD): 7.0 (4.1) Interval analyzed: 3.0 (10th percentile)−10	WJTA (math and reading scores) Age at outcome: 11 yr	Sex, caregiver education, family income, race/ethnicity, test language.	Math score: −2.5 (−4.6, −0.38) Reading score: −2.9 (−4.4, −1.4)
Lanphear et al. (2000) United States 1988–1994 Cross-sectional	U.S. NHANES n = 4,853 children ages 6–16 yr (born 1972–1988) Large U.S. representative study of multiple risk factors and outcomes	Blood Concurrent GM (SD): 1.9 (7.0) 63.5% <2.5 Detection limit = 0.5 Interval analyzed: 1–5	WRAT (arithmetic and reading scores) Age at outcome: 6–16 yr Linear regression	Child sex, race/ethnicity, poverty index ratio, reference adult education, serum ferritin and cotinine levels. Did not consider potential confounding by parental cognitive function or caregiving quality.	−0.05 (−0.09, −0.01)
Krieg et al. (2010) United States 1991–1994 Cross-sectional	U.S. NHANES n = 773 children ages 12–16 yr (born 1972–1982) Large U.S. representative study of multiple risk factors and outcomes	Blood Concurrent GM (SD): 1.9 (7.0) 63.5% <2.5 Detection limit = 0.5 Interval analyzed: 1–5	WRAT (arithmetic and reading scores) Age at outcome: 6–16 yr Log-linear regression	Child sex, caregiver education, family income, race/ethnicity, test language. Did not consider potential confounding by parental cognitive function or caregiving quality.	−0.34 (−0.59, −0.08)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIsa
Surkan et al. (2007) Boston, Massachusetts and Farmington, Maine United States Cross-sectional	n = 389 children 6–10 yr Recruitment from trial of amalgam fillings	Blood Concurrent Group 1: 1–2 Group 2: 3–4 Group 3: 5–10 Mean (SD): 2.2 (1.6)	WIAT (reading and math composites) Age at outcome: 6–10 yr	Caregiver IQ, child age, SES, race, birth weight. Also considered potential confounding by site, sex, birth order, caregiver education and marital status, parenting stress, and maternal utilization of prenatal and annual health care but not parental caregiving quality.	−0.69 (−4.4, 3.0) −6.7 (−12, −1.2)
Chiodo et al. (2007) Detroit, Michigan United States Cross-sectional	n = 495 children (born 1989–1991) age 7 yr	Blood Concurrent Mean (SD): 5.0 (3.0)	Test of Early Reading Ability−2 MAT (math and reading scores) Age 7 yr	Maternal psychopathology, IQ, prenatal smoking, prenatal marijuana, SES, HOME score, caretaker education and marital status, # children in home, child sex. Also considered child age, maternal age, custody, cocaine use, prenatal alcohol use.	−0.19 (−0.30, −0.08)[c]
Fergusson et al. (1997) Christchurch New Zealand 1977 (birth) Followed to age 18 Cohort	n = 881 children Christchurch Health and Development Study birth cohort	Tooth Pb (age 6–8 yr) Mean (SD): 6.2 (3.7) µg/g	Percent leaving school without school certificate Ages 16–18 yr	Maternal age, punitiveness, standard of living, breastfeeding duration, parental conflict, grade, residence on busy roads. Also considered potential confounding by sex, ethnicity, maternal education, family size, HOME, SES, ethnicity, parental change, birth order, single parent.	0–2 µg/g: 15.6 3–5 µg/g: 16.7 6–8 µg/g: 18.1 9–11 µg/g: 19.7 12+ µg/g: 24.1 p < 0.05

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIsa
Needleman et al. (1990) Chelsea and Somerville, MA United States 1975–1978 (enrollment) followed to age 18 yr Cohort	n = 132 children (1st/2nd grade) in Massachusetts schools	Tooth Pb (1st/2nd grade) distribution <10 ppm: 50% 10–19.9 ppm: 22.7% >20 ppm: 27.3%	Failure to graduate high school Highest grade achieved Logistic regression	Maternal age at birth, education, and IQ, family size, SES, sex, age at testing, birth order, alcohol use, mother and child left hospital together. Did not examine potential confounding by parental caregiving quality.	Failure to graduate: 7.4 (1.4, 41) d OR >20 ppm vs. <10 ppm Highest grade achieved: −0.03 (−0.05, −0.01) per natural log increase in tooth Pb

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIsa
†Zhang et al. (2013) Detroit, Michigan United States 1990–2008 (born) Followed through grade 3–8 (2008–2010) Cohort	Students in public schools in Detroit n: 21281 (8831- 3rd grade, 7708- 5th grade, 4742- 8th grade) At least 1 of the 3 tests (math, science and reading) taken and BLL before 6 yr of age	Blood Venous blood collected for surveillance by Detroit Department of Health and Wellness Promotion Age at measurement: Before 6 yr of age (mean age: 3.1) Max: Highest BLL before age 6 yr: 7.12 µg/dL	Academic achievement (math, science and reading) in grade 3, 5, and 8 Educational attainment in math, science and reading on MEAP. Age at outcome: 3, 5, and 8 grades	Grade level, gender, race, language, maternal education, SES (i.e., school lunch status).	**ORs of Scoring "Less Than Proficient" on MEAP Tests *(Ref = ≤1 µg/dL)*** ***1−5 µg/dL*** Mathematics: 1.42 (1.24, 1.63) Science: 1.33 (1.10, 1.62) Reading: 1.45 (1.27, 1.67) ***6−10 µg/dL*** Mathematics: 2.00 (1.74, 2.30) Science: 2.22 (1.82, 2.72) Reading: 2.21 (1.92, 2.55) ***>10 µg/dL*** Mathematics: 2.40 (2.07, 2.77) Science: 2.26 (1.84, 2.78) Reading: 2.69 (2.31, 3.12)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIsa
†Evens et al. (2015) Chicago metropolitan area, 6 counties U.S. 1994–1998 (born) Followed 9–10 yr, 2003–2006 Cohort	Chicago public school children n: 46796	Blood BLLs obtained from Chicago Blood Pb Surveillance program; ICP-MS or AAS. Age at measurement: ≤72 mo (mean age: 45 mo) Mean: 4.81 µg/dL	Academic achievement 3rd grade ISAT scores in Reading and Math; 4 score categories, i.e., failure, below standard, meets standard and exceeds standard. Age at outcome: 9–10 yr	Sex, mother's education, low-income, very low birth weight/preterm, child's age at time of BLL, ISAT vs. Iowa, race (Interaction with race ethnicity explored).	**RR** ***Reading Failure*** ***1 µg/dL increase*** All Children: 1.06 (1.05, 1.07) NH White: 1.14 (1.08, 1.20) NH Black: 1.05 (1.04, 1.06) Hispanic: 1.08 (1.05, 1.11) ***Math Failure*** ***1 µg/dL increase*** All Children: 1.06 (1.05, 1.07) NH White: 1.11 (1.05, 1.18) NH Black: 1.05 (1.04, 1.06) Hispanic: 1.09 (1.06, 1.12)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIsa
†Blackowicz et al. (2016) Chicago U.S. 1994–1998 (birth) Followed through 2003–2006 (3rd grade) Cohort	School children n: 12319 Chicago Public Schools.	Blood Chicago Blood Pb Registry provided data on BLL measured between birth and 2006 Age at measurement: between birth and 2006 (most recent was used in analysis) 4.16 µg/dL	School performance 3rd grade performance based on ISAT scores Age at outcome: 3rd grade	Child sex, maternal education, low-income, preterm birth, small for gestational age, child's age at time of BLL, ISAT vs. Iowa, and Hispanic subgroup (Mexican-American vs. other Hispanic and Puerto Rican vs. Other Hispanic);	Beta Reading scores: −0.11 (−0.134, −0.086) Math scores: −0.096 (−0.12, −0.072) RR Reading failure: 1.07 (1.05, 1.10) Math failure: 1.09 (1.06, 1.12)
†Shadbegian et al. (2019) North Carolina Statewide U.S. 1990–2004 (birth) Followed 6 yr (3–8 grade) Cohort	NC Pb Poisoning Prevention Program Cohort n: 560,624 (54% of the Pb surveillance registry) Living in NC between 2000–2012 with BLL ≤10 µg/dL at 0–5 yr	Blood Child blood (BLL ≤10, BLL ≤5, and a matched group via CEM with BLL ≤5 µg/dL) Age at measurement: 0–5 yr Full sample (BLL ≤10 µg/dL) mean: 3.66, Full sample (BLL ≤5 µg/dL) mean: 2.89, CEM Matched sample (BLL ≤5 µg/dL) mean: 2.40	Academic achievement Percentile scores on standardized EOG tests for math and reading Age at outcome: Grade 3 and Grade 8	Child's sex, race/ethnicity, SES, Medicaid enrollment, birth month, and age upon entry to grade 3, mother's age, marital status, parental alcohol and tobacco use, highest educational achievement at the time of the child's birth, vector representing school, grade and year combination CEM to balance distributions between groups 2- and 3-way interactions for BLL*grade, covariates*grade, BLL*grade*covariates.	**Beta** Decrease in Test-Score Percentile in Children with 5-6 µg/dL vs. BLL ≤ 1 µg/dL Math: 0.95 (0.66, 1.24) Reading: 1.41 (1.12, 1.70)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIsa
†Skerfving et al. (2015) Landskrona and Trelleborg Sweden 1978–2007 (enrollment during primary school) Followed through age 16 Cohort	Primary school children n: 3176	Blood Child venous blood; flame or electrothermal atomization AAS Age at measurement: 7–12 yr 34 µg/L; Median: 30 75th: 44 90th: 60 Max: 162	School performance (see also Section 3.6.1 [adult cognitive function]) School performance after nine-year compulsory schooling. 4–5 categories from not passing to passing with merit (based on ranking) Age at outcome: 16 yr	Child and parent country of birth, parental education, total family income, father's IQ.	**Beta** *Merits* Children (BLL ≤ 5 µg/dL): −10.9 (−15.486, −6.314) All Children: −6.36 (−9.986, −2.734) *Grades* Children (BLL ≤ 5 µg/dL): −0.112 (−0.177, −0.047) All Children: −0.155 (−0.21, −0.1) Note: CIs estimated from p-values.

AAS = atomic absorption spectrometry; BLL = blood lead level; CEM = coarsened exact matching; CI = confidence interval; EOG = end of grade; GM = geometric mean; HOME = Health Outcomes and Measures of the Environment; ICP-MS = inductively coupled plasma mass spectrometry; ISAT = Illinois Standard Achievement Test; IQ = intelligence quotient; MAT = Metropolitan Achievement Test; MEAP = Michigan Educational Assessment Program; MI = Michigan; NHANES = National Health and Nutrition Examination Survey; NR = not reported; Pb = lead; SD = standard deviation; SES = socioeconomic status; WIAT = Wechsler Individual Achievement Test; WJTA = Woodcock-Johnson Test of Achievement; WRAT = Wide Range Achievement Test; yr = year(s).

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

[b]Results are not standardized (e.g., BLL distribution data needed to calculate the standardized estimate was not reported or categorical data was analyzed).

[c]The CI was calculated from a p-value and the true CI may be wider or narrower than calculated.

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

Table 3-6E Epidemiologic studies of Pb exposure and cognitive effects: population or group mean blood Pb levels >5 µg/dL

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Al-Saleh et al. (2020) Saudi Arabia 2011–2013 (enrollment) Followed through 2011–2013 and 2017–2018 Cohort	Lactating mother-infant pairs n: 82 (36 males and 46 female children).	Blood, Hair, Urine, Breast Milk Maternal blood, spot urine, breast milk, and hair, child spot urine and hair; AAS with electrothermal atomizer Age at measurement: Maternal measurements made during lactation Infants at 3–12 mo (lactation) and children at 5–8 yr old Lactation: GM: maternal urine :5.881 µg/L, hair :1.717 µg/g, blood GM: 2.346 µg/dL, breastmilk: 46.483 µg/L; Infant urine: 4.946 µg/L, hair: 2.894 µg/g; Early childhood: GM: urine: 2.563 µg/L, hair: 0.850 µg/g max: urine: 20.826 µg/L, hair: 4.470 µg/g	Neurodevelopmental performance and visual-motor integration (Test of Nonverbal Intelligence 2nd edition and Beery VMI 3rd edition, respectively.) Age at outcome: 5–8 yr old	Child's age and sex, maternal age, BMI, parity, lifestyle, educational level, SES, residential characteristics, urinary cotinine levels (an index of exposure to secondhand smoke).	**Beta (95% CI)[a]** BVMI: 0.012 (−1.989, 2.014) TONI: −0.044 (−1.809, 1.721)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Barg et al. (2018) Montevideo Uruguay Study years NR Cross-sectional	n: 206 Children living in areas considered high risk for metal exposure.	Blood Child venous blood; flame AAS or GFAAS Age at measurement: 5–8 yr 4.2 µg/dL	Executive function BRIEF (teacher rating) Age at outcome: 5–8 yr	Child IQ, iron status, and BMI, blood Pb testing method, household possessions, maternal education, current parent smoking.	**PR (95% CI)[b]** *BRIEF- Global Executive Composite* Children with BLL ≥5 vs. <5 µg/dL: 1.02 (0.96, 1.09) Boys: 1.00 (0.98, 1.01) Girls: 1.01 (0.99, 1.04)
Cai et al. (2021) Guangxi China Study years NR Cross-sectional	School children n: 255 Participants living near a Pb and zinc mine (~500 m distance between school and mine).	Blood Child venous blood (Pb intoxication and non-Pb intoxication groups); GFAAS Age at measurement: 7–12 yr Median Pb level: Rice samples: 0.10 mg/kg, Blood: 84.8 µg/L 75th: Blood: 115.4 µg/L Max: Rice: 0.53 mg/kg	Perception and reasoning Raven's SPM Age at outcome: 7–12 yr	Age, gender, physical condition, lifestyle habits, educational attainment and smoking habit of parents, family environment and economy.	**Beta (95% CI)[b]** IQ, RSPM: -0.58 (−1.031, -0.129)
Jeong et al. (2015) Multi-center South Korea Cross-sectional May 2006-Dec 2010	MOCEH study n: 194 Birth cohort- mother-infant pairs followed through 60 mo of age. Cross-sectional analysis conducted.	Blood Child venous blood; GFAAS Age at measurement: 60 mo GM: 13.01 µg/L Max: 35.05 µg/L	FSIQ, VIQ, PIQ (Korean WPPSI-R) Age at outcome: 60 mo	Sex, parental education, family income, breastfeeding status, CRP level, mother's BLL during pregnancy Note: Mediation analysis to examine the relationship of BLL, iron deficiency and IQ.	Beta (95% CI)[b] Verbal IQ and ln-BLL (µg/L): −9.587 (−16.829, −2.344)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Kao et al. (2021) Taipei Taiwan 2011−2014 Cross-Sectional	recruited from Taipei MacKay Memorial Hospital n:139 children less than 3 yr of age	Hair, fingernails Child hair, fingernails; ICP-MS Age at Measurement: Mean (SD) 2.8 (0.4) years (children under 3 yr) Mean (SD): hair 2.9 (4.8) µg/g, nails 0.8 (5.1) µg/g	BSID-III cognitive and language development scores Age at outcome: 2.8 ± 0.4 yr	General linear models adjusted for sex, gestational age at birth, age of the house (years), leafy-vegetable intake (servings/week), and the area of surface roads within 100 m of the residence	Regression results were not reported because they were not statistically significant.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Kordas et al. (2011) Mexico City, Mexico Jan 1994-June 1995 Followed for 48 mo Cohort	Birth cohort n: 24 mo = 220, 48 mo = 186 Mother-infant pairs from 3 hospitals serving low- and middle-income women	Blood Maternal, cord blood, and child blood; GFAAS Age at measurement: Delivery (maternal, cord), 24 and 48 mo (child) Mean: Maternal BLL at delivery: 8.6 µg/dL, Cord blood: 6.6, BLL at 24 mo: 8.1, BLL at 48 mo: 8.1	Neurodevelopment using BSID-II (MDI), MSCA (general cognitive index and memory scale). Age at outcome: 24 (BSID) and 48 mo (MSCA) OLS linear regression	Birth weight, gestational age, child sex; maternal age, years of schooling, IQ, smoking status, marital status crowding in the house, type of floor in the house. (Stratified analysis by child development 48 mo and gene polymorphism also conducted.)	**Beta (95% CI)[b]** ***McCarthy Scales of Children's Abilities, 48 mo*** ***GCI*** Concurrent BLL: −0.6 (−0.992, −0.208) Cord BLL: −0.2 (−0.788, 0.388) ***Memory Score*** Concurrent BLL: −0.3 (−0.496, −0.104) Cord BLL: 0.1 (−0.096, 0.296) ***Bayley Scales of Infant Development II, 24 mo*** ***MDI*** Concurrent BLL: −0.1 (−0.492, 0.292) Cord BLL: −0.7 (−1.288, −0.112)
Kuang et al. (2020) Nanjing China 2012 Cross-sectional	Public primary school children n: 742 Excluded students with congenital mental retardation (third-degree relatives included) and diseases.	Blood Child venous blood; ICP-MS Age at measurement: 7–11 yr Mean: 30.4 µg/L; Median: 26.1 µg/L	School performance Standardized scores on Chinese, Math and English added for total scores. Age at outcome: 7–11 yr	Age and sex (tests administered on the same day).	**Beta (no p-value, Cis, or SE reported)[b]** Total: −0.168 Chinese: −0.042 Math: −0.039 English: −0.087

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Lee et al. (2017) Korea Enrolled 2006−2015, followed to age 5 (2015) Cohort	Mothers' and Children's Environmental Health (MOCEH) n: 251	Maternal Blood GFAAS with Zeeman background correction Age at Measurement: At birth (cord blood) GM 0.957 µg/dL Max: 3.17 µg/dL	Cognitive Development The mental developmental index (MDI) of the Korean BSID-II (K-BSID-II) was administered to infants who were 6, 12, 24, and 36 mo-old. The Korean language version of the Wechsler Preschool and Primary Scale of Intelligence - Revised (K-WPPSI-R) was administered to children at 60 mo.	Partial correlation analysis adjusted for maternal education, sex of child, and family income.	Strongest correlations between scores measured at closest time. Scores more stable in those at extreme ends of cognitive development.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Liu et al. (2013a) Jiangsu province China 2004–2005 (enrollment) followed 5 yr Cohort	China Jintan Child Cohort Study n: 1341 children (603 girls and 738 boys) Community based cohort of preschool children.	Blood Early child blood; GFAAS. Age at measurement: 3, 4 or 5 yr mean: 6.43 µg/dL	FSIQ, VIQ, PIQ (Chinese version of WPPSI-R). See also Table 3-5 (School performance was assessed by standardized tests on 3 major subjects: Chinese, English and Math.) Age at outcome: 6 yr (IQ), 8–10 yr (school performance)	Child age at blood Pb test, child gender, residence as defined as school location, blood iron level, parent education, parent occupation, and father's smoking.	Beta for log-transformed BLL (95% CI)[b] (ref: <8 µg/dL) FSIQ 8−10 µg/dL: −1.28 (−4.01, 1.46) ≥10 µg/dL: −1.45 (−3.50, 0.67) Chinese score 8−10 µg/dL: −3.20 (−5.78, −0.63) ≥10 µg/dL: −4.02 (−7.11, −0.93) Math score 8−10 µg/dL: −5.25 (−8.14, −2.36) ≥10 µg/dL: −5.27 (−8.73, −1.81) English score 8−10 µg/dL: −4.33 (−7.32, −1.34) ≥10 µg/dL: −5.18 (−8.76, −1.59)
Liu et al. (2018b) Mexico City, Mexico Followed for 24 mo Cohort	PROGRESS study n: 665 Mother-infant pairs.	Blood Maternal blood; joint exposure to Mn, Pb, Co, Cr, Cs, Cu, As, Cd, and Sb Age at measurement: Prenatal exposure (2nd trimester) NR	Cognitive development using BSID-III. BSID scores were centered and scaled and presented as z-scores normalized to expected mean of 100 and SD of 15. Age at outcome: 6, 12, 18, and 24 mo	SES, mother's hemoglobin during the second trimester of pregnancy, mother's educational level, child gender, mother's WASI IQ, and Fenton's birth weight z-scores.	NR

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Marques et al. (2014) State of Rondonia, Western Amazon Brazil Cohort 2007–2012	Population-based cohort n: 96 (TOKS = 51 and Itapua = 45) Low SES populations living in rural and urban areas including children living in the vicinity of TOKS (i.e., multiple metal exposure).	Breastmilk Breastmilk; GFAAS Age at measurement: 6 mo of breastfeeding (from Marques 2013c) TOKS: 10.04 µg/L (mean), 8.2 µg/L (median); 29.4 µg/L (max) Itapua: 3.89 µg/L (mean), 2.5 µg/L (median), 16.2 µg/L (max)	Neurodevelopment (milestones including age of walking and talking, Bayley MDI and PDI); milestones assessed based on mothers' recollection at the time of visit. Age at outcome: 6 and 24 mo (Bayley MDI, PDI)	Birth weight, income, maternal education, breastfeeding status.	Beta (95% CI)[b] MDI 6 M −0.293 (−0.50, 0.08) MDI 24 M −0.234 (−0.60, 0.13) PDI 6 M −0.062 (−0.28, 0.16) PDI 24 M −0.129 (−0.34, 0.08) Age of walking −0.219 (−0.43, 0.002) Age of talking −0.066 (−0.28, −0.16)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Magzamen et al. (2015) Wisconsin (Milwaukee or Racine) United States Enrollment: born during 1996−2000 (Follow-up of blood lead level: before child's third birthday; Follow-up for WKCE scores: 4th grade) Cohort	Wisconsin Children's Lead Levels and Educational Outcomes Project (CLLEO) n: 1076	Blood Blood lead records used to categorize children as not exposed (<5 µg/dL) or exposed (>10 µg/dL and <20 µg/dL) Age at Measurement: 18-36 mo 43% of sample defined as exposed	Academic achievement: Wisconsin Knowledge and Concepts Exam (WKCE) math and reading scores WKCE reading and math scores obtained from the Wisconsin Department of Public Instruction with parental consent.	Child gender, race, parental < HS education, free lunch program, English language learner, and child health rating by parents (excellent vs. other); interactions with Pb tested for each covariate	**Beta for entire distribution of math scores[b]** OLS = −8.94 (−14.84, −3.05) **Beta for math scores in quantiles[b]** 10th percentile = −17.00 (−32.13, −3.27) 50th percentile = −8.00 (−15.24, −0.36) 90th percentile = −4.50 (−10.55, 4.50) **Beta for entire distribution of reading scores[b]** OLS = −13.66 (−19.94, -7.37) **Beta for reading scores in quantiles[b]** 10th percentile = −18.00 (−48.72, −3.32) 50th percentile = −14.50 (−20.72, −5.61) 90th percentile = −7.50 (−15.58, 2.07)

Rawat et al. (2022) India Not reported Cross-Sectional	n: 43	Blood Blood Pb was measured via LeadCare II testing analyser Age at Measurement: 4−12 yr GM (SD) 19.93 (9.22) ug/dL Max: 37.4 µg/dL	IQ level, performance on Draw-A-Person Test The Draw-A-Person test and the IQ test were administered in the study setting Age at Outcome: 4−12 yr	There were no adjustments for confounders, as simple statistics were employed.	IQ - Mean (SD) score[b] Group A (<10 µg/dL Pb, n = 9): 122.33 (4.03) Group B (>10 µg/dL Pb, n = 34): 96.03 (12.76) p-value for difference = 0.006 % change in results from Draw-A-Person test for Group B compared to Group A: Line characteristic: Thick and sharp = 41%; Soft = −32% Detailing: With = 32%; Without = −9% Shading: With = −21%; Without = 24% Distortion: With = 50%; Without = −17% Colours: Warm = 41%; Cool = −27% Group A (<10 µg/dL, n = 9) vs. Group B (>10 µg/dL, n = 34) drawings had the following characteristics: Thick and sharp lines = 33% vs. 47%; Soft lines = 78% vs. 53%%

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
					With detailing = 22% vs. 29%%; Without detailing = 78% vs. 71%% With shading = 33% vs. 26%; Without shading = 67% vs. 82% With distortion = 33% vs. 50%; Without distortion = 89% vs. 74% Warm colors = 67% vs. 94%; Cool colors = 89% vs. 65%
Rodrigues et al. (2016) Sirajdikhan and Pabna districts Bangladesh 2008–2011 (enrollment) Cross-sectional	Birth cohort in Bangladesh n: 525 (Sirajdikhan: 239; Pabna: 286) Pregnant women (gestational age <16 wk).	Blood Child concurrent whole blood tested using the Pb Care II Water samples from tube well tested for As and Mn during first trimester of pregnancy and follow-up visits at age of 1 mo, 12 mo and 20–40 mo. Age at measurement: 20–40 mo Median: Sirajdikhan: 7.6 µg/dL; Pabna: <LOD 75th: Sirajdikhan: 10.4 µg/dL; Pabna: 3.8 µg/dL Max: Sirajdikhan: 43.0 µg/dL; Pabna: 13.8 µg/dL	Cognitive development using the culturally adapted BSID-III. Age-adjusted Z-scores Age at outcome: 20–40 mo of age	Maternal age and education, child's sex, ETS, HOME score, maternal Raven score, child hematocrit levels, As, Mn.	**Beta (95% CI)** *Cognitive development* Pabna region[a]: 0.02 (SE: 0.12) per ln-transformed BLL* Sirajdikhan region[b]: −0.02 (−0.04, 0.00) *Unable to standardize because P25 and median BLL were <LOD

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Roy et al. (2011) Chennai, India (4 representative industrial and traffic zones) 2005–2006 Cross-sectional	School Children (3–7 yr) n: 725 3 schools from each of the 4 zones randomly selected (12 schools total); children lower and upper kindergarten and first grades.	Blood Postnatal venous blood; PbCare Analyzer Age at measurement: 3–7 yr of age Overall mean: 11.5 µg/dL; mean by genotypes: Taq A1/A1: 11.66 µg/dL; Taq A1/A2+A2/A2: 11.42 µg/dL Max: Overall: 40.5 µg/dL	IQ using BKT (mental age divided by chronological age and multiplied by 100) Tamil-translated Binet-Kamat Scales of Intelligence Age at outcome: 3–7 yr of age	Age + age 2, sex, midarm circumference, average monthly family income, and family size, parental education. Note: stratified analysis by genotypes (3 categories) conducted.	Beta (95% CI)[b] IQ (BKT, Tamil-translated): −4.22 (−7.10, −1.36)
†Rygiel et al. (2021) Mexico City Mexico 1997–2005 Cohort	ELEMENT project n: 85 Mother-child pairs recruited at the Mexican Social Security Institute	Blood Maternal and child venous blood; ICP-MS, GFAAS Age at measurement: T1, T2, T3 (maternal); 12, 24 mo (child) Maternal blood GM (SD): T1: 5.27 (1.93) µg/dL T2: 4.74 (1.96) µg/dL T3: 4.98 (1.93) µg/dL Infant blood GM (SD): 12 mo: 3.92 (1.80) µg/dL 24 mo: 3.49 (1.93) µg/dL	MDI assessed using BSID-II (Spanish version) Age at outcome: 12–24 mo	Maternal IQ (WAIS), maternal age, infant weight, length, SES, infant age and sex, current infant BLL.	Beta (95% CI) for 12-month MDI[b] T1: 0.31 (0.00, 0.62) T2: 0.11 (−0.63, 0.86) T3: 0.41 (−0.34, 1.17) Beta (95% CI) for 24-month MDI[b] T1: -0.16 (−0.99, 0.66) T2: -0.23 (−1.05, 0.59) T3: 0.28 (−0.50, 1.06)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Sánchez et al. (2011) Mexico City Mexico 1997–1999 (enrollment) Followed through 24 mo Cohort	ELEMENT study n: 169 Mother-child pairs recruited during pregnancy or before conception.	Blood Maternal blood; ICP-MS Age at measurement: each trimester of pregnancy Mean (SD): 1st trimester (n = 139): 13.7 (3.4) µg/dL 2nd trimester (n = 159): 24.5 (2.8) µg/dL 3rd trimester (n = 147): 35.2 (1.9) µg/dL Max: 1st trimester: 20.4 µg/dL 2nd trimester: 33.7 µg/dL 3rd trimester: 39.0 µg/dL.	MDI assessed using BSID-II (Spanish version) Scores standardized for mother's age, mother's IQ, duration of breastfeeding, sex, and weight and height z-score at 24 mo Age at outcome: 24 mo	Maternal age, IQ, duration of breastfeeding, sex, weight, and height Z-score at 24 mo.	Beta (95% CI)[b] T1: -5.42 (−10.2, -0.64) T2: 0.88 (−5.34, 7.09) T3: 1.22 (−3.65, 6.08)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Saxena et al. (2022) Araihazar Bangladesh 2012 - 2016 Cross-Sectional	Metals, Arsenic, & Nutrition in Adolescents study (MANAs) n: 572	Blood Whole blood Pb quantified using ICP-MS. Age at Measurement: Mean (SD) = 14.6 (0.7) years Mean = 98.7 µg/L; Median = 91.29 µg/L	Cognitive Effects The Cambridge Neuropsychological Test Automated Battery (CANTAB) was administered to the adolescents to assess aspects of executive function.	Linear regression models adjusted for BMI, head circumference, child's years of education, maternal intelligence (WASI), paternal years of education, wall type, sex, and other blood metals - arsenic, cadmium, manganese, and selenium.	**Beta (95% CI)[c]** Delayed Match to sample: -3.67 (−6.59, -0.75) Planning: -0.05 (−0.42, 0.32) Rapid visual processing: -0.01 (−0.03, 0.01) Reaction time: 0.03 (−0.01, 0.07) Spatial recognition memory: 1.9 (−0.88, 4.68) Spatial span: -0.16 (−0.43, 0.11) Spatial working memory: 1.09 (−2.54, 4.72)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Soetrisno and Delgado-Saborit (2020) West Java (Depok, Bogor and Bekasi) Sukatani village (control) Indonesia Cross-sectional	School children living in urban locations near e-waste facility; control site n: 44 (22 from Bogor and 22 from Sukatani) Children selected from schools per teachers/ principal recommendation.	Hair, soil, water Hair samples from children in Bogor and Sukatani village. BLLs from 36 children in Bogor area (2010). Age at measurement: 6–9 yr Soil Pb mean: Depok-Bekasi: 3653 mg/kg; Sukatani: 93.2 mg/kg; Water Pb: all 10 samples below LOD; Hair Pb: Depok-Bekasi: 0.155 mg/g; Sukatani: 0.0729 mg/kg Max: Soil Pb: Depok-Bekasi: 7662 mg/kg; Sukatani: 115 mg/kg; Hair Pb: Depok-Bekasi: 0.841 mg/g; Sukatani: 0.255 mg/kg	Academic achievement (see also Section 3.5.1.4, executive function) Performance on reading, math, writing expression and oral language, arts, science, social sciences, and sports collected from the school official alumni report. TMT B. Age at outcome: 6–9 yr	Age, parental education, environmental tobacco smoke at home, and residential traffic exposure.	**Beta (95% CI)[d]** Change in TMT-B (seconds) per mg/g unit of hair Pb: 54 (−3.8, 114)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Sun et al. (2015) Jiangsu Province China Nov 2011 Cross-sectional	Chinese National Health Research Program n: 446 Participants recruited from three primary schools located in the three towns.	Blood, Urine Child venous blood samples; ICP-MS method. Morning urine samples collected was tested for heavy metals. Age at measurement: 9–13 yr GM BLL: 33.13 µg/L; Arithmetic mean BLL: 36.99 µg/L 75th: 43.39 µg/L 90th: 56.85 µg/L Max: 101 µg/L	IQ (CRT). Primary score was converted to standard IQ scores. Age at outcome: 9–13 yr	Father's education, mother's education, BMI, annual family income, gender, age.	Beta (95% CI)[b] −6.61 (−13.15, −0.07)
Tassiopoulos et al. (2017) 22 PHACS clinical research sites in the United States, including Puerto Rico USA Enrollment began in 2007; BLL data available from 1998−2014, developmental data available from 1996−2010, developmental data available from 1996−2010 Cohort	Surveillance Monitoring of ART Toxicities (SMARTT) n: 546 children with a Bayley-III at one year of age who had a BPb between 9 mo of age and up to 3 mo after the Bayley-III; 634 children with a Bayley Screen at 3 yr of age and a BPb between 9 mo of age and up to 3 mo after the Bayley Screen	Blood Blood lead obtained between the ages of 1 and 3 yr as part of standard of care or local guidelines are abstracted from the medical chart when available Age at Measurement: 1 yr (n = 546) and 3 yr (n = 634)	Cognitive Effects Cognition and language neurodevelopment using BSID-III. Age at outcome: 1 yr At 3 yr of age, developmental function was assessed with the Bayley Screening Test (Bayley Screen),19 which includes a subset of items from the Bayley-III with the domains of cognition, receptive communication, expressive communication, and fine and gross motor development.	Sex; race; ethnicity; maternal IQ (evaluated with the Wechsler Abbreviated Scale of Intelligence); maternal education, primary language, living arrangement, and living situation; household income; geographic region; prenatal tobacco exposure; postnatal tobacco exposure within the home; age at the developmental evaluation; and help from others caring for the child.	OR (95% CI)[b] (for BLLs >=5 vs. <5 µg/dL) Cognitive delay 1.64 (0.95, 2.90) Receptive communication 0.83 (0.47, 1.43) Expressive communication 0.91 (0.52, 1.58)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Tung et al. (2022) Providence, Rhode Island United States Mother-newborn assessed for exposure and outcome within 2 hrs of delivery and 24 hrs of delivery, respectively. Cross-Sectional	Rhode Island Health Study (RICHS) n: 192	Placental Blood Pb Placental Pb concentrations quantified using ICP-MS. Age at Measurement: 24 hrs Mean = 4.49 ng/g among those with detectable Pb	BSID Newborns' neurologic integrity, behavioral function, and signs of stress assessed by NICU Network Neurobehavioral Scale (NNNS). Latent Profile Analyses used to place children in subgroups with discrete profiles.	Multinomial regression models adjusted for infant gender, maternal age, maternal race, maternal BMI, education status, and smoking status during pregnancy.	OR (95% CI)[b] for neurobehavioral profile membership associated with detectable Pb (>LOD, dichotomized) vs. Profile 2 membership Profile 1: 0.95 (0.38, 2.35) Profile 3: 0.97 (0.42, 2.25) Profile 4: 0.91 (0.38, 2.20) Profile 5: 3.42 (0.88, 13.32), p <0.1 Profile characteristics: 5 = Highest arousal, excitability and hypertonicity with lowest quality of movement and regulation (most extreme). Other profiles: 1 = High attention and quality of movement; 2 [referent] = Average with lowest lethargy; 3 = Average, required more handling; 4 = More signs of lethargy, hypotonicity, nonoptimal reflexes, low attention and arousal. *Unstandardized due to BLL distribution information

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Wan et al. (2021) China Cross-Sectional	n: 333	Blood Blood samples were collected from a previous study and analyzed for Pb. Authors did not report analytical method. Age at Measurement: Children aged 9 - 11 yr; exposure group mean (SE) = 9.93 (0.85) years; control group (SE) = 9.62 (0.73) Median for exposure group = 7.163 µg/dL; median for control group = 3.703 µg/dL	FSIQ Intelligence was tested using the Combined Raven's Test in China (CRT-C2).	Multivariable linear regression adjusted for children's age and gender, father's and mother's age, education levels and occupations, passive smoking of the children, and annual family incomes.	Beta (95% CI)[a] −1.2 (−1.7, −0.60)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Wang et al. (2012) Taizhou region (Luqiao city and Lanxi city), Zhejiang Province (for exposure site) and Chun'an, Zhejiang province (reference site) China June 2010 Cross-sectional	School-based study n: 329 (Luqiao: 108, Lanxi: 151, Chun'an: 70) Schools located near e-waste recycling center and tinfoil manufacturing area (Luqiao and Lanxi cities). Comparison group schools in area dominated by agriculture (Chun'an).	Blood, urine Child's venous blood, urine; ICP-MS. Age at measurement: 11–12 yr GM: Luqiao: 6.97 µg/dL, Lanxi: 8.11 µg/dL, Chun'an: 2.78 µg/dL (42%–53% had BLL ≥10 µg/dL in Luqiao and Lanxi and no one had BLL ≥10 in Chun'an) Max: Luqiao: 57.24 µg/dL, Lanxi: 59.98 µg/dL, Chun'an: 7.59 µg/dL	IQ (CRT) calculated from raw score. Age at outcome: 11–12 yr	Child's sex, birth weight, BMI, gestation at delivery and the mother's age at delivery, years of education, yearly income, tobacco exposure during pregnancy and alcohol exposure during pregnancy.	**Beta (95% CI)[b]** *IQ (CRT)* Female: −0.097 (−0.178, −0.016) Male: −0.096 (−0.175, −0.016)

AAS = atomic absorption spectrometry; ADHD = attention deficit/hyperactivity disorder; As = arsenic; BASC = Behavior Assessment System for Children; BKT = Binet Kamat Test Of Intelligence; BLL = blood lead level; BMI = body mass index; BRIEF = Behavior Rating Inventory of Executive Functions; BSID = Bayley Scales of Infant and Toddler Development; CANTAB = Cambridge Neuropsychological Test Automated Battery; CBLI = cumulative blood lead index; CI = confidence interval; Co = cobalt; Cr = chromium; CRS = Conners' Rating Scales; CRT = Combined Raven's Test; Cs = cesium; Cu = copper; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; ETS = environmental tobacco smoke; Fe = iron; FSIQ = full-scale intelligence quotient; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; Hg = mercury; HNES = Home Nurture Environment Scale; HOME = Health Outcomes and Measures of the Environment; ICP-MS = inductively coupled plasma mass spectrometry; ICP-MS-DRC = inductively coupled plasma mass spectrometry; K-XRF = K-shell X-ray fluorescence; LOD = limit of detection; MDAT = Malawi Developmental Assessment Tool; MDI = Mental Developmental Index; Mn = manganese; mo = month(s); MOCEH = Mothers' and Children's Environmental Health; MSCA = McCarthy Scales of Children's Abilities; NR = not reported; OLS = ordinary least squares; Pb = lead; PDI = Psychomotor Developmental Index; PIQ = performance intelligence quotient; PROGRESS = Programming Research in Obesity, Growth, Environment and Social Stressors; Sb = antimony; SES = socioeconomic status; SPM = Standard Progressive Matrices; TMT = Trail Making Test; TOKS = tin, ores, kiln, smelters; VIQ = verbal intelligence quotient; VMI = visual-motor integration WAIS = Wechsler Adult Intelligence Scale-Revised; WASI = Wechsler Abbreviated Scale of Intelligence; WISC = Weschler Intelligence Scale for Children; WPPSI = Wechsler Preschool and Primary Scale of Intelligence; WRAT = Wide Range Achievement Test.

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

[b]Effect estimates are not standardized because data pertaining to the BLL distribution and/or base for the log-transformation were not reported.

[c]Per natural log increased in centered BLLs (i.e., BLL/median).

[d]Results are unstandardized due to the biomarker (hair).

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

Table 3-7E Epidemiologic studies of Pb exposure and performance on neuropsychological tests of attention, impulsivity, and hyperactivity, ADHD-related behaviors, and clinical ADHD in children

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Neugebauer et al. (2015) Duisburg Germany 2000–2002 (enrollment) Followed through 2009–2011 Cohort	Duisburg birth cohort study n: 114 Pregnant women and their offspring	Blood Maternal venous blood; AAS Age at measurement: 32 wk gestation (prenatal) Mean (SD): 2.216 (1.083) µg/dL Med: 2.0 µg/dL 95th: 4.2 µg/dL Max: 6.3 µg/dL	Attentional performance using KiTAP with 5 subtests: alertness, distractibility, Go/No-go, divided attention, flexibility; ADHD-associated behavior using FBB-ADHS Age at outcome: Mean: 8.5 yr (KiTAP); 9.5 yr (FBB-ADHS)	SES, maternal diseases, parental lifestyle, childbirth outcomes, HOME Score	gMR: KITAP Inattention (omissions): 1.15 (1.00, 1.33) Attention (performance speed): 1.14 (0.98, 1.33) FBB-ADHS Overall ADHD: 1.061 (1.009, 1.115) Impulsivity 1.133 (1.055, 1.216) Hyperactivity 1.047 (0.992, 1.106) Inattention 1.054 (0.989, 1.123)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Ethier et al. (2015) Arctic Quebec (Puvirnituq) Canada 1993–1998 (enrollment) Followed through 2009–2020 Cohort	NCDS n: 27 Subsample of school-aged children who participated in the Cord Blood Monitoring Program	Blood Cord blood and concurrent venous blood; GFAAS Age at measurement: Delivery (cord); 8.6–12.6 yr old (concurrent) Mean (SD): 5.4 (4.1) µg/dL Max: 17.8 µg/dL	Selective spatial attention Visuo-spatial attention-shift task (adapted from Posner paradigm) Age at outcome: 8.6–12.6 yr	Sex, age at testing time, SES, breastfeeding duration, maternal alcohol, marijuana, cigarettes use (Each model used a different set of confounders)	Beta per SD increase in ln-transformed Pb: **Cord Blood** Reaction time: 0.02[b] Omission Error: −0.02[b] False Alarm: 0.42 (0.08, 0.76)[c] Accuracy: −0.27[b] Validity Effect: −0.05[b] **Concurrent Blood** Reaction time: 0.52 (−0.10, 1.14)[c] Omission Error: −0.10[b] False Alarm: −0.16[b] Accuracy: −0.17[b] Validity Effect: −0.13[b]
†Tatsuta et al. (2014) Sendai, Tohoku region Japan Study years NR Followed through 42 mo Cohort	TSCD birth cohort n: 387 Mother-infant pairs urban areas of the Tohoku district	Blood Cord blood; ICP-MS. Age at measurement: Delivery Median: 1.0 µg/dL Max: 1.8 µg/dL	Sequential processing and mental processing scores (K-ABC) Age at outcome: 42 mo	Child sex, birth order, alcohol and smoking habits, duration of breastfeeding, annual family income at 42 mo, and maternal IQ (Raven SPM)	Betas: K-ABC Sequential Processing: −2.136 (−12.80, 8.531)[d] Mental Processing: −3.319 (−12.41, 5.774)[d]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Yorifuji et al. (2011) Faroese island Denmark 1986–1987 (enrollment) Followed through 7-14 yr Cohort	Faroese birth cohort n: 896 (7 yr), 808 (14 yr) Mother-infant pairs	Blood Cord blood; electrothermal AAS with Zeeman background correction. Age at measurement: Delivery GM: 1.57 µg/dL 75th: 2.2 µg/dL	Attention/working memory assessed using WISC-R digit span Age at outcome: 7, 14 yr	Child age, sex, maternal IQ (RPM), paternal employment and education, maternal education, daycare at age 7, medical risk, and maternal alcohol use and smoking during pregnancy	Beta per log-transformed Pb: **7 yr** Digit span forward: −0.11 (−0.29, 0.07)[d] <2.61 µg/g Hg: −1.70 (−3.12, −0.28) **14 yr** Digit span: −0.21 (−0.53, 0.11)[d] Digit span forward: −0.04 (−0.23, 0.14)[d] Digit span backward: −0.17 (−0.37, 0.04)[d] <2.61 µg/g Hg: −2.73 (−4.32, −1.14)
†Ruebner et al. (2019) 46 centers United States Study Years: NR Followed through 1–16 yr Cohort	CKiD Cohort study n: 412 Children ages 1–16 yr at recruitment with mild to moderate CKD	Blood Child venous blood; ICP-MS. The BLL measurement closest to the time of neurocognitive testing was used for analysis (concurrent). Age at measurement: NR; 2, 4, or 6 yr after study entry Median: 1.2 µg/dL 75th: 1.8 µg/dL Max: 5.1 µg/dL	Attention, hyperactivity, and response inhibition Age-specific neurocognitive assessments (K-CPT, CPT III, BASC-2) administered 3, 5, 7 or 9 yr after study entry. The last available test results were used to evaluate long-term effects. Mean time between BLL and neurocognitive testing was 2.3 yr. Age at outcome: 1 to >18 yr; median: 15.4 yr	Child age, sex, race, poverty, and maternal education	Beta: K-CPT/CPT Attention: 1.8 (0.15, 3.45) Adjusted BRIEF and BASC-2 results were not reported because they were not statistically significant.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Rooney et al. (2018) Lisbon Portugal 1997–2005 (enrollment age 8-12 yr) Followed 7 yr age 15-19 yr Cohort	Casa Pia Clinical Trial of Dental Amalgams in Children n: 330 Children aged 8−12 yr at baseline in the Casa Pia school system	Blood Child venous blood; flameless AAS Age at measurement: 8–12 yr old (baseline) Mean (SD): Boys: 5.26 (2.73) µg/dL Girls: 4.42 (2.19) µg/dL Max: 15.0 µg/dL	Neuropsychological tests of attention Stroop word, Stroop color, Stroop color/word, WISC-III Digitspan, WAIS-III, WMS-III, Trail Making A, Adult Trail Making A Age at outcome: 15–19 yr (annual assessment for 7 yr)	Age at baseline, race, and nonverbal IQ (home environment, parent's SES, medical histories similar across subjects	Median beta: Boys Stroop word: −0.118 (−0.257, 0.021) Stroop color: −0.114 (−0.246, 0.018) Stroop color/word: −0.117 (−0.232, −0.001) WAIS-III digitspan: −0.049 (−0.112, 0.015) WMS-III spatialspan: −0.012 (−0.077, 0.054) Adult Trailmaking A: −0.02 (−0.148, 0.108) Median beta: Girls Stroop word: −0.01 (−0.182, 0.162) Stroop color: 0.033 (−0.142, 0.208) Stroop color/word: −0.019 (−0.165, 0.126) WAIS-III digitspan: −0.06 (−0.139, 0.02) WMS-III spatialspan: −0.019 (−0.103, 0.066) Adult Trailmaking A: −0.165 (−0.35, 0.021)

†Choi et al. (2020) Seoul Korea Aug. 2010 - Feb. 2015 Case-control	n = 355 (259 ADHD, 96 controls) 5−18 yr old patients at a child and adolescent psychiatry outpatient clinic of Seoul National University Hospital ADHD status diagnosed with K-SADS-PL (neuropsychological testing by board certified child/adolescent psychiatrist)	Blood Child venous blood; GFAAS with Zeeman background correction Age at measurement: 5−18 yr Mean: 1.4 (cases) vs. 1.3 (controls) µg/dL	Inattention and hyperactivity/impulsvity assed using ADHD-RS IV (parent rating) Attention and executive function assessed using computerized SCWT and CPT Age at outcome: 5–18 yr	Age, sex, IQ	Beta direct effects: ADHD-RS Total ADHD severity: 2.254 (−0.278, 4.785) Inattention: 1.053 (−0.387, 2.493) Hyperactivity/Impulsivity: 1.259 (−0.042, 2.560) Beta direct effects: Conners' CPT Inattention (errors of omission): 3.748 (0.091, 7.404) Impulsivity (errors of commission): −0.925 (−4.412, 2.562) Response Time: 2.515 (0.013, 5.017) Response Time Variability: 2.647 (−0.846, 6.140) Beta direct effects: Stroop Stroop word: −1.143 (−3.316, 1.031) Stroop color: −0.729 (−2.832, 1.375) Stroop color/word: 0.491 (−1.876, 2.857) Stroop color/word interference: 1.618 (−0.963, 4.199) Beta interaction: Stroop DAT1 × Pb on Inattention (errors omission): 10.613 (−0.237, 21.463)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					DAT1 × Pb on Response Time Variability: −0.198 (−10.527, 10.132) DRD4 × Pb on Inattention (errors omission): −0.911 (−7.380, 5.558) DRD4 × Pb on Response Time Variability: −4.065 (−10.166, 2.036) ADRA2A MspI × Pb on Inattention (errors omission): 2.870 (−2.340, 8.079) ADRA2A MspI × Pb on Response Time Variability: −1.588 (−6.526, 3.350) ADRA2A DraI × Pb on Inattention (errors omission): 5.066 (0.197, 9.934) ADRA2A DraI × Pb on Response Time Variability: 3.392 (−1.233, 8.017)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Boucher et al. (2012a) Nunavik region, Montreal Canada 1993−1998 (enrollment) Followed through Sep. 2005 – Apr. 2007 Cohort	Cord Blood Monitoring Program (CBMP) One child from the Environmental Contaminants and Child Development Study (1996−2000) n: 196 School children without known neurodevelopmental disorder or medication for attention problems	Blood Cord and child blood; GFAAS with Zeeman background correction (cord), ICP-MS (child). Age at measurement: Delivery (cord), 9–13 yr (child) Cord: 4.8 µg/dL (mean), 3.7 µg/dL (med); 20.9 µg/dL (max) Concurrent child: 2.2 µg/dL (mean), 2.0 µg/dL (med), 12.8 µg/dL (max)	Impairment in response inhibition (Go/No-Go, ERPs measured by EEG) Electro-oculogram was recorded from bipolar miniature electrodes placed vertically above and below the right eye. Age at outcome: 9–13 yr	Child age, sex, status as adoptee; transport by plane from remote to larger village for assessment; time of assessment; maternal age at delivery; SES; maternal nonverbal reasoning abilities; breastfeeding duration; maternal smoking, marijuana use, binge drinking during pregnancy; docosahexaenoic acid concentrations in cord and child plasma samples; Hg, PCBs	Beta per log-transformed Pb: **Cord blood** Mean Reaction Time (RT), correct go trials: −0.05[b] Mean RT, incorrect no-go trials: −0.10[b] Percent correct go trials: −0.21 (−0.36, −0.06)[c] Percent correct no-go trials: −0.17 (−0.29, −0.05)[c] **Concurrent blood** Mean RT, correct go trials: 0.03[b] Mean RT, incorrect no-go trials: 0.03[b] Percent correct go trials: −0.12[b] Percent correct no-go trials: −0.16 (−0.27, −0.05)[c]
Rabinowitz et al. (1992) Taiwan Study period NR Cross-sectional.	N: 493 Mix of children residing in urban or rural environments or near a smelter Children grades 1–3 recruited from schools	Tooth Child deciduous tooth; method NR Age at measurement: grades 1–3 Mean (SD): 4.6 (3.5) µg/g	Hyperactivity Syndrome Boston Teacher Questionnaire (BTQ) Age at Outcome: Grades 1–3	Sex, # adults at home. Also considered grade, child longest hospital stay parental education, SES, birth outcomes, handedness, language at home, and prenatal maternal medicine, alcohol, and smoking.	OR vs. <2.3 µg/g as reference 2.3–7 µg/g: 1.9 (0.53, 6.5) >7 µg/g: 2.8 (0.68, 12)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Chandramouli et al. (2009) Avon U.K Jul. – Dec. 1992 (birth) Followed through 8 yr Cohort	10% random subsample of Avon Longitudinal Study of Parents and Children (ALSPAC) n = 488 School children	Blood Earlier childhood venous blood; AAS using micro sampling flame atomization Age at measurement: 30 mo Mean (SD): NR Group 1: 0-<2 µg/dL Group 2: 2-<5 µg/dL Group 3: 5-<10 µg/dL Group 4: >10 µg/dL	Parent and teacher rated hyperactivity and attention SDQ (7 yr), Development and Well-Being Assessment (DAWBA) (8 yr), Test of Everyday Attention for Children (TEACh) (8 yr) Age at outcome: 7–8 yr	Maternal education and smoking, home ownership, home facilities score, family adversity index, paternal SES, parenting attitudes at 6 mo, child sex. Also considered child IQ.	OR for increased score: TEACh Group 1: reference Group 2: 1.03 (0.66, 1.61) Group 3: 0.99 (0.62, 1.57) Group 4: 1.14 (0.54, 2.40) SDQ hyperactivity Group 1: reference Group 2: 0.84 (0.47, 1.52) Group 3: 1.25 (0.67, 2.33) Group 4: 2.82 (1.08, 7.35)
†Sioen et al. (2013) Flanders Belgium Oct. 2002 – Dec. 2003 (enrollment) Followed through June 2011 Cohort	Flemish Health and Environment Study (FLEHS 1) n: 270 Birth cohort of Flemish children living in either rural or urban areas	Blood Cord blood, HR-ICP-MS Age at measurement: Delivery median = 14.3 µg/L 75th: 25.3 µg/L	Hyperactivity SDQ with 5 domains: emotional, conduct, hyperactivity, peer and social problems Age at outcome: 7-8 yr	Maternal and paternal BMI, maternal age, weight increase of mother during pregnancy, smoking during pregnancy, smoking behavior of maternal grandmother before birth of mother, parental education, current parental smoking, child sex, serious infections of child since birth (also tested interaction by sex)	OR per doubling of log-transformed Pb: Hyperactivity: 2.940 (1.172, 7.380)[d] Total difficulties: 2.167 (0.741, 6.334)[d]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Fruh et al. (2019) Eastern Massachusetts U.S. 1999–2002 (enrollment) Followed through age 7 yr Cohort	Project Viva n: 1006 Birth cohort of mother-child pairs	Blood Maternal venous blood; ICP-MS Age at measurement: T2 Median: 1.1 µg/dL	Parent teacher ratings of hyperactivity using SDQ Standardized for child age and sex Age at outcome: 7 yr	Maternal 2nd trimester Hg and Mn levels, nulliparity, smoking during pregnancy, IQ, and education; paternal education; HOME composite score and household income; and child race/ethnicity	Beta per ln-transformed Pb for hyperactivity: SDQ-parent: 0.10 (−0.21, 0.41) SDQ-teacher: 0.20 (−0.24, 0.64)
†Horton et al. (2018) Mexico City Mexico born 1994–2006 and followed through age 6–16 Cohort	ELEMENT Project n: 133 healthy, low to moderate income mother (18–39 yr old)-child pairs	Teeth tooth Pb (prenatal, postnatal metrics derived); laser ablation ICP-MS Age at measurement: tooth Pb concentration corresponded to prenatal and 300 days after birth Figure 1c	Externalizing behavior (attention and hyperactivity) BASC-2: BSI, hyperactivity and attention symptoms Age at outcome: 8–11 yr old	Maternal age at delivery, maternal education, smoking, SES, maternal IQ	Beta per ln-transformed Pb: Attention: 0.19 (0.02, 0.37)[e] BSI (composite): 0.22 (0.06, 0.38)[e]
†Rasnick et al. (2021) Cincinnati, OH Born: Oct 2001–Jul 2003 Exposure: 2001–2005 Cohort	CCAAPS n: 263	Air LURF, air sampling at 24 sites (C-V R2 = 0.89), predicted air concentration at child's residence. Children residing >1,500 m or <400 m from major highway eligible. Median: 0.51 ng/m^3 (range 0–10.8 ng/m^3)	Attention problems using BASC-2 Age at outcome: 12 yr	Maternal education, community-level deprivation, blood Pb concentrations, greenspace, and traffic related air pollution.	Beta per 1 ng/m^3 increase in monthly air Pb exposure: Attention: 0.8 (0.1, 1.5)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Liu et al. (2014b) Jintan, Jiangsu province China Sep. 1, 2004 – Apr. 30, 2005 (age 3−5 yr) Followed to age 6 yr Cohort	China Jintan Child Cohort Study n: 1025 children Chinese preschool children	Blood Venous child blood; GFAAS Age at measurement: 3–5 yr old Mean (SD): 6.4 (2.6) µg/dL median = 6.0 µg/dL 75th: 7.5 µg/dL 90th: 9.4 µg/dL Max: 32 µg/dL	Attention and ADHD problems CBCL (Chinese version); Caregiver-Teacher Report Form; normalized T scores Age at outcome: 6 yr	Age at BLL test, sex, preschool residence, father's educational level, mother's educational level, father's occupation, parents' marital status, single child status, and child IQ	Beta: **CBCL** Attention: 0.001 (−0.002, 0.002) ADHD: 0.136 (−0.115, 0.386) **C-TRF** Attention: 0.001 (−0.002, 0.002) ADHD: 0.073 (−0.177, 0.322) OR: **C-TRF** ADHD all: 1.08 (0.99, 1.18) Boys: 1.04 (0.94, 1.16) Girls: 1.15 (0.98, 1.35)
†Winter and Sampson (2017) Chicago, Illinois U.S. 1995–1997 (birth) Followed through 2013 (age 17 yr) Cohort	PHDCN n: 254 Children and caregivers living in Chicago	Blood Avg BLL before age 6; methods NR Age at measurement: 6 yr old or younger Mean: 6.4 µg/dL	Impulsivity score CBCL PC questionnaire Age at outcome: Mean: 17 yr old	Age at CBCL assessment, sex, race/ethnicity, primary caregiver immigrant generational status, marital status, education level, Temporary Assistance for Needy Families receipt, and the proportion of residential neighborhood that is non-Hispanic Black, Hispanic, below the poverty line, and tested for Pb exposure	Beta: CBCL Impulsivity: 0.06 (0.005, 0.115)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Choi et al. (2016) 10 Cities South Korea 2006–2010 (enrollment at 1st−2nd grade) Followed through age 7−9 yr Cohort	CHEER n: 2195 Elementary school children	Blood Child venous blood; AAS with Zeeman background correction Age at measurement: 7–9 yr GM: 1.56 µg/dL	ADHD symptomology DuPaul's ADHD rating scale per DSM-IV Age at outcome: After age 7–9 yr	Age, sex, residential area, monthly household income, parental marital status, family history of psychiatric disorders (anxiety disorder, ADHD, autism and schizophrenia), preterm birth and birth weight	RR (BLL >2.17 vs. ≤2.17 µg/dL) for ADHD symptoms: 1.552 (1.002, 2.403) Single parent home and BLL >2.17 µg/dL vs. 2-parent home and BLL ≤2.17 µg/dL: 3.567 (1.595, 7.980)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Boucher et al. (2012b) Nunavik, Arctic Quebec Canada 1993–2000 (enrollment) Sep. 2005–Feb. 2010 (follow-up) Cohort	Cord Blood Monitoring Program and Environmental Contaminants and Child Development Study n: 279 Inuit Children	Blood Cord and child venous blood; AAS (cord), ICP-MS (child) Age at measurement: delivery (cord), 11.3 yr (child) Mean (SD): 4.7 (3.3) µg/dL (cord); 2.7 (2.2) µg/dL (child) Median: 3.7 µg/dL (cord); 2.1 µg/dL (child) Max: 20.9 µg/dL (cord); 12.8 µg/dL (child)	ADHD symptomology assessed using the TRF from CBCL and the DBD rating scale Age at outcome: 11.3 yr (average)	Child age and sex, SES, age of the biological mother at birth, maternal tobacco use during pregnancy, and birth weight, Hg	Cord Blood: Attention problems Beta (95% CI) per log-transformed Pb: 0.05 (–0.10, 0.19)[d] OR (95% CI) ADHD inattentive type 1st tertile referent 2nd tertile 2.77 (1.00, 7.65)[d] 3rd tertile 2.87 (1.04, 7.94)[d] ADHD hyperactive-impulsive type 1st tertile referent 2nd tertile 0.95 (0.30, 3.00)[d] 3rd tertile 2.92 (1.07, 8.04)[d] Child Blood: Attention problems Beta (95% CI) per log-transformed Pb: 0.08 (–0.05, 0.21)[d] OR (95% CI) ADHD inattentive type 1st tertile referent 2nd tertile 1.06 (0.42, 2.66)[d] 3rd tertile 1.01 (0.38, 2.64)[d] ADHD hyperactive-impulsive type 1st tertile referent 2nd tertile 4.01 (1.06, 15.23)[d] 3rd tertile 5.52 (1.38, 22.12)[d]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Desrochers-Couture et al. (2019) Nunavik, Northern Quebec Canada Nov. 1993–Mar. 2002 (enrollment) Sep. 2005–Feb. 2010 (1st follow-up) Jan. 2013–Feb. 2016 (2nd follow-up) Cohort	NCDS-childhood n: 212 Inuit children from 14 coastal villages in Nunavik, Quebec, subsample from the Cord Blood Monitoring Program and NIH-infancy study	Blood Cord and child venous blood; GFAAS (cord), ICP-MS (child) Age at measurement: Delivery (cord), 11.4, 18.5 yr (child) GM (GSD): 3.80 (1.84) µg/dL (cord); 2.34 (1.86) µg/dL (child); 1.63 (2.00) µg/dL (adolescent) Median:3.73 µg/dL (cord); 2.07 µg/dL (child); 1.52 µg/dL (adolescent) Max: 17.80 µg/dL (cord); 12.83 µg/dL (child); 18.13 µg/dL (adolescent)	Teacher-rated ADHD symptomology Teacher assessed DBD and TRF, Achenbach's YSR, BAARS Age at outcome: 11.4, 18.5 yr (average)	Child age, sex, SES, maternal age at delivery, maternal tobacco smoking during pregnancy, and birth weight	Beta (95% CI): Child Blood: Child externalizing behavior: 0.23 (0.08, 0.38) Child ADHD: 0.45 (0.13, 0.78) Direct effect: 0.09 (−0.11, 0.28) Indirect effect: −0.02 (−0.06, 0.03) Adolescent externalizing behavior mediated through child externalizing behavior (β: 0.09, 95% CI: 0, 0.17)
†Hong et al. (2015) 5 administrative regions South Korea Study years NR Case-control	n: 1001 General population of children in 3rd to 4th grades	Blood Child venous blood; GFAAS with Zeeman background correction Age at measurement: 8–11 yr Median: 1.81 µg/dL 75th: 2.25 µg/dL, 95th: 3.01 µg/dL Max: 6.16 µg/dL	ADHD symptomology Teacher/parent ratings ADHD symptoms (ADHD-RS); CPT Age at outcome: 8–11 yr	Age, gender, residential region, paternal education level, and yearly income log10-transformed blood Hg, Mn, urine concentrations of cotinine, phthalate metabolites full-scale IQ	Beta (95% CI) Child blood: ADHD-RS, parent-rated 1.04 (0.18, 1.90) ADHD-RS, teacher-rated 1.90 (0.74, 3.05) Additionally adjusted for FSIQ, Mn, and Hg: ADHD-RS, parent-rated 0.68 (−0.20, 1.56) ADHD-RS, teacher-rated 1.49 (0.32, 2.67)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Nigg et al. (2016) Michigan United States Study years NR Case-control	n: 386 children, 6–17 yr old from 267 families (148 singletons, 119 sibling pairs) Non-ADHD: 147 ADHD: 122	Blood Child venous blood; ICP-MS Age at measurement: 6–17 yr Non-ADHD: mean (SD) = 0.74 (0.35) µg/dL ADHD: mean (SD) = 0.94 (0.52) µg/dL	Composite parent and teacher ratings of ADHD symptoms using 3 scales: ADHD-RS: inattention and hyperactivity-impulsivity symptom scores CRS-R: cognitive (inattention) and hyperactivity problems subscales SWAN: inattention and hyperactivity symptom scores Age at outcome: 6–17 yr	Gross annual income, HFE mutations, race, parenting behavior, OD/CD, Fe hemoglobin level, sex	Betas of hyperactivity-impulsivity scores per z-score increase in Pb modified by HFE C282Y mutation Parent ratings: Mutation: 0.74 (0.52, 0.96)[e] Wild-type: 0.28 (0.15, 0.41)[e] Male: 0.31 (0.14, 0.48)[e] Female: 0.09 (−0.16, 0.34)[e] Teacher ratings: Mutation: 0.47 (0.22, 0.72)[e] Wild-type: 0.29 (−0.04, 0.12)[e] Male: 0.19 (0.07, 0.31)[e] Female: 0.11 (−0.03, 0.25)[e]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Joo et al. (2018) Seoul, Ulsan, Cheonan South Korea 2006–2011 (enrollment) Followed through 5 yr Cohort	MOCEH n: 575 mother-child pairs Pregnant women at 12–20 wk of pregnancy in prenatal clinics and public health centers	Blood Maternal venous, cord, and child venous blood; AAS Age at measurement: 20 wk (maternal); delivery (maternal and cord); 2, 3, and 5 yr (child) GM: Maternal 1.28 µg/dL (early), 1.24 (late) 0.9 (cord); Child 1.55 (age 2), 1.43 (age 3), 1.29 (age 5)	Attention and aggressive behavior combined K-CBCL: Externalizing behavior (attention and aggressive behavior combined); Age at outcome: 5 yr	Maternal age at childbirth, parity, maternal educational level, household income, residential area, and breastfeeding	Beta (95% CI): Externalizing behavior at 5 yr Maternal-early pregnancy Male: −0.72 (−3.12, 1.69) Female: −0.45 (−2.16, 1.26) Maternal-late pregnancy Male: 2.99 (0.55, 5.43) Female: 0.24 (−2.18, 2.66) Cord blood Male: 3.09 (−0.08, 6.26) Female: −0.16 (−3.33, 3.01) Child blood–2 yr Male: 0.55 (−1.52, 2.62) Female: 3.50 (0.97, 6.03) Child blood–3 yr Male: 1.13 (−1.42, 3.68) Female: 2.05 (−1.35, 5.45) Child blood–5 yr (concurrent) Male: 1.42 (−2.12, 4.95) Female: 4.53 (−0.81, 9.86)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Ji et al. (2018) Boston, Massachusetts U.S. 1998−2013 (enrollment) Followed through 2016 Cohort	Boston Birth Cohort n: 299 ADHD cases, 1180 neurotypical controls Mother-infant pairs	Blood Child blood; method NR, BLLs obtained from electronic medical records Age at measurement: ≤4 yr; the earlier BLL was selected where multiple BLLs were recorded Mean (SD): 2.2 (1.6) µg/dL	Diagnosed ADHD Physician-diagnosed ADHD from electronic medical records Age at outcome: Median: 6 yr	Maternal age at delivery, maternal race/ethnicity, maternal education, smoking during pregnancy, intrauterine infection, parity, child's sex, mode of delivery, preterm birth, and birth weight	OR (95% CI) **Continuous BLL:** 1.118 (1.003, 1.247) **Categorical BLL:** 2−4 vs. <2 µg/dL: 1.08 (0.81, 1.44)[e] 5−10 vs. <2 µg/dL: 1.73 (1.09, 2.73)[e] **Sex-stratified:** Girls 5−10 vs. <5 µg/dL: 0.68 (0.27, 1.69)[e] Boys 5−10 vs. <5 µg/dL: 2.49 (1.46, 4.26)[e] **Joint Effects of sex and BLL category:** Girls*5−10 µg/dL: 0.69 (0.28, 1.71)[e] Boys*<5 µg/dL: 3.02 (2.24, 4.06)[e] Boys*5−10 µg/dL: 7.48 (4.29, 13.02)[e]
†Park et al. (2016) Busan South Korea Apr.-Sep. 2013 Case-control	n: 114 cases (diagnosed ADHD), 114 controls Recruitment from child psychiatric and pediatric clinics from four university hospitals	Blood Child venous blood; GFAAS with Zeeman background correction Age at measurement: 6–12 yr GM (GSD): 1.90 (0.86) µg/dL (cases); 1.59 (0.68) µg/dL (controls)	Diagnosed ADHD Diagnosed ADHD (confirmed by [K-SADS-PL-K]); CPT and parent-rated ADHD symptoms among ADHD cases Age at outcome: 6–12 yr	Age, sex-matched controls; gestational age, birth weight, SES, parental education, and parents' smoking behavior	OR (95% CI) per log-transformed Pb: ADHD total 1.60 (1.04–2.45)[d]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Kim et al. (2013a) Omaha, Nebraska U.S. Aug 2007–Dec 2009 Case-control	n: 71 cases (diagnosed ADHD); 58 controls Children living near a former refinery	Blood Child venous blood; ICP-MS Age at measurement: 5–12 yr GM: 1.29 µg/dL (cases); 1.33 µg/dL (controls); 1.65 µg/dL (inside Pb investigation area); 1.01 µg/dL (outside Pb investigation area)	ADHD Physician-diagnosed according to DSM-IV Age at outcome: 5–12 yr	Matched on age, sex, race and adjusted for maternal smoking, SES, and environmental tobacco exposure	OR (95% CI) per ln-transformed Pb ADHD Overall 2.52 (1.07–5.92)[e]
†Geier et al. (2018) Representative sample U.S. 2003–2004 Cross-sectional	NHANES n: 2109 Children	Blood Child venous blood: ICP-MS Age at measurement: 10–19 yr Mean (SD): 1.16 (1.27) µg/dL	ADD Self-reported doctor diagnosed ADD Age at outcome: 10–19 yr	Sex, age, SES, race	OR (95% CI): ADD 1.292 (1.025–1.545)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Braun et al. (2006) Representative sample U.S. 1999–2002 Cross-sectional	NHANES n: 4704 Children 4–15 yr	Blood Venous blood: GFAAS Age at measurement: 4–15 yr old Quintiles: ND–0.7 µg/dL: 679 0.8–1.0 µg/dL: 795 1.1–1.3 µg/dL: 857 1.4–2.0 µg/dL: 745 ≥2.0 µg/dL: 995	Parent-reported ADHD with prescription stimulant use Age at outcome: 4–15 yr old	Age, sex, race, prenatal ETS exposure, postnatal ETS exposure, BLLs, preschool or childcare attendance, health insurance coverage, and ferritin levels	AOR (95% CI) Child blood: 2nd quintile (0.8–1.0): 1.1 (0.4–3.4)[e] 3rd quintile (1.1–1.3): 2.1 (0.7–6.8)[e] 4th quintile (1.4–2.0): 2.7 (0.9–8.4)[e] 5th quintile (>2.0): 4.1 (1.2–14.0)[e]

AAS = atomic absorption spectrometry; ADHD = attention deficit/hyperactivity disorder; ADHD-RS = ADHD rating scale; ADRA2A = adrenoceptor alpha 2A; AOR = adjusted odds ratio; BAARS = Barkley Adult ADHD-IV Rating Scale; BASC = Behavior Assessment System for Children; BLL = blood lead level; BMI = body mass index; BRIEF = Behavior Rating Inventory of Executive Functions; BSI = Behavioral Symptoms Index; CARES = Communities Actively Researching Exposure Study; CBCL = Child Behavior Check List; Cd = cadmium; CHEER = Children's Health and Environmental Research; CI = confidence interval; CKiD = Chronic Kidney Disease in Children Study; CPT = Continuous Performance Test; CRS-R = Conners' Rating Scale-Revised; C-TRF = Caregiver-Teacher Report Form; DAT1 = dopamine transporter; DBD = Disruptive Behavior Disorders; DRD2 = dopamine receptor D2; DSM = Diagnostic and Statistical Manual of Mental Disorders; EEG = electroencephalogram; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; ERP = event-related potentials; FBB-ADHS = Fremdbeurteilungsbogen für Aufmerksamkeitsdefizit/Hyperaktivitätstörungen; Fe = iron; FLEHS = Flemish Health and Environment Study; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; GMR = geometric mean ratio; HFE = hemochromatosis gene; Hg = mercury; HOME = Health Outcomes and Measures of the Environment; ICP-MS = inductively coupled plasma mass spectrometry; K-ABC = Kaufman Assessment Battery For Children; K-CPT = Conners' Kiddie Continuous Performance; KiTAP = Test of Attentional Performance for Children; K-SADS-PL-K = Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime – Korean Version; LURF = Land Use Random Forest; Mn = manganese; mo = month(s); MOCEH = Mothers' and Children's Environmental Health; NCDS = Nunavik Child Development Study; NR = not reported; OD/CD = oppositional defiant and conduct disorder; OR = odds ratio; Pb = lead; PCBs = polychlorinated biphenyls; PHDCN = Project on Human Development in Chicago Neighborhoods; RR = relative risk; RT = reaction time; SCWT = Stroop Color-Word Test; SD = standard deviation; SDQ = Strengths and Difficulties Questionnaire; SE = standard error; SES = socioeconomic status; SPM = Standard Progressive Matrices; SRS = Social Responsiveness Scale; SWAN = Strengths and Weaknesses of ADHD Symptoms and Normal Behavior Scale; T1 = first trimester of pregnancy; T2 = second trimester of pregnancy; T3 = third trimester of pregnancy; TEACh = Test of Everyday Attention for Children; TSCD = Tohoku Study of Child Development; WAIS = Wechsler Adult Intelligence Scale; wk = week(s); WMS = Weschler Memory Scale; yr = year(s).

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

[b]Results are unstandardized because they did not have an associated SE, CI, or p-value reported in the study.

[c]The CI was calculated from a p-value and the true CI may be wider or narrower than calculated.

[d]Results are unstandardized because the log base used for exposure transformation was unspecified in the study.

[e]Results are unstandardized because the Pb level distribution data was not available.

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

Table 3-7T Animal toxicological studies of Pb exposure and externalizing and internalizing behaviors

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Externalizing Behavior					
Tartaglione et al. (2020)	**Rat (Wistar)** Control (tap water), M/F n = 16 (9/7) 50 mg/L, M/F, n = 16 (9/7)	GD 28 to PND 23	Oral, lactation In utero	PND 23: 0.007 µg/mL (0.7 µg/dL) for Control 0.255 µg/mL (25.5 µg/dL) for 50 mg/L	PND 4, 7, 10, 12: Ultrasonic Vocalizations
Internalizing Behavior					
Cory-Slechta et al. (2013)	**Mouse (C57BL/6)** Control (distilled deionized water) – NS, M/F, n = 8–16 Control (distilled deionized water) – prenatal stress (PS), M/F, n = 8–16 100 ppm (NS), M/F, n = 8–16 100 ppm (PS), M/F, n = 8–16	GD −60 to 12 mo	Oral, drinking water Oral, lactation In utero	PND 75 – Females: <LOD for Control (NS) <LOD for Control (PS) 8.42 µg/dL for 100 ppm (NS) 9.94 µg/dL for 100 ppm (PS) PND 75 – Males: <LOD for Control (NS) <LOD for Control (PS) 7.05 µg/dL for 100 ppm (NS) 7.16 µg/dL for 100 ppm (PS) 12 mo – Females:	7–12 mo: FST

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				<LOD for Control (NS) <LOD for Control (PS) 9.38 µg/dL for 100 ppm (NS) 10.1 µg/dL for 100 ppm (PS) 12 mo – Males: <LOD for Control (NS) <LOD for Control (PS) 6.94 µg/dL for 100 ppm (NS) 8.03 µg/dL for 100 ppm (PS)	
Zou et al. (2015)	**Mouse (ICR)** Control (distilled water), M, n = 10 250 mg/L solution, M, n = 10	~5 wk to 8 wk	Oral, drinking water	8 wk: 1.8 µg/dL for Control 21.7 µg/dL for 250 mg/L	8 wk: Locomotor Activity
Betharia and Maher (2012)	**Rat (Sprague Dawley)** PND 24: Control (RO DI water), M/F, n = 11–13 10 µg/mL, M/F, n = 11–13 PND 59:	GD 0 to PND 20	Oral, lactation In utero	PND 2: 1.77 ng/g (0.188 µg/dL) for Control 85.17 ng/g (9.02 µg/dL) for 10 µg/mL PND 25: 0.83 ng/g (0.088 µg/dL)	PND 24, 59: OFT

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
	Control (RO DI water), M/F, n = 10–11 10 µg/mL, M/F, n = 10–11			for Control 9.21 ng/g (0.98 µg/dL) for 10 µg/mL PND 60: 0.23 ng/g (0.024 µg/dL) for Control 0.30 ng/g (0.032 µg/dL) for 10 µg/mL	
Faulk et al. (2014)	**Mouse (Agouti)** Control (distilled water), M/F, n = 30 2.1 ppm, M/F, n = 28 16 ppm, M/F, n = 33 32 ppm, M/F, n = 29	GD −14 to PND 21	Oral, lactation In utero	PND 21 (Maternal BLL): <LOD for Control 4.1 µg/dL for 2.1 ppm 25.1 µg/dL for 16 ppm 32.1 µg/dL for 32 ppm	PND 90, 180, and 270: Locomotor Activity
Basha et al. (2014)	**Rat (Not Specified)** Control (deionized water), M, n = 6 0.2% solution, M, n = 6	PND 1 to PND 21	Oral, lactation	PND 45: 0.42 µg/dL for Control 49.5 µg/dL for 0.2% solution 4 mo: 0.56 µg/dL for Control 14.4 µg/dL for 0.2% solution 12 mo: 0.46 µg/dL for Control	PND 45, 4 mo, 12 mo, 18 mo: OFT, Locomotor Activity, Hole Board Test

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				6.96 µg/dL for 0.2% solution 18 mo: 0.12 µg/dL for Control 11.2 µg/dL for 0.2% solution	
Mansouri et al. (2012)	**Rat (Wistar)** Control (distilled water), M/F, n = 16 (8/8) 50 mg/L, M/F, n = 16 (8/8)	PND 70 to PND 100	Oral, drinking water	PND 100 – Males: 2.05 µg/dL for Control 8.8 µg/dL for 50 mg/L PND 100 – Females: 2.17 µg/dL for Control 6.8 µg/dL for 50 mg/L	PND 100: OFT
Duan et al. (2017)	**Mouse (CD1)** Control (distilled water), M/F, n = 5 27 ppm, M/F, n = 5 109 ppm, M/F, n = 5	PND 1 to PND 21	Oral, lactation	PND 21: 16.2 µg/L (1.6 µg/dL) for Control 191.8 µg/L (19.2 µg/dL) for 27 ppm 283.4 µg/L (28.3 µg/dL) for 109 ppm PND 35: 14.3 µg/L (1.4 µg/dL) for Control 283.4 µg/L (28.3 µg/dL) for 27 ppm	PND 7, 11, 15, 19: TST, OFT

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				376.9 µg/L (37.7 µg/dL) for 109 ppm	
Wang et al. (2016)	**Rat (Sprague Dawley)** Control (tap water), M, n = 7 100 ppm, M, n = 9	PND 24 to PND 56	Oral, drinking water	PND 56: 11 µg/L (1.1 µg/dL) for Control 133 µg/L (13.3 µg/dL) for 100 ppm	PND 60–66: OFT
Shvachiy et al. (2018)	**Rat (Wistar)** Control (tap water), M/F, n = 8 0.2% (p/v) solution (distilled water), M/F, n = 9 – Intermittent exposure 0.2% (p/v) solution, M/F, n = 9 – Continuous exposure	Intermittent Exposure: GD 7 to PND 84, PND 140 to PND 196 Continuous Exposure: GD 7 to PND 196	Oral, drinking water Oral, lactation In utero	PND 196: <0.1 µg/dL for Control 18.8 µg/dL for 0.2% (Intermittent) 24.4 µg/dL for 0.2% (Continuous)	PND 189: OFT, EPM
Basha and Reddy (2015)	**Rat (Wistar)** Control (deionized water), M, n = 8 0.2 % solution, M, n = 8	GD 6 to GD 21	In utero	PND 21: 0.21 µg/dL for Control 11.2 µg/dL for 0.2% solution PND 28: 0.33 µg/dL for Control 12.3 µg/dL for 0.2% solution 4 mo: 0.19 µg/dL for Control	PND 21, PND 28, 4 mo: OFT, Hole Board Test

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				5.9 µg/dL for 0.2% solution	
Stansfield et al. (2015)	**Rat (Long-Evans)** Control (chow), M/F, n = 11–23 1500 ppm, M/F, n = 11–23	GD 0 to PND 50	Oral, diet Oral, lactation In utero	PND 50: 0.6 µg/dL for Control 22.2 µg/dL for 1500 ppm	PND 50: Locomotor Activity
Flores-Montoya and Sobin (2015)	**Mouse (C57BL/6)** Control (distilled water), M/F, n = 19 (8/11) 30 ppm, M/F, n = 26 (16/10) 230 ppm, M/F, n = 16 (12/4)	PND 0 to PND 28	Oral, drinking water Oral, lactation	≥PND 28 Males: 0.2 µg/dL for Control 3.93 µg/dL for 30 ppm 9.39 µg/dL for 230 ppm ≥PND 28 Females: 0.19 µg/dL for Control 3.19 µg/dL for 30 ppm 12.14 µg/dL for 230 ppm	≥PND 28 Hole Board Test, OFT
Neuwirth et al. (2019a)	**Rat (Long-Evans)** Control (tap water), M/F, n = NR 150 ppm, M/F, n = NR 1000 ppm, M/F, n = NR	GD 0 to PND 22	Oral, lactation In utero	PND 22: <LOD for Control 3.3–10.7 µg/dL for 150 ppm 9.0–17.8 µg/dL for 1000 ppm PND 55: <LOD for Control <LOD for 150 ppm	PND 36–45: OFT PND 37–46: EPM

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
				<LOD for 1000 ppm	
Mansouri et al. (2013)	**Rat (Wistar)** Control (tap water or water + NaAc), M/F, n = 16 (8/8) 50 ppm, M/F, n = 16 (8/8)	PND 55 to PND 181	Oral, drinking water	PND 178–181 – Females: NR for Control 10.6 µg/dL for 50 ppm PND 178–181 – Males: NR for Control 18.9 µg/dL for 50 ppm	PND 150–152: OFT
Tartaglione et al. (2020)	**Rat (Wistar)** Control (tap water), M/F n = 16 (9/7) 50 mg/L, M/F, n = 16 (9/7)	GD −28 to PND 23	Oral, lactation In utero	PND 23: 0.007 µg/mL (0.7 µg/dL) for Control 0.255 µg/mL (25.5 µg/dL) for 50 mg/L	PND 30: OFT PND 60: EPM
Sobolewski et al. (2020)	**Mouse (C57BL/6)** F0: Control (distilled DI water), F, n = 10 100 ppm, F, n = 10 F1: see Figure 1, n = 12 F2: see Figure 1, n = 12	F1: GD −60 to PND 23–27	Oral, lactation In utero	F1 PND 6–7: 0 µg/dL for Control 12.5 µg/dL for 100 ppm (F0 dosing) F3 PND 120: 0 ng/dL for Control 0 µg/dL for 100 ppm (F0 dosing)	PND 60–120 (variable by endpoint): EPM, Locomotor Activity

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
	F3: see Figure 1, n = 8–10				
Singh et al. (2019)	**Rat (Wistar)** Control (distilled water), M, n = 5 2.5 mg/kg, M, n = 5	3 mo to 6 mo	Oral, gavage	6 mo: 5.76 µg/dL for Control 28.4 µg/dL for 2.5 mg/kg	6 mo: EPM, Locomotor Activity
Al-Qahtani et al. (2022)	**Mouse (Albino)** Control (distilled water), M, n = 10 0.2 mg/kg, M, n = 10	8–9 wk to 14–15 wk	Oral, gavage	14–15 wk: 1.2 µg/100 mL (1.2 µg/dL) for Control 7.1 µg/100 mL (7.1 µg/dL) for 0.2 mg/kg	NR: EPM, Locomotor Activity

BLL = blood lead level; EPM = elevated plus maze; F = female; FST = forced swim test; GD = gestational day; LOD = limit of detection; M = male; MRI = magnetic resonance imaging; mo = month(s); NR = not reported; NS = no stress; OFT = open-field test; Pb = lead; PG = pregestation; PND = postnatal day; PS = prenatal stress; TST = tail suspension test; wk = week(s); yr = year(s).

Table 3-8E Epidemiologic studies of Pb exposure and performance on neuropsychological tests of attention, impulsivity, and hyperactivity, attention deficit/hyperactivity disorder-related behaviors, and clinical attention deficit/hyperactivity disorder in children; group or population mean blood Pb level >5 µg/dL, any study design

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Arbuckle et al. (2016a) representative population Canada 2007–2009 Cross-sectional	CHMS n: 1080 Representative sample of children	Blood Child venous blood; analytic method NR Age at measurement: 6–11 yr old GM: 0.90 95th: 1.96 µg/dL	ADHD symptoms SDQ, parent-reported ADD/ADHD Age at outcome: 6–11 yr old	Age, sex, neonatal unit, maternal smoking child age (Supplemental Table 1)	**OR[b]** *Parent-Reported Outcomes* ADD/ADHD: 2.08 (1.01, 4.25) Any Learning Disability: 1.41 (0.73, 2.70) Psychotropic Medicine Taken: 2.91 (1.47, 5.79) *SDQ* Total Difficulties, Prenatal Smoking: 10.57 (2.81, 39.69) Total Difficulties, No Prenatal Smoking: 1.98 (1.41, 2.79) Emotional Symptoms: 1.25 (0.60, 2.59) Hyperactivity/Inattention: 2.75 (1.46, 5.16)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Arbuckle et al. (2016b) representative sample Canada 2007–2009 Cross-sectional	CHMS n: 2097 Representative sample of children	Blood Child venous blood Age at measurement: 6–19 yr old	ADHD symptomology SDQ, reported ADD or ADHD Age at outcome: 6–19 yr old	Smoking, sex, income	**OR[b]** *Parent or Self-Reported Outcomes, Ages 6−19* ADD/ADHD: 2.39 (1.32, 4.32) Learning Disability (Low Income): 0.81 (0.37, 1.81) Learning Disability (High Income): 2.78 (1.40, 5.51) Medicine Taken (Fasting Sample): 0.83 (0.34, 2.02) Medicine Taken (Non-Fasting): 4.20 (1.92, 9.17) *SDQ, Ages 6−17* Total Difficulties: 2.16 (1.33, 3.51) Emotional Symptoms: 1.08 (0.68, 1.71) Hyperactivity/Inattention: 2.33 (1.59, 3.43)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Barg et al. (2018) Montevideo Uruguay Cross-sectional	n: 206 Children living in areas considered high risk for metal exposure	Blood Child venous blood; flame AAS or GFAAS Age at measurement: 5–8-year-old 4.2 µg/dL	teacher-rated ADHD and hyperactive behavior CRS-R: hyperactive, oppositional, cognitive, and ADHD-like behaviors (teacher ratings) Age at outcome: 5–8-year-old	Child IQ, iron status, and BMI, blood Pb testing method, household possessions, maternal education, current parent smoking	**PRs** *Cognitive Problems/Inattention* Total population (≥5 vs. 5 µg/dL): 1.02 (0.967, 1.076) Girls: 1.01 (0.995, 1.025) Boys: 1.01 (0.99, 1.03) *Hyperactivity* Total population (≥5 vs. 5 µg/dL): 1.01 (0.947, 1.077) Girls: 1.02 (1, 1.04) Boys: 0.99 (0.97, 1.01) *ADHD Index* Total population (≥5 vs. 5 µg/dL): 1.01 (0.952, 1.072) Girls: 1.01 (0.99, 1.03) Boys: 1.00 (0.98, 1.02)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Chan et al. (2015) 10 locations U.S. Cohort	National Institute of Child Health and Human Development, Study of Early Child Care and Youth Development n: 266 School children	Teeth (Shed molars) ICP-OES Mean: 0.46 µg/g	Disruptive behavior and ADHD subscales TBD completed by 3rd grade teachers; scores for (1) Total Disruptive Behavior; (2) subscale scores for ADHD, hyperactivity/impulsivity, inattention, and OD Age at outcome: teeth collected at 8–11 yr old (body burden)	Race, sex, paternal education, maternal education, marital status, and family SES	**Change in behavior score per µg/g of Pb concentration in teeth:[c]** DBD: −0.05 ADHD: −0.03 Impulsive: −0.06 Inattention: 0.00 Defiance: −0.09
†Forns et al. (2014) Catalonia Spain Cohort	INMA n: 385 Children of mothers enrolled in the population-based cohort as part of the INMA (Environment and Childhood) Project	Urine Maternal urine; ICP-MS, values below LOD were imputed Age at measurement: T1, T3 Median: 3.44, 1st; 3.63 3rd 75th: 4.64 1st, 4.84	ADHD symptoms ADHD-DSM-IV criteria and MSCA Age at outcome: 4 yr old	Age, maternal social class, and maternal mental health	**Change in neuropsychological outcomes per ng/mL increase in mother's urinary Pb concentration:** *T1* GCI MSCA: 1.46 (−2.76, 5.69) EF MSCA: 0.34 (−3.95, 4.63) *T3* GCI MSCA: −1.27 (−5.71, 3.17) EF MSCA: −0.74 (−5.24, 3.75) **IRR:** *T1* Inattention: 0.92 (0.57, 1.46) Hyperactivity: 1.04 (0.65, 1.65) *T3* Inattention: 0.71 (0.43, 1.18) Hyperactivity: 1.04 (0.64, 1.70)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Gu et al. (2018) Wuhan China Case-control	Hospital based case-control, recruitment: n: 389 cases; 392 controls Children 6–18 yr old	Blood Venous sample, whole blood, AAS Median: 5.685 µg/dL	ADHD, subtypes inattention, hyperactivity and impulsivity and combined Cases: ADHD DSM-IV (subtypes defined by inattention, hyperactivity and impulsivity [HI] and combined type [C]); WISC and Parent Symptom Questionnaire Age at outcome: 6–18 yr old	Age, sex (cases and controls compared on IQ, maternal alcohol, smoking, parental relationship, breastfeeding)	**OR[b]** BLL <56.85 µg/L, GG: Reference BLL >56.85 µg/L, GG: 1.865 (1.132, 3.075) BLL <56.85 µg/L, GA/AA: 1.255 (0.806, 1.954) BLL >56.85 µg/L, GA/AA: 1.871 (1.014, 3.451)
†Gump et al. (2017) Upstate New York U.S. Cross-sectional	Environmental Exposures and Child Health Outcomes n: 203 children residing in low- to middle-income communities	Blood venous blood; Age at measurement: 9–11 yr old	Externalizing behavior: attention, impulsivity, hyperactivity DBD for ADHD inattentive type and ADHD hyperactive-impulsive type; ASQ:I questionnaire for ASD (parent-rated); acute vagal response for stress (heart rate variability) Age at outcome: 9–11 yr old	Sex, race, age, and SES and Hg	Beta (95%)[b] ADHD-Inattention (Score) 0.01 (−0.14, 0.15) ADHD-Hyperactivity (Score) 0.16 (0.02, 0.30) Oppositional Defiant Disorder (Score) 0.16 (0.02, 0.31)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Huang et al. (2016) Mexico City Mexico 1997–2001 Cross-sectional	ELEMENT n: 578 Mother-child pairs	Blood Venous blood; ICP-MS Age at measurement: 6–13 yr old Mean: 3.4 µg/dL	ADHD symptomology CRS-R, CRS-R DSM-IV Age at outcome: 6–13 yr old	Maternal marital status, age, educational years, SES, smoking during pregnancy, child's age, sex, birth weight.	Adjusted associations between a 1-µg/dL increase in blood lead Cognitive Problem/Inattention –0.03 (–0.3, 0.2) Hyperactivity 1.2 (0.3, 2.0) ADHD Index 0.02 (–0.2, 0.3) CGI Restless-Impulsive 1.2 (0.3, 2.0) CRS-R DSM-IV Inattentive 0 (–0.3, 0.3) Hyperactive-Impulsive 1.1 (0.2, 2.0) Total 0.03 (–0.2, 0.3)
†Joo et al. (2017) Cheonan South Korea 2008–2010 Case-Control	n: 214 cases (=19 on the K-ARS or ADHD diagnosis); 214 control (49 elementary schools) Elementary school children	Blood Venous blood, AA spectrophotometry GM: 1.65 (cases) µg/dL; 1.49 µg/dL (controls)	ADHD symptomology K-ARS Age at outcome: 6 to 10 yr old	Maternal education, family history of ADHD, parental marital status, and teenage mother	**OR[b]** All ADHD: 1.28 (0.89, 1.83) Inattention: 1.63 (1.03, 2.58) Hyperactivity/impulsivity: 1.04 (0.53, 2.07)
†Kicinski et al. (2015) Flanders Belgium 2008 and 2011 Cross-sectional	n: 606 Third year secondary school students in two industrial areas in Flanders, Belgium	Blood venous blood, ICP-MS Age at measurement: 13.6–17 yr old Mean: 13.8 µg/dL 95th: 28.1 µg/dL	Sustained attention, short-term memory, manual motor speed CPT, NES Age at outcome: 13.6–17 yr old	R gender, age, smoking, passive smoking, household income per capita, the highest occupational category of either parent, and the education level of the mother	Effect estimates between BLL and neurobehavioral outcomes not reported due lack of statistical significance

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Lin et al. (2019) Xinhua China Aug. 2014 – Aug. 2015 Cross-sectional	n: 164 Children who visited a lead specialty clinic in Xinhua Hospital from August 2014-August 2015	Blood, Bone Child venous blood; AAS Tibia bone; XRF Age at measurement: 3–15 yr GM: Blood: Low: 4.3 µg/dL High: 19.6 µg/dL Bone: Low: 0.3 µg/g High: 12.8 µg/g	ADHD symptoms and comorbidities Vanderbilt-ADHD Diagnostic-Parent-Rating Scale Age at outcome: 3–15 yr	Children's age, sex, passive smoking (the frequency of smoking by parents and other household members in the presence of children), parity, maternal education levels and family yearly income	**OR[b]** *Inattention* BLL <10 µg/dL: Reference BLL ≥10 µg/dL: 3.3 (0.9, 12.4) *Hyperactivity/impulsivity* BLL <10 µg/dL: Reference BLL ≥10 µg/dL: 2.0 (0.5, 7.5) *Oppositional defiant disorder* BLL <10 µg/dL: Reference BLL ≥10 µg/dL: 2.7 (0.8, 8.9)
†Liu et al. (2014e) Guiyu China 2009 - 2011 Cross-sectional	n: 240 Native 3-7 yr old kindergarten children who have resided in Guiyu for more than 2 yr after birth	Blood Child venous blood; GFAAS Age at measurement: 3–7 yr Median: 7.33 µg/dL 75th: 9.13 µg/dL	ADHD symptomology ADHD (H,I,C) per DSM-IV; CPRS-R, CTRS-R, Rutter Child Behavior Questionnaire (antisocial behavior, neurotic) Age at outcome: 3–7 yr	Age and gender, residential site, time, heavy metal exposure	Measures of association for blood lead and attention outcomes not reported. Study only reports correlation analyses.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Lucchini et al. (2012) Valcamonica and Garda Lake areas in Province of Brescia Italy Cross-sectional	Junior high school-age children from 20 local public schools n: 299	Blood Child venous blood; GFAAS Age at measurement: 11–14 yr 1.71 µg/dL, Median: 1.50 75th: 2.10 µg/dL Max: 10.2 µg/dL	Conners'-Wells' Adolescent Self-Report Scale Long Form 10 subscales: family problems, emotional problems, conduct problems, cognitive problems/inattention, anger control problems, hyperactivity, ADHD index, DSM-IV (disattention), DSM-IV (hyperactivity/impulsivity), and DSM-IV (Total) Age at outcome: 11–14 yr	Sex, age at testing, parental education, SES, family size, parity order, BMI	**Betas** Performance IQ: −1.991 (−3.918, −0.064) Verbal IQ: −1.863 (−3.79, 0.064) Total IQ (Table 4): −2.237 (−4.101, −1.372) Total IQ (Table 5): −2.248 (−4.111, −0.385)
†Muñoz et al. (2020) Arica Chile 2009–2015 Cross-sectional	n: 2656 Children enrolled in a heavy metal intervention program	Blood Child venous blood; AAS Age at measurement: 3–17 yr Median: 1.0 µg/dL 75th: 2.0 µg/dL	Parent-reported attention deficit and hyperactivity recorded in medical records Age at outcome: 3–17 yr	Age, sex, parents' report of children exposure to secondhand tobacco smoke, housing material quality	**OR[b]** BLL ≥5 µg/dL: 2.33 (1.32, 4.12)
†Rodrigues et al. (2018) Salvador, Bahia Brazil Cross-sectional	n: 225 Children living near alloy plant	Blood GFAAS Age at measurement: 7–12 yr 1.2 µg/dL Max: 15.6 µg/dL	Child behavior CBCL: 8 domains including attention Age at outcome: 7–12 yr	Sex, age, height-for-age Z-score, maternal schooling, socioeconomic classification, and community violence index, as well as maternal IQ	*Change in Behavior (Total raw score) per log-µg/dL decrease in BLL:* −1.08 (−11.5, 9.3) *Change in Behavior (Total score T) per log-µg/dL decrease in BLL:* −0.74 (−5.3, 3.8)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Skogheim et al. (2021) Norway 2002–2009 Case-control	Norwegian Mother, Father and Child Cohort Study (MoBa) n: 397 ASD cases, 1034 controls Children	Blood Maternal whole blood; ICP-SFMS at wk 17 of gestation Age at Measurement: Prenatal, Week 17 og gestation GM (95% CI) (cases): 0.835 (0.797, 0.875) µg/dL GM (95% CI) (controls): 0.882 (0.860, 0.905) µg/dL	ADHD Diagnosis of ADHD (NPR) Age at outcome: 3 or less	Child sex, birth weight, birth year, and SGA, maternal age at delivery, education, parity, pre-pregnancy BMI, kg/m^2), self-reported smoking and alcohol intake during pregnancy, FFQ-based estimates of seafood intake (g/day), and dietary iodine intake (µg/day)	**OR[b]** *ADHD* Q1 (Reference): Q2: 1.15 (0.87, 1.52) Q3: 0.84 (0.63, 1.12) Q4: 1.09 (0.82, 1.45)
†Sobin et al. (2015) U.S. Cross-sectional	n: 421 Elementary school children	Blood 2 samples 60 days apart averaged; ICP-MS or Pb Care I Age at measurement: 5.1–11.8 yr old Mean: 2.7 µg/dL (males); 2.4 µg/dL (females)	Attention Age at outcome: 5.1–11.8 yr old	Sex, age and mother's level of education	**Beta** Motor dexterity non-dominant hand time (s): 1.93 (−1.343, 5.203) Working memory misses: 0.11 (0.051, 0.169) Working memory false alarms errors: 0.05 (−0.009, 0.109) Visual attention 5-choice movement time (ms): 26.07 (11.331, 40.809)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Soetrisno and Delgado-Saborit (2020) West Java (Depok, Bogor and Bekasi) Sukatani village (control) Indonesia Cross-sectional	School children living in urban locations near e-waste facility; control site n: 44 (22 from Bogor and 22 from Sukatani) Children selected from schools per teachers/ principal recommendation	Hair, soil, water hair samples from children in Bogor and Sukatani village. BLLs from 36 children in Bogor area (2010). Age at measurement: 6–9 yr Soil Pb mean: Depok-Bekasi: 3653 mg/kg; Sukatani: 93.2 mg/kg; Water Pb: all 10 samples below LOD; Hair Pb: Depok-Bekasi: 0.155 mg/g; Sukatani: 0.0729 mg/kg Max: Soil Pb: Depok-Bekasi: 7662 mg/kg; Sukatani: 115 mg/kg; Hair Pb: Depok-Bekasi: 0.841 mg/g; Sukatani: 0.255 mg/kg	Visual attention TMT A Age at outcome: 6–9 yr	Age, parental education, environmental tobacco smoke at home, and residential traffic exposure	Change in TMT-A (seconds) per mg/g unit of hair Pb 2.5 (−55, 60)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Zhang et al. (2015a) Guangdong China Jan. 2012–May 2012 Cross-sectional	n: 243 Preschool children residing near e-recycling plant	Blood Child venous blood, GFAAS Median: 7.9 µg/dL 95th: 16.9 µg/dL	ADHD symptomology Parent rating per DSM-IV ADHD criteria Age at outcome: 3–7 yr	Age, sex, father's work in e-waste, Serum ferritin, E-waste workshops around the house	**OR** ADHD: 2.4 (1.1, 5.2)

ADD = attention deficit disorder; ADHD = attention deficit/hyperactivity disorder; ASD = autism spectrum disorder; ASQ:I = Ages and Stages Questionnaire Inventory; BLL = blood lead level; BMI = body mass index; BRIEF = Behavior Rating Inventory of Executive Functions; CBCL = Child Behavior Check List; CHMS = Child Health Monitoring System; CI = confidence interval; CPRS-R = Conners' Parent Rating Scale-reformed; CPT = Continuous Performance Test; CTRS = Conners' Teacher Rating Scale; DBD = Disruptive Behavior Disorders; DSM = Diagnostic and Statistical Manual of Mental Disorders; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; FFQ = Food Frequency Questionnaire; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; Hg = mercury; ICP-MS = inductively coupled plasma mass spectrometry; ICP-OES = inductively coupled plasma optical emission spectrometry; ICP-SFMS = inductively coupled plasma sector field mass spectrometry; INMA = Infancia y Medio Ambiente (Environment and Childhood); IQ = intelligence quotient; K-ARS = Korean ADHD Rating Scale; LOD = limit of detection; mo = month(s); NPR = Norwegian Patient Registry; NR = not reported; OFT = open-field test; OD = oppositional defiant; Pb = lead; SDQ = Strengths and Difficulties Questionnaire; SES = socioeconomic status; SGA = small for gestational age; TBD = to be determined; TMT A = Trail Making Test: attention; XRF = X-ray fluorescence; yr = year(s).

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

[b]Effect estimate is unstandardized due to insufficient blood lead distribution information or insufficient information regarding log transformation.

[c]Result did not report confidence interval nor p-value

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

Table 3-9E Epidemiologic studies of Pb exposure and externalizing behaviors including conduct disorders, aggression, and criminal behavior in children and adolescents

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Tatsuta et al. (2012) Tohoku district Japan Study years NR Followed through 30 mo Cohort	TSCD birth cohort n: 306 Mother/child pairs in Japan	Blood Cord blood, HR-ICP-MS Age at measurement: delivery Median = 1.0 µg/dL 95th: 1.7 µg/dL	Externalizing behavior composite (oppositional, aggressive) CBCL Age at Outcome: 2.5 yr	Child age, birth weight, sex, maternal age at pregnancy, delivery type, birth order, drinking/smoking habits in pregnancy, duration of breastfeeding, maternal IQ, Evaluation of Environmental Stimulation score	Externalizing behavior beta = −0.032[b] (not significant)
†Sioen et al. (2013) Flanders Belgium Oct. 2002–Dec. 2003 (enrollment) Followed through June 2011 Cohort	Flemish Health and Environment Study (FLEHS 1) n: 270 Birth cohort of Flemish children living in either rural or urban areas	Blood Cord blood, HR-ICP-MS Age at measurement: delivery Median = 14.3 µg/L 75th: 25.3 µg/L	Conduct problems SDQ with 5 domains: emotional, conduct, hyperactivity, peer and social problems Age at outcome: 7 - 8 yr	Maternal and paternal BMI, maternal age, weight increase of mother during pregnancy, smoking during pregnancy, smoking behavior of maternal grandmother before birth of mother, parental education, current parental smoking, child sex, serious infections of child since birth (also tested interaction by sex)	OR per doubling of log-transformed Pb: Conduct problems: 1.182 (0.319, 4.385)[c]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Liu et al. (2014b) Jintan, Jiangsu province China Sep. 1, 2004–Apr. 30, 2005 (age 3−5 yr) Followed through age 6 yr Cohort	China Jintan Child Cohort Study n: 1025 children Chinese preschool children	Blood Child venous blood; GFAAS Age at measurement: 3–5 yr Mean (SD): 6.4 (2.6) µg/dL median = 6.0 µg/dL 75th: 7.5 µg/dL 90th: 9.4 µg/dL Max: 32 µg/dL	Aggressive behavior and oppositional defiant problems CBCL (Chinese version); Caregiver-Teacher Report Form; normalized T scores Age at outcome: 6 yr	Age at BLL test, sex, preschool residence, father's educational level, mother's educational level, father's occupation, parents' marital status, single child status, and child IQ	**Parent:** Aggressive β (95% CI): −0.018 (−0.264, 0.229) Oppositional β (95% CI): −0.03 (−0.28, 0.22) **Teacher:** Aggressive β (95% CI): 0.001 (−0.001, 0.003) Oppositional β (95% CI): 0.223 (−0.038, 0.484) Aggressive OR (95% CI): overall 1.07 (0.98, 1.17); boys 1.03 (0.93, 1.14); girls 1.21 (0.99, 1.47) Oppositional OR (95% CI): overall 1.06 (0.98, 1.15); boys 1.02 (0.92, 1.13); girls 1.12 (0.97, 1.29)
†Nkomo et al. (2017) Soweto/Johannesburg South Africa Apr. 23–Jun. 8, 1990 (enrollment) Followed 15–16 yr Cohort	BT20+ n: 1322 684 females, 87.2% Black African; 10.4% mixed ancestry urban residents; white and Indian participants excluded due to low numbers	Blood Child venous blood; GFAAS with Zeeman background correction Age at measurement: 13 yr Mean (SD) = 5.76 (2.42) µg/dL median = 5.62 µg/dL 75th: 7.08 µg/dL Max: 28 µg/dL	Violent behavior YSR – violent behavior Age at outcome: 15–16 yr	Child sex, ethnicity, maternal education, public/private hospital, SES (unclear covariate adjustment reporting)	physical violence β (95% CI): 0.05 (0.04, 0.05)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Nkomo et al. (2018) Soweto/Johannesburg South Africa Apr. 23–Jun. 8, 1990 (enrollment) Followed 14–15 yr Cohort	BT20+ n: 1086 Black African and mixed ancestry urban residents; white and Indian participants excluded due to low numbers	Blood Child venous blood; GFAAS with Zeeman background correction Age at measurement: 13 yr mean (SD) = 5.6 (2.3) µg/dL GM = 5.1 µg/dL median = 5.4 µg/dL	Aggressive behavior YSR Age at outcome: 14–15 yr	Child sex, maternal age, maternal education at birth, marital status, public/private hospital, SES	β Direct aggression (BLLs ≥10 µg/dL vs. <5 µg/dL): 0.43 (0.08, 0.78)[d]
†Boucher et al. (2012b) Nunavik, Arctic Quebec Canada 1992–2000 (enrollment) 2005–2010 (follow-up) Cohort	Cord Blood Monitoring Program and Environmental Contaminants and Child Development Study n: 279 Inuit Children	Blood Cord blood; AAS Child venous blood; ICP-MS Age at measurement: Avg: delivery (cord) 11.3 yr (child) Mean: 4.7 (cord); 2.7 (child) Max: 20.9 (cord); 12.8 (child)	Externalizing behavior and OD/CD problems CBCL and DBD rating scale Age at outcome: Avg: 11.3 yr old	Child age and sex, SES, age of the biological mother at birth, maternal tobacco use during pregnancy, and birth weight, Hg	β Externalizing behavior Cord: 0.09 (−0.05, 0.23)[c] Child: 0.14 (0.01, 0.26)[c] OR OD/CD 2nd vs. 1st tertile: 1.90 (0.88, 4.11)[c] 3rd vs. 1st tertile: 1.53 (0.67, 3.49)[c]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Beckwith et al. (2018) Cincinnati, OH U.S. 1979–1984 (enrollment) Followed through 19−24 yr Cohort	CLS n: 250 Young adults from birth cohort Recruited pregnant women in 1st or 2nd trimester from inner city neighborhoods with historically elevated incidence of childhood lead poisoning	Blood Child venous blood; ASV (see (Roda et al., 1988)) Age at measurement: 78 mo Mean: 7.99 µg/dL Max: 24.75 µg/dL	PPI score and gray and white matter volume in cingulate and ventromedial prefrontal cortex PPI; high resolution anatomical MRI with Voxel Based Morphometry to calculate brain volume changes Age at outcome: 19–24 yr old	Sex, race, age at time of imaging, gestational age at birth, weight at birth, maternal IQ, participant IQ, HOME score, adult marijuana usage, maternal prenatal alcohol use, maternal prenatal cigarette use, maternal narcotic use, and maternal prenatal marijuana use	Beta PPI Overall: 0.22 (0.06, 0.38)[e] Female: 0.16 (−0.05, 0.37)[e] Male: 0.22 (−0.02, 0.47)[e]
†Desrochers-Couture et al. (2019) Nunavik, Northern Quebec Canada Nov. 1993–Mar. 2002 (enrollment) Sep. 2005–Feb. 2010 (1st follow-up) Jan. 2013–Feb. 2016 (2nd follow-up) Cohort	NCDS-childhood n: 212 Inuit children from 14 coastal villages in Nunavik, Quebec, subsample from the Cord Blood Monitoring Program and NIH-infancy study	Blood Cord and venous child blood; GFAAS (cord), ICP-MS (child) Age at measurement: Cord: delivery; Avg child: 11.4 and 18.5 yr GM (GSD): 3.80 (1.84) µg/dL (cord); 2.34 (1.86) µg/dL (child); 1.63 (2.00) µg/dL (adolescent) Median:3.73 µg/dL (cord); 2.07 µg/dL (child); 1.52 µg/dL (adolescent) Max: 17.80 µg/dL (cord); 12.83 µg/dL (child); 18.13 µg/dL (adolescent)	Externalizing behavior; behavior problems; substance use Behaviors – externalizing (CBCL), hyperactivity-impulsivity (DBD, BAARS), oppositional defiant/conduct disorder (DBD, DISC); substance use Age at outcome: childhood (11 yr); adolescence (18 yr)	Child age, sex, SES, age of biological mother at delivery, maternal tobacco smoking during pregnancy, birth weight, blood Hg, house crowding, education of primary caregiver	Beta (95% CI): Child Blood: Child externalizing behavior: 0.23 (0.08, 0.38) Direct effect on adolescent externalizing: 0.34 (−0.38, 1.06) Indirect effect on adolescent externalizing: 0.18 (0, 0.36) Child OD/CD: 0.37 (0.06, 0.69) Direct effect on adolescent CD: 0.01 (−0.10, 0.13) Indirect effect on adolescent CD (0.01, −0.01, 0.03)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Tlotleng et al. (2022) Johannesburg South Africa April-June 1990 (birth), sub-cohort established at age 9 yr, followed through 23–24 yr Cohort	Young adults, n = 100 Sub-cohort (Bone Health Cohort) of singleton children (born April-June 1990) from BT20 Cohort enrolling women in 2nd and 3rd trimester residing in Soweto-Johannesburg	Bone Child tibia; K-XRF Age at measurement: NR Mean (SD), min, med (IQR), max: 8.7 (5.3), 0, 9 (5–12.5), 21 µg/g Males (n = 53): 8.1 (4.4), 0, 8 (5–11), 18 µg/g Females (n = 47): 9.4 (6.1), 0, 10 (4–14), 21 µg/g	Aggression scores (anger, physical, verbal, hostility) BPAQ Age at outcome: 23–24 yr	Age, sex, exposure to family violence, attitude toward neighborhood, exposure to crime and violence in the neighborhood Level of schooling, alcohol and drug abuse, presence of both parents at home, home environment, and SES (maternal education, housing type, participant's education/occupation) also considered.	Beta per 1 µg/g increase in bone Pb Anger aggression: 0.25 (0.04, 0.37) Physical aggression: 0.093 (−0.01, 0.27) Verbal aggression: 0.093 (−0.05, 0.23) Hostility: 0.03 (−0.19, 0.26)
†Reuben et al. (2019) Dunedin New Zealand Apr. 1, 1972–Mar. 31, 1973 (enrollment) Followed through Dec. 2012 Cohort	Dunedin Multidisciplinary Health and Development Study N: 579 Birth cohort of nationally representative (majority white) children with high rates of participation and follow-up	Blood Child venous blood; GFAAS Age at measurement: 11 yr Mean: 11.08 µg/dL (94% above 5 µg/dL)	Antisocial behavior in children Rutter Child Scale (averaged parent/teacher ratings) Age at outcome: 11 yr	Sex, childhood SES, maternal IQ, and family history of mental illness.	Beta Antisocial behavior: 0.02 (0.00, 0.04)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Chandramouli et al. (2009) Avon U.K. Jul. – Dec. 1992 (enrollment) Followed through 8 yr Cohort	10% random subsample of Avon Longitudinal Study of Parents and Children (ALSPAC) n = 488 Birth cohort	Blood Child venous blood; AAS with micro sampling flame atomization Age at measurement: 30 mo Mean (SD): NR Group 1: 0-<2 µg/dL Group 2: 2-<5 µg/dL Group 3: 5-<10 µg/dL Group 4: >10 µg/dL	Antisocial activities Parent/teacher ratings on Antisocial Behavior Interview Age at outcome: 8 yr	Maternal education and smoking, home ownership, home facilities score, family adversity index, paternal SES, parenting attitudes at 6 mo, child sex. Also considered child IQ.	ORs for increased score Group 1 (0–<2 µg/dL): ref Group 2 (2–<5 µg/dL): 0.93 (0.47, 1.83) Group 1 (5–<10 µg/dL): 1.44 (0.73, 2.84) Group 1 (>10 µg/dL): 2.90 (1.05, 8.03)
Wright et al. (2008) Cincinnati, OH United States 1979–1984 (enrollment) Followed through 19–24 yr Cohort	CLS n: 250 Young adults from birth cohort Recruited pregnant women in 1st or 2nd trimester from inner city neighborhoods with historically elevated incidence of childhood lead poisoning	Blood Child blood; ASV Age at measurement: 6 yr Median (5th–95th): 6 yr: 6.8 (3.4–18) µg/dL 0–6 yr avg: 12 (6.0–26) µg/dL	Criminal arrests County records Age at outcome: 19–24 yr	Maternal IQ and education, sex, SES. Also considered potential confounding by maternal prenatal smoking, marijuana use, narcotic use, and prior arrests, HOME score, birth weight, # children in the home, public assistance in childhood.	RRs (yes/no) Age 6 blood Pb: 1.05 (1.01, 1.09) Age 0–6 yr avg blood Pb: 1.01 (0.98, 1.05)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Fruh et al. (2019) Eastern Massachusetts U.S. 1999–2002 (enrollment) Followed through age 7 yr Cohort	Project Viva n: 1006 Birth cohort of mother-child pairs	Blood Maternal venous blood; ICP-MS Age at measurement: T2 Median: 1.1 µg/dL	Parent teacher ratings of conduct problems using SDQ Standardized for child age and sex Age at outcome: 7 yr old	Maternal 2nd trimester Hg and Mn levels, nulliparity, smoking during pregnancy, IQ, and education; paternal education; HOME composite score and household income; and child race/ethnicity	Parent ratings: Overall β (95% CI): 0.10 (−0.10, 0.30) Boys: 0.07 (−0.18, 0.32) Girls: 0.13 (−0.13, 0.40) Teacher ratings: Overall β (95% CI): 0.18 (−0.08, 0.44) Boys: 0.18 (−0.17, 0.53) Girls: 0.17 (−0.13, 0.46)
†Ruebner et al. (2019) 46 centers U.S. Study Years: NR Follow-up: NR Cohort	CKiD Cohort study n: 412 Children ages 1–16 yr at recruitment with mild to moderate CKD	Blood Child venous blood; ICP-MS. The BLL measurement closest to the time of neurocognitive testing was used for analysis (concurrent). Age at measurement: NR; 2, 4, or 6 yr after study entry Median: 1.2 µg/dL 75th: 1.8 µg/dL Max: 5.1 µg/dL	Externalizing behaviors, composite index on the BASC-2 (see also 3.5.1 and 3.5.2) The last available test results were used to evaluate long-term effects. Mean time between BLL and neurocognitive testing was 2.3 yr. Age at outcome: 1–16 yr	Age, sex, race, poverty, and maternal education	Adjusted BASC-2 results were not reported because they were not statistically significant.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Naicker et al. (2012) Johannesburg South Africa Apr. – Jun. 1990 (enrollment) Followed through 20 yr Cohort	Birth to Twenty cohort (Bt20) n: 1041 (487 boys, 554 girls) Singleton children representative of South Africa population	Blood Child venous blood; GFAAS Age at measurement: 13 yr median = 5.4 µg/dL; GM = 5.2 µg/dL Max: 28.1 µg/dL	Rule-breaking behavior, aggressive behavior YSR (adapted from CBCL for use in adolescents) Age at outcome: 13 yr	SES, maternal education, demographic factors	Attacking people – boys β (95% CI): 0.54 (0.09, 0.98)[d]
†Rodrigues et al. (2018) Simoes Filho, Salvador, Bahia Brazil Study years NR Cross-sectional	Simoes Filho, Brazil n: 225 Children aged 7–12 yr, attending public in town near ferro-Mn alloy plant	Blood Child venous blood; GFAAS Age at measurement: 7–12 yr median = 1.2 µg/dL Max: 15.6 µg/dL	Behavioral problems/disruptive behavior (externalizing behavior, aggressive behavior, rule-breaking behavior) CBCL Age at outcome: 7–12 yr	Gender, age, SES, community violence score, maternal IQ	Attacking people – Adjusted total T-score β (95% CI): –0.74 (−5.3, 3.8)[d]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Barg et al. (2018) Montevideo Uruguay Study years NR Cross-sectional	Montevideo sample n: 206 Children in urban area	Blood Child venous blood (fasting); AAS with flame or graphite furnace ionization Age at measurement: 6–8 yr (mean = 6.75 yr) mean = 4.2 µg/dL	Behavior problems (e.g., oppositional) CRS-R; BRIEF Age at outcome: 6–8 yr (mean = 6.75 yr)	Child IQ, iron status, BMI, household possessions, maternal education, current parent smoking (also looked at sex and Pb evaluation method in sensitivity analyses)	BRIEF: Behavioral Regulation Index (PR [95% CI]): overall = 1.01 (1.00, 1.03); girls = 1.03 (1.00, 1.05); boys = 0.99 (0.97, 1.01) CTRS-R: Oppositional (PR [95% CI]): overall = 1.00 (0.98, 1.02); girls = 1.01 (0.99, 1.04); boys = 0.99 (0.96, 1.02)
†Liu et al. (2022b) Philadelphia County, PA; Suburbs of Philadelphia, PA United States Study years NR Cross-sectional	Healthy Brains and Behavior n: 131	Blood Child blood; HR-ICP-MS. Age at Measurement: 11−12 yr Mean = 2.2 µg/dL; Median = 1.10 µg/dL 75th: 1.8 µg/dL Max: 35.4 µg/dL	Parent-report and child-report of externalizing behavior (composite) Scores derived from factor analyses of 14 validated measures of antisocial/ aggressive behavior (RPQ, CBCL, YSR, APSD, CODDS, AQ from BPAQ) Age at outcome: 11−12 yr	OLS regression adjusted for sex and race.	Beta for externalizing behavior: Parent-reported: 0.20 (0.05, 0.34) Child-reported: 0.20 (0.04, 0.35)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Nigg et al. (2010) Study location and year NR Case-control	n = 326 Recruitment by community advertisements, mailings, outreach to clinics	Blood Child venous blood; ICP-MS Age at Measurement: 6−17 yr Mean (SE) = 0.73 (0.04) µg/dL	Externalizing composite score (oppositional and conduct symptoms) on parent K-SADS Oppositional behavior on parent and teacher CRS Age at Outcome: 6−17 yr	Household income, maternal smoking, child age, sex, blood hemoglobin, child FSIQ (WISC-IV)	Beta for SD increase in scores per SD increase in log-10 Pb Parent ratings: K-SADS externalizing composite: 0.21 (0.05, 0.37) CRS oppositional behavior: 0.09 (−0.09, 0.27) Teacher ratings: CRS oppositional behavior: 0.11 (−0.01, 0.23)
†Amato et al. (2013) Milwaukee, WI United States Study years NR Followed 7–10 yr (blood Pb before age 3, outcome assessment at 4th grade) Cohort	Wisconsin Childhood Pb Poisoning Prevention Project / Milwaukee Public School n: 1076 unexposed; 2687 exposed; 3763 total Exposed individuals were more likely to be Black or Hispanic, and be on assisted lunch programs	Blood Maximum child blood Pb, methods varied by providers Age at measurement: <3 yr Mean NR; reported exposed (BLL 10–20 µg/dL) vs. unexposed (<5 µg/dL) Max: 20 µg/dL	School suspensions Unduplicated suspension count Age at outcome: 10 yr (4th grade)	Gender, race/ethnicity, income (free/reduced lunch)	Suspensions OR for exposed (10−20 µg/dL) vs. unexposed (<5 µg/dL): 2.66 (2.12, 3.32)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Boutwell et al. (2017) St. Louis City, MO United States Study years: NR 16-year period Other – ecological study	106 census tracts in St. Louis City, MO n: 59,645 children; 15,734 violent crimes St Louis residents	Blood NR Age at measurement: <72 mo age NR	Violent crime (crimes with firearm, assault crimes, robbery crimes, homicides, rape) Police department/uniform crime report – violent crime (crimes with firearm, assault crimes, robbery crimes, homicides, rape)	Concentrated disadvantage; mean age of housing; proportion occupied by renters; domestic assaults	RR for 1% increase in proportion of elevated blood tests in the census tract. Firearm crimes: 1.03 (1.025, 1.035) Assault: 1.03 (1.025, 1.035) Robbery: 1.03 (1.02, 1.04) Homicides: 1.03 (1.015, 1.045) Rape: 1.01 (0.99, 1.03)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Beckley et al. (2018) Apr. 1, 1972–Mar. 31, 1973 (enrollment) Followed through 38 yr Cohort	Dunedin Multidisciplinary Health and Development Study N: 553 Birth cohort of nationally representative (majority white) children with high rates of participation and follow-up	Blood Child venous blood; GFAAS Age at measurement: 11 yr mean = 11.01 µg/dL Max: 31 µg/dL	Criminal offending (criminal conviction, recidivism, conviction for violent offense, self-reported criminal offending) Official conviction records from central police computer; self-reported offending interview Age at outcome: 38 yr	Sex, age	OR (ref: no conviction) Any criminal conviction: 1.042 (1, 1.086) One-time: 1.046 (0.99, 1.104) Recidivistic: 1.039 (0.986, 1.095) Nonviolent: 1.051 (1.003, 1.101) Violent offense: 1.025 (0.962, 1.092) Beta (self-report offending) 15 yr: 0.1 (0.015, 0.185) 18 yr: 0.06 (−0.02, 0.14) 21 yr: 0.01 (−0.065, 0.085) 26 yr: 0.06 (−0.015, 0.135) 32 yr: 0.04 (−0.04, 0.12) 38 yr: 0.02 (−0.06, 0.1)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Wright et al. (2021) Cincinnati, OH United States 1979–1984 (enrollment) Followed through 2013 Cohort	CLS n: 254 Young adults from birth cohort Recruited pregnant women in 1st or 2nd trimester from inner city neighborhoods with historically elevated incidence of childhood lead poisoning	Blood Maternal blood (n = 219) and child blood; ASV Age at measurement: prenatal, <60 mo (avg child), 60–78 mo (avg late child), 78 mo (late child) Mean (SD): Average child (0–60 mo): 14.4 (6.6) µg/dL	Total number of arrests for each subject (2003–2013 and lifetime), violent crimes, drug crimes, and property crimes Hamilton County public records Age at outcome: 18–24 yr, 27–33 yr	Birth weight (grams), maternal age at delivery, Appearance, Pulse, Grimace, Activity, and Respiration scores taken at 1 min, self-reported maternal drug use during pregnancy that includes reports of alcohol, marijuana and tobacco use, maternal IQ measured by the WAIS-R, and HOME Inventory scores across the first 3 yr	IRR Arrests 2003−2013 for 6-year blood Pb, controlling for prior arrests 1998−2003: 1.008 (0.995, 1.021) 6 yr blood Pb Lifetime Arrests: 1.016 (1.002, 1.03) Property Arrests: 1 (0.977, 1.023) Drug Arrests: 1.032 (1.005, 1.06) Violent Arrests: 1.016 (0.992, 1.039) Adult Arrests: 1.014 (1, 1.027) EEs for other blood Pb sources are available but not listed for the sake of space.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Emer et al. (2020) Milwaukee, WI Born June 1 1986-Dec 31, 2005 Outcome assessed January 1, 2005-December 31 2015 Cohort	Adolescents enrolled in Milwaukee public school (2004–2016) with BLL before age 6 N = 82,612	Capillary or venous BLLs measured by the Milwaukee Health department Male: Mean (IQR) 5.6 (5.8) Peak (IQR): 7.0 (7.0) Female: Mean (IQR): 5.3 (5.0) Peak (IQR): 6.0 (8.0) Age: < 6 yr	Firearm violence perpetration (i.e., coded as arrestee, suspect or person of interest by Milwaukee police department; victim of firearm violence assessed using police records	Sex, race; socioeconomic status, and year of birth	Perpetration: OR (mean Pb): 1.03 (1.02, 1.04) OR (peak Pb): 1.02 (1.01, 1.02) Victimization OR (mean Pb): 1.04 (1.03, 1.05) OR (peak Pb): 1.02 (1.01, 1.03)

BASC-2 = Behavior Assessment System for Children; BLL = blood lead level; BMI = body mass index; BRIEF = Behavior Rating Inventory of Executive Functions; BT20+ = Birth to Twenty Plus; CBCL = Child Behavior Check List; CI = confidence interval; CKD = chronic kidney disease; CKiD = Chronic Kidney Disease in Children Study; CLS = Cincinnati Lead Study; CTRS-R = Conners' Teacher Rating Scale-Revised; DBD = Disruptive Behavior Disorder; DISC = Disrupted-in-Schizophrenia; EES = Evaluation of Environmental Stimulation; FLEHS = Flemish Environment and Health Study; GFAAS = graphite furnace atomic absorption spectrometry; Hg = mercury; HOME = Health Outcomes and Measures of the Environment; ICP-MS = inductively coupled plasma mass spectrometry; IQ = intelligence quotient; IQR = interquartile range; K-SADS = Kiddie Schedule for Affective Disorders and Schizophrenia; Mn = manganese; mo = month(s); NCDS = Nunavik Child Development Study; NR = not reported; Pb = lead; PPI = Psychopathic Personality Inventory; RR = relative risk; SDQ = Strengths and Difficulties Questionnaire; SE = standard error; SES = socioeconomic status; T2 = second trimester of pregnancy; TSCD = Tohoku Study of Child Development; WAIS-R = Weschler Adult Intelligence Scale-Revised; yr = year(s); YSR = Youth Self-Report.

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

[b]Results are unstandardized because they did not have an associated SE, CI, or p-value reported in the study.

[c]Results are unstandardized because the log base used for exposure transformation was unspecified in the study.

[d]Results are unstandardized because the Pb level distribution data was not available.

[e]The CI was calculated from a p-value and the true CI may be wider or narrower than calculated.

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

Table 3-10E Epidemiologic studies of Pb exposure and internalizing behaviors in children

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Wasserman et al. (2001) Pristina Yugoslavia 1984−1985 (enrollment) Followed through 1999 Cohort	N: 191 Recruitment from prenatal clinics	Blood Child blood; method NR Age at outcome: Delivery to 4−5 yr Lifetime (to age 4−5 yr) avg blood Mean (SD) of log−10 Pb: 0.86 (0.12) µg/dL, Mean: ~7.2 µg/dL	Internalizing behavior scores and subscores (i.e., anxious/depressed, somatic complaints, and withdrawn) assessed using maternal ratings of CBCL Age at Outcome: 4−5 yr	Sex, ethnicity, age, maternal education and smoking history, HOME score, birth weight	Betas for log−10 change in outcome: Internalizing composite: 0.152 (0.023, 0.281) Anxious/depressed: 0.041 (−0.089, 0.17) Somatic complaints: 0.107 (−0.062, 0.276) Withdrawn: 0.066 (−0.073, 0.205)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Burns et al. (1999) Port Pirie Australia May 1979-May 1982 (enrollment) Followed to age 11−13 yr Cohort	Port Pirie Cohort Study (PPCS) N: 322 Recruited 90% of live births in a lead smelting community	Blood Lifetime avg (to age 11−13 yr) blood GM (95% CI) µg/dL Boys: 14.3 (13.5, 15.1) Girls: 13.9 (13.2, 14.6)	Internalizing behavior scores and subscores (i.e. anxious/depressed, somatic complaints, and withdrawn) assessed using maternal ratings of CBCL Age at Outcome: 11−13 yr	Maternal age, prenatal smoking status, IQ, concurrent psychopathology, and education, birth weight, type of feeding, length of breastfeeding, paternal education and occupation, birth order, family functioning, parental smoking, marital status, HOME score, child IQ	Beta Male: Internalizing composite: 0.8 (−0.9, 2.4)[b] Anxious/depressed: 0.8 (−0.2, 1.8)[b] Somatic complaints: −0.1 (−0.7, 0.4)[b] Withdrawn: 0.1 (−0.4, 0.7)[b] Female: Internalizing composite: 2.1 (0.0, 4.2)[b] Anxious/depressed: 1.3 (0.1, 2.5)[b] Somatic complaints: 0.3 (−0.4, 0.9)[b] Withdrawn: 0.6 (0.0, 1.1)[b]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Bellinger et al. (1994b) Boston, MA US 1979−1980 (birth) followed to age 8 yr Cohort	N: 1782 Recruitment at birth hospital	Blood, Tooth Cord blood and shed deciduous teeth. Dentin taken from zone representing cumulative postnatal deposition; ASV Age at Measurement: 6 yr Tooth mean (SD): 3.4 (2.4) µg/dL Range: 0.1−28.9 10th−90th percentiles: 1.2−6.3 95th percentile: 7.4 Cord blood mean (SD): 6.8 (3.1) µg/dL Interval analyzed: 0.1−35.1 95th percentile: 12.2	Internalizing behavior T scores and subscores (i.e. anxious/depressed, somatic complaints, and withdrawn) assessed using teacher ratings of CBCL Age at Outcome: 8 yr old	Prepregnant weight, race, Cesarean section, maternal marital status, prenatal care, paternal education, colic, child current medication use, sibship size, sex, birth weight. Also considered potential confounding by public assistance, prenatal smoking, maternal education but not parental caregiving quality.	Betas for ln-transformed change in internalizing T score: Cord blood: −0.07 (−0.23, 0.10) Tooth: 0.43 (0.09, 0.77)
†Winter and Sampson (2017) Chicago, Illinois U.S. born 1995–1997 to 2013, followed through 17 yr old Cohort	PHDCN n: 254 Children and caregivers living in Chicago	Blood Child venous and capillary blood; methods NR Age at measurement: before 6 yr Avg BLL before 6 yr Mean: 6.4 µg/dL	Internalizing on the CBCL (i.e., anxiety and depression); see also Section 3.5.2 (impulsivity) PC questionnaire) Age at outcome: Mean: 17 yr old	Age, sex, race/ethnicity; PC's immigrant generational status, marital status, education, Temporary Assistance for Needy Families receipt; proportion residential neighborhood that is non-Hispanic Black, Hispanic, and below the poverty line; proportion of the child's residential neighborhood tested for Pb exposure	Beta Anxiety/depression: 0.09 (0.03, 0.16)

†Liu et al. (2014b) Jintan, Jiangsu province China Sep. 1, 2004 – Apr. 30, 2005 (age 3−5 yr) Followed to age 6 yr Cohort	China Jintan Child Cohort Study n: 1025 children Chinese preschool children	Blood Child venous blood; GFAAS Age at measurement: 3–5 yr old Mean (SD): 6.4 (2.6) µg/dL median = 6.0 µg/dL 75th: 7.5 µg/dL 90th: 9.4 µg/dL Max: 32 µg/dL	Internalizing problems composite and subscores (emotionally reactive, anxious/depressed, somatic complaints, withdrawn, and sleep) CBCL (Chinese version); Caregiver-Teacher Report Form; normalized T scores Age at outcome: 6 yr	Age at BLL test, sex, preschool residence, father's educational level, mother's educational level, father's occupation, parents' marital status, single child status, and child IQ	Internalizing problems Parent beta: −0.029 (−0.280, 0.222) Teacher beta: 0.223 (−0.037, 0.484) Teacher OR: 1.10 (1.03, 1.18) Emotionally Reactive Parent beta: −0.117 (−0.365, 0.131) Teacher beta: 0.322 (0.058, 0.587) Teacher OR: 1.10 (1.02, 1.19) Anxiety/Depression: Parent beta: 0.101 (−0.151, 0.354) Teacher beta: 0.001 (−0.001, 0.003) Teacher OR: 1.12 (1.03, 1.23) Somatic Complaints Parent beta: −0.171 (−0.436, 0.094) Teacher beta: 0.001 (−0.003, 0.001) Teacher OR: 1.01 (0.90, 1.13) Withdrawn Parent beta: 0.096 (−0.158, 0.349)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Teacher beta: 0.001 (−0.001, 0.003) Teacher OR: 1.02 (0.93, 1.12) Clinically significant anxiety Parent beta: 0.044 (−0.212, 0.299) Teacher beta: 0.253 (0.016, 0.500) Teacher OR: 1.12 (1.03, 1.23)
†Joo et al. (2018) Seoul, Ulsan, Cheonan South Korea 2006–2011 (enrollment) Followed through 5 yr Cohort	MOCEH n: 575 mother-child pairs pregnant women	Blood Maternal venous blood, cord blood, and child blood; AAS Age at measurement: 20 wk gestation (maternal); delivery (cord); 2,3 and 5 yr (child) GM: Maternal 1.28 µg/dL (early), 1.24 (late) 0.9 (cord) Child 1.55 (age 2), 1.43 (age 3), 1.29 (age 5)	Internalizing behavior K-CBCL (emotional reactivity, anxious/ depressed, somatic complaints, and withdrawn/depressed states) See also Section 3.5.2 Age at outcome: 5 yr old	Maternal age at childbirth, parity, maternal educational level, household income, residential area, and breastfeeding	Beta (95% CI): Internalizing at 5 yr Maternal-early pregnancy Male: −0.16 (−2.54, 2.23) Female: −0.13 (−1.86, 1.60) Maternal-late pregnancy Male: 2.55 (0.22, 4.88) Female: −0.18 (−2.66, 2.31) Cord blood Male: 2.44 (−0.74, 5.63) Female: −1.00 (−4.30, 2.29)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Child blood–2 yr Male: −0.03 (−2.07, 2.00) Female: 2.94 (0.36, 5.52) Child blood–3 yr Male: 0.25 (−2.33, 2.82) Female: 2.76 (−0.73, 6.26) Child blood–5 yr (concurrent) Male: 1.23 (−2.10, 4.56) Female: 5.65 (0.50, 10.80)
†Fruh et al. (2019) Eastern Massachusetts U.S. 1999–2002 (enrollment) Followed through age 7 yr Cohort	Project Viva n: 1006 Birth cohort of mother-child pairs	Blood Maternal venous blood; ICP-MS Age at measurement: T2 Median: 1.1 µg/dL	Parent teacher ratings of emotional problems SDQ Standardized for child age and sex Age at outcome: 7 yr old	Maternal 2nd trimester Hg and Mn levels, nulliparity, smoking during pregnancy, IQ, and education; paternal education; HOME composite score and household income; and child race/ethnicity	Parent ratings: Overall β (95% CI): 0.30 (0.05, 0.55) Boys: 0.17 (−0.17, 0.50) Girls: 0.52 (0.18, 0.86) Teacher ratings: Overall β (95% CI): 0.07 (−0.22, 0.35) Boys: 0.02 (−0.33, 0.37) Girls: 0.12 (−0.31, 0.54)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Sioen et al. (2013) Flanders Belgium Oct. 2002 – Dec. 2003 (enrollment) Followed through June 2011 Cohort	Flemish Health and Environment Study (FLEHS 1) n: 270 Birth cohort of Flemish children living in either rural or urban areas	Blood Cord blood, HR-ICP-MS Age at measurement: delivery median = 14.3 µg/L 75th: 25.3 µg/L	Emotional problems SDQ with 5 domains: emotional, conduct, hyperactivity, peer and social problems Age at outcome: 7 - 8 yr	Maternal BMI, age at pregnancy, weight increase during pregnancy, smoking, paternal BMI, if parents smoke, smoking behavior maternal grandmother before the birth of the mother, parental education, child sex, serious child infections	OR per doubling of log-transformed Pb: Emotional problems: 0.900 (0.524, 1.547)[b]
†Rokoff et al. (2022) New Bedford, MA Born: 1993–1998 Cohort	Children residing near Superfund site n: 468 of 788 mother-infant pairs.	Blood Cord blood; ICP-MS Child blood; medical records, method NR Age at measurement: delivery Mean (SD) cord BLL CPRS: 1.37 µg/dL (0.94) BASC-2: 1.37 µg/dL (0.95) Mean (SD) peak postnatal BLL CPRS: 6.68 µg/dL (3.95) BASC-2: 6.58 µg/dL (3.87)	Internalizing Behavior Anxiety, Depression, Somatization, and Internalizing Problems on BASC-2 SRP Anxious-Shy and Psychosomatic on CPRS Anxious-Shy on CTRS Age(s) at outcome: 8 yr (CPRS and CTRS) and 15-years (BASC-2)	Maternal age, marital status, parity, parental education), household income, maternal smoking, alcohol consumption during pregnancy, pre-pregnancy weight, height, and gestational weight gain, BMI, prenatal social disadvantage index, HOME score, maternal IQ No interactions between chemicals; linear regression models adjusted for Mn and organochlorines,	β BASC-2 SRP Anxiety: 1.78 (0.58, 2.99) Depression: 0.79 (−0.39, 1.97) CPRS Psychosomatic Boys: 2.08 (0.07, 4.10) Girls: 0.48 (−1.00, 1.97) C-R functions presented

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Rasnick et al. (2021) Cincinnati, OH Born: Oct 2001–Jul 2003 Exposure: 2001–2005 Cohort	CCAAPS n: 263	Air LURF, air sampling at 24 sites (C-V R^2 = 0.89), predicted air concentration at child's residence. Children residing >1,500 m or <400 m from major highway eligible. Median: 0.51 ng/m^3 (range 0–10.8 ng/m3)	Internalizing and Externalizing Behavior BASC-2; internalizing behaviors (anxiety, depression, somatization), externalizing behaviors (aggression, conduct problems, and hyperactivity), behavioral symptoms index (attention problems, atypicality, and withdrawal) Age at outcome: 12 yr	Maternal education, community-level deprivation, blood Pb concentrations, greenspace, and traffic related air pollution.	B (anxiety score) = 3.1 (95% CI: 0.4, 5.7) per ng/m^3 Note: no association with depression, somatization, conduct problems, hyperactivity, withdrawal behaviors
†Ruebner et al. (2019) 46 centers U.S. Study Years: NR Follow-up: 1–16 yr Cohort	CKiD Cohort study n: 412 Children with mild to moderate CKD	Blood Child venous blood; ICP-MS. The BLL measurement closest to the time of neurocognitive testing was used for analysis (concurrent). Age at measurement: NR; 2, 4, or 6 yr after study entry Median: 1.2 µg/dL 75th: 1.8 µg/dL Max: 5.1 µg/dL	Internalizing behaviors, composite index on the BASC-2 (see also 3.5.1 and 3.5.2) The last available test results were used to evaluate long-term effects. Mean time between BLL and neurocognitive testing was 2.3 yr. Age at outcome: 1–16 yr	Age, sex, race, poverty, and maternal education	Adjusted BASC-2 results were not reported because they were not statistically significant.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Horton et al. (2018) Mexico City Mexico born 1994–2006 and followed through age 6–16 Cohort	ELEMENT Project n: 133 healthy, low to moderate income mother (18–39 yr old)-child pairs	Tooth Tooth Pb (prenatal, postnatal metrics derived); laser ablation ICP-MS Age at measurement: tooth Pb concentration corresponded to prenatal and 300 days after birth Figure 1c	Internalizing behavior on the BASC-2. See Section 3.5.2 (attention and hyperactivity) and BSI Age at outcome: 8–11 yr old	Maternal age at delivery, maternal education, smoking, SES, maternal IQ	Beta: BASC-2 Internalizing (10 mo): NR Anxiety (12 mo): 0.4 (95% CI NR)[c] Internalizing composite result was not reported because it was not statistically significant.
†Doherty et al. (2020) New Hampshire U.S. 2009 to 2014–2019 Cohort	NHBCS n: 371 (SRS−2); 318 (BASC-2) Mother-child pairs	Toenails Maternal and infant toenails; Median (maternal prenatal): 0.14 µg/g (SRS−2), 0.13 µg/g (BASC-2); Median (maternal postnatal): 0.10 µg/g (SRS), 0.11 µg/g (BASC-2); Median (infant): 0.35 µg/g (SRS−2), 0.37 µg/g	Internalizing Behaviors on the BASC-2; see also Section 3.5.2.2 Age at outcome: 3 yr	Maternal age, maternal BMI, parental education, maternal smoking, marital status, parity, child age at last breastfeeding, Healthy Eating Index score, year of birth, sex, and age of the child at testing	Exposure was $\log_2$ transformed. Betas per 1 µg/g increase in toenail Pb concentration. Total Maternal prenatal: −0.14 (−0.28, 0.00)[d] Maternal postnatal: 0.06 (−0.05, 0.18)[d] Child: 0.01 (−0.14, 0.16)[d] Males Maternal prenatal: −0.17 (−0.36, 0.01)[d] Maternal postnatal: 0.31 (0.15, 0.47)[d] Child: 0.09 (−0.13, 0.31)[d] Females

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Maternal prenatal: −0.16 (−0.33, 0.01)[d] Maternal postnatal: −0.04 (−0.20, 0.13)[d] Child: −0.15 (−0.36, 0.06)[d]

BASC = Behavioral Assessment System for Children; BLL = blood lead level; BMI = Body Mass Index; BRIEF = Behavior Rating Inventory of Executive Functions; CBCL = Child Behavior Check List; CCAAPS = Cincinnati Childhood Allergy and Air Pollution Study; CI = confidence interval; CKD = chronic kidney disease; CKiD = Chronic Kidney Disease in Children Study; CPRS = Conners' Parent Rating Scale; C-TRF = Caregiver-Teacher Report Form; CTRS = Conners' Teacher Rating Scale; C-V R^2 = cross validated R-square; DSM = Diagnostic and Statistical Manual of Mental Disorders; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; FSIQ = full-scale intelligence quotient; GFAAS = graphite furnace atomic absorption spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; HOME = Health Outcomes and Measures of the Environment; IQ = intelligence quotient; K-CBCL = Korean Child Behavior Check List; LURF = Land Use Random Forest; MOCEH = Mothers' and Children's Environmental Health; NHBCS = New Hampshire Birth Cohort Study; NR = not reported; OR = odds ratio; Pb =lead; PC = primary caregiver; PHDCN = Project on Human Development in Chicago Neighborhoods; SDQ = Strengths and Difficulties Questionnaire; SRP = Self-Report of Personality; SRS = Social Responsiveness Scale; yr = year(s); T2 = second trimester of pregnancy.

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

[b]Results are unstandardized because the log base used for exposure transformation was unspecified in the study.

[c]Results are unstandardized because they did not have an associated SE, CI, or p-value reported in the study.

[d]Results are unstandardized because the biomarker used for Pb exposure measurement is toenails.

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

Table 3-11E Epidemiologic studies of Pb exposure and motor function in children

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Ris et al. (2004) Cincinnati, OH US 1979−1985 (enrollment) Cohort	Cincinnati Lead Study (CLS) N: 195 Birth cohort recruited prenatally from obstetrical clinics	Blood Prenatal maternal blood: NR Average Childhood blood (mean of 20 quarterly concentrations obtained from 3−60 mo): NR 78 mo blood lead: NR	Visuoconstruction (Block Design Subtest, ROCF-Accuracy) and Fine-Motor (Grooved Pegboard Test, Finger Tapping Test) factors Age at outcome: 15−17 yr	Maternal IQ, SES, total average HOME scores, and adolescent marijuana consumption	Beta Visuoconstruction Prenatal: −0.157 (−0.277, −0.037)[b] Average: 0.028 (−0.052, 0.108)[b] 78-month: 0.014 (−0.088, 0.116)[b] Fine-motor Prenatal: −0.017 (−0.056, 0.022)[b] Average: −0.016 (−0.041, 0.009)[b] 78-month: −0.046 (−0.077, −0.015)[b]
Bhattacharya et al. (1995) Cincinnati, OH US 1979−1984 (enrollment) Cohort	Cincinnati Lead Program Project N: 202 Pregnant mothers living in older houses in poor condition and with chipping lead-based paint and lead laden dust	Blood GM (SD) (min-max) ug/dL: Prenatal maternal blood: 8.0 (1.58) (2−22) Average Childhood blood (mean of 20 quarterly concentrations obtained from birth to 5 yr): 11.9 (1.5) (4−28)	Postural balance, including sway area (SA) and sway length (SL) Age at outcome: 5 yr	Age, height, weight, birth length, birth weight, Hgb, TIBC, Minimum middle-ear pressure, smoking during pregnancy, HOME score at 36 mo, foot area, sports participation, race, known occurrences of bilateral otitis media	Betas Eyes open SA: 0.059 (0.024, 0.093) SL: 0.145 (0.088, 0.201) Eyes closed SA: 0.043 (0.01, 0.076) SL: 0.121 (0.069, 0.173) Eyes open, foam SA: 0.046 (−0.175, 0.266) SL: 0.113 (0.065, 0.16) Eyes closed, foam SA: 0.055 (0.018, 0.091) SL: 0.86 (0.277, 1.443)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Dietrich et al. (1993) Cincinnati, OH US 1979−1984 (enrollment) Cohort	N: 245 Pregnant mothers living in older houses in poor condition and with chipping lead-based paint and lead laden dust	Blood Maternal and child venous blood Age at measurement: T1 (maternal), delivery, 1 2, 3, 4, 5, 6 yr (child) Mean (SD) (min-max) ug/dL: T1: 8.4 (3.8) (1−27) Neonatal: 4.8 (3.1) (1−22) 1 yr: 10.5 (4.9) (3−35) 2 yr: 17.1 (8.3) (6−49) 3 yr: 16.2 (7.6) (4−50) 4 yr: 14.0 (7.1) (4−45) 5 yr: 11.9 (6.4) (3−38) 6 yr: 10.1 (5.6) (2−33)	Bilateral coordination, visual-motor contol, upper-limb speed and dexterity, and fine motor composite assessed using BOTMP Age at outcome: 6 yr	NR	Beta Bilateral coordination Prenatal: −0.04 (−0.197, 0.117)[b] Neonatal: −0.15 (−0.326, 0.026)[b] Average (3−60 mo): −0.11 (−0.188, −0.032)[b] Concurrent: −0.18 (−0.258, −0.102)[b] Visual-motor control Prenatal: 0.06 (−0.097, 0.217)[b] Neonatal: −0.1 (−0.296, 0.096)[b] Average (3−60 mo): −0.05 (−0.148, 0.048)[b] Concurrent: −0.12 (−0.218, −0.022)[b] Upper-limb speed and dexterity Prenatal: −0.2 (−0.435, 0.035)[b] Neonatal: −0.45 (−0.724, −0.176)[b] Average (3−60 mo): −0.19 (−0.327, −0.053)[b] Concurrent: −0.31 (−0.447, −0.173)[b] Fine motor composite Prenatal: −0.14 (−0.552, 0.272)[b] Neonatal: −0.49 (−0.96, −0.02)[b] Average (3−60 mo): −0.28 (−0.515, −0.045)[b] Concurrent: −0.46 (−0.715, −0.205)[b]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Wasserman et al. (2000) K. Mitrovica and Pristina Kosovo, Yugoslavia 1985−1986 (enrollment) Followed 54 mo Cohort	Yugoslavia Prospective Study N: 283 children Pregnant women recruited from K. Mitrovica (lead smelter, refinery, and battery factory) and Pristina (town 40 km south)	Blood Prenatal maternal, delivery, and subsequent 6-month interval venous blood: NR	Fine motor and gross motor composites assessed using BOTMP Visual motor integration assessed using Beery Test of VMI Age at outcome: 54 mo	Maternal age, parental education, number of siblings, living arrangement, HOME score at 3 yr, maternal intelligence at 2 yr (RSPM), birthweight, BMI at 54 mo, child sex, opportunities to practice motor skill, incomplete lateralization	Beta for log−10 transformed Pb Fine motor composite: −0.17 (−1.503, 1.163)[c] Gross motor composite: 0.03 (−1.538, 1.598)[c] VMI: −0.24 (−0.632, 0.152)[c]
†Kim et al. (2013c) and Kim et al. (2013b) Seoul, Cheonan and Ulsan Korea 2006–2010 Followed 6 mo Cohort	MOCEH study n: 884 Mothers recruited before 20th wk of pregnancy between and were in locations (Seoul, Cheonan and Ulsan)	Blood Maternal blood samples measured for Pb, Cd in early (<20 wk) pregnancy and late (med = 39 wk) pregnancy Age at measurement: Early and late pregnancy Early pregnancy: 1.4 (GM), 2.1 (90th), 9.8 (max) µg/dL Late pregnancy: 1.3 (GM); 2.1 (90th), 4.3 (max) µg/dL GM also available separately by 3 sites	PDI assessed using BSID-II (Korean version) Age at outcome: 6 mo	Birth weight, infant sex, maternal age and education, family income, breastfeeding status, residential area.	Beta Early: 0.28 (−1.19, 1.75) Late: −1.38 (−3.31, 0.55) Early: Cd <1.47 µg/L: 2.70 (0, 5.39) Cd >1.47 µg/L: −1.17 (−3.27, 0.94) Late: Cd <1.51 µg/L: 0.18 (−2.70, 3.07) Cd >1.51 µg/L: −2.86 (−5.55, −0.16)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Kim et al. (2018b) 4 cities: Seoul, Anyang, Ansan and Jeju Korea 2011–2012 (enrollment) Followed through 24 mo Cohort	CHECK cohort n: 140 birth cohort-pregnant women recruited from 4 cities in Korea before delivery	Blood Maternal blood; method NR Age at measurement: delivery Median (IQR): Maternal: 2.7 (3.5, 5.7) µg/dL Cord: 1.2 (0.8, 1.7) µg/dL	PDI assessed using BSID-II (Korean version) Age at outcome: 13–24 mo	BPA, and phthalates, maternal age (continuous), birth delivery mode (categorical), monthly household income (categorical), child's sex, and BDI (continuous) of the mother, gestational age (continuous), primiparous (categorical), and pre-pregnancy BMI (categorical)	Beta (maternal blood) Overall: −15.45 (−30.12, −0.79) Boys: −18.32 (−45.35, 8.71) Girls:−7.48 (−42.10, 27.15)
†Y Ortiz et al. (2017) Mexico City Mexico Jul 2007-Feb 2011 Followed through 24 mo Cohort	PROGRESS birth cohort n: 536 Women <20 wk of gestation and planning to reside in Mexico City for the next 3 yr.	Blood Maternal blood analyzed using ICP-MS. Age at measurement: T2, T3 Mean: T2: 3.7 µg/dL T3: 3.9 µg/dL	Motor development assessed using BSID-III. Standardized scores (mean: 100, SD: 15). Age at outcome: 24 mo	Infant sex, birth weight, gestational age, maternal age, maternal IQ (WAIS Spanish version), HOME score.	Beta for log-transformed Pb Motor Development: T2: 1.97 (−2.46, 6.40)[b,c] T3: −11.01 (−17.55, −4.48)[b,c]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Liu et al. (2014c) Pearl River Delta Region, Guangdong China Jan 2009–Jan 2010 (enrollment) Followed for 3 yr Cohort	Birth cohort from 3 medical centers n: 362 mother-infant pairs (141 high Pb group with cord BLL ≥3.92 µg/dL and 102 low Pb group ≤1.89 µg/dL)	Blood Cord blood and child blood analyzed using GFAAS. 2 exposure groups created based on cord BLL below 25th percentile (low) and above the 75th percentile (high). Age at measurement: At birth (cord), 6, 12, 24 and 36 mo (postnatal child) High and low Pb groups: cord BLLs: 5.63 and 1.35 µg/dL; 6 mo BLL: 4.03 and 2.85 µg/dL; 12 mo: 4.87 and 3.79 µg/dL; 24 mo: 4.39 and 3.31 µg/dL; 36 mo: 3.94 and 3.28 µg/dL	PDI assessed using BSID-II (Chinese version) Age at outcome: 36 mo	Birth weight, sex, maternal education, IQ (WISC-R), hemoglobin level, smoking, age, parental occupations, household annual income, HNES total score	Beta comparing PDI score at 36 mo in high exposed (Cord BLL ≥3.92 µg/dL) vs. low exposed (Cord BLL ≤1.89 µg/dL): −1.302 (−1.572, −1.031)
†Rygiel et al. (2021) Mexico City Mexico 1997–2005 Cohort	ELEMENT project n: 85 Mother-child pairs recruited at the Mexican Social Security Institute	Blood Maternal and child venous blood; ICP-MS, GFAAS Age at measurement: T1, T2, T3 (maternal); 12, 24 mo (child) Maternal blood GM (SD): T1: 5.27 (1.93) µg/dL T2: 4.74 (1.96) µg/dL T3: 4.98 (1.93) µg/dL Infant blood GM (SD): 12 mo: 3.92 (1.80) µg/dL 24 mo: 3.49 (1.93) µg/dL	PDI assessed using BSID-II (Spanish version) Age at outcome: 12–24 mo	Maternal IQ (WAIS), maternal age, infant weight, length, SES, infant age and sex, current infant BLL	A large number of results were obtained from the mediation analysis. In summary, T1, T2, and T3 BLLs were associated with nonsignificant decreases in 12-month PDI. This association persisted for 24-month PDI at less magnitude for T2 Pb. Beta for 12-month PDI T1:−0.24 (−0.95, 0.48) T2: −0.38 (−1.10, 0.35) T3: −0.33 (−1.06, 0.40) Beta for mediation by GCNT1 cg18515027 methylation of ln-transformed T2 BLLs and 12-month PDI: Indirect: 1.25 (−0.11, 3.32)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Shekhawat et al. (2021) Western Rajasthan India 2018–2019 (enrollment) Follow-up at 6.5 mo (average) Cohort	n:117 Mother-child pairs in third trimester or at delivery	Blood Cord blood; ICP-OES GM = 4.14 µg/dL; mean = 4.77 ± 3.3 µg/dL; median = 4.23 µg/dL 75th: 5.1 µg/dL	Motor development assessed using BSID-III Age at outcome: 6.5 mo	Maternal age, gravida, gestational age, maternal education, child sex and weight, preterm birth, maternal food intake during pregnancy, smoking, alcohol consumption, maternal residential and occupational history, delivery type	β (95 % CI) **Umbilical cord Pb level <5 µg/dL (n = 70)** Composite motor: −0.048 (−0.28, 0.19) Subscale fine motor: −0.10 (−1.80, 0.68) Subscale gross motor: 0.14 (−0.84, 0.94) **Umbilical cord Pb level 5.0–10.5 µg/dL (n = 47)** Composite motor: 0.01 (−1.19, 0.23) Subscale fine motor: 0.03 (−3.34, 4.1) Subscale gross motor: −0.29 (−5.00, 0.11)
Henn et al. (2012) Mexico City Mexico 1997−2000 (enrollment) Followed for 24 mo Cohort	N: 455 Women recruited during pregnancy or at delivery	Blood Child venous blood, ICP-MS Age at measurement: 12, 24 mo 12 mo mean (SD): 5.1 (2.6) µg/dL 24 mo mean (SD): 5.0 (2.9) µg/dL	PDI assessed using BSID-II (Spanish version) Age at Outcome: 12, 18, 24, 30, 36 mo	Sex, gestational age, hemoglobin, maternal IQ, maternal education, and visit	Beta 12-month BLL: −0.27 (−0.56, 0.02) 24-month BLL: −0.18 (−0.53, 0.17)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Parajuli et al. (2015a) Chitwan, Bharatpur District Nepal Sep-Oct 2008 Followed through 24 mo Cohort	Pregnant women visiting the Bharatpur General Hospital n: 100 Birth cohort: women were selected if living in the study area for at least 2 yr and were at term pregnancy (>37 wk of gestation)	Blood Cord blood; ICP-MS, measured for Pb, As and Zn Age at measurement: At birth Median: 2.06 µg/dL Max: 22.08 µg/dL	PDI assessed using BSID-II Age at outcome: 24 mo	Maternal age and education, BMI, gestational age, family income, parity, birth weight, weight at 24 mo, child age assessment, As, Zn, HOME score (smoking and alcohol consumption not included given low prevalence)	Beta −4.83 (−16.53, 6.86)
†Parajuli et al. (2015b) Chitwan, Bharatpur district Nepal Sep-Oct 2008 Followed through 36 mo Cohort	Birth cohort from Bharatpur General Hospital n: 100 Resided in area for at least 2 yr delivered at term (i.e., >37 wk)	Blood Cord blood; ICP-MS, measured for Pb, As and Zn Age at measurement: At birth Median: 2.06 µg/dL Max: 22.08 µg/dL	PDI assessed using BSID-II Age at outcome: 36 mo	Maternal age and education, BMI, gestational age, family income, parity, birth weight, weight at 24 mo, child age at assessment, As, Zn, HOME score (smoking and alcohol consumption not included given low given low prevalence)	Beta −2.56 (−9.71, 4.59)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Jiang et al. (2022) Taipei Taiwan August 2008-December 2009 (enrollment) Follow-up 3 yr Cohort	N: 53 children Meconium (n = 36) Hair (n = 52) Fingernail (n = 43) Longitudinal birth cohort study at a medical center hospital in northern Taiwan	Meconium, Hair, Fingernail All metals analyzed using ICP-MS. Child meconium collected at birth Child hair and fingernails collected at age 1 mo Median (min, max): Meconium: 25.6 (2.00, 8815) ng/g Hair: 3.61 (0.31, 25.1) µg/g Fingernail: 0.84 (0.06, 24.3) µg/g	Motor development assessed using BSID-III. Raw total motor scores were standardized to expected mean of 100 and SD of 15. Raw fine motor and gross motor scores were standardized to expected mean of 10 and SD of 3. Age at Outcome: 3 yr	Maternal age and education, newborn birth head circumference and sex, and As and Cd levels	Beta for log−10 transformed Pb and log−10 transformed motor development score Meconium Motor: −0.00001 (−0.021, 0.021)[e] Fine motor: 0.009 (−0.048, 0.065)[e] Gross motor: −0.014 (−0.064, 0.036)[e] Hair Motor: 0.020 (−0.009, 0.049)[e] Fine motor: 0.046 (−0.015, 0.107)[e] Gross motor: 0.006 (−0.043, 0.054)[e] Fingernails Motor: −0.003 (−0.025, 0.019)[e] Fine motor: −0.001 (−0.053, 0.052)[e] Gross motor: −0.004 (−0.046, 0.037)[e]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Zhou et al. (2017) Shanghai China 2010–2012 (enrollment) Followed for 24–36 mo after birth Cohort	Shanghai Stress Birth Cohort Study n: 139 Women enrolled in prenatal clinics of maternity hospitals during mid-to-late pregnancy.	Blood Maternal blood Pb measured using AAS. Age at measurement: 28–36 wk of gestation GM: 3.30 µg/dL	Gross motor and fine motor development assessed using GDS (Chinese version) Age at outcome: 24–36 mo	Maternal age at enrollment, economic status, maternal education, gestational week, child sex, birth weight and age	Beta per log−10 transformed BLL Gross motor development: 3.31 (−6.11, 12.73)[c] Fine motor development: 0.49 (−11.27, 12.24)[c]
†Liu et al. (2022a) Guangxi region China July-September 2015 (enrollment) Followed until July-September 2018 (3 yr) Cohort	Guangxi Birth Cohort Study N: 703 children Pregnant women recruited from eight maternity and child healthcare hospitals in six cities of Guangxi	Blood, urine Prenatal maternal serum (first, second, and third trimesters) Infant urine Age at measurement: NR Maternal serum med (25th, 75th): 0.78 (0.54, 1.24) µg/L Infant urine med (25th, 75th): 0.22 (0.14, 0.37) µg/L	Gross motor development using GDS (Chinese version) Age at outcome: 2.57 (SD: 0.14) yr	Maternal age, pre-pregnancy BMI, children's age, children's gender, blood sampling time, delivery mode, delivery gestational week, birth head circumference.	Beta per ln-transformed µg/L increase in Pb Overall: −2.321 (−3.614, −1.029)[c] Male: −3.426 (−6.162, −0.691)[c] Female: −1.182 (−2.805, 0.442)[c]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Taylor et al. (2015) Avon UK Apr. 1, 1991 – Dec. 31, 1992 (expected delivery date) Followed 10 yr Cohort	Subsample of ALSPAC Study N: 582 child blood N: 4285 prenatal maternal blood Pregnant women in former Avon Health Authority	Blood Maternal blood collected in early pregnancy (med: 11 wk of gestation); ICP-MS Child venous blood Age at measurement: 30 mo Mean (SD) Prenatal: 3.67 (1.47) µg/dL Child: 4.22 (3.12) µg/dL	Balance (heel-to-toe test) from the Movement Assessment Battery for Children (Movement ABC) Age at outcome: 7 yr Static and dynamic balance tests based on BOTMP Age at outcome: 10 yr	Sex, passive smoking at 77 or 103 months old (weekdays and weekends), and concurrent Ca and Fe intakes	OR for ≥5 µg/dL vs. <5 µg/dL Pb **Prenatal Pb:** Heel-to-toe test: 1.01 (0.95, 1.01) Dynamic balance: 1.02 (0.95, 1.09) Static balance: 0.98 (0.92, 1.06) **Child Pb:** Heel-to-toe test: 0.98 (0.92, 1.05) Dynamic balance: 1.01 (0.93, 1.09) Static balance: 1.03 (0.94, 1.12)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Taylor et al. (2018) Avon UK Apr. 1, 1991 – Dec. 31, 1992 (expected delivery date) Followed 10 yr Cohort	Subsample of ALSPAC Study N: 1558 Pregnant women in former Avon Health Authority	Blood Maternal blood; ICP-MS Age at measurement: Early pregnancy (med: wk 11 of gestation) Mean (SD) Prenatal: 3.66 (1.55) µg/dL	Balance (heal-to-toe test), ball skills (beanbag toss), and manual dexterity (threading lace and placing pegs) Movement Assessment Battery for Children (Movement ABC) Age at outcome: 7 yr	Sex, maternal education, smoking in pregnancy, alcohol in pregnancy, maternal age and parity	OR for ≥5 µg/dL vs. <5 µg/dL Pb Balance: 0.99 (0.74, 1.33) Ball skills: 0.88 (0.58, 1.32) Threading lace: 1.12 (0.83, 1.50) Peg board − preferred hand: 1.19 (0.88, 1.60) Peg board – non-preferred hand: 1.14 (0.85, 1.54) OR for highest quartile (NR) vs. lowest quartile (<5 µg/dL) of Pb Balance: 0.98 (0.73, 1.31) Ball skills: 1.07 (0.71, 1.63) Threading lace: 1.01 (0.75, 1.35) Peg board − preferred hand: 1.23 (0.92, 1.66) Peg board – non-preferred hand: 0.99 (0.73, 1.32)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Boucher et al. (2016) Nunavik, Québec Canada October 2005 – February 2010 (outcome assessment) Cohort	Nunavik Child Development Study N: 265 school children Phone recruitment of children with umbilical cord blood samples obtained under the Arctic Cord Blood Monitoring Program	Blood Cord blood and child concurrent venous blood, ICP-MS Age at measurement: birth (cord), 11.3 yr (child) Cord mean, median (SD): 4.7, 3.7 (3.4) µg/dL Child blood mean, median, SD: 2.7, 2.0 (2.1) µg/dL	Fine motor performance on Santa Ana Form Board (manual dexterity), Finger Tapping (fine motor speed), and Stanford-Binet Copying (visuo-motor integration) Age at outcome: 11.3 yr (SD: 0.8)	Form Board: child age and sex, social environment, maternal age, parity, marital status, smoking during pregnancy; Finger Tapping: child age and sex, social environment; Stanford-Binet: child age and sex, social environment, marital status Others considered: adoption status, primary caregiver's years of education, Peabody Picture Vocabulary Test, RPM, parity, mother fluency in English/French, assimilation to Western culture, alcohol and illicit drug use during pregnancy, other contaminants, nutrient biomarkers	Beta for log-transformed Pb Cord blood Manual dexterity: −0.08[d,f] Fine motor speed: −0.19 (−0.33, −0.05)[b,f] Visuo-motor integration: −0.01[d,f] Child blood Manual dexterity: −0.17 (−0.34, 0)[b,f] Fine motor speed: −0.21 (−0.37, −0.05)[b,f] Visuo-motor integration: 0.1[d,f]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Parajuli et al. (2013) Chitwan Valley Nepal Sep-Oct 2008 Cross-sectional	n: 79 women living in the study area (i.e., Chitwan) for at least 2 yr, at term pregnancy when the mothers visited the hospital (more than 37 wk of gestation), age of 18–40 yr, singleton birth, and no report of diabetes, hypertension, or preeclampsia	Blood Cord blood Pb concentrations determined using ICP-MS. Age at measurement: delivery mean: 31.7 µg/L; median: 20.6 µg/L 75th: 35.1 µg/L Max: 220.8 µg/L	Neurodevelopment assessed using Brazelton NBAS III Age at outcome: 1 day old	Maternal age, parity, mother's education level; annual family income, mother's BMI, birth weight, gestational age, age of baby at NBAS assessment	ß (95 % CI) change in score per 1 µg/L increase in blood Pb Habituation: 1.44 (−1.19, 4.07) Orientation: −0.12 (−8.34, 8.10) Motor system: −2.15 (−4.27, −0.03) State organization: 2.15 (−1.58, 5.88) State regulation: −0.75 (−3.86, 2.36) Autonomic Stability: 0.71 (−0.48, 1.90) Abnormal reflex: 1.07 (−1.32, 3.46)
†Liu et al. (2014d) Shenzhen, Guangdong China Jan 2009–Jan 2010 Followed for 26–30 wk Cohort	Birth cohort n: 415 mother-child pair (219 high Pb group ≥4.89 µg/dL at first trimester and 196 low Pb group ≤1.96 µg/dL) Pregnant women recruited during the early pregnancy (10–14 wk)	Blood Maternal, cord blood analyzed using GFAAS. Maternal BLL classified as low or high Age at measurement: First, second and third trimester and at delivery Low and High BLL groups: First trimester: 1.22 µg/dL and 6.49 µg/dL; second trimester: 1.01 µg/dL and 5.63 µg/dL; third trimester: 1.19 µg/dL and 6.31 µg/dL; and delivery: 1.26 µg/dL and 6.65 µg/dL	Neurodevelopment assessed using NBNA Age at outcome: 3 days	Infant sex, maternal hemoglobin, IQ, tobacco use and parents' occupation, education, yearly household income.	Beta for change in NBNA score per log-transformed Pb T1: −4.86 (−8.831, −0.889)[f] T2: −3.98 (−8.180, 0.220)[f] T3: −3.65 (−6.609, 1.309)[f] Cord: −3.39 (−7.531, 0.751)[f]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Nozadi et al. (2021) Navajo Nation United States Enrollment February 2013 - June 2018 Follow-up at age 10−13 mo Cohort	Navajo Birth Cohort Study (NBCS) n: 327	Blood Maternal blood Pb from the 36-week visit or at the time of delivery was processed using ICP-DRC-MS. Age at Measurement: Mean (SD) maternal age at birth = 27.4 (5.87) years. Children assessed at 10 and 13 mo. GM = 0.410 µg/dL; median = 0.37 µg/dL 75th: 0.51 µg/dL 95th: 1.20 µg/dL	Neurodevelopment assessed using Ages and Stages Questionnaire Inventory (ASQ:I) Age at outcome: 10, 13 mo	Multivariable linear regression for fine motor adjusted for blood cadmium, urine cesium, urine arsenic, and mother's education; gross motor adjusted for urine strontium	Beta Fine motor: −0.63 (−1.19, −0.08) Gross motor: 0.14 (−0.47, 0.75)
†Kao et al. (2021) Taipei Taiwan 2011−2014 Cross-Sectional	recruited from Taipei MacKay Memorial Hospital n:139 children less than 3 yr of age	Hair, fingernails Pb concentrations in hair and fingernails were measured using ICP-MS Age at Measurement: Mean (SD) 2.8 (0.4) years (children under 3 yr) GM (SD): hair 2.9 (4.8) Î¼g/g, nails 0.8 (5.1) Î¼g/g	Motor development assessed using BSID-III Age at outcome: 2.8 ± 0.4 yr	Sex, gestational age at birth, age of the house (years), leafy-vegetable intake (servings/week), and the area of surface roads within 100 m of the residence	Regression results were not reported because they were not statistically significant.

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Nyanza et al. (2021) Northern Tanzania Tanzania 2015–2017 (enrollment) Followed for 12 mo Cohort	Mining and Health Prospective Longitudinal Study in Northern Tanzania n: 439 Birth cohort of mother-child pairs recruited in 2nd trimester	Maternal dried blood spots; ICP-MS, measured for Pb, Hg, and Cd Age at measurement: T2 Median: 2.72 µg/dL 75th: 4.25 µg/dL Max: 14.5 µg/dL	Gross motor and fine motor development assessed using MDAT. Scores in each domain classified as normal (≥90th percentile on all items in that domain or <90th percentile on one or two items in the domain) or impaired (<90th percentile on more than two items in a domain). Age at outcome: between 6 and 12 mo	Maternal age and education, maternal and paternal occupation, number siblings under 5 yr at home, and family SES, infant sex, age, birth weight, height and weight as a proxy for nutritional status. (Covariates with p < 0.20 retained in the final models.)	Prevalence ratio Gross motor development: 1.0 (0.9, 1.0) Fine motor development: 1.0 (0.9, 1.0)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
†Palaniappan et al. (2011) Chennai India 2003−3006 Cross-sectional	n = 755 school children (age 3–7 yr) Children attending public schools in Chennai (kindergarten – 1st grade)	Blood Child venous blood; LeadCare Analyzer Age at measurement: 3–7 yr Mean (SD): 11.5 (5.3) µg/dL	Visual-motor (drawing), visual-spatial (matching), fine motor (pegboard) subtests and composite assessed using WRAVMA Age at outcome: 3–7 yr Standardized scores (mean: 100, SD: 15)	Gender, age, hemoglobin level, average monthly income of the family (categorical) and parent education (categorical)	Beta Drawing: −0.29 (−0.51, −0.07) Matching: −0.14 (−0.31, 0.02) Pegboard: −0.19 (−0.38, 0.01) Composite: −0.26 (−0.45, −0.07)

AAS = atomic absorption spectrometry; As = arsenic; BASC = Behavior Assessment System for Children; BDI = Beck Depression Inventory; BLL = blood lead level; BOTMP = Bruininks–Oseretsky Test of Motor Proficiency; BPA = bisphenol A; BRIEF = Behavior Rating Inventory of Executive Functions; BSID = Bayley Scales of Infant and Toddler Development; CBCL = Child Behavior Check List; CCAAPS = Cincinnati Childhood Allergy and Air Pollution Study; CHECK = Health and Environmental Chemicals in Korea; CI = confidence interval; CKD = chronic kidney disease; CKiD = Chronic Kidney Disease in Children; CPRS = Conners' Parent Rating Scale; C-TRF = Caregiver-Teacher Report Form; CTRS = Conners' Teacher Rating Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; FSIQ = full-scale intelligence quotient; GDS = Gesell Development Schedules; GFAAS = graphite furnace atomic absorption spectrometry; GM = geometric mean; Hgb = hemoglobin; HOME = Health Outcomes and Measures of the Environment; IQ = intelligence quotient; MOCEH = Mothers' and Children's Environmental Health; NBAS = Neonatal Behavioral Assessment Scales; NBNA = Neonatal Behavioral Neurological Assessment; NHBCS = New Hampshire Birth Cohort Study; NR = not reported; OR = odds ratio; Pb = lead; PDI = Psychomotor Developmental Index; PHDCN = Project on Human Development in Chicago Neighborhoods; SDQ = Strengths and Difficulties Questionnaire; SES = socioeconomic status; SRP = self-report of personality; SRS = Social Responsiveness Scale; T1 = first trimester of pregnancy; T2 = second trimester of pregnancy; T3 = third trimester of pregnancy; WAIS = Weschler Adult Intelligence Scale; WISC-R = Wechsler Intelligence Scale for Children; WRAVMA = Wide Range Assessment of Visual-Motor Abilities; Zn = zinc.
[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.
[b]The CI was calculated from a p-value and the true CI may be wider or narrower than calculated.
[c]Results are unstandardized because the Pb level distribution data was not available.
[d]Results are unstandardized because they did not have an associated SE, CI, or p-value reported in the study.
[e]Results are unstandardized because the biomarker used for Pb exposure measurement is not blood, tooth, or bone.
[f]Results are unstandardized because the log base used for exposure transformation was unspecified in the study.
†Studies published since the 2013 Integrated Science Assessment for Lead.

Table 3-11T Animal toxicological studies of Pb exposure and motor function

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Flores-Montoya and Sobin (2015)	**Mouse (C57BL/6)** Control (distilled water), M/F, n = 19 (8/11) 30 ppm, M/F, n = 26 (16/10) 230 ppm, M/F, n = 16 (12/4)	PND 0 to PND 28	Oral, drinking water Oral, lactation	PND 28 − Males: 0.2 µg/dL for Control 3.93 µg/dL for 30 ppm 9.39 µg/dL for 230 ppm PND 28 − Females: 0.19 µg/dL for Control 3.19 µg/dL for 30 ppm 12.14 µg/dL for 230 ppm	PND 28: OFT, Rotarod Test
Zou et al. (2015)	**Mouse (ICR)** Control (distilled water), M, n = 10 250 mg/L solution, M, n = 10	~5 wk to 8 wk	Oral, drinking water	8 wk: 1.8 µg/dL for Control 21.7 µg/dL for 250 mg/L	8 wk: Rotarod Test, Locomotor Activity
Rao Barkur and Bairy (2016)	**Rat (Wistar)** Control (tap water), M, n = 12 0.2% solution, PG, M, n = 12 0.2% solution, G, M, n = 12 0.2% solution, L, M, n = 12	PG: GD −30 to GD 0 G: GD 1 to GD 21 L: PND 1 to PND 21	Oral, lactation In utero	PND 22: 0.19 µg/dL for Control 3.03 µg/dL for PG 5.51 µg/dL for G 26.86 µg/dL for L	PND 3, 4, 5: Surface Righting Reflex, PND 6, 8, 10, 12: Swimming Performance, PND 8, 10, 12: Negative Geotaxis, PND 14–18: Ascending Wire Mesh,

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Betharia and Maher (2012)	**Rat (Sprague Dawley)** PND 24: Control (RO DI water), M/F, n = 11–13 10 µg/mL, M/F, n = 11–13 PND 59: Control (RO DI water), M/F, n = 10–11 10 µg/mL, M/F, n = 10–11	GD 0 to PND 20	Oral, lactation In utero	PND 2: 1.77 ng/g (0.188 µg/dL) for Control 85.17 ng/g (9.02 µg/dL) for 10 µg/mL PND 25: 0.83 ng/g (0.088 µg/dL) for Control 9.21 ng/g (0.98 µg/dL) for 10 µg/mL PND 60: 0.23 ng/g (0.024 µg/dL) for Control 0.30 ng/g (0.032 µg/dL) for 10 µg/mL	PND 1–10: Surface Righting Reflex, PND 24, 59: OFT

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Basha and Reddy (2015)	**Rat (Wistar)** Control (deionized water), M, n = 8 0.2 % solution, M, n = 8	GD 6 to GD 21	In utero	PND 21: 0.21 µg/dL for Control 11.2 µg/dL for 0.2% solution PND 28: 0.33 µg/dL for Control 12.3 µg/dL for 0.2% solution 4 mo: 0.19 µg/dL for Control 5.9 µg/dL for 0.2% solution	PND 4–7: Surface Righting Reflex, PND 8–10: Negative Geotaxis, PND 12 –16: Forelimb Hang, PND 21, PND 28, 4 mo: Locomotor Activity
Tartaglione et al. (2020)	**Rat (Wistar)** Control (tap water), M/F n = 16 (9/7) 50 mg/L, M/F, n = 16 (9/7)	GD −28 to PND 23	Oral, lactation In utero	PND 23: 0.007 µg/mL (0.7 µg/dL) for Control 0.255 µg/mL (25.5 µg/dL) for 50 mg/L	PND 4, 7, 10, 12: Neonatal Spontaneous Movement, PND 4, 7, 10, 12: Surface Righting Reflex, PND 4, 7, 10, 12: Negative Geotaxis, PND 30: OFT
Faulk et al. (2014)	**Mouse (Agouti)** Control (distilled water), M/F, n = 30 2.1 ppm, M/F, n = 28 16 ppm, M/F, n = 33 32 ppm, M/F, n = 29	GD −14 to PND 21	Oral, lactation In utero	PND 21 (Maternal BLL): <LOD for Control 4.1 µg/dL for 2.1 ppm 25.1 µg/dL for 16 ppm 32.1 µg/dL for 32 ppm	PND 90, 180, and 270: Locomotor Activity

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Basha et al. (2014)	**Rat (Not Specified)** Control (deionized water), M, n = 6 0.2% solution, M, n = 6	PND 1 to PND 21	Oral, lactation	PND 45: 0.42 µg/dL for Control 49.5 µg/dL for 0.2% solution 4 mo: 0.56 µg/dL for Control 14.4 µg/dL for 0.2% solution 12 mo: 0.46 µg/dL for Control 6.96 µg/dL for 0.2% solution 18 mo: 0.12 µg/dL for Control 11.2 µg/dL for 0.2% solution	PND 45, 4 mo, 12 mo, 18 mo: OFT, Locomotor Activity
Mansouri et al. (2012)	**Rat (Wistar)** Control (distilled water), M/F, n = 16 (8/8) 50 mg/L, M/F, n = 16 (8/8)	PND 70 to PND 100	Oral, drinking water	PND 100 − Males: 2.05 µg/dL for Control 8.8 µg/dL for 50 mg/L PND 100 − Females: 2.17 µg/dL for Control 6.8 µg/dL for 50 mg/L	PND 100: OFT, Rotarod Test

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Duan et al. (2017)	**Mouse (CD1)** Control (distilled water), M/F, n = 5 27 ppm, M/F, n = 5 109 ppm, M/F, n = 5	PND 1 to PND 21	Oral, lactation	PND 21: 16.2 µg/L (1.6 µg/dL) for Control 191.8 µg/L (19.2 µg/dL) for 27 ppm 283.4 µg/L (28.3 µg/dL) for 109 ppm PND 35: 14.3 µg/L (1.4 µg/dL) for Control 283.4 µg/L (28.3 µg/dL) for 27 ppm 376.9 µg/L (37.7 µg/dL) for 109 ppm	PND 7, 11, 15, 19: OFT
Wang et al. (2016)	**Rat (Sprague Dawley)** Control (tap water), M, n = 7 100 ppm, M, n = 9	PND 24 to PND 56	Oral, drinking water	PND 56: 11 µg/L (1.1 µg/dL) for Control 133 µg/L (13.3 µg/dL) for 100 ppm	PND 60–66: OFT
Shvachiy et al. (2018)	**Rat (Wistar)** Control (tap water), M/F, n = 8 0.2% (p/v) solution (distilled water), M/F, n = 9 − Intermittent exposure 0.2% (p/v) solution, M/F, n = 9 − Continuous exposure	Intermittent Exposure: GD 7 to PND 84, PND 140 to PND 196 Continuous Exposure: GD 7 to PND 196	Oral, drinking water Oral, lactation In utero	PND 196: <0.1 µg/dL for Control 18.8 µg/dL for 0.2% (Intermittent) 24.4 µg/dL for 0.2% (Continuous)	PND 189: OFT

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Stansfield et al. (2015)	**Rat (Long-Evans)** Control (chow), M/F, n = 11–23 1500 ppm, M/F, n = 11–23	GD 0 to PND 50	Oral, diet Oral, lactation In utero	PND 50: 0.6 µg/dL for Control 22.2 µg/dL for 1500 ppm	PND 50: Locomotor Activity
Neuwirth et al. (2019a)	**Rat (Long-Evans)** Control (tap water), M/F, n = 48 (30/18) 150 ppm, M/F, n = 62 (32/30) 1000 ppm, M/F, n = 49 (30/19)	GD 0 to PND 22	Oral, lactation In utero	PND 22: <LOD for Control 3.3–10.7 µg/dL for 150 ppm 9.0–17.8 µg/dL for 1000 ppm PND 55: <LOD for Control <LOD for 150 ppm <LOD for 1000 ppm	PND 36–45: OFT
Mansouri et al. (2013)	**Rat (Wistar)** Control (tap water or water + NaAc), M/F, n = 16 (8/8) 50 ppm, M/F, n = 16 (8/8)	PND 55 to PND 181	Oral, drinking water	PND 178–181 − Females: NR for Control 10.6 µg/dL for 50 ppm PND 178–181 − Males: NR for Control 18.9 µg/dL for 50 ppm	PND 155–159: Rotarod Test

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Sobolewski et al. (2020)	**Mouse (C57BL/6)** F0: Control (distilled DI water), F, n = 10 100 ppm, F, n = 10 F1: see Figure 1, n = 12 F2: see Figure 1, n = 12 F3: see Figure 1, n = 8–10	F1: GD −60 to PND 23–27	Oral, lactation In utero	F1 PND 6–7: 0 µg/dL for Control 12.5 µg/dL for 100 ppm (F0 dosing) F3 PND 6–7: 0 ng/dL for Control 0 µg/dL for 100 ppm (F0 dosing)	PND 60–120 (variable by endpoint): Locomotor Activity
Singh et al. (2019)	**Rat (Wistar)** Control (distilled water), M, n = 5 2.5 mg/kg, M, n = 5	3 mo to 6 mo	Oral, gavage	6 mo: 5.76 µg/dL for Control 28.4 µg/dL for 2.5 mg/kg	6 mo: Locomotor Activity, Rotarod Test
Vigueras-Villaseñor et al. (2021)	**Rat (Wistar)** Control (tap water), M, n = 8 320 ppm, M, n = 8	GD 0 to PND 21	Oral, lactation In utero	PND 110: 2.04 µg/dL for Control 26.3 µg/dL for 320 ppm	PND 90 to PND 110: Locomotor Activity

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Al-Qahtani et al. (2022)	**Mouse (Albino)** Control (distilled water), M, n = 10 0.2 mg/kg, M, n = 10	8–9 wk to 14–15 wk	Oral, gavage	14–15 wk: 1.2 µg/100 mL (1.2 µg/dL) for Control 7.1 µg/100 mL (7.1 µg/dL) for 0.2 mg/kg	NR: Locomotor Activity

BLL = blood lead level; F# = filial generation; F = female; GD = gestational day; LOD = limit of detection; M = male; MRI = magnetic resonance imaging; mo = month(s); NaAc = sodium acetate; NR = not reported; OFT = open-field test Pb = lead; PG = pregestation; PND = postnatal day; wk = week(s); yr = year(s).
[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.

Table 3-12E Epidemiologic studies of Pb exposure and sensory organ function in children

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Dietrich et al. (1992) Cincinnati, U.S. Cross-sectional	The Cincinnati lead study cohort n: 259	Blood Age at measurement: prenatal−5 yr Mean (SD) µg/dL: Prenatal 8.2 (3.8) Neonatal 4.8 (3.3)	Central auditory processing abilities and cognitive developmental status Age at outcome: 5 yr	Measures of fetal distress and growth, perinatal complications, postnatal indices of health and nutritional status, sociodemographic characteristics, and psychosocial features of the home environment	Beta[b] Filtered Word Score (total number of words correctly identified in both ears) Prenatal: −0.12 Neonatal: −0.26 Mean lifetime through 5 yr: −0.07
Schwartz and Otto (1991) HHANES, U.S. Cross-sectional	Hispanic Health and Nutrition Examination Survey n: 3545	Blood Age at measurement: 6−19 yr Median (25th, 75th) µg/dL: Mexican Americans 8 (6, 11) Cuban American 8 (6, 10) Puerto Ricans 8 (6, 11)	Elevated hearing threshold Audiometric evaluations were performed for all subjects Beltone model 200-C audiometers were used in the survey; Hearing threshold was defined as the lowest intensity of a pure tone that was just audible to the subject. Age at outcome: 6−19 yr	NR	An increase[b] in BLL from 7 ~microg/dl to 18 µg/dl was associated with an approximately 2-dB loss of hearing at all frequencies

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Schwartz and Otto (1987) NHANES II U.S. Cross-sectional	NHANES II n: 4519	Blood Age at measurement: 4−19 yr Range of Pb: 6 to 47 µg/dL	Hearing thresholds Standard Beltone Model 200C audiometers were used and ca liberated weekly with B&K Model 2203 sound level meters in accordance with 1969 ANSI specifications. Tests were conducted at 500, 1000, 2000, and 4000Hz on each ear. Age at outcome: 4−19 yr	Race, lead, ear discharge, cold in last 2-week, other ear condition, chronic ear discharge, income, dietary calcium, sex, current cold, ringing in ear(s), earache, previous running ear, diagnosed hearing impairment, degree of urbanization, head of household education level	The risk of elevated hearing thresholds at 500, 1000, 2000 and 4000 Hz increased with increasing PbB for both ears
†Yin et al. (2021)	n: 234–7596 in 8 studies	Blood Age at measurement: 3−87 yr	Hearing loss	All studies included in the meta-analysis controlled for age and sex. Adjustment for other potential confounders varies by studies, but includes monthly income, education levels, smoking status, BMI, ethnicity, work duration, ototoxic medication, blood lead, occupational noise, loud noise, and firearm noise, and hypertension and diabetes	OR (95% CI)[b] 1.53 (1.24,1.87)
†Choi and Park (2017) Korea 2010−2012	KNHANES n: 5187 adults and 853 adolescents	Blood	Hearing loss (>15dB) at speech frequency; Hearing loss (>15dB) at high frequency	Age, age squared, sex, education, BMI, current cigarette smoking	**OR (95% CI)[b]** *Hearing Loss (>15 dB) High-frequency PTA* Pb Quartile 2 (0.978–1.260): 0.89 (0.39, 2.03)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Cross-sectional		Graphite furnace atomic absorption spectrometry Age at Measurement: adolescents 12–19 yr (mean±SE 15.6 ± 0.10) Geometric mean (95% CI) (age-adjusted): 1.26 µg/dL (1.22, 1.30)	Pure-tone air conduction hearing thresholds were obtained for each ear at frequencies of 0.5, 1, 2, 3, 4, and 6 kHz over an intensity range of −10 to 110 dB −10 to 110 dB. Age at outcome: 12–19 yr		Pb Quartile 3 (1.261–1.557): 1.88 (0.83, 4.25) Pb Quartile 4 (1.562–5.904): 1.38 (0.63, 3.02) Per doubling of Pb: 1.26 (0.73, 2.16) *Hearing Loss (>15 dB) Speech-frequency PTA* Pb Quartile 2 (0.978–1.260): 1.17 (0.41, 3.32) Pb Quartile 3 (1.261–1.557): 1.08 (0.38, 3.08) Pb Quartile 4 (1.562–5.904): 1.24 (0.34, 4.49) Per doubling of Pb: 1.2 (0.48, 3.05)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Xu et al. (2020) China October-December 2014 Cross-sectional	n: 116	Blood Graphite furnace atomic absorption spectrometry (GFAAS, Jena Zeenit 650, Germany) Age at measurement: 3–7 yr Median ± SEM (P_{25}, P_{75}): Exposed group 5.29 ± 0.29 (3.61, 7.40) Refence group 3.63 ± 0.24 (2.98, 4.77)	DNA methylation and hearing loss Age at outcome: 3–7 yr	Both continuous variables for child age, gender, weight, height and BMI, and categorical variables for presence of family member smoking, residence distance to the road, residence nearby noise, residence renovation noise within a year, often listening music with earphones within a year, often watching television programs in loud noise, and often play (i.e., toys or music, etc.) in loud noise	**Beta (95% CI)[b]** Q1 0.139 (0.007, 2.968 Q2 0.051 (0.003, 0.977) Q3 0.16 (0.016, 1.58) Q4 2.765 (1.795, 15.237) **OR (95% CI)** *Hearing loss in both ears* 1.40 (1.06, 1.84) *Left ear* 1.46 (1.12, 1.91)
†Shargorodsky et al. (2011) NHANES, U.S. 2005−2008 Cross-sectional	NHANES n: 2535	Blood Inductively coupled plasma mass spectrometry Age at Measurement: 12−19 yr Weighted Mean (95% CI): Age 12−13: 1.00 µg/dL (0.92−1.09 µg/dL) Age 14−15: 0.93 µg/dL (0.87−0.99 µg/dL) Age 16−17: 0.85 µg/dL (0.79−0.91 µg/dL) Age 18−19: 0.93 µg/dL (0.84−1.03 µg/dL)	Any Hearing Loss (>15 dB), High-Frequency Hearing Loss, Low-Frequency Hearing Loss Age at outcome: 12−19 yr	Age, sex, race-ethnicity, PIR, history of 3 or more ear infections, loud noise exposure, and smoking	**OR (95% CI)[b] (<1 µg/dL reference)** *Any >15 dB* 1−1.99 µg/dL 0.99 (0.67−1.46) ≥2 µg/dL 1.95 (1.24−3.07) *High-Frequency* 1−1.99 µg/dL 1.20 (0.80−1.80) ≥2 µg/dL 2.22 (1.39−3.56) *Low-Frequency* 1−1.99 µg/dL 1.24 (0.82−1.86) ≥2 µg/dL 1.13 (0.61−2.07)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Liu et al. (2018c) Guiyu (e-waste recycling area) & Haojing (exposure control, no e-waste processing), China 2014 Cross-sectional	n: 234 (146 exposed; 88 reference)	Blood Graphite furnace atomic absorption spectrometry (GFAAS, Jena Zeenit 650, Germany) Age at Measurement: 3–7 yr Median± SE: 4.94 ± 0.20 µg/dL in exposed; 3.85 ± 1.81 µg/dL in reference	Hearing loss, Low frequency hearing loss, High frequency hearing loss Age at outcome: 3–7 yr	Child age, gender, weight, height, BMI, parent education level, family member smoking, family monthly income, residence distance to the road, residence nearby noise, residence renovation noise within a year, often listening to music with earphones within a year, often watching television programs in loud noise, and often play (*i.e.,* toys or music, *etc.*) in loud noise	**OR (95% CI)[b]** Hearing loss total 1.24 (1.029, 1.486) Low frequency 1.02 (0.869, 1.190) High frequency 1.08 (0.839, 1.379)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Pawlas et al. (2015) Upper Silesia, Poland 1996−2001 and 2008−2010 Cross-sectional	Two cohorts merged n: 483	Blood Graphite furnace atomic absorption spectrometry Age at Measurement: 4−13 yr Median: 4.50 µg/dL	Pure-tone audiometry (PTA), Brainstem auditory evoked potentials (BAEP), Acoustic otoemission Age at Outcome: 4−13 yr	Cohort, mother's education (dichotomized into 'secondary school or higher', or 'less', corresponding to primary and apprenticeship) and smoking during pregnancy, and the child's sex, birth weight, apgar score, history of mumps, age, and pressure in middle ear on both sides	**Beta (95% CI)[b]** ALAD Msp/ ALAD1−1 0.3 (0.15, 0.45) ALAD*2 0.42 (−0.03, 0.87) ALAD Rsa1 TT+TC 0.3 (0.1, 0.5) CC 0.2 (−0.05, 0.45) VDR BsmI bb 0.03 (−0.22, 0.28) Bb+BB 0.4 (0.25, 0.55) VDR taq1 TT 0.04 (−0.21, 0.29) Tt+tt 0.4 (0.2, 0.6) VDR fok1 FF+Ff 0.4 (0.25, 0.55) ff −0.1 (−0.6, 0.4)

†Silver et al. (2016) Sanhe County, Hebei Province, China November 2009- November 2011 Cohort	n: 391 (ARB: auditory brainstem response), 1148 (VA: visual acuity)	Maternal Blood AAS Age at Measurement: Pregnant woman 18 yr or older *Mean (SD) gestational age at mid-pregnancy visit* ABR subset 15.7 (2.2) weeks VA subset 15.5 (1.9) weeks *Mean (SD) gestational age at late-pregnancy* ABR subset 38.8 (1.3) weeks VA subset 39.3 (1.3) weeks *Mean (SD) gestational age at birth* ABR subset 39.2 (1.1) weeks VA subset 39.7 (1.1) weeks ABR Pb median 2.9 µg/dL at mid-pregnancy 3.0 µg/dL at late-pregnancy <2.0 µg/dL at birth (cord blood) GM (SD) 2.4 (2.5) µg/dL at mid-pregnancy 2.7 (2.3) µg/dL at late-pregnancy <2.0 µg/dL at birth (cord blood); VA median 2.9 µg/dL at mid-pregnancy, 3.3 µg/dL at late-pregnancy, 2.1 µg/dL at birth (cord blood) GM (SD) 2.4 (2.6) µg/dL at mid-pregnancy 2.9 (2.2) µg/dL at late-pregnancy <2.0 µg/dL at birth (cord blood)	ABR; Grating visual acuity (VA) Age at Outcome: ABR mean 2 d old VA mean 6 wk old	Sex, age at testing, cord blood iron status, gestational age, birth weight, head circumference	**Beta (95% CI)[b]** *ARB C-P ratio* Mid pregnancy lead High (>3.8 µg/dL) 0.02 (−0.01, −0.05) Mid pregnancy lead Med. (2–3.8 µg/dL) 0.02 (−0.01, −0.05) Late-pregnancy lead High (>3.8 µg/dL) 0.05 (0.02, 0.08) Late-pregnancy lead Med. (2–3.8 µg/dL) 0.03 (0.01, 0.06) Cord lead High (>3.2 µg/dL) 0 (−0.02, 0.03) Cord lead Med. (2–3.2 µg/dL) 0 (−0.03, 0.03)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Alvarenga et al. (2015) Brazil Followed 35.5 mo Contemporary cross-sectional cohort	n: 130 children (80 males & 50 females)	Blood AAS with graphite furnace Age at Measurement: 18 mo–14 yr (Mean: 6 yr 8 mo ± 2 yr 3 mo) Mean: 12.2 µg/dL; SD = 5.7 µg/dL Median: 10.2 µg/dL	Auditory brainstem response Age at outcome: 18 mo–14 yr	Age, gender, cumulative blood lead levels, and date of the audiological assessment	**Beta (95% CI)[b]** *Wave III, in relation to wave I* Constant 4.00 (3.97, 4.04) Wave I RE 0.58 (0.44, 0.72) Male RE 0.09 (0.05, 0.13) Constant 4.03 (3.99, 4.06) Wave I LE 0.61 (0.45, 0.77) Male LE 0.07 (0.03, 0.11) *Wave V, in relation to wave III* Constant 5.77 (5.74, 5.80) Wave I RE 0.81 (0.68, 0.94) Male RE 0.073 (0.03, 0.11) Constant 5.78 (5.75, 5.81) Wave I LE 0.85 (0.73, 0.97) Male LE 0.08 (0.05, 0.12)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Fillion et al. (2013) Lower Tapajos River Basin, State of Para, Brazil May to July 2006 Cross-sectional	n: 228	Blood Inductively coupled plasma mass spectrometry (ICP-MS, Perkin Elmer DRC II) Age at Measurement: 15−66 yr (median = 33.0 yr) Mean = 12.8 ± 8.4 µg/dL; Median = 10.5 µg/dL	Contrast sensitivity (cycles per degree, cpd); Acquired color vision loss (color confusion index, CCI) Age at outcome: 15−66 yr	Age, sex, current smoking (yes vs. no), current drinking (yes vs. no)	**Beta (95% CI)[b]** *Spatial frequency with %EPA* 1.5 cpd −1.32 (−4.30; 1.65) 3 cpd 2.06 (−2.87; 6.99) 6 cpd 0.60 (−6.04; 7.25) 12 cpd −13.33 (−23.28; −3.49) 18 cpd −2.43 (−6.64; 1.79) CCI 0.16 (−0.03; 0.33)

AAS = Atomic absorption spectrometry; ABR = Auditory brainstem response; BLL = blood lead level; CI = confidence interval; OR = odds ratio; Pb = lead; PTA = pure-tone average.
[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.
[b]Effect estimates are not standardized because data pertaining to the BLL distribution and/or base for the log-transformation were not reported.
†Studies published since the 2013 Integrated Science Assessment for Lead.

Table 3-13E Epidemiologic studies of Pb exposure, social cognition, and behavior in children

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Kim et al. (2016) South Korea 2005–2006 (enrollment); 2009–2010 (follow-up) Cohort	CHEER study n: 2,437 Children recruited from 33 elementary schools across 10 Korean cities	Blood Child blood; GFAAS Age at measurement: 7–8 yr old, 9–10 yr old, and 11–12 yr old GM (µg/dL): 7–8 y: 1.64; 9–10 y: 1.58; 11–12 y: 1.58 75th (µg/dL): 7–8 y: 2.36; 9–10 y: 2.08; 11–12 y: 2.05 95th (µg/dL): 7–8 y: 3.47; 9–10 y: 3.05; 11–12 y: 3.05	Autistic behaviors Parent responses to ASSQ and SRS Age at outcome: 11–12 yr	Child sex, fetal and environmental tobacco smoke, parental education levels, family income, low birth weight, breastfeeding, gestational age, fish intake, and blood Hg level	Change in SRS Scores* Exposure at 7−8 yr 1.37 (0.75, 1.98) Exposure at 9−10 yr 0.56 (−0.33, 1.44) Exposure at 11−12 yr 0.39 (−0.47, 1.25) Change in ASSQ Scores* Exposure at 7−8 yr 0.09 (0.03, 0.14) Exposure at 9−10 yr −0.02 (−0.09, 0.05) Exposure at 11−12 yr 0.03 (−0.04, 0.10) *Higher score indicates more autistic behaviors OR Autism (ASSQ ≥17) Exposure at 7−8 yr 1.45 (1.10, 1.93) Exposure at 9−10 yr 0.86 (0.60, 1.23) Exposure at 11−12 yr 0.97 (0.70, 1.35)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Arora et al. (2017) Sweden 2011–2016 (enrollment) Cohort	Roots of Autism and ADHD Twin Study in Sweden n: 32 twin pairs and 12 individual twins Monozygotic and dizygotic twins discordant for ASD; discordance defined as >2 points differences on the Autism-Tics, ADHD and other Comorbidities subscale	Tooth Shed deciduous teeth, validated by maternal, cord, and serial child blood Pb; laser ablation ICP-MS Age at measurement: estimating various timepoints from 20 wk prenatal to 30 wk postnatal Mean NR	ASD diagnosis ADOS−2, SRS−2 among discordant twins for ASD (ICD10 [Autism or Asperger's]; DSM−5 [ASD]) Age at outcome: 8–12 yr	Genetic factors Child sex, zygosity, gestational age, the average birth weight of the twin pairs, and the SD of the birth weight in the twin pairs.	OR of log-transformed Pb for ASD case vs. non-ASD twin control: 1.5 (0.9, 2.5)[b,d] More quantitative results depicted graphically (see Figure 3-2)
†Skogheim et al. (2021) Nationwide Norway 2002–2009 (enrollment) Case-control	Norwegian Mother, Father and Child Cohort Study (MoBa) n: 397 ASD cases, 1034 controls Children from a birth cohort	Blood Maternal whole blood; ICP-SFMS Age at measurement: wk 17 of gestation Exposure Quartiles: Q1: 0.16–0.65 µg/dL Q2: 0.65–0.86 µg/dL Q3: 0.86–1.12 µg/dL Q4: 1.12–8.24 µg/dL	ASD diagnosis NPR Age at outcome: NR	Birth year and child sex-matched controls Child sex, birth weight, birth year, and SGA, maternal age at delivery, education, parity, pre-pregnancy BMI, kg/m^2), self-reported smoking and alcohol intake during pregnancy, FFQ-based estimates of seafood intake (g/day), and dietary iodine intake (µg/day)	OR for ln-transformed Pb Q1: Ref. Q2: 0.80 (0.57, 1.12)[b] Q3: 0.79 (0.56, 1.12)[b] Q4: 0.81 (0.57, 1.15)[b]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Rahbar et al. (2015) Kingston Jamaica December 2009–March 2012 (enrollment) Case-control	Jamaican Autism Study n: 100 cases; 100 controls Children 2−8 yr at enrollment	Blood Child venous blood; ICP-MS Age at measurement: 2–8 yr GM (SD) (cases): 2.25 (2.23) µg/dL GM (SD) (controls): 2.73 (1.85) µg/dL	ASD diagnosis DSM-IV-TR criteria, ADOS Age at outcome: 2–8 yr	Age, sex-matched controls maternal age, parental education levels, parish at child's birth, SES (i.e., car ownership by the family), consumption of shellfish (lobsters, crabs), and Teflon use (pots, pans, and dishes) for cooking	GMD for ln-transformed Pb (ASD Cases vs. Controls): −0.17 (−0.86, 0.52)[b,c]
†Rahbar et al. (2021) Karachi Pakistan Study years NR Case-control	n: 30 cases; 30 controls children at clinics affiliated with Aga Khan University	Blood Child venous blood; ICP-MS Age at measurement: 2–8 yr GM (cases): 7.11 µg/dL; GM (controls): 8.48 µg/dL	ASD diagnosis DSM-IV-TR criteria, ADOS Age at outcome: 2–12 yr	Age, sex-matched controls maternal age, parental education level, and SES (i.e., car ownership by the family) and dietary consumptions dummy variables that represented the matched pairs	GMD for ln-transformed Pb (ASD Cases vs. Controls): −1.37 µg/dL (−3.28, 0.54)[b,c]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Dong et al. (2022) Northeast China October 2017 – January 2020 (enrollment) Case-Control	n: 512 children with ASD Children diagnosed with ASD at First Hospital of Jilin University	Blood Child serum Age at measurement: 2–13 yr Mean (SD) Mild Autism: 2.58 (1.08) µg/dL Moderate/severe: 2.58 (1.08) µg/dL	ASD severity Severity of autism symptoms determined by CARS Age at outcome 2–13 yr	Age, place of residence, caregivers, parental education level, gastrointestinal problems. Also considered sex, siblings, parental age at pregnancy, household income, family history of mental illness, vitamin intake during pregnancy, eating problems, sleeping problems, gastrointestinal problems, ADHD comorbidity	Beta 0.03 (0.01, 0.05)[c]
†Rygiel et al. (2021) Mexico City Mexico 1997–2005 (enrollment) Cohort	ELEMENT project n: 85 Mother-child pairs recruited at the Mexican Social Security Institute	Blood Maternal and child venous blood; ICP-MS, GFAAS Age at measurement: T1, T2, T3 (maternal); 12, 24 mo (child) Maternal blood GM (SD): T1: 5.27 (1.93) µg/dL T2: 4.74 (1.96) µg/dL T3: 4.98 (1.93) µg/dL Infant blood GM (SD): 12 mo: 3.92 (1.80) µg/dL 24 mo: 3.49 (1.93) µg/dL	Orientation/engagement and emotional regulation ORIEN and EMOCI scores from BRS of BSID-IIS Age at outcome: 12–24 mo	Maternal IQ (WAIS), maternal age, infant weight, length, SES, infant age and sex, current infant BLL	A large number of results were obtained from the mediation analysis. In summary, T2 BLLs were consistently inversely associated with 24-month EMOCI and ORIEN scores Beta 24-month EMOCI at T2: −1.13% (−2.63, 0.37) 24-month ORIEN at T2: −0.98% (−2.83, 0.88)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Shekhawat et al. (2021) Western Rajasthan India 2018–2019 (enrollment) Followed through 6.5 mo (average) Cohort	n:117 Mother-child pairs in third trimester or at delivery	Blood Cord blood; ICP-OES Age at measurement: Delivery GM = 4.14 µg/dL; mean = 4.77 ± 3.3 µg/dL; median = 4.23 µg/dL 75th: 5.1 µg/dL	Social-emotional development score using BSID-III Age at outcome: 6.5 mo	Maternal age, gravida, gestational age, maternal education, child sex and weight, preterm birth, maternal food intake during pregnancy, smoking, alcohol consumption, maternal residential and occupational history, delivery type	ß (95 % CI) for socio-emotional development scores Pb < 5 µg/dL: 0.19 (−0.46, 0.46) Pb 5.0–10.5 µg/dL: −0.05 (−0.60, 0.86)
†Nozadi et al. (2021) Navajo Nation United States February 2013–June 2018 (enrollment) Followed through 10–13 mo Cohort	Navajo Birth Cohort Study (NBCS) n: 327 Children of mothers (age 14–45 yr) living across Navajo Nation with community exposure to metal mixtures from abandoned uranium mines	Blood Maternal blood, child blood; ICP-DRC-MS. Age at measurement: Delivery or 36-wk visit (maternal); 10, 13 mo (child) GM = 0.410 µg/dL; median = 0.37 µg/dL 75th: 0.51 µg/dL 95th: 1.20 µg/dL	Communication and personal-social domain scores using the ASQ:I. Age-adjusted scores. Age at outcome: 10–13 mo	Age. Also considered maternal age, marital status, maternal occupation and education, household income, concentrations of various metals in urine, blood, and serum	Beta (95% CI) Communication: −0.15 (−0.58, 0.28) Personal-Social: −0.11 (−0.72, 0.50)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Lin et al. (2013) Taipei, Taiwan April 2004-Jan 2005 (enrollment) Followed through 2 yr Panel Study	TBPS n: 230 Singleton full-term children of non-smoking mothers without occupational exposure attending medical center, hospital, and clinics in Taipei	Blood Maternal blood, cord blood; ICP-MS, measured for Pb, Mn, As, and Hg. Pb categories: Low: <16.45 µg/L High: ≥16.45 µg/L Mn categories: Low: <59.59 µg/L High: ≥59.59 µg/L Age at measurement: Delivery Mean: 13 µg/L, GM: 10.61 µg/L 75th: 16.45 µg/L Max: 43.22 µg/L	Social and self-help ability DQs CDIIT Age at outcome: 2 yr	Maternal age, maternal education, child sex, environmental tobacco smoke during pregnancy and after delivery, fish intake, and HOME Inventory score	Beta Social High vs. Low Pb: −5.89 (−10.81, −0.97)[c] High Mn x low Pb: 2.83 (−3.442, 9.102)[c] Low Mn x high Pb: −2.9 (−9.231, 3.431)[c] High Mn x high Pb: −7.01 (−14.144, 0.124)[c] Self-help High vs. Low Pb: −1.26 (−5.905, 3.385)[c] High Mn x low Pb: 0.49 (−5.429, 6.409)[c] Low Mn x high Pb: 0.35 (−5.608, 6.308)[c] High Mn x high Pb: −2.38 (−9.103, 4.343)[c]
†Nyanza et al. (2021) Northern Tanzania Tanzania 2015–2017 (enrollment) Followed through 12 mo Cohort	Mining and Health Prospective Longitudinal Study in Northern Tanzania n: 439 Birth cohort of mother-child pairs recruited in 2nd trimester	Maternal dried blood spots; ICP-MS, measured for Pb, Hg, and Cd Age at measurement: second trimester Median: 2.72 µg/dL 75th: 4.25 µg/dL Max: 14.5 µg/dL	Social development domain using MDAT. Scores classified as normal (≥90th percentile on all items in the domain or <90th percentile on one or two items in the domain) or impaired (<90th percentile on more than two items in the domain). Age at outcome: 6–12 mo	Maternal age and education, maternal and paternal occupation, number siblings under 5 yr at home, and family SES, infant sex, age, birth weight, height and weight as a proxy for nutritional status (covariates with p < 0.20 retained in the final models)	Prevalence ratio: Social status development: 1.01 (1.00, 1.02)

†Doherty et al. (2020) New Hampshire U.S. 2009 to 2014–2019 Cohort	NHBCS n: 371 (SRS−2); 318 (BASC-2) Mother-child pairs	Toenails Maternal and infant toenails; Median (maternal prenatal): 0.14 µg/g (SRS), 0.13 µg/g (BASC); Median (maternal postnatal): 0.10 µg/g (SRS), 0.11 µg/g (BASC); Median (infant): 0.35 µg/g (SRS), 0.37 µg/g	Composite score (Social Awareness, Social Cognition, Social Communication, Social Motivation, and Restricted Interests and Repetitive Behavior) on SRS−2. Adaptive skills composite on BASC-2; see also Section 3.5.2.2 Age at outcome: 3 yr old	Maternal age, maternal BMI, parental education, maternal smoking, marital status, parity, child age at last breastfeeding, Healthy Eating Index score, year of birth, sex, and age of the child at testing	Beta per log_2-transformed µg/g increase in toenail Pb Total SRS−2 Maternal prenatal: −0.08 (−0.20, 0.04)[e] Maternal postnatal: 0.03 (−0.08, 0.13)[e] Child: −0.06 (−0.19, 0.06)[e] Males Maternal prenatal: −0.06 (−0.23, 0.11)[e] Maternal postnatal: −0.01 (−0.14, 0.13)[e] Child: −0.08 (−0.25, 0.10)[e] Females Maternal prenatal: −0.04 (−0.19, 0.11)[e] Maternal postnatal: 0.07 (−0.08, 0.21)[e] Child: −0.05 (−0.21, 0.11)[e] Total Adaptive Skills Maternal prenatal: −0.06 (−0.19, 0.07)[e] Maternal postnatal: 0.08 (−0.03, 0.19)[e] Child: 0.08 (−0.06, 0.22)[e] Males Maternal prenatal: −0.01 (−0.19, 0.18)[e] Maternal postnatal: 0.08 (−0.07, 0.24)[e]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
					Child: 0.10 (−0.13, 0.32)[e] Females Maternal prenatal: −0.19 (−0.34, −0.04)[e] Maternal postnatal: 0.07 (−0.08, 0.23)[e] Child: 0.26 (0.07, 0.45)[e]
†Zhou et al. (2017) Shanghai China 2010–2012 Followed through 24–36 mo Cohort	Shanghai Stress Birth Cohort study n: 139 Mother-infant pairs in prenatal clinics of maternity hospitals during mid-to-late pregnancy	Blood Maternal whole blood Age at measurement: wk 28–36 of gestation GM (95% CI): 3.30 (3.05, 3.57) µg/dL	Adaptive and social behavior domain DQs from GDS Age at outcome: 24–36 mo	Maternal age at enrollment, SES, maternal education, gestational week, child sex, birth weight and age	Beta per log−10 transformed BLL Adaptive: Overall: 3.60 (−3.64, 10.83)[b] Low stress: 7.57 (−0.12, 15.27)[b] High stress: −17.93 (−35.83, −0.03)[b] Social: Overall: −6.45 (−15.55, 2.65)[b] Low stress: −0.07 (−9.57, 9.44)[b] High stress: −41.00 (−63.11, −18.89)[b]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Ruebner et al. (2019) 46 centers U.S. Study Years: NR Cross-sectional	CKiD Cohort study n: 412 Children (age 1–16 yr) with mild to moderate CKD	Blood Child venous blood; ICP-MS. The BLL measurement closest to the time of neurocognitive testing was used for analysis (concurrent). Age at measurement: NR; 2, 4, or 6 yr after study entry Median: 1.2 µg/dL 75th: 1.8 µg/dL Max: 5.1 µg/dL	Adaptive skills, composite index on the BASC-2 (see also 3.5.1 and 3.5.2) The last available test results were used to evaluate long-term effects. Mean time between BLL and neurocognitive testing was 2.3 yr. Age at outcome: 3, 5, or 7 yr after study entry	Child age, sex, race, poverty, and maternal education	Adjusted BASC-2 results were not reported because they were not statistically significant.
†Vigeh et al. (2014) Tehran Iran October 2006 – March 2011 Followed through 36 mo Cohort	Birth cohort n: 174 Mother-infant pairs recruited in first trimester (8–12 wk).	Blood Maternal blood, cord blood; ICP-MS Age at measurement: 3 trimesters during pregnancy and delivery Mean: 1st trimester: 4.15 µg/dL, 2nd trimester: 3.44, 3rd trimester: 3.78, umbilical cord: 2.86 Max: 1st trimester: 20.5 µg/dL, 2nd trimester: 7.5, 3rd trimester: 8.0, umbilical cord: 6.9	Mental development assessed using the ECDI by Harold Ireton (language comprehension, expressive language, gross motor, self-help, social interaction). Cutoff point scores for development delay was score <20% of that expected for children's age. Age at outcome: 36 mo	Maternal educational, BMI, family income, gestational age, birth weight, birth order (first born)	OR Total ECDI: 1.74 (1.18, 2.5)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Kim et al. (2018b) 4 cities: Seoul, Anyang, Ansan and Jeju Korea Pregnancy (2011–2012) through 24 mo of age Cohort	CHECK cohort n: 140 birth cohort-pregnant women recruited from 4 cities in Korea before delivery,	Blood Prenatal maternal blood collected during hospital visit: 2.7 µg/dL Cord blood: 1.2 µg/dL	Adaptive behaviors assessed using SMS Association was examined using multiple linear regression analysis. Age at outcome: 13–24 mo	BPA, and phthalates, maternal age (continuous), birth delivery mode (categorical), monthly household income (categorical), child's sex, and BDI (continuous) of the mother, gestational age (continuous), primiparous (categorical), and pre-pregnancy BMI (categorical)	Associations of blood Pb concentrations and SQ were assessed but not reported because they lacked statistical significance.

AAS = atomic absorption spectrometry; ADHD = attention deficit/hyperactivity disorder; ADOS = Autism Diagnostic Observation Schedule; ASD = autism spectrum disorder; ASQ = Ages and Stages Questionnaire Inventory; ASSQ = Autism Spectrum Screening Questionnaire; BASC = Behavior Assessment System for Children; BDI = Beck Depression Inventory; BLL = blood lead level; BMI = body mass index; BPA = bisphenol A; BRS = behavioral rating scale; BSID = Bayley Scales of Infant and Toddler Development; CARS = Childhood Autism Rating Scale; CDIIT = Comprehensive Developmental Inventory for Infants and Toddlers; CHECK = Children's Health and Environmental Chemicals in Korea; CHEER = Children's Health and Environmental Research; CKiD = Chronic Kidney Disease in Children; DQ = development quotient; DSM = Diagnostic and Statistical Manual of Mental Disorders; GM = geometric mean; ECDI = Early Child Development Inventory; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; GDS = Gesell Developmental Schedules; GFAAS = graphite furnace atomic absorption spectrometry; HOME = Home Observation Measurement of the Environment; ICP-MS = inductively coupled plasma mass spectrometry; ISAT = Illinois Standard Achievement Test; MAT = Metropolitan Achievement Test; MEAP = Michigan Educational Assessment Program; MDAT = Malawi Development Assessment Tool; Mn = manganese; mo = month(s); NHANES = National Health and Nutrition Examination Survey; NHBCS = New Hampshire Birth Cohort Study; NHNPR = Norwegian Patient Registry; NR = not reported; OR = odds ratio; Pb = lead; SD = standard of deviation; SES = socioeconomic status; SGA = small for gestational age; SMS = Social Maturity Scale; SRS = Social Responsiveness Scale; SQ = social quotient; TBPS = Taiwan Birth Panel Study; wk = week(s); yr = year(s).
[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.
[b]Results are unstandardized because the Pb level distribution data was not available.
[c]The CI was calculated from a p-value and the true CI may be wider or narrower than calculated.
[d]Results are unstandardized because the log base used for exposure transformation was unspecified in the study.
[e]Results are unstandardized because the biomarker used for Pb exposure measurement is not blood, tooth, or bone.
†Studies published since the 2013 Integrated Science Assessment for Lead.

Table 3-14E Epidemiologic studies of exposure to Pb and cognitive function in adults

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Power et al. (2014) Boston, MA, U.S 1993–2008 Cohort	Participants selected from cohort study (Nurse's Health Study) and part of case-control ancillary study n: 584	Bone, Blood Bone Pb: K-XRF at the midtibial shaft and the patella. blood Pb concentrations; GFAAS with Zeeman background correction in year 1993–2004 Age at measurement: registered nurses aged 45–74 yr Tibia Pb conc: 10.5 ± 9.7 µg/g, Patella Pb conc: 12.6 ± 11.7 µg/g. Blood Pb conc: 2.9 ± 1.9 µg/dL	Cognitive decline Cognitive decline assessed using a telephone battery of cognitive tests during 2–4 waves over the period of follow-up, 1995–2008. All 9 cognitive scores were Z-transformed with high score representing better performance.	Alcohol consumption, smoking status, education, husband's education, menopausal status/hormone therapy use, physical activity, ibuprofen use, aspirin use, vitamin E supplementation, the % of residential census tract of white race/ ethnicity, and median income of residential census track.	**Beta (95% CI)[a]** *Tibia* Verbal Memory −0.002 (−0.006, 0.003) Overall Cognition −0.002 (−0.005, 0) *Patella* Verbal Memory −0.001 (−0.005, 0.002) Overall Cognition −0.001 (−0.004, 0.001) *Blood* Verbal Memory 0.003 (−0.021, 0.027) Overall Cognition −0.007 (−0.023, 0.009)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Farooqui et al. (2017) Boston, MA, U.S. 1993–2007 Cohort	Participants selected from cohort study (Veterans Affairs NAS n: 741 subjects in MMSE and 715 in Global cognition	Bone Patella (trabecular bone) and tibia (cortical bone) bone Pb was measured using K-XRF spectroscopy in 1993 Age at measurement: healthy men aged 51–98 yr Patella Pb conc: 30.6 ± 19.44 µg/g, and tibia Pb conc: 21.6 ± 13.33 µg/g	Changes in cognition Cognition was assessed using the MMSE, NES2, CERAD and WAIS-R during 3–5 visits over the period of 15 yr of follow-up.	Age at first cognitive test, past education level, baseline smoking status and alcohol intake.	**Beta (95% CI)[a] Pb and MMSE over time** *Tibia* *IQR change in Pb* −0.051 (−0.137, 0.035) *IQR change in Pb*time* −0.007 (−0.018, 0.004) *Patella* *IQR change in Pb* −0.061 (−0.12, −0.002) IQR change in Pb*time −0.008 (−0.015, 0) **HR (95% CI)[b]** *Patella* 1.095 (0.993, 1.207) *Tibia* 1.033 (0.875, 1.22) **Beta (95% CI)[b] Pb and Global Cognition over time** *Patella* −0.119 (−0.247, 0.009) *Tibia* −0.137 (−0.318, 0.043)

†Weuve et al. (2013) Boston, MA, United States 2003−2007 Cross-sectional	PD cases confirmed by movement disorder specialists using the U.K. Brain Bank criteria n: 151 subjects (101 cases and 50 controls)	Bone Bone Pb measured using K-XRF spectrometric estimates of Pb concentrations in Tibia and Patella bones. Age at measurement: cases and controls (spouses, in-laws, or friends of the cases) aged 54–81 yr Patella Pb conc by age at cognitive interview categories: 54–64.9 yr: 5.9 ± 10.3 µg/g 65–69.9 yr: 9.2 ± 7.8 µg/g 70–74.9 yr: 7.7 ± 10.5 µg/g 75–80.9 yr: 15.2 ± 10.2 µg/g Tibia Pb conc by age at cognitive interview categories: 54–64.9 yr: 4.4 ± 11.1 µg/g 65–69.9 yr: 8.8 ± 10.5 µg/g 70–74.9 yr: 6.8 ± 8.8 µg/g 75–80.9 yr: 9.2 ± 11.5 µg/g	Cognition function Cognitive function assessed using a telephone cognitive assessment battery of 9 tests based on a validated telephone battery for assessing age-related cognitive decline. Added test of cognitive domains that typically decline in PD. All 9 cognitive scores were z-transformed with high score representing better performance.	Age at cognitive assessment, sex, race, education, smoking history	**Adjusted difference (95% CI)[b]** *Patella* Telephone interview for cognitive assessment (TICS) −0.08 (−0.32 to 0.15) Delayed 10-word recall 0.05 (−0.18 to 0.28) Delayed 10-word recognition 0.01 (−0.22 to 0.24) Animal naming −0.11 (−0.32 to 0.10) “F” naming −0.07 (−0.30 to 0.17) Digit span forward −0.02 (−0.27 to 0.22) Digit span backward 0.05 (−0.17 to 0.27) Oral trails B minus A 0.03 (−0.23 to 0.28) Global score −0.01 (−0.14 to 0.13) *Tibia* Telephone interview for cognitive status (TICS) −0.20 (−0.40 to −0.00) Delayed 10-word recall −0.04 (−0.23 to 0.16) Delayed 10-word recognition −0.01 (−0.21 to 0.20) Animal naming −0.11 (−0.29 to 0.07) “F” naming −0.19 (−0.39 to 0.01) Digit span forward

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
					−0.23 (−0.43 to −0.03) Digit span backward −0.19 (−0.37 to −0.00) Oral trails B minus A −0.06 (−0.29 to 0.17) Global score −0.13 (−0.25 to −0.01)
†Skerfving et al. (2015) Landskrona and Trelleborg, Southern Sweden 1978–2007 followed for 4–12 yr Cohort	n: 927	Blood Between 1978 and 1994, B-Pb levels were determined using flame or electrothermal atomization atomic absorption spectrometry; between 1995 and 2007, B-Pb levels were determined using inductively coupled plasma mass spectrometry Age at measurement: 7−12 yr Mean: 34 µg/L	IQ assessed for military conscription IQ (measured logical, verbal, spatial abilities, and technical understanding) assessed as a part of military conscription examinations. Age at outcome: 18−19 yr	Age at blood sampling, sex, parents' education, family economy, and country of birth of child and parents	Beta (SE)[a] IQ All subjects −0.127 (−0.209, −0.045) Blood Pb ≤50 µg/L −0.204 (−0.392, −0.016)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Reuben et al. (2017) Dunedin, New Zealand 1972/73–2012 Cohort	Dunedin Multidisciplinary Health and Development Study n: 565	Blood Graphite fumance atomic absorption spectrophotometry Age at measurement: 11 yr Mean (SD): 10.99 ± 4.63 µg/dL	Full -scale IQ (other domains such as verbal comprehension, perpetual reasoning, working memory, processing speed) Cognitive function assessed using Wechsler Adult Intelligence Scale – IV (WAIS-IV) at the age of 38 yr.	Childhood IQ scores (age 7 and 9 yr), their mothers' IQ score, and their socioeconomic background	Change in IQ[a] (95% CI) Adjusted by sex −0.394 (−0.669, −0.119) Fully adjusted −0.322 (−0.496, −0.148) Change in perceptual reasoning[a] (95% C) −0.414 (−0.627, −0.201) Change in working memory[a] (95% CI) −0.252 (−0.476, −0.028) Change in socioeconomic status[a] (95% CI) −0.358 (−0.635, −0.081)
†Reuben et al. (2020) Dunedin, New Zealand 1972/73–2019 Cohort	Dunedin Multidisciplinary Health and Development Study n: 564	Blood Furnace atomic absorption spectrophotometry Age at measurement: 11 yr Mean (SD): 10.99 ± 4.63 µg/dL	Full-scale IQ and self-reported information) Cognitive performance assessed objectively using Wechsler Adult Intelligence Scale – IV (WAIS-IV) and subjectively via informant and self-reports at the age of 45 yr.	Childhood IQ scores (age 7 and 9 yr), their mothers' IQ score, and their socioeconomic background	Change in IQ[a] (95% CI) −0.414 (95% CI: −0.679, −0.149) Residualized Change in IQ[a] (95% CI) −0.394 (−0.583, −0.205)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Khalil et al. (2014) Multicity (6 clinical sites), U.S. May 2007 to Nov 2008 Cross-sectional	Population-based cohort study (MrOS) n: 445	Blood Venous blood samples tested for Pb levels using AAS Age at measurement: non-Hispanic Caucasian men aged ≥65 yr Mean (SD) 2.25 ± 1.20 µg/dL	Cognitive function assessed using 3 MS Age at outcome: ≥65 yr	Age, education, smoking, alcohol consumption and BMI	Beta (95% CI)[b] Cognitive Function in Adults 3MS −0.01 (−1.10,1.07) Cognitive Function in Adults Trail Making B 2.72 (−7.65, 13.09)
†Souza-Talarico et al. (2017) Sao Paulo City, Brazil Cross-sectional	n: 125 (104 women and 21 men)	Blood Venous blood samples tested for heavy metals (Cd and Pb) levels using ICP-MS Age at measurement: Healthy older adults between 50 and 82 yr (M = 65.9) Mean (SD) 2.1 ± 0.970 µg/dL	MMSE and Informant Questionnaire on Cognitive Decline used to rule out cognitive and functional impairments. Age at outcome: 50 and 82 yr (M = 65.9)	Age, sex, income, education, hemoglobin, hematocrit	Beta[b] WMC Pb 0.106 (ΔR: 0.057) BCd × BPb interaction-term and WMC −0.378 (p ≤ 0.001) Table 3 adjusted EE for Pb and WMC, with and without controlling for Oxygen Radical Absorbance Capacity total: standardized

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†van Wijngaarden et al. (2011) Nationwide, U.S. 1999–2008 Cross-sectional	NHANES 1999–2008 (for self-reported confusion and memory problems) and NHANES 1999– 2002 (for DSST) n: 9526 participants (7277 from NHANES 1999–2008 and 2299 participants from NHANES 1999–2002)	Blood Venous blood samples tested for Pb concentration using AAS with Zeeman background correction. Age at measurement: ≥60 yr Blood Pb conc: 2.46 µg/dL (range 0.18–54.00 µg/dL)	Cognitive function Cognitive function assessed by self-reported responses on limitation in cognitive functioning, and DSST (a subset of the WAIS-III) for subset of participants. Age at outcome: ≥60 yr	Age, sex, ethnicity, education level, PIR, self-reported general health status	OR (95% CI)[b] 1.01 (0.65, 1.56)
†Przybyla et al. (2017) Nationwide, U.S. 1999–2002 Cross-sectional	NHANES cycles 1999–2000 and 2001 −2002; n: 498	Blood Blood samples tested for chemicals (Pb, Cd and PCBs) concentrations; Pb and Cd measured using ICP-MS. Age at measurement: 60–84 yr Mean 2.17 µg/dL (95% CI: 2.07, 2.27)	Cognitive function Cognitive function assessed using the DSC Module of the WAIS-III. Age at outcome: 60–84 yr	Race/ethnicity, age, education level, PIR, sex and smoking status	Betas per natural log increase in BLL Cognitive Functioning All Participants: −0.10 (−0.20, −0.01) Females: −0.12 (−0.26, 0.01) Males: −0.09 (−0.24, 0.06) Age 60–69: −0.13 (−0.28, 0.01) Age 70–74: −0.08 (−0.2, 0.04)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Sasaki and Carpenter (2022) Nationwide, U.S. 2011–2014 Cross-sectional	NHANES cycles 2011–12 and 2013–14 and tested for different sets of chemicals for different subgroups n: 3042	Blood and Urine Venous blood samples and urine samples tested for seven metals and metalloids (including Pb) using ICP-MS Age at measurement: 60–80 yr Blood mean Pb: 19.0 µg/L Urine mean Pb: 0.72 µg/dL	Cognitive function Immediate and delayed memory assessed using the CERAD, and working memory assessed using the DSST. Age at outcome: 60–80 yr	Age, sex, ethnicity, education level, depression, diabetes, alcohol consumption, and smoking	**Beta (95% CI)[b]** *Blood* CERAD Immediate recall: −0.58 (−0.91, −0.24) CERAD Delayed recall: −0.19 (−0.35, −0.02) Digit symbol substitution: −1.08 (−2.12, −0.05) CERAD immediate recall as a function of age 60s Years Old Group: −0.37 (−0.87, 0.13) ≥70 Years Old Group: −0.85 (−1.44, −0.27) *Urine* CERAD Immediate recall: −0.26 (−0.58, 0.06) CERAD Delayed recall: −0.03 (−0.19, 0.13) Digit symbol substitution: −1.03 (−2.01, −0.06)
†Xiao et al. (2021) Guangxi, southern China Aug 2016–July 2018 Cross-sectional	n: 2879	Blood Venous blood samples tested for 22 metals (including Pb) using ICP-MS. Age at measurement: ≥60 yr Blood Pb: Median: 51.5 µg/L	Cognitive function Cognitive function assessed using the MMSE. Age at outcome: ≥60 yr	Age, gender, education attainment, annual income, BMI, smoking, alcohol drinking, insomnia, and physical activity	Beta (95% CI)[a] Cognitive function Single-pollutant model −0.018 (−0.06, 0.023) Multi-pollutant model −0.019 (−0.063, 0.025)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Meramat et al. (2017) Malaysia May 2013 to January 2014 Cross-sectional	Neuroprotective Model for Healthy Longevity among Malaysia Older adult n: 317	Nail Toenails (clipped from all toes) assessed for trace elements (Al, Ca, Cd, Co, Fe, Pb, Zn, Se, Cu and Cr) using ICP-MS. Age at measurement: ≥60 yr Pb conc: Cognitive impaired group (n = 197): 0.55 ± 0.03 µg/g; and Normal cognitive group (n = 120): 0.35 ± 0.013 µg/g	Cognitive impairment assessed using Montreal Cognitive Assessment - a Malay version Age at outcome: ≥60 yr	Age, sex, years of education and smoking habits	OR (95% CI)[a] Cognitive impairment 2.471 (1.535−3.980)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Yu et al. (2021) Nationwide, U.S. Jan 2015–Sep 2017 Cohort	SPHERL longitudinal study n: 260 (260: DSST cohort and 168: SCWT cohort) with baseline and annual follow-up blood Pb measurements and neurocognitive function assessments.	Blood Venous blood samples tested for Pb concentration using ICP-MS. Age at measurement: mean age 29.4 yr Blood Pb conc: DSST cohort: Geo mean: 3.97 (5–95th percentage interval (PI) 0.90–14.3) µg/dL at baseline, 13.4 (PI 3.70–30.3) µg/dL and 12.8 (PI 2.80–29.2) µg/dL at the first and second follow-up visits, respectively.	Cognitive function Cognitive function changes assessed using the DSST and ST at baseline and annual follow-up visits. Age at outcome: mean age 29.4 yr	Age, sex, ethnicity, change in age, baseline BMI, changes in body weight, education, baseline blood Pb, baseline neurocognitive function test, baseline values and changes in smoking status, total/HDL ratio, cholesterol and alcohol consumption	OR (95% CI)[a] DSST 1.012 (0.997, 1.028)

3MS = Modified Mini Mental State Examination; BrainAGE = Brain Age Gap Estimation; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; DSC = Digital Symbol Coding; DSST = Digit Symbol Substitution Test; EE = effect estimate(s); K-XRF = K-shell X-ray fluorescence; MMSE = mini mental status exam; MrOS = Osteoporotic Fractures in Men Study; NAS = Normative Aging Study; NES2 = Neurobehavioral Evaluation System 2; PD = Parkinson's disease; WAIS-III = Wechsler Adult Intelligence Scale, Third Edition; WAIS-R = Wechsler Adult Intelligence Scale-Revised; WMC = working memory capacity; SPHERL = Study for Promotion of Health in Recycling Lead; SCWT = Stroop Color-Word Test.
[a]Effect estimates are standardized to a 1 µg/dL increase in BLL or a 10 µg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.
[b]Result not standardized because data pertaining to the BLL distribution and/or base for the log-transformation were not reported.

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

Table 3-15E Epidemiologic studies of Pb exposure and psychopathological effects in adults

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Rajan et al. (2007) Boston, MA, U.S. 1991–2002 Cohort	Veterans Affairs NAS n: 1,075 Closed cohort of male volunteers with no chronic medical conditions at entry. 97% white	Bone Bone Pb measured in the mid-tibia shaft and patella using K-XRF Age at measurement: 21–80 yr Mean: ~67.5 yr old Mean (SD): Tibia: 22.1 (13.8) µg/g Patella: 31.4 (19.6) µg/g	Depression and anxiety Depressive and anxiety symptoms were measured using the BRIEF Symptom Inventory (depression and anxiety were determined to be present for participants that scored 1 SD above the mean for a normal population). Participant followed up was 3 yr.	Age, alcohol consumption, education, time between assessments, and cumulative smoking	*Anxiety OR (95% CI)*[a] Tibia: 1.13 (0.99, 1.29) Patella: 1.09 (0.99, 1.19) *Depression OR (95% CI)*[a] Tibia: 1.11 (0.98, 1.38) Patella: 1.05 (0.96, 1.16)
Bouchard et al. (2009) U.S. 1999–2004 Cross-sectional	NHANES n: 1,987	Blood Blood Pb measured in venous whole blood samples using ICP-MS Age at measurement: 20–39 yr old Geo. mean: 1.24 µg/dL 20th %ile: 0.7 µg/dL 40th %ile: 1.0 µg/dL 60th %ile: 1.4 µg/dL 80th %ile: 2.1 µg/dL	Depression WHO CIDI was administered. Major depressive disorder diagnosed according to DSM-IV criteria. Age at outcome: 20–39 yr	Age, sex, race/ethnicity, education, and PIR	Major Depressive Disorder **OR (95% CI)**[a] Q1: Ref. Q2: 1.39 (0.71, 2.72) Q3: 1.28 (0.69, 2.38) Q4: 1.41 (0.76, 2.6) Q5: 2.32 (1.13, 4.75)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Peters et al. (2011) Boston, MA U.S 1991–1997 (Bone Pb measurements); 1993–2003 (Psychological measurements) Cohort	Veterans Affairs NAS n: 412 Closed cohort of male volunteers with no chronic medical conditions at entry. 97% white	Bone Bone Pb measured in the mid-tibia shaft using K-XRF Age at measurement: Mean: ~65.3 yr old Mean: 20.6 µg/g	Pessimism and Depression A subscale of the Life Orientation Test was used to assess pessimistic attitudes. Depressive symptoms were measured using the BRIEF Symptom Inventory (depression was determined to be present for participants that scored 1 SD above the mean for a normal population). Age at outcome: Mean ~68.3 yr	Age, health behaviors, childhood SES, adult SES	Difference in Pessimism Level on the Life Orientation Test (95% CI) 0.21 (0.00, 0.43)
†Reuben et al. (2019) Dunedin, New Zealand Enrollment: 1972–73; Follow-up through 2012 Cohort	Dunedin Multidisciplinary Health and Development Study Cohort of children 3 yr old at enrollment followed through 32 yr of age. Study population was nationally representative (majority white) and had high rates of participation and follow-up.	Blood Blood Pb measured in venous blood samples using GFAAS Age at measurement: 11 yr Mean: 11.08 µg/dL (94% above 5 µg/dL)	General Psychopathology, Externalizing Symptoms, Internalizing Symptoms, and Thought Disorder Symptoms in Adults Psychopathology symptoms were assessed using the Diagnostic Interview Schedule. Factor loadings from each of 11 disorders were used to create hierarchical measures for psychopathology and each of its constituent psychiatric spectra Age at outcome: 18, 21, 26, 32, and 38 yr	Sex, childhood SES, maternal IQ, and family history of mental illness.	**Change in symptom scores (95%CI) (standardized to a mean [SD] of 100 [15])[a]** *General Psychopathology* 0.27 (0.02, 0.51) *Externalizing Symptoms* 0.15 (−0.10, 0.40) *Internalizing Symptoms* 0.28 (0.04, 0.53) *Thought Disorder* 0.26 (0.01, 0.51)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†McFarlane et al. (2013) Port Pirie, Australia 1979–1982 (enrollment); 2008–2009 (follow-up) Cohort	Port Pirie cohort Study n: 210 Mother-singleton infant pairs enrolled in Pb-smelting town from 1979–1982. Assessed periodically from birth to 7 yr, again from 11 to 13 yr, and for this study, at 25 to 29 yr	Blood Blood Pb measured in capillary blood samples using GFAAS Age at measurement: 6, 15, and 24 mo; 3–7 yr Mean: 17.2 µg/dL (birth to 7-yr average)	Drug and alcohol abuse, DSM-IV Disorders (Alcohol abuse, drug abuse, social phobia, specific phobia, PTSD, alcohol dependence, panic attack, major depressive disorder) and adult self-report DMV-IV oriented subscale (anxiety, somatic problems, depressive problems, hyperactivity, inattention, antisocial personality problems, avoidant personality problems) Age at outcome: 25 to 29 yr	HOME, maternal education, paternal occupation, mothers' age at birth, breastfeeding, and single parent family status	**OR (95% CI)[a]** *Social Phobia* Women: 1.05 (0.93, 1.188) Men: 0.96 (0.80, 1.15) *Specific Phobia* Women: 1.13 (0.99, 1.29) Men: 1.02 (0.71, 1.47) *Major Depressive Disorder* Women: 0.89 (0.77, 1.03) Men: 0.89 (0.68, 1.16)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Li et al. (2017) Shanghai (inner and outer districts) China 2010 Cross-sectional	n: 1,701 Stratified cluster sampling of pregnant women (gestational wk 28–36)	Blood Blood Pb measured in venous blood samples using GFAAS Geo mean: 3.97 µg/dL Max: 14.84 µg/dL	Maternal stress Life Event Stress Scale for Pregnant Women, Symptom Checklist-9-Revised (GSI [measure of psychological distress], anxiety and depression scores) Age at outcome: 13–42 yr old (wk 28–36)	Maternal age at enrollment, ethnicity, maternal education, and family monthly income, years residing in Shanghai	Change in maternal stress, anxiety, and depression scores per 10-fold increase in BLLs (results from piecewise linear models)[a] *Maternal Stress* ≤2.57 µg/dL: 0.22 (0.05, 0.4) >2.57 µg/dL: −0.07 (−0.16, 0.01) *Depression* ≤2.57 µg/dL: 0.34 (0.12, 0.56) >2.57 µg/dL: −0.09 (−0.19, 0.02) *Anxiety* ≤2.57 µg/dL: 0.25 (0.04, 0.46) >2.57 µg/dL: −0.08 (−0.18, 0.02)
†Ishitsuka et al. (2020) Japan 2011–2014 Cross-sectional	Japan Environment and Children's Study n: 17,267 Pregnant women recruited out of 15 regional centers across Japan	Blood Blood Pb measured in whole blood samples using ICP-MS Age at measurement: 31 yr (mean) Geo. mean: 0.58 µg/dL Max: 6.75 µg/dL	Maternal Depression K6. Depression measured as scores ≥5 or 13 (two cutoff points for sensitivity). Age at outcome: Mean age: 31 yr	Age, parity, marital status, education, employment status, household income, and smoking and alcohol status	**OR (95% CI)[b]** *K6 ≥13* 1.00 (0.76, 1.32) *K6 ≥5* 0.98 (0.88, 1.09)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Berk et al. (2014) U.S. 2005–2010 Cross-sectional	NHANES n: 15,140 General population, ≥18 yr old	Blood Blood Pb measured in venous whole blood samples using ICP-MS Age at measurement: ≥18 yr old Mean: NR	Depression Depression measured as >9 on the nine-item depression module of the Patient Health Questionnaire Age at outcome: ≥18 yr old	Age, sex, poverty, family income, ethnicity, and country of birth	Depression OR (95% CI) **Q4 vs. Q1*:** 0.98 (0.78, 1.25) *Quartile levels NR
†Nguyen et al. (2022) South Korea 2009–2013 and 2016–2017 Cross-Sectional	KNHANES n: 16,371 General population; mean age: 42.6 yr old (SD: 18.12)	Blood Blood Pb was measured in venous whole blood using GFAAS Age at measurement (mean): 42.6 yr old (SD: 18.12) Geo. Mean: 1.84 µg/dL (w/o depression) 1.85 µg/dL (w/ depression)	Depression Self-reported physician's diagnosis or treatment for depression Age at outcome (mean): 42.6 yr old (SD: 18.12)	Sex, urbanicity, household income, physical activity, occupation, BMI, alcohol consumption, education level, and smoking status	OR (95% CI)[a] 1.02 (0.90, 1.16)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Eum et al. (2012) Boston, MA United States Subsample 1: Bone Pb Measure 1993–1995; Subsample 2: Bone Pb Measure 2001–2004. Psychological Questionnaires: 1988, 19992,1996, 2000, 2004 Cohort	Nurses' Health Study n: 617 Women from two subsample studies of the NHS cohort	Bone Midtibial shaft and patella bone Pb measured using K-XRF Age at measurement: Mean: 60.9 yr Mean: Tibia: 10.3 µg/g; Patella:12.5 µg/g Tibia Tertiles: T1: <7.0 µg/g T2: 7.0–11.5 µg/g T3: >11.5 µg/g Patella Tertiles: T1: <8.5 µg/g T2: 8.5–14.5 µg/g T3: >14.5 µg/g	Phobic anxiety and depressive symptoms Depression symptoms measured using MHI−5; Anxiety symptoms measured using phobic anxiety scale of the Crown-Crisp Experiential Index (CCEI) Age at outcome: Mean: MHI−5: 59.4 yr CCEI: 59.2 yr	Substudy group, age at bone Pb measure, age at MHI−5 or CCEI measurement, education, husband's education, alcohol consumption, pack-years of smoking, and employment status at MHI−5 or CCEI assessment	**OR (95% CI)[b] (Tertile 3 vs. Tertile 1)** *CCEI ≥4* *All women* Tibia: 1.10 (0.73, 1.64) Patella: 0.75 (0.49, 1.15) *Women on HRT* Tibia: 2.79 (1.02, 7.59) Patella: 0.23 (0.07, 0.69) *MHI−5 Point Difference (lower scores indicate worse symptoms)* *All women (T3 vs. T1)* Tibia: −1.06 (−3.05, 0.94) Patella: −7.78 (−11.73, −3.83) *Women on HRT (T3 vs. T1)* Tibia: 0.61 (−1.55, 2.78) Patella: 0.51 (−3.91, 4.94)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Fan et al. (2020) Luan city, Anhui province, China 2016 Cross-sectional	Cohort Study of Elderly Health and Environmental Controllable Factors n: 994 Older adults (≥60 yr old) selected using cluster sampling from two communities in Luan, China	Blood Blood Pb measured in venous whole blood samples using ICP-MS Age at measurement: ≥60 yr old Quartiles Q1: <2.03 µg/dL Q2: 2.03–2.68 µg/dL Q3: 2.68–3.06 µg/dL Q4: ≥3.06 µg/dL	Depressive symptoms Chinese revision of the geriatric depression scale Age at outcome: ≥60 yr old	Age, gender, region, marital status, monthly income, education level, alcohol intake, smoking, and BMI	OR (95% CI)[b] **Depression** Q1: Ref. Q2: 1.28 (0.79, 2.08) Q3: 1.36 (0.84, 2.22) Q4: 2.03 (1.23, 3.35)
†Ma et al. (2019) Hebei Province China 2018–2019 Case-control	n: 190 (95 cases, 95 controls) First-episode drug-naive patients ages 18 to 60 yr old were recruited from a psychiatric hospital. Age and sex-matched controls without known psychiatric problems recruited from an affiliated hospital	Blood Serum Pb measured in venous blood samples using ICP-MS Age at measurement: 18–60 yr old Median: 0.61 ng/mL (serum) 75th: 0.79 ng/mL (serum)	Schizophrenia Physician-diagnosed schizophrenia using ICD−10 criteria Age at outcome: 18–60 yr old	Marital status (others not specified). Population matched on age and sex	OR (95% CI)[b] per 1 ng/mL increase 3.15 (1.24, 7.99)

AAS = atomic absorption spectrometry; BLL = blood lead level; BMI = body mass index; CCEI = Crown-Crisp Experiential Index; CI = confidence interval; CIDI = Composite International Diagnostic Interview; GFAAS = graphite furnace atomic absorption spectrometry; K6 = Kessler Psychological Distress Scale; K-XRF = K-shell X-ray fluorescence; MHI−5 = Mental Health Index 5-item; NAS = Normative Aging Study; NR = not reported; Pb = lead; PIR = poverty-income ratio; PTSD = post-traumatic stress disorder; Q = quartile; SD = standard deviation; SES = socioeconomic status; WHO = World Health Organization; wk = week(s); yr = year(s).

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

[b]Result not standardized because data pertaining to the BLL distribution and/or base for the log-transformation were not reported.

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

Table 3-16E Epidemiologic studies of Pb exposure and sensory organ function in adults

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Park et al. (2010) Eastern Massachusetts U.S. Enrollment and outcome assessment: 1962–1996; bone Pb measurements: 1991–1996 Cohort	NAS n: 448	Bone Bone Pb levels measured in the midtibial shaft and patella with a K-XRF instrument. Age at measurement: Mean (SD) at bone Pb measurement = 64.9 (7.3) yr; mean (SD) at first audiometric test = 42.5 (8.4) yr Mean (SD) in tibia = 22.5 (14.2) µg/g; mean (SD) in patella = 32.5 (20.4) µg/g	Sensory Organ Function Pure-tone averages assessed by audiologists with the modified Hughson-Westlake procedure. Air conduction hearing thresholds measured for each ear by audiologists using either a Beltone 15C or a Grason-Stadler 1701 audiometer.	Cross-sectional analyses and logistic regression analyses adjusted for age, race, education, BMI, pack-years of cigarettes, diabetes, hypertension, occupational noise, and noise notch.	Hearing loss OR (95% CI)[b] Tibia 1.19 (0.92, 1.53) Patella 1.48 (1.14, 1.91) EE in Hearing thresholds (dB HL) with one interquartile range Increment in bone lead measure Tibia PTA 0.83 (−0.18, 1.83) Patella PTA 1.58 0.62, 2.55
†Shiue (2013) U.S. 2003–2004 Cross-sectional	NHANES n: 712 (vision); 732 (hearing); 669 (balance) NHANES age 50 and above	Urine Urinary Pb was detected by mass spectrometry Age at measurement: 50 yr Not Reported	Vision: excellent, good, and fair eyesight (self-reported) were classified as good; poor and very poor were classified as poor Hearing: good and little trouble hearing (self-reported) were classified as good; lots of trouble and deaf were classified as poor Balance: “During the past 12 mo, have you had dizziness, difficulty with balance, or difficulty with failing?”	Age, sex, ethnicity, urine creatinine, survey weighting	OR (95% CI)[b] Vision 1.15 (0.67–1.97) Hearing 0.97 (0.63–1.51) Balance 0.68 (0.51–0.91)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
			Ear ringing: "ears ringing, roaring, or buzzing in the last year" Age at outcome: 50 yr		
†Kang et al. (2018) Korea 2010–2013 Cross-sectional	KNHANES n: 6409 Representative sample of the entire Korean population. Study participants were at least 20 yr old and underwent pure-tone audiometry and blood Pb test.	Blood Blood Pb was measured using GFAAS and classified into quartiles by sex Age at measurement: 20–87 yr (mean ± SE: 47.1 ± 0.3 yr) Weighted mean ± SE (Men): Q1 = 1.56 ± 0.01 µg/dL; Q2 = 2.22 ± 0.01 µg/dL; Q3 = 2.82 ± 0.01 µg/dL; Q4 = 4.22 ± 0.08 µg/dL; Weighted mean ± SE (Women): Q1 = 1.12 ± 0.01 µg/dL; Q2 = 1.61 ± 0.01 µg/dL; Q3 = 2.11 ± 0.01 µg/dL; Q4 = 3.03 ± 0.03 µg/dL	Low-frequency hearing impairment; High-frequency hearing impairment Pure-tone audiometry was performed on both ears at 0.5, 1, 2, 3, 4, and 6 kHz. A binaural pure-tone average threshold was used and two binaural averages were computed, one across 0.5, 1, and 2 kHz and the other across 3, 4, and 6 kHz to determine the low- and high-frequency thresholds. Hearing impairment was then determined according to whether an average threshold exceeded 25 dB in the respective frequency band. Age at outcome: 20–87 yr (mean ± SE: 47.1 ± 0.3 yr)	Age, BMI, education, smoking, alcohol consumption, exercise, diabetes mellitus, hypertension, noise exposure	**OR (95% CI)[b]** *Hearing Loss – Low Frequency* **Females** Q2: 1.271 (0.726, 2.224) Q3: 1.308 (0.784, 2.183) Q4: 0.932 (0.541, 1.605) **Males** Q4: 1.026 (0.813, 1.295) Q3: 1.028 (0.661, 1.598) Q2: 1.17 (0.772, 1.773) *Hearing Loss – High Frequency* **Females** Q2: 0.947 (0.608, 1.475) Q3: 1.013 (0.698, 1.471) Q4: 1.502 (1.027, 2.196) **Males** Q2: 1.368 (1.006, 1.86) Q3: 1.402 (1.005, 1.955) Q4: 1.629 (1.161, 2.286)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Choi and Park (2017) Korea National Health and Nutrition Examination Survey (KNHANES), Korea 2010−2012 Cross-sectional	KNHANES n: 5187 adults	Blood Measured using Graphite furnace atomic absorption spectrometry Age at Measurement: 20–87 yr 90th: Adults: Geometric mean (age-adjusted) 2.12 µg/dL (95% CI: 2.08, 2.15) Adolescents: Geometric mean (age-adjusted) 1.26 µg/dL (95% CI: 1.22, 1.30)	Hearing loss (>25dB) at speech frequency; Hearing loss (>25dB) at high frequency Pure-tone air conduction hearing thresholds were obtained for each ear at frequencies of 0.5, 1, 2, 3, 4, and 6 kHz over an intensity range of −10 to 110 dB −10 to 110 dB. Age at outcome: 20−87 yr	Adjusted for age; age squared; sex; education; BMI; current cigarette smoking; current diagnosis of hypertension and diabetes; and occupational, recreational, and firearm noise exposures	**OR (95% CI)[b]** *Hearing Loss (>25 dB) High-frequency PTA* Pb Quartile 2 (1.594–2.146): 1.13 (0.83, 1.53) Pb Quartile 3 (2.48–2.822): 1.35 (1, 1.81) Pb Quartile 4 (2.823–26.507): 1.7 (1.25, 2.31) Per doubling of Pb: 1.3 (1.08, 1.57) *Speech-Frequency PTA* Pb Quartile 2: 0.94 (0.65, 1.35) Pb Quartile 3: 1.29 (0.92, 1.78) Pb Quartile 4: 1.25 (0.87, 1.79) Per doubling of Pb: 1.15 (0.94, 1.41)
†Wang et al. (2020) Zhejiang Province (Hangzhou, Jiangshan, Tonglu, Jiaxing, Anji, Jinyun), China 2016 to 2018 Case-control	n: 2016	Blood Measured by graphite furnace atomic absorption spectrometry Age at Measurement: 21−89 yr	Hearing loss The devices utilized in this research were an audiometer (AT235, Interacoustics AS, Assens, Denmark) and standard headphones (TDH−39, Telephonics Corporation, Farmingdale, USA)	Income, education, hypertension, diabetes, hyperlipidemia, otitis media, migraine, anemia, smoking, alcohol consumption, daily fruit and vegetable intake, and workplace noise exposure	OR (95% CI)[b] Q1 Ref Q2 1.135 (0.806, 1.599) Q3 1.038 (0.731, 1.475) Q4 1.016 (0.7, 1.475)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
		Logarithmic-transformed levels of Pb Case group (1.58 ± 0.17 µg/dL) and control group (1.57 ± 0.16 µg/dL)	Age at outcome: 21−89 yr		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Choi et al. (2012) NHANES, U.S. 1999–2004 Cross-sectional	NHANES n: 3698	Blood Simultaneous multielement atomic absorption spectrometer (SIMAA 6000; PerkinElmer, Norwalk, CT) with Zeeman background correction Age at Measurement: 20−69 yr Age-adjusted geometric mean (95% CI) = 1.54 µg/dL (1.49, 1.60)	Hearing threshold; Hearing loss Pure-tone air conduction hearing thresholds were obtained for both ears at frequencies of 0.5–8 kHz over an intensity range of –10 to 120 dB. Age at outcome: 20−69 yr	Age and age^2, sex, race/ethnicity [non-Hispanic white (reference), Mexican American, non-Hispanic Black, other], education [< high school (reference), high school, > high school], BMI (continuous), ototoxic medication use (yes/no), cigarette smoking [never smoker (reference), < 20 pack-years, ≥ 20 pack-years], hypertension (yes/no), type 2 diabetes (yes/no), and either blood lead or blood cadmium (for the corresponding cadmium or lead model), occupational noise exposure (O*NET score, continuous), nonoccupational firearm noise (yes/no) and any recreational noise (yes/no)	OR (95% CI)[b] Hearing Loss: Quintile 2 (0.90–1.30 µg/dL) 1.08 (0.55, 2.12) Quintile 3 (1.4–1.8 µg/dL) 1.1 (0.58, 2.05) Quintile 4 (1.90–2.70 µg/dL) 1.21 (0.67, 2.22) Quintile 5 (2.80–54 µg/dL) 1.36 (0.75, 2.48) Per doubling of Pb 1.09 (0.95, 1.26)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Yin et al. (2021) Iran, Korea, China, United States Other	n: 234–7596 in 8 studies	Blood Age at measurement: 3−87 yr	Hearing loss	All studies included in the meta-analysis controlled for age and sex. Adjustment for other potential confounders varies by studies, but includes monthly income, education levels, smoking status, BMI, ethnicity, work duration, ototoxic medication, blood lead, occupational noise, loud noise, and firearm noise, and hypertension and diabetes	OR (95% CI)[b] 1.34 (1.18, 1.52)
†Tu et al. (2021) NHANES, U.S. 2011–2012 Cross-sectional	NHANES n: 1503	Blood Measured by plasma mass spectrometry Age at measurement: 20−69 yr Median = 1.07 µg/l 95th: 1.62 µg/l	Speech-frequency hearing loss; High-frequency hearing loss For each ear, 0·5, 1, 2, 3, 4 and 6 kHz frequencies were used for assessing pure-tone air conduction hearing thresholds over a –10 to 110 dB intensity ranges. The average of four audiometric frequencies (0·5, 1, 2 and 4 kHz) was used to identify	Age, sex, education, marital status, BMI, smoking, noise exposure, hypertension and diabetes	OR (95% CI)[b] HFHL 1·98 (1·27, 3·10) SFHL 1.46 (0.81, 2.64)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
			speech-frequency hearing loss (SFHL), while the average of three audiometric frequencies (3, 4 and 6 kHz) was used to identify high-frequency hearing loss (HFHL). SFHL or HFHL ≥25 dB in either ear was sued to define hearing loss, based on the WHO definition for this condition Age at outcome: 20−69 yr		
†Paulsen et al. (2018) Beaver Dam Offspring Study Beaver Dam, Wisconsin, U.S. Baseline data collection June 8, 2005, through August 4, 2008 with two follow-up examinations occurred at 5-year intervals: one was conducted between July 12, 2010, and March 21, 2013, and the other between July 1, 2015, and November 13, 2017 Cohort	BOSS n: 1983	Blood Measured by Inductively coupled plasma mass spectrometry Age at Measurement: 21−84 yr Central tendency BLL: NR	Contrast sensitivity impairment	Age, alcohol consumption, smoking, AMD, cataract, plaque site, VA impairment, and sex	HR (95% CI)[b] 0.91 (0.696, 1.19)
†Fillion et al. (2013)	n: 228	Blood Measured by Inductively coupled plasma mass spectrometry (ICP-MS)	Contrast sensitivity (cycles per degree, cpd); Acquired color vision loss (color confusion index, CCI)	Age, sex, current smoking (yes vs. no), current drinking (yes vs. no)	Beta (95% CI)[b] Spatial frequency with %EPA

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Lower Tapajos River Basin, State of Para Brazil May to July 2006 Cross-sectional		Age at Measurement: 15−66 yr (median = 33.0 yr) Mean = 12.8 ± 8.4 µg/dL; Median = 10.5 µg/dL	Age at outcome: 15−66 yr		1.5 cpd −1.32 (−4.30; 1.65) 3 cpd 2.06 (−2.87; 6.99) 6 cpd 0.60 (−6.04; 7.25) 12 cpd −13.33 (−23.28; −3.49) 18 cpd −2.43 (−6.64; 1.79) CCI 0.16 (−0.03; 0.33)

BLL = blood lead level; CI = confidence interval; CIDI = Composite International Diagnostic Interview; EPA = eicosapentaenoic acid (; K-XRF = K-shell X-ray fluorescence; NAS = Normative Aging Study; OR = odds ratio; Pb = lead; PTA = pure tone average; Q = quartile; RR= relative risk; SD = standard deviation; SE = standard error; WHO = World Health Organization; yr = year(s).

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

[b]Result not standardized because data pertaining to the BLL distribution and/or base for the log-transformation were not reported.

†Studies published since the 2013 Integrated Science Assessment for Lead

Table 3-16T Animal toxicological studies of Pb exposure and sensory organ function

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Jamesdaniel et al. (2018)	**Mouse (C57BL/6)** Control (tap water), M, n = 6 2 mM, M, n = 6	PND 33 to PND 61	Oral, drinking water	PND 61: 10 µg/L (1 µg/dL) for Control 293 µg/L (29.3 µg/dL) for 2 mM	PND 61: Auditory threshold (via BAEP)
Carlson et al. (2018)	**Mouse (CBA/CaJ)** Control (deionized water), M, n = 16 0.03 mM, M, n = 8	5 wk to 16 wk	Oral, drinking water	16 wk: <LOD for Control 2.89 µg/dL for 0.03 mM	16 wk: Auditory threshold (via BAEP)
Zhu et al. (2016)	**Rat (Sprague Dawley)** Control (tap water), M/F, n = 15 58 mg/L, M/F, n = 17	PND 1 to PND 21	Oral, lactation	PND 9: 0 µg/dL for Control 7.9 µg/dL for 58 mg/L PND 21: 0 µg/dL for Control 8.2 µg/dL for 58 mg/L	PND 60: Histopathology, Cortical Temporal Processing, Sound Discrimination Testing, Auditory threshold (via BAEP)

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Liu et al. (2019)	**Rat (Sprague Dawley)** Control (tap water), F, n = 12 58 mg/L, F, n = 11	PND 1 to PND 21	Oral, drinking water	PND 9: 0 µg/dL for Control 7.9 µg/dL for 58 mg/L PND 21: 0 µg/dL for Control, 8.2 µg/dL for 58 mg/L PND 40: 0 µg/dL for Control 0 µg/dL for 58 mg/L	PND 93: Sound-Azimuth Discrimination Training

BAEP = brainstem auditory evoked potentials; BLL = blood lead level; F = female; KNHANES = Korea National Health and Nutrition Examination Survey; M = male; Pb = lead; PND = postnatal day; wk = week(s).

Table 3-17E Epidemiologic studies of exposure to Pb and neurodegenerative disease in adults

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Wang et al. (2007) NAS US Bone Pb measurement (1991–1999), Mini-Mental State Examination (MMSE) twice (1993–1998 and 1995–2000) Cross-sectional	NAS n: 358	Tibia and patella Measured by K-XRF Age at measurement 21–81 yr Median: 19 and 23 μg/g for tibia and patella	Cognitive decline cognitive assessment battery was the MMSE, a global examination of cognitive function that assesses orientation, immediate and short-term recall, verbal and written skills, and attention and ability to follow commands Age at outcome: 21−81 yr	Adjusted for age, years of education, nonsmoker, former smoker, pack-years, nondrinker, alcohol consumption, English as first language, computer experience, and diabetes	Change in MMSE score per IQR (15 μg/g) increase in tibia Pb by class of *HFE* genotype[a] Wild-type –0.02 (–0.10 to 0.07) One *HFE* variant allele –0.14 (–0.33 to 0.04) Two *HFE* variant alleles –0.63 (–1.04 to –0.21)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Weisskopf et al. (2004) Normative Aging Study, U.S. 1991 and 2002 Cross-sectional	NAS n: 466	Tibia, patella, and blood Bone Pb measured by ABIOMED K-XRF instrument and blood Pb measured by Zeeman background-corrected flameless atomic absorption (graphite furnace) Age at measurement 21–81 yr Median µg/g (interquartile range) Patella 27 (19, 40) µg/g Tibia 21 (15, 29) µg/g Blood 5 (3, 7) µg/dL	Cognitive decline cognitive assessment battery was the MMSE, a global examination of cognitive function that assesses orientation, immediate and short-term recall, verbal and written skills, and attention and ability to follow commands	Age at first MMSE test, alcohol intake, and days between the two MMSE tests as continuous variables, as well as education (<12 yr, 12 yr, 13–15 yr, ≥16 yr), smoking status (never, former, current), computer experience (yes/no), and English as a first language (yes/no)	Difference in change in MMSE score per IQR increase in Pb[a] –0.25 (–0.45, –0.05)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
(Wright et al., 2003) Normative Aging Study, U.S. 1991−1997 Cross-sectional	NAS n: 1033	Tibia, patella, and blood Bone Pb measured by ABIOMED K-XRF instrument and blood Pb measured by Zeeman background-corrected flameless atomic absorption (graphite furnace) Age at measurement 21–81 yr Mean (SD) Patella 29.5 (21.2) µg/g Tibia 22.4 (15.3) µg/g Blood 4.5 (2.5) µg/dL	Cognitive decline cognitive assessment battery was the MMSE, a global examination of cognitive function that assesses orientation, immediate and short-term recall, verbal and written skills, and attention and ability to follow commands	Age, alcohol intake, and education history	OR (95% CI)[a] MMSE <24 Tibia 1.02 (1.00,1.04) Patella 1.02 (1.00, 1.03)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
(Weuve et al., 2006) Normative Aging Study, U.S. 1991 and 2002 Cross-sectional	NAS n: 1171	Tibia, patella, and blood Measured by graphite furnace atomic absorption with Zeeman background correction Age at measurement 21–81 yr Median (and first and third quartiles) of tibia and patella were 19 (13, 28) and 27 (18, 39) µg/g Blood 5.2 (⩽1–28) µg/dl	*ALAD* genotype modifications on cognition cognitive assessment battery was the MMSE, a global examination of cognitive function that assesses orientation, immediate and short-term recall, verbal and written skills, and attention and ability to follow commands	Age at cognitive assessment and age-squared, years of education (⩽8, 9–11, 12, 13–15, 16, ⩾17 yr), computer experience (an additional measure of socioeconomic status), and length of time between the lead and cognitive assessments, were smoking status (current *v* past or never), alcohol consumption (none, 0.1–4.9 g/day, 5.0–9.9 g/day, ⩾10 g/day, or missing), calorie adjusted calcium intake (in tertiles), regular energy expenditure on leisure time physical activity (in tertiles), and diabetes (physician diagnosed or fasting blood glucose >126 mg/dl)	Mean difference in MMSE score per IQR increase in Pb (95% CI)[a] Tibia Among *ALAD−2* carriers −0.16 (−0.58 to 0.27) Among *ALAD* wildtypes −0.05 (−0.21 to 0.12) Patella Among *ALAD−2* carriers −0.26 (−0.64 to 0.12) Among *ALAD* wildtypes −0.07 (−0.23 to 0.09) Blood Among *ALAD−2* carriers −0.26 (−0.54 to 0.01) Among *ALAD* wildtypes −0.04 (−0.16 to 0.07)
(Nordberg et al., 2000) Stockholm 1994−1996 Cross-sectional	Kungsholmen project n: 762	Blood Measured using Graphite furnace atomic absorption spectrometry Age at measurement: 75+ (mean age of 88.4 yr) Mean (SD) 3.7 (2.3) µg/dl	Mental Performance MMSE	Age and BMI	No association was reported (quantitative estimate NR)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Farooqui et al. (2017) Boston, MA, United States 1993–2007 Cohort	Participants selected from cohort study (Veterans Affairs NAS); healthy men aged 51–98 yr n: 741 subjects in MMSE and 715 in Global cognition	Bone Patella (trabecular bone) and tibia (cortical bone) bone Pb was measured using K-XRF spectroscopy in 1993 Patella mean (SD) 30.6 ± 19.44 µg/g, and tibia mean (SD) 21.6 ± 13.33 µg/g	Changes in cognition Cognition was assessed using the MMSE, NES2, CERAD and WAIS-R during 3–5 visits over the period of 15 yr of follow-up.	Age at first cognitive test, past education level, baseline smoking status and alcohol intake.	**HR (95% CI)[b]** Cognition MMSE < 25 Tibia 1.05 (0.82, 1.35) Patella 1.21 (0.99, 1.49) **Beta (95% CI)[b]** Global Cognition (Summary score of NES2, CERAD and WAIS-R) Tibia −0.206 (−0.453, 0.089) Patella −0.25 (−0.518, 0.019) Cognition MMSE Tibia −0.077 (−0.206, 0.052) Patella −0.128 (−0.251, −0.0004)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Yang et al. (2018) Multicity (Taichung city, Changhua, and Nantou County), Taiwan Feb 2015–Oct 2016 Case-control	Participants were recruited from the China Medical University Hospital. Cases recruited the Department of Neurology, and controls from the Department of Family Medicine who were receiving general health check-up; aged ≥50 yr. n: Full sample: 434 (170 AD and 264 controls); Propensity-score-matched sample: 84 AD and 84 controls.	Blood assessed for heavy metals Blood samples tested for heavy metals (Pb, Cd, Se, Hg). Blood Pb measured through ICP-MS Blood Pb conc: Full samples: AD: 2.50 ± 1.35 µg/dL, Controls: 2.36 ± 1.02 µg/dL Propensity matched samples: AD: 2.58 ± 1.35 µg/dL, Controls: 2.50 ± 1.18 µg/dL	AD risk Physician AD diagnosis based on definition of the Diagnostic and Statistical Manual Fourth Edition Criteria; MMSE test of cognitive function	Age, gender, education, exercise habits, hypertension, diabetes, cardiovascular diseases, depression, anxiety	**OR (95% CI)[b]** *Full population* Total: 1.05 (0.86–1.28) Tertile 2 vs. 1: 1.00 (0.56–1.79) Tertile 3 vs. 1: 0.87 (0.49–1.55) *Propensity score-matched population* Total: 1.06 (0.83–1.35) Tertile 2 vs. 1: 1.16 (0.55–2.47) Tertile 3 vs. 1: 1.12 (0.53–2.39)
†Horton et al. (2019) Nationwide, United States 1999–2008 followed till 2014 Cohort	Participants selected from the five NHANES cycles and included 1999 to 2008 who were followed till 2014 for death; aged ≥60 yr. n: 8,080 subjects	Blood assessed for Pb Blood samples collected during the NHANES mobile examination center visit assessed for Pb using ICP-DRC-MS. Blood Pb conc: Geo mean and 95% CI: 2.1 (2.02, 2.11) µg/dL	AD mortality The identification of AD mortality is based on the immediate cause of death in the National Death Index record. Cause of death was coded according to the ICD−10, revision 10; G30 was used to indicate AD.	Age, sex, poverty status, race/ethnicity, and smoking status, and competing risks for AD mortality.	HRR (95% CI)[b] 0.3 µg/dL: ref 0.5 µg/dL: 1.1 (0.89, 1.3) 1 µg/dL: 1.2 (0.77, 1.8) 1.5 µg/dL: 1.2 (0.7, 2.1) 2 µg/dL: 1.3 (0.66. 3) 3 µg/dL: 1.3 (0.6, 3.0) 5 µg/dL: 1.4 (0.54, 3.8)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
(Vinceti et al., 1997) Santa Mafia Nuova Hospital in Reggio Emilia, northern Italy December 31st, 1994 Case-control	n: 15 cases and 36 controls	Blood Age at measurement: (mean ±SD) Patients 65.9 ± 14.0 yr Controls 64.4 ± 12.9 Mean (SD) Controls 108.3 ± 44.4 µg/l Patients 127.1 ± 67.8 µg/l	ALS measured by ALS severity scale	Patients and controls matched on year of birth and gender, confounders NR	Correlation coefficient ALSSS (p-value)[b] Total −0.440 (0.101)
(Kamel et al., 2002) New England and U.S. 1993−1996 Case-control	n: 109 cases and 256 controls	Blood and bone Blood lead was measured using graphite furnace atomic absorption spectrometry. Bone lead was measured using *in vivo* K-XRF Age at measurement: 30−80 yr Mean (SE) Blood µg/dl Cases 5.2 (0.4) Controls 3.4 (0.4) Patella µg/g Cases 20.5 (2.1) Controls 16.7 (2.0) Tibia µg/g Cases 14.9 (1.6) Controls 11.1 (1.6)	ALS A board-certified neurologist (T. L. M. or J. M. S.) evaluated potential cases. Diagnosis of ALS was based on criteria published by the World Federation of Neurology.	Cases and controls matched on age, sex, and region	OR (95% CI)[b] Blood 1.9 (1.4, 2.6) Tibia 2.3 (0.4, 14.5) Patella 3.6 (0.6, 20.6)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
Kamel et al. (2008) New England and U.S. Enrollment: 1993 - 1996; follow-up through December 31, 2003 Cohort	n: 110	Bone and blood Bone Pb measured in the tibia and patella using K-XRF; blood Pb measured using atomic absorption spectrometry Age at Measurement: Median (range) = 60 (30–79) years Blood Pb median = 4 µg/dL; patella Pb median = 15 µg/g; tibia Pb mean = 13 µg/g Max: Blood Pb max = 14 µg/dL; patella Pb max = 107 µg/g; tibia Pb max = 61 µg/g	Neurodegenerative Disease - ALS Amyotrophic lateral sclerosis (ALS) was diagnosed by board-certified neurologists and based on the World Federation of Neurology El Escorial criteria; related symptoms were documented from interviews. Cause of death was identified by the National Death Index (NDI).	Cox proportional hazard analyses adjusted for age, sex, and ever smoked, except for sex-stratified models, which included age and ever smoked.	HR (95% CI)[a] Diagnosis to death 0.9 (0.8 to 1.0) Symptoms to death 0.9 (0.8 to 1.0)
(Fang et al., 2010) U.S. 2003−2007 Case-control	n: 184 cases and 194 controls	Blood Pb measured by inductively coupled plasma mass spectrometry Age at measurement: mean (SD) Cases 63.3 (34–83) Controls 63.4 (34–84) Pb Mean (SD) 3.4 µg/dL (2.5)	ALS Neurologists with expertise in ALS reviewed medical records to determine motor neuron disease diagnosis in accordance with the original El Escorial Criteria, including ALS (*International Classification of Diseases*, Ninth Revision (ICD-9) code 335.20), progressive muscular atrophy (ICD-9 code 335.21), progressive bulbar palsy (ICD-9 code 335.22), pseudobulbar palsy (ICD-9 code 335.23), primary lateral sclerosis (ICD-9 code 335.24), and other motor neuron diseases (ICD-9 code 335.29).	Age	OR (95% CI)[b] Overall 1.9 (1.3, 2.7)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Fang et al. (2017) Nationwide, United States 2007–2013 Cohort	Veterans with ALS in the U.S. National Registry of Veterans, and other veterans with ALS not treated within the Veterans Affairs healthcare system. with ALS from April 2003 to September 2007 and followed till the date of death or July 25, 2013; **non-Hispanic Caucasian men** aged 34–83 yr n: 145 U.S. Veterans with ALS, who were male, diagnosed with ALS by neurologist.	Blood assessed for Pb Whole blood collected during Jan-Sep 2007 assessed for Pb using ICP-MS. Biomarkers for bone formation measured in plasma. Bone formation was measured using procollagen type I N-terminal propeptide and bone resorption measured using C-terminal collagen crosslinks. Blood Pb conc: 2.35 ± 1.28 µg/dL	ALS survival Trained neurologist with expertise in ALS assigned diagnoses using an algorithm based on the revised El Escorial Criteria	Age at diagnosis, diagnostic certainty, site of onset, diagnostic delay and revised ALS Functional Rating Scale Score	HR (95% CI)[a] 1.234 (1.021, 1.49)
†Peters et al. (2020) EPIC Multi-center, Europe 1993–1999 Nested case-control	N = 107 cases identified after 8 yr of follow-up 3 controls per case	Pb concentration in erythrocytes analyzed using ICP-MS	ALS: Motor neuron disease (ICD10 G12.2) as underlying cause of death	Matched by age at recruitment, sex, study center	OR (95%CI) Reference: ≤56.8 ng/g >56.8–≤89.0: 1.83 (0.99, 3.35) >89.0: 1.89 (0.97, 3.67)
†Vinceti et al. (2017) Emilia-Romagna, Italy May 1998–April 2011 Case-control	Cases were ALS patients and controls were selected from hospital-admission of no ALS; mean age cases: 52 yr n: 76 (38 ALS cases and 38 controls)	Cerebral spinal fluid assessed for heavy metals CSF evaluated for heavy metals (Pb, Cd, Hg) using ICP-MS Median Pb conc: Cases: 155 ng/L, Controls: 132 ng/L	ALS Probable ALS diagnosis using the revised El Escorial Criteria.	Age, sex, and total selenium	In the highest tertile of exposure, OR (95% CI)[b] 1.39 (0.48, 4.25)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Andrew et al. (2022) Nationwide, United States 2013–2019 Case-control	Participants are from the healthcare claims dataset from Symphony Health with ALS diagnosis after 6 mo enrollment in the database prior to the first ALS ICD code. Controls are individuals similar to ALS cases based on age, sex, and length of database history with min of 6 mo in database; cases and controls age 18–80 yr (63% were 55–75 yr) n: Cases: 26,199 and controls: 78,597	268 Airborne contaminants Airborne exposure to Pb and other contaminants assessed from U.S. EPA's NEI database for 2008 to estimate exposure prior to ALS onset. Data was used to estimate residential exposure at the zip3 locations of the ALS patients and controls.	ALS ALS based on the healthcare claims	Family income, race, age, and sex	OR (95% CI)[b] **Discovery and Validation Cohorts** 1.39 (95% CI 0.48–4.25) **New Hampshire/Vermont** [Q1+Q2: ≤1.37 tons (Ref) Q3: 1.37–26.1 Q4: >26.1] *5-year Exposure History* Q3: 1.79 (1.32, 2.43) Q4: 1.11 (0.8, 1.55) *10-year Exposure History* Q3: 2.42 (1.76, 3.33) Q4: 2.03 (1.46, 2.8) *15-year Exposure History* Q3: 1.83 (1.34, 2.52) Q4: 1.73 (1.26, 2.38) **Ohio** [Q1+Q2: ≤14.7 tons (Ref) Q3: 14.7–50.8 Q4: >50.8]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
					5-year Exposure History Q3: 0.48 (0.37, 0.61) Q4: 0.39 (0.3, 0.51) *10-year Exposure History* Q3: 1.05 (0.83, 1.33) Q4: 1.6 (1.28, 1.98) *15-year Exposure History* Q3: 0.94 (0.74, 1.18) Q4: 1.07 (0.86, 1.34)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Paul et al. (2021) Australia and New Zealand, and Central California Case-control	Participants for this study comes from two publicly available PD studies: SGPD consortium of three studies across Australia and New Zealand with cases and controls. PEG a population-based study from three agricultural counties of Central California with cases and controls. n: SGPD cohort: 959 cases and 930 controls; PEG cohort: 569 cases and 238 controls	Epigenetic biomarkers for PD cumulative Pb exposure (tibia and patella), i.e., DNAm Pb Epigenetic biosensors identified with site-by-sire analysis and combined via machine learning algorithm on K-XRF in vivo measures of bone Pb. To determine Pb biomarker level in two cohorts, the regression coefficients were extracted from NAS and applied to the DNAm beta matrices. DNAm tibia Pb: SGPD cohort: cases: 3.41 ± 0.4, controls: 3.48 ± 0.4; PEG cohort: cases: 3.06 ± 0.4, controls: 3.03 ± 0.3		Age (DNAm Age in SGPD), sex, ancestry (PEG only), smoker (PEG only), blood cell composition, and mean Meth By Sample	OR (95% CI)[b] Tibia SPGD 1.54 (1.22, 1.95) Patella SPGD 0.70 (0.53, 0.93) Tibia PEG 1.52 (1.25, 1.86)
†Ji et al. (2015) Boston, MA, United States NAS Cohort	Participants selected are subgroup of participants from cohort study (Veterans Affairs NAS); healthy men aged 50–98 yr. n: 807	Blood, Bone assessed for Tremor Pb Blood samples tested for Pb concentration using Zeeman background-corrected flameless atomic absorption graphite furnace. Bone Pb concentration measured with K-XRF at both the tibia and the patella starting in 1991. Blood Pb concentration: 5.01 ± 2.72 µg/dL		Age, age squared, alcohol consumption, smoking status, education level	OR (95% CI)[b] Blood Quintile 2 vs. 1 0.09 (–0.10, 0.29) Quintile 3 vs. 1 0.06 (–0.16, 0.28) Quintile 4 vs. 1 0.07 (–0.13, 0.27) Quintile 5 vs. 1 0.07 (–0.16, 0.30) Patella Quintile 2 vs. 1

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
		Tibia Pb conc: 21.23 ± 13.29 µg/g (); patella Pb conc: 27.98 ± 18.38 µg/g)	Tremor score was created based on an approach using hand-drawing samples that were derived from figure copying testing performed as part of larger cognitive test battery (CERAD, MMSE, and VMI) assessed over a mean follow-up of 8.0 ± 3.2 yr after bone Pb measurement. ALAD genotype was determined by amplifications of 0.5 µL of whole blood using two sets of primers specific for a portion of the ALAD gene.		–0.07 (–0.30, 0.15) Quintile 3 vs. 1 –0.14 (–0.37, 0.09) Quintile 4 vs. 1 –0.22 (–0.45, 0.01) Quintile 5 vs. 1 –0.02 (–0.27, 0.22) Tibia Quintile 2 vs. 1 0.03 (–0.20, 0.26) Quintile 3 vs. 1 0.03 (–0.20, 0.26) Quintile 4 vs. 1 0.13 (–0.11, 0.36) Quintile 5 vs. 1 –0.07 (–0.32, 0.17)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Khalil et al. (2014) Pittsburgh, PA United States 2007–2009 Cross-sectional	MrOS n: 445 Non-Hispanic Caucasian men (community dwelling non-institutionalized) at least 65 yr of age enrolled in MrOS at the University of Pittsburgh clinic. Eligibility criteria included the ability to walk unaided and without bilateral hip replacements.	Blood Blood Pb measured using AAS Age at measurement: Mean = 79.5 ± 5 yr Mean = 2.25 µg/dL; SD = 1.20 µg/dL; Median = 2 µg/dL Max: 10 µg/dL	Grip strength (kg); Leg extension power (watts); Walking speed (m/s); Narrow-walk pace (m/s); Use arms to stand up (yes/no) Grip strength was measured on a Jamar dynamometer; Leg extension power was measured with the Nottingham power rig; Walking speed was assessed on a standard 6-m walking course; Narrow-walk pace (an indirect measure of dynamic balance) was assess while keeping each foot within a 20-centimeter wide lane on the 6-m walking course; Stand from a chair without using the arms was measured as yes/no. Age at outcome: 65 yr	Age, education, smoking, alcohol consumption, BMI	Beta (95% CI)[a] Leg extension power −0.03 (−1.97, 2.03) Ability to stand from a chair without using their arms 0.97 (0.88, 1.07)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Shiue (2013) United States 2003–2004 Cross-sectional	NHANES n: 712 (vision); 732 (hearing); 669 (balance) NHANES age 50 and above	Urine Urinary Pb was detected by mass spectrometry Age at measurement: 50 yr Not Reported	Vision; Hearing; Balance; Ear ringing Vision: excellent, good, and fair eyesight (self-reported) were classified as good; poor and very poor were classified as poor Hearing: good and little trouble hearing (self-reported) were classified as good; lots of trouble and deaf were classified as poor Balance: "During the past 12 mo, have you had dizziness, difficulty with balance, or difficulty with failing?" Ear ringing: "ears ringing, roaring, or buzzing in the last year" Age at outcome: 50 yr	Age, sex, ethnicity, urine creatinine, survey weighting	OR (95% CI)[b] Vision 1.15 (0.67–1.97) Hearing 0.97 (0.63–1.51) Balance 0.68 (0.51–0.91)

†Casjens et al. (2018) Ruhr area, a German industrial region with a high volume of steel production Germany Baseline recruitment 2000–2003; Follow-up 2011–2014 Cohort	HNRS n: 1188 Men from the Heinz Nixdorf Recall Study. Recruitment details not provided.	Blood Blood Pb was measured in aliquots of whole blood archived at baseline and at follow-up using ICP-MS Age at measurement: Median = 58 yr at baseline (range 45–75 yr) and 68 yr (range 55–86) yr at follow-up Median = 3.29 (IQR 2.55–4.32) µg/dL at baseline; 2.59 (IQR 1.99–3.39) µg/dL at follow-up Max: 67.73 µg/dL at baseline; 39.68 µg/dL at follow-up	Odor identification; Tapping hits; Aiming errors; Line tracing errors; Steadiness errors Odor identification: Sniffin sticks odor identification test of 12 odors, participants classified as normosmic if >9 odors identified, hyposmic if 7–9 odors identified, and functionally anosmic if <7 odors identified Tapping hits: tapping a stylus within 32 s as fast as possible; hits <10th percentile were considered as substantially impaired manual dexterity Aiming errors: 20 small plates with a diameter of 5 mm standing in a line (distance 4 mm) had to be touched with a stylus as fast as possible; errors >90th percentiles were considered as substantially impaired manual dexterity Line tracing errors: drawing a stylus through a curvy course of a groove without touching side walls or bottom; errors >90th percentiles were considered as substantially impaired manual dexterity Steadiness errors: maintain a precise arm-hand position by holding a stylus for 32 s in a 5.8 mm hole without touching sides or bottom; errors >90th percentiles were considered as substantially impaired manual dexterity Age at outcome: 55–86 yr	Occupational qualification, age, smoking status, alcohol consumption, total test time	OR (95% CI)[b] Group 1: <5 µg/dL (Ref) Group 2: 5–<9 µg/dL Group 3: ≥9 µg/dL **Odor identification** *baseline* G2: 0.91 (0.65, 1.28) G3: 1.96 (0.94, 4.11) *follow-up* G2: 1.04 (0.55, 1.94) G3: 1.57 (0.47, 5.19) **Motor Performance Series** **Steadiness Errors** *baseline* G2: 0.99 (0.62, 1.59) G3: 1.36 (0.5, 3.66) *follow-up* G2: 1.16 (0.5, 2.69) G3: 1.75 (0.41, 7.58) **Line tracing errors** *baseline* G2: 1.09 (0.68, 1.76) G3: 0.93 (0.32, 2.74) *follow-up* G2: 1.01 (0.41, 2.48) G3: 0.59 (0.08, 4.11) **Aiming errors** *baseline* G2: 1.07 (0.75, 1.53) G3: 0.56 (0.22, 1.42)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
					follow-up G2: 1.35 (0.73, 2.51) G3: 0.42 (0.09, 2.08) **Tapping Hits** baseline G2: 0.87 (0.53, 1.44) G3: 1.35 (0.49, 3.7) follow-up G2: 2.63 (1.26, 5.49) G3: 0.8 (0.14, 4.59)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Ji et al. (2013) United States 1999–2002 Cross-sectional	NHANES n: 3,593 (1,798 women; 1,795 men) NHANES data from the 1999–2000 and 2001–2002 surveys, participants were 50 yr of age	Blood Blood Pb was measured using AAS Age at measurement: 50–85 yr (Median = 61.2 yr) Mean ± SD: Women = 2.17 ± 0.04 µg/dL; Men = 3.18 ± 0.08 µg/dL (*there's a slight discrepancy in the SDs in Table 1 vs. text on p. 712) Median: Women = 1.72 µg/dL; Men = 2.41 µg/ dL	Walking speed (ft/sec) Time to walk 20 ft (at usual walking pace) Age at outcome: 50–85 yr (median = 61.2 yr)	Model 4 (fully adjusted): age, education, ethnicity, height, waist circumference, alcohol, smoking, physical activity, arthritis, diabetes, heart condition, hypertension, homocysteine, C-reactive protein	Beta (95% CI) Walking Speed-Men 4.4 to ≤54.0 −0.029 (−0.155, 0.097) Walking Speed-Women 3.0 to ≤53.0 −0.114 (−0.191, −0.038) Walking Speed-Men 3.1 to < equal to 4.3 0.082 (−0.012, 0.176) Walking Speed-Women 2.2 to ≤2.9 −0.104 (−0.187, −0.021) Walking Speed-Men 2.4 to ≤3.0 −0.17 (−0.26, −0.08) Walking Speed-Women 1.7 to ≤2.1 −0.024 (−0.118, −0.063) Walking Speed-Men 1.8 to ≤2.3 0.057 (−0.051, 0.165) Walking Speed-Women 1.3 to ≤1.6 −0.027 (−0.055, 0)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Min et al. (2012) United States 1999–2004 Cross-sectional	NHANES n: 5574 Adults who participated in the NHANES Balance Component and had blood Pb and Cd measurements and data for all covariate variables	Blood Blood Pb was measured using a multielement AAS with Zeeman background correction. Age at measurement: 40 yr Weighted mean (participant without balance dysfunction): 2.09 µg/dL (95% CI: 2.01, 2.18); Weighted mean (participants with balance dysfunction): 2.39 µg/dL (95% CI: 2.29, 2.49) Max: 48 µg/dL	Balance dysfunction Balance dysfunction was evaluated by the Romberg Test of Standing Balance on Firm and Compliant Support Surfaces, which measured the participant's ability to maintain balance under four test conditions: Test 1) maintain balance while standing (with feet together and arms folded across the waist, holding each elbow with the opposite hand) for 15 sec.; Test 2) maintain balance while standing for 15 sec with eyes closed so that only vestibular and proprioceptive (i.e., leg muscle position sense) information is available; Test 3) maintain balance while standing for 30 sec on a foam-padded surface, which reduces proprioceptive input but does not affect visual or vestibular input; Test 4) maintain balance while standing for 30 sec on a foam-padded surface with eyes closed, so that input is available from the vestibular system only. Each condition was scored on a pass or fail basis. The time to failure (i.e., loss of balance) was also recorded for test condition 4, with those who passed the test assigned the maximum value of 30 sec. Age at outcome: 40 yr	Age, sex, race/ethnicity, education, pack-years of smoking, alcohol consumption, histories of stroke and diabetes, intakes of Ca^{2+} and iron	OR (95% CI) Balance Dysfunction (Quintile 5 [3.3–48 µg/dL]) 33.334 (1.939, 573.157) Balance Dysfunction (Quintile 4 [2.3–3.2 µg/dL]) 5.234 (0.59, 46.429) Balance Dysfunction (Quintile 3 [1.8–2.2 µg/dL]) 0.665 (0.05, 8.783) Balance Dysfunction (Quintile 2 [1.3–1.7 µg/dL]) 3.707 (0.544, 25.282)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs
†Grashow et al. (2013) Greater Boston area, MA, United States Grooved pegboard May 2005- December 2009 Neuroskill July 2004 and November 2007 Cohort	Normative Aging Study n: 362 for grooved pegboard test; 328 for the Neuroskill test Elderly, majority Caucasian men originally recruited from the greater Boston, Massachusetts area in the 1960s	Bone Bone Pb was measured at the patella and the midtibial shaft using an ABIOMED K-XRF instrument. "Tibia and patella bone Pb concentrations reflect cumulative Pb exposure over different time windows: patella Pb reflects exposure over the last decade, while tibia Pb half-life is on the order of decades" Age at measurement: NR Mean patella Pb = 25.0 mg/g bone (SD = 20.7); Mean tibia Pb = 19.2 mg/g bone (SD = 14.6)	Grooved pegboard (completion time, seconds); Neuroskill (Signature score, %); Neuroskill (lm pattern score, %) Grooved pegboard test: Subjects were asked to insert the metal pegs into each of the 25 holes in sequence as quickly as possible with their dominant hand without practice trials; Neuroskill tests (signature score, %): Subjects were asked to provide five samples of their signature in succession, written in their natural manner; Neuroskill tests (lm pattern score, %): Subjects were asked to provide five samples of a series of cursive lms (lm pattern) using the instrumented pen Age at outcome: Mean age = 69.1 yr (SD = 7.2)	Age, smoking, education, computer experience, income	**Beta (95% CI)[a]** *Neuroskill-lm pattern score* Patella 0.45 (0.178, 0.723) Tibia 0.847 (0.163, 1.53) *Neuroskill-Signature Score* Patella 0.08 (−0.47, 0.63) Tibia −0.293 (−1.063, 0.477) *Grooved pegboard-dominant hand completion time* Patella 1.965 (0.553, 3.378) Tibia 3.107 (1.157, 5.057)

AAS = atomic absorption spectrometry; BLL = blood lead level; Cd = cadmium; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; CI = confidence interval; CSF = cerebrospinal fluid; EE = effect estimate(s); HNRS = Heinz Nixdorf Recall Study; HRR = hazard rate ratio; K-XRF = K-shell X-ray fluorescence; MMSE = Mini Mental State Examination; mo = month(s); MrOS = Osteoporotic Fractures in Men Study; NAS = Normative Aging Study; NEI = National Emissions Inventory; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; SD = standard deviation; sec = second(s); VMI = visual-motor integration; yr = year(s).
[a]Effect estimates are standardized to a 1 μg/dL increase in BLL or a 10 μg/g increase in bone Pb level, unless otherwise noted. For studies that report results corresponding to a change in log-transformed Pb biomarkers, effect estimates are assumed to be linear within the 10th to 90th percentile interval of the biomarker and standardized accordingly.
[b]Result not standardized because data pertaining to the BLL distribution and/or base for the log-transformation were not reported.
†Studies published since the 2013 Integrated Science Assessment for Lead.

Table 3-17T Animal toxicological studies of Pb exposure and neurodegeneration

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Zhou et al. (2018)	**Rat (Sprague Dawley)** Control (distilled water), M, n = 10 0.5% solution, M, n = 10 1.0% solution, M, n = 10 2.0% solution, M, n = 10	PND 24 to PND 52	Oral, drinking water	PND 52: 13.3 µg/L (1.3 µg/dL) for Control 148.9 µg/L (14.9 µg/dL) for 0.5% solution 231.3 µg/L (23.1 µg/dL) for 1.0% solution 293.4 µg/L (29.3 µg/dL) for 2.0% solution	PND 24, 31, 38, 45, 52: Amyloid protein expression, Brain Cholesterol, Expression of BACE1 and APP
Li et al. (2016c)	**Mouse (Kunming)** Control (distilled water), M/F, n = 10 0.1% solution (mass fraction), M/F. n = 10 0.2% solution (mass fraction), M/F, n = 10 0.5% solution (mass fraction), M/F, n = 10	GD to PND 21	Oral, lactation In utero	PND 21: 10.62 µg/L (1.1 µg/dL) for Control 40.71 µg/L (4.1 µg/dL) for 0.1% solution 81.77 µg/L (8.2 µg/dL) for 0.2% solution 103.36 µg/L (10.3 µg/dL) for 0.5% solution	PND 21: Amyloid protein expression
Gu et al. (2012)	**Mouse (Tg-SwDI)** Control (Na-acetate water), NR, n = 4–7 50 mg/kg, NR, n = 4–7	4–8 wk to 10–14 wk	Oral, gavage	10–14 wk: 1.83 µg/dL for Control 29.5 µg/dL for 50 mg/kg	10–14 wk: Beta-amyloid and APP expression
Wu et al. (2020b)	**Mouse (C57BL/6)** Control (distilled deionized water), M, n = 7–10 0.2% solution, M, n = 7–10	4 wk to 4 mo	Oral, drinking water	16 mo: 66.4 µg/L (6.6 µg/dL) for Control 278.9 µg/L (27.9 µg/dL) for 0.2% solution	16 mo: Expression of BACE1 and APP, Phosphorylated tau expression

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Sun et al. (2014)	**Rat (Sprague Dawley)** Control (tap water), NR, n = 20 580 ppm, NR, n = 20	NR (230–260 g) – 3 mo of treatment	Oral, drinking water	After 3 mo treatment: 3.0 µg/L (0.3 µg/dL) for Control 56.8 µg/L (5.7 µg/dL) for 580 ppm	After 3 mo treatment: Immunohistochemistry of APP
Gąssowska et al. (2016b)	**Rat (Wistar)** Control (tap water), M/F, n = 8 0.1% solution, M/F, n = 8	GD 0 to PND 21	Oral, lactation In utero	PND 28: 0.93 µg/dL for Control 6.86 µg/dL for 0.1% solution	PND 28: Tau protein expression and phosphorylation
Rahman et al. (2012b)	**Rat (Wistar)** Control (tap water), M/F, n = 6–10 0.2% solution, M/F, n = 6–12	PND 1 to PND 30	Oral, drinking water Oral, lactation	PND 21: 1.4 µg/dL for Control 12.1 µg/dL for 0.2% solution PND 30: 1.2 µg/dL for Control 12.8 µg/dL for 0.2% solution	PND 21, 30: Tau protein expression and phosphorylation
Zhang et al. (2012)	**Rat (Sprague Dawley)** Control (deionized water), M, n = 10 100 ppm, M, n = 10 200 ppm, M, n = 10 300 ppm, M, n = 10	NR (40–60 g)	Oral, drinking water	+8 wk from start of exposure 49.9 ng/mL (5 µg/dL) for Control 100.9 ng/mL (10.1 µg/dL) for 100 ppm 128.6 ng/mL (12.9 µg/dL) for 200 ppm 147.7 ng/mL (14.8 µg/dL) for 300 ppm	+8 wk from start of exposure: Phosphorylated tau expression, Alpha-Synuclein expression
Bihaqi and Zawia (2013)	**Monkey (*Macaca fascicularis*)** Control, F, n = 4 1.5 mg/kg/day, F, n = 5	PND 0 to PND 400	Oral, infant formula Oral, gelatin capsules	PND 400: 3–6 µg/dL for Control 19–26 µg/dL for 1.5 mg/kg/day	23 yr: Tau protein expression and phosphorylation, Tau phosphorylation

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Feng et al. (2019)	**Rat (Sprague Dawley)** Control (deionized water), M/F, n = 8 0.8 g/L (maternal) and 0.3 g/L (pup), M/F, n = 8 1.5 g/L (maternal) and 0.9 g/L (pup), M/F, n = 8	GD −10 to PND 490	Oral, drinking water Oral, lactation In utero	PND 21: 0 mg/L (0 µg/dL) for Control 0.29 mg/L (29 µg/dL) for 0.8 g/L 0.69 mg/L (69 µg/dL) for 1.5 g/L PND 287: 0 mg/L (0 µg/dL) for Control 0.29 mg/L (29 µg/dL) for 0.8 g/L 0.61 mg/L (61 µg/dL) for 1.5 g/L PND 490: 0 mg/L (0 µg/dL) for Control 0.31 mg/L (31 µg/dL) for 0.8 g/L 0.58 mg/L (58 µg/dL) for 1.5 g/L	PND 21, 287, 490: Neuronal Density, Brain Volume
Mansouri et al. (2012)	**Rat (Wistar)** Control (distilled water), M/F, n = 16 (8/8) 50 mg/L, M/F, n = 16 (8/8)	PND 70 to PND 100	Oral, drinking water	PND 100 - Males: 2.05 µg/dL for Control 8.8 µg/dL for 50 mg/L PND 100 - Females: 2.17 µg/dL for Control 6.8 µg/dL for 50 mg/L	PND 100: Open Field Test, Rotarod Test

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details	BLL as Reported (µg/dL)	Endpoints Examined
Mansouri et al. (2013)	**Rat (Wistar)** Control (tap water or water+NaAc), M/F, n = 16 (8/8) 50 ppm, M/F, n = 16 (8/8)	PND 55 to PND 181	Oral, drinking water	PND 178–181 - Females: NR for Control 10.6 µg/dL for 50 ppm PND 178–181 - Males: NR for Control 18.9 µg/dL for 50 ppm	PND 155–159: Rotarod Test
Singh et al. (2019)	**Rat (Wistar)** Control (distilled water), M, n = 5 2.5 mg/kg, M, n = 5	3 mo to 6 mo	Oral, gavage	6 mo: 5.76 µg/dL for Control 28.4 µg/dL for 2.5 mg/kg	6 mo: Locomotor Activity, Rotarod Test
Al-Qahtani et al. (2022)	**Mouse (Albino)** Control (distilled water), M, n = 10 0.2 mg/kg, M, n = 10	8–9 wk to 14–15 wk	Oral, gavage	14–15 wk: 1.2 µg/100 mL (1.2 µg/dL) for Control 7.1 µg/100 mL (7.1 µg/dL) for 0.2 mg/kg	NR: Locomotor Activity

APP = amyloid precursor protein; BACE1 = beta-secretase 1; F = female; GD = gestational day; M = male; mo = month(s); NR = not reported; Pb = lead; PND = postnatal day; wk = week(s); yr = year(s).

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