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Integrated Science Assessment for Lead

Appendix 8: Reproductive and Developmental Effects

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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

2PN	oocytes with two pronuclei
AAS	atomic absorption spectrometry
AD	abdominal diameter
AGD	anogenital distance
AGDap	anopenile distance
AGDas	anoscrotal distance
ALAD	δ-aminolevulinic acid dehydratase
ALSPAC	Avon Longitudinal Study of Parents and Children
AMH	anti-Müllerian hormone
AQCD	Air Quality Criteria Document
ART	assisted reproductive technology
As	arsenic
BKMR	Bayesian kernel machine regression
BL	birth length
BLL	blood lead level
BMI	body mass index
BMIZ	BMI-for-age Z-score
BT20+	Birth to Twenty Plus
BW	birth weight
BWGA	birth weight-for-gestational age
BWZ	birth weight Z-score
C-ABCS	China-Anhui Birth Cohort Study
CANDLE	Conditions Affecting Neurocognitive Development and Learning in Early Childhood
CC	chest circumference
CCG	Charlotte-Concord-Gastonia
Cd	cadmium
CD	cephalic diameter
CHD	congenital heart disease
CHECK	Children's Health and Environmental Chemicals in Korea
CHL	crown-heel length
CI	confidence interval
CMS	Charlotte Motor Speedway
Cr	chromium
d	day(s)
DBP	diastolic blood pressure
E2	estradiol
E3G	estrone-3-glucuronide
EAAS	electrothermal atomic absorption spectrometry
ELEMENT	Early Life Exposure in Mexico to Environmental Toxicants
ELISA	enzyme-linked immunosorbent assay
EMASAR	Study on the Environment and Reproductive Health
e-REACH	e-waste Recycling Exposure and Community Health
ETS	environmental tobacco smoke
fE2	free estradiol
FLEHS	Flemish Environment and Health Study
FSH	follicle stimulating hormone
FT	free testosterone
FT3	free triiodothyronine
FT4	free thyroxine
GA	gestational age
GD	gestational day
GDM	gestational diabetes mellitus
GEE	generalized estimating equation
GFAAS	graphite furnace atomic absorption spectrometry
GnRH	gonadotropin-releasing hormone
GSI	Global Severity Index
HAZ	height-for-age Z-score
HC	head circumference
HCAZ	head circumference for age Z-score
hCG	human chorionic gonadotropin
HFIAS	Household Food Insecurity Access Scale
Hg	mercury
HOME	Health Outcomes and Measures of the Environment
HR	hazard ratio
HR-ICP-MS	high resolution inductively coupled plasma mass spectrometry
HTZ	height Z-score
hr	hour(s)
ICP-AES	inductively coupled plasma atomic emission spectroscopy
ICP-MS	inductively coupled plasma mass spectrometry
ICP-QQQ	inductively coupled plasma triple quad
IgE	immunoglobulin E
IGF-1	insulin-like growth factor 1
IGT	impaired glucose tolerance
IL-33	interleukin-33
INMA	Instituto de Nanociencia y Materiales de Aragón
IQR	interquartile range
ISA	Integrated Science Assessment
IUGR	intrauterine growth restriction

IVF	in vitro fertilization
JECS	Japan Environment and Children's Study
K6	Kessler Psychological Distress Scale
KNHANES	Korea National Health and Nutrition Examination Survey
K-XRF	K-shell X-ray fluorescence
LA-ICP-MS	laser ablation-inductively coupled plasma-mass spectrometry
LBW	low birth weight
LESPW	Life Event Scale for Pregnant Women
LGA	large for gestational age
LH	luteinizing hormone
LIFE	Longitudinal Investigation of Fertility and the Environment
LMP	last menstrual period or last missed period
ln	natural log
LOD	limit of detection
MAL-ED	Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development
MII	metaphase II
min	minute(s)
MIREC	Maternal-Infant Research on Environmental Chemicals
miRNA	micro RNA
MMP	matrix metalloproteinase
Mn	manganese
mo	month(s)
MOCEH	Mothers' and Children's Environmental Health
MSA	Metropolitan Statistical Area
mtDNA	mitochondrial DNA
mtDNAcn	mitochondrial DNA copy number
NASCAR	National Association for Stock Car Auto Racing
NHANES	National Health and Nutrition Examination Survey
NICE	Nutritional impact on Immunological maturation during Childhood in relation to the Environment
NR	not reported
NS	non-stress
NTD	neural tube defect
OFC	orofacial cleft
OGTT	oral glucose tolerance test
OR	odds ratio
Pb	lead
PECOS	Population, Exposure, Comparison, Outcome, and Study Design
PI	Ponderal Index
PIR	poverty-income ratio
$PM_{2.5}$	fine particulate matter
PND	postnatal day
PROGRESS	Programming Research in Obesity, Growth, Environment and Social Stressors
PROM	premature rupture of membranes
PROTECT	Puerto Rico Test site for Exploring Contamination Threats
QL	lower quartile
QUS	quantitative ultrasound
ROS	reactive oxygen species
RR	relative risk
rTL	relative telomere length
SA	semen analysis
SBP	systolic blood pressure
SCL-90-R	Symptom-Checklist-90-Revised
SD	standard deviation
Se	selenium
SE	standard error
SES	socioeconomic status
SGA	small for gestational age
SHBG	sex hormone binding globulin
SNP	single nucleotide polymorphism
SPECT	Survey on the Prevalence in East China for Metabolic Diseases and Risk Factors
T	testosterone
T#	tertitle #
TL	telomere length
TPOAb	thyroid peroxidase antibody
TRI	Toxics Release Inventory
TSH	thyroid-stimulating hormone
TSLP	thymic stromal lymphopoietin
tT	total testosterone
tT3	total triiodothyronine
tT4	total thyroxine
TV	testicular volume
UCB	umbilical cord blood
WAZ	weight for age Z-score
WC	waist circumference
wk	week(s)
WHEALS	Wayne County Health, Environment, Allergy and Asthma Longitudinal Study
WHO	World Health Organization
yr	year(s)

APPENDIX 8 REPRODUCTIVE AND DEVELOPMENTAL EFFECTS

Summary of Causality Determinations for Pb Exposure and Reproductive and Developmental Effects

This appendix characterizes the scientific evidence that supports causality determinations for Pb exposure and reproductive and developmental 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 chapter supports the following causality conclusions:

Outcome Group	Causality Determination
Pregnancy and Birth Outcomes	Likely to be Causal
Development	Causal
Female Reproductive Function	Likely to be Causal
Male Reproductive Function	Causal

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.

8.1 Introduction and Summary of the 2013 Integrated Science Assessment

This appendix evaluates the epidemiologic and toxicological literature related to the potential effects of lead (Pb) on reproductive and developmental outcomes, divided into four sections: (1) effects on pregnancy and birth outcomes; (2) effects on development; (3) effects on female reproductive function; and (4) effects on male reproductive function. Based on the epidemiologic and toxicological studies reviewed in the 2013 Pb Integrated Science Assessment (ISA) (U.S. EPA, 2013), the determination for effects on pregnancy and birth outcomes was based on the mix of inconsistent results of the epidemiologic and toxicological studies on various birth outcomes, but with some associations observed in some epidemiologic studies of preterm birth and low birth weight and fetal growth. The

determination for developmental effects was informed by evidence from toxicological studies reporting delayed female sexual maturity and supported by epidemiologic studies of delayed pubertal onset for both girls and boys. The determination for effects on female reproductive effects was based on epidemiologic and toxicological studies for reproductive function among females reviewed including endpoints of hormone levels, fertility, estrous cycle changes, and morphology or histology of female reproductive organs including the placenta. Of the epidemiologic and toxicological studies reviewed for effects on female reproductive function, the studies were high-quality and well-designed and examined different exposure periods in conjunction with a number of outcomes related to female reproductive effects. The determination for effects on male reproductive function were based on strong toxicological evidence that showed detrimental effects on semen quality, sperm, and fecundity/fertility, with supporting evidence in epidemiologic studies of associations between Pb exposure and detrimental effects on sperm. The summary of the determinations from the 2013 Pb ISA is detailed below.

8.1.1 Effects on Pregnancy and Birth Outcomes

The 2013 Pb ISA (U.S. EPA, 2013) reported the associations between Pb exposure and birth outcomes (infant mortality and embryogenesis; birth defects; preterm birth; and low birth weight/fetal growth) were inconsistent overall. There were some associations observed between Pb and low birth weight when epidemiologic studies used measures of postpartum maternal bone Pb or air exposures. The associations were less consistent for maternal blood Pb measured during pregnancy or at delivery or umbilical cord and placenta Pb (maternal blood Pb or umbilical cord and placenta Pb were the biomarkers most commonly used in studies of low birth weight) but some associations between increased Pb biomarker levels and decreased low birth weight/fetal growth were observed. Animal studies investigating the effects of Pb exposure during gestation on litter size, implantation, and birth weight had varying results between studies. Based on the mix of inconsistent results of studies on various birth outcomes but some associations observed in select epidemiologic studies of preterm birth and low birth weight/fetal growth, the evidence in the 2013 Pb ISA was suggestive of a causal relationship between Pb exposure and birth outcomes.

8.1.2 Effects on Development

The 2013 Pb ISA (U.S. EPA, 2013) reported Pb associated effects on development in epidemiologic and toxicological studies. Previous toxicological studies indicated that delayed pubertal onset may be one of the more sensitive developmental effects of Pb exposure with effects observed after gestational exposures leading to blood Pb levels (BLLs) in the female pup of 1.3–13 μg/dL (Iavicoli et al., 2006; Iavicoli et al., 2004). Toxicological studies have reported delayed male sexual maturity as measured with sex organ weight, seeing significant decrements at BLLs of 20–34 μg/dL (Ronis et al., 1998c; Sokol et al., 1985). The 2013 Pb ISA also presented findings from a toxicological study that

suggests Pb may act through disruption of insulin-like growth factor 1 (IGF-1) to delay the onset of puberty, demonstrated by the attenuation of Pb-induced delays in pubertal onset in female rats supplemented with IGF-1 (Pine et al., 2006). Thus, data from the toxicological literature and from epidemiologic studies demonstrated that puberty onset in both males and females is delayed with Pb exposure. Findings from epidemiologic studies of the effect of Pb on postnatal growth were inconsistent and findings from the toxicological literature of the effect of Pb exposure were mixed with recent growth findings showing adult-onset male obesity after gestational and lactational Pb exposure. The 2013 Pb ISA concluded that, based on the findings of delayed pubertal onset among males and females, there was sufficient evidence to conclude a causal relationship between Pb exposure and developmental effects.

8.1.3 Effects on Female Reproductive Function

The 2013 Pb ISA (U.S. EPA, 2013) found some evidence of a potential relationship between Pb exposure and female fertility; however, findings were inconsistent. Epidemiologic studies were largely cross-sectional and adjustments for important confounding factors were not included in all studies. Some toxicological studies reported effects on placental pathology and inflammation, decreased ovarian antioxidant capacity, and altered hormone levels. Overall, the relationship observed with female reproductive outcomes, such as fertility, placental pathology, and hormone levels in some epidemiologic and toxicological studies was sufficient for the 2013 Pb ISA to conclude that evidence was suggestive of a causal relationship between Pb exposure and female reproductive function.

8.1.4 Effects on Male Reproductive Function

The 2013 Pb ISA (U.S. EPA, 2013) reported multiple studies in rodents and non-human primates that observed Pb-induced sperm DNA damage, reduced sperm quality, reduced sperm production, and histological and ultrastructural damage to male reproductive organs. Other toxicological studies reported that Pb exposure was associated with decreases in reproductive organ weights, histological changes in the testes and germ cell, and subfecundity. The 2013 Pb ISA also presented toxicological evidence suggesting that Pb may damage sperm cells and sex organ tissue through induction of oxidative stress (Salawu et al., 2009; Shan et al., 2009; Madhavi et al., 2007; Rubio et al., 2006; Wang et al., 2006). Specifically, one study reported Pb-induced increases in oxidative stress markers and reductions of levels of antioxidant enzymes in testicular plasma (Salawu et al., 2009). In addition, several studies reported attenuation of Pb-induced reductions in sperm count, motility, and viability when animals were co-administered substances with known antioxidant properties (Salawu et al., 2009; Shan et al., 2009; Madhavi et al., 2007; Rubio et al., 2006; Wang et al., 2006). Epidemiologic studies were limited due to lack of consideration of potential confounding factors or the use of men attending a fertility clinic, which could result in a biased sample. However, a well-conducted epidemiologic study that enrolled men going to a clinic for either infertility issues or to make a semen donation and controlled for other metals as well as smoking reported a positive

association with various detrimental effects in sperm (Telišman et al., 2007). Studies in the 2013 Pb ISA that investigated the effects of Pb on hormone levels reported inconsistent results, resulting in uncertainty as to whether Pb exerts its toxic effects on the reproductive system by affecting the responsiveness of the hypothalamic-pituitary-gonad axis, by suppressing circulating hormone levels, or by some other pathway. Based on the consistency and coherence of findings of the detrimental effects of Pb exposure on sperm and semen in the toxicological literature from animal studies, the support from epidemiologic studies, and biological plausibility provided by mode of action evidence; however, the evidence in the 2013 Pb ISA was sufficient to conclude a causal relationship between Pb exposures and male reproductive function.

8.2 Scope

The scope of this section is defined by Population, Exposure, Comparison, Outcome, and Study Design (PECOS) statements. The PECOS statements define the objectives of the review and establishes study inclusion criteria thereby facilitating identification of the most relevant literature to inform the Pb ISA.[1] In order to identify the most relevant literature, the body of evidence from the 2013 Pb ISA was considered in the development of the PECOS statements for this Appendix. Specifically, well-established areas of research; gaps in the literature; and inherent uncertainties in specific populations, exposure metrics, comparison groups, and study designs identified in the 2013 Pb ISA inform the scope of this Appendix. The 2013 Pb ISA used different inclusion criteria than the current ISA, and the studies referenced therein often do not meet the current PECOS criteria (e.g., due to higher or unreported biomarker levels). Studies 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. With exception of supporting evidence used to demonstrate the biological plausibility of Pb-associated effects on reproductive and developmental health, studies evaluated and subsequently discussed within this section were only included if they satisfied all the components of the following discipline-specific PECOS statement:

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

[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 (NAAQS) review (e.g., longitudinal studies designed to examine recent versus historical Pb exposure).

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: Reproductive effects, including but not limited to altered age of puberty onset, reduced fertility, poor semen quality/motility, and miscarriage. Developmental effects including but not limited to adverse pregnancy outcomes (e.g., reduced fetal growth, preterm birth, small for gestational age [SGA], birth defects), as well as postnatal developmental effects.

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

Experimental Studies:

Population: Laboratory nonhuman mammalian animal species (i.e., mouse, rat, Guinea pig, minipig, rabbit, cat, dog; whole organism) 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.

Outcomes: Reproductive and developmental effects.

Study design: Controlled exposure studies of animals in vivo.

8.3 Effects on Pregnancy and Birth Outcomes

The 2013 Pb ISA reported inconsistent findings in the epidemiologic and toxicological literature for birth outcomes (infant mortality and embryogenesis; birth defects; preterm birth; and low birth weight/fetal growth). Among the epidemiologic studies, there were inconsistent associations between Pb

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

[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 BLLs. The 95th percentile of the 2011–2016 National Health and Nutrition Examination Survey (NHANES) distribution of BLL in children (1–5 years; n = 2,321) is 2.66 µg/dL (CDC, 2019) and the proportion of individuals with BLLs 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.

exposure and preterm birth. A single study of neural tube defects (NTDs) found no associations in the 2013 Pb ISA, but studies within the 2006 Air Quality Criteria Document for Lead (Pb AQCD) (U.S. EPA, 2006) reported associations between Pb exposure and NTDs. There were some associations reported between Pb and low birth weight when epidemiologic studies used measures of postpartum maternal bone Pb or air exposures. There were less consistent associations for maternal blood Pb measured during pregnancy or at delivery or umbilical cord and placenta Pb (maternal blood Pb or umbilical cord and placenta Pb were the biomarkers most commonly used in studies of low birth weight). The effects of Pb exposure during gestation in animal toxicological studies included mixed findings, but most studies reported reductions in birth weight of pups or birth weight of litters when dams were treated with Pb.

The recent epidemiologic and toxicological studies are detailed in the following sections. Effects on pregnancy and birth outcomes encompass a large range of outcomes. The following sections relating to pregnancy and outcomes are categorized into seven main sections: (1) maternal health during pregnancy; (2) prenatal growth; (3) preterm birth; (4) birth defects; (5) spontaneous abortion and pregnancy loss and fetal and infant mortality; (6) placental function; and (7) other pregnancy and birth outcomes.

8.3.1 Maternal Health During Pregnancy

Maternal health during pregnancy encompasses a wide range of health effects. The details of the recent epidemiologic and toxicological studies evaluating the association between Pb exposure and maternal health during pregnancy are provided in Table 8-2 and Table 8-3, respectively.

8.3.1.1 Epidemiologic Studies on Maternal Health During Pregnancy

The main maternal health outcomes evaluated in this section are gestational diabetes mellitus (GDM) and epigenetic studies. Although there are a limited number of epigenetic studies, these studies may help to add support for biological plausible pathways for which Pb exposure may affect maternal health during pregnancy.

8.3.1.1.1 Epidemiologic Studies on Gestational Diabetes Mellitus

There were no studies on GDM in the 2013 Pb ISA. There were several recent epidemiologic studies that evaluated the association between Pb exposure and GDM and/or impaired glucose tolerance (IGT) (Tatsuta et al., 2022a; Zheng et al., 2021; Zhou et al., 2021b; Oguri et al., 2019; Soomro et al., 2019; Wang et al., 2019; Shapiro et al., 2015). Generally, across the studies there were null associations between Pb exposure and GDM and IGT, and/or GDM or IGT. In studies that evaluated Pb in maternal blood with GDM outcomes, the timing of when Pb was measured differed between trimesters, but the difference in what trimester Pb was measured did not impact the associations (Oguri et al., 2019; Soomro

et al., 2019; Wang et al., 2019; Shapiro et al., 2015). These studies all reported median BLLs less than 5 µg/dL (range: 1.7–2.8 µg/dL) or geometric mean BLLs less than 5 µg/dL (range: 0.6–1.62 µg/dL or 6.05–6.13 ng/g). Additionally, while maternal blood was the primary biomarker used to measure Pb exposure, some studies have used other biomarkers such as maternal serum (Zhou et al., 2021b) and maternal erythrocytes (Zheng et al., 2021); however, the type of biomarker measurement did not influence the pattern of associations. Only one study reported a decrease of 0.5 (95% confidence interval [CI]: −1.6, −0.6) mg/dL difference in mid-gestational glucose concentration associated with an interquartile range (IQR) (17.6 ng/g) change in blood erythrocyte Pb exposure (Zheng et al., 2021). Furthermore, multiple studies also considered co-exposure to other metals in addition to Pb, but the associations remained null (Zheng et al., 2021; Zhou et al., 2021b; Oguri et al., 2019; Wang et al., 2019). Overall, the associations between Pb exposure and GDM, IGT, and GDM or IGT were null, and the null associations persisted across the different trimesters of when Pb levels were measured, the different biomarkers for Pb exposure, and adjustment for co-exposure to other metals.

8.3.1.1.2 Epidemiologic Studies on Epigenetic Effects During Pregnancy

There were no studies on epigenetic effects during pregnancy evaluated in the 2013 Pb ISA. The recent epidemiologic studies on epigenetic effects during pregnancy are limited but provide insight on potential mechanistic pathways in which Pb exposure may impact pregnancy. A single study by Sanders et al. (2015) assessed the association between maternal Pb levels in blood, patella, and tibial bone and altered micro RNA (miRNA) expression in the cervix during the second trimester of pregnancy in a subset of 60 women enrolled in a prospective birth cohort, Programming Research in Obesity, Growth, Environment and Social Stressors (PROGRESS), in Mexico City. Changes in cervical miRNA expression are a potential mechanism that could alter gene expression leading to aberrant changes in cervix tissue function and subsequently impact parturition (Sanders et al., 2015). Expression of certain miRNAs in the cervix during pregnancy have been associated with subsequent gestational age (GA) at delivery (Sanders et al., 2015). During mid-pregnancy (16–19 weeks gestation), samples from cervical exams were collected and analyzed for the expression profiles of 800 miRNAs. Overall, there were distinct miRNAs measured in cervical samples during pregnancy that are associated with the subsequent GA of offspring. Sanders et al. (2015) also identified differentially expressed miRNAs with respect to preterm compared term birth in a subset of women. There were two miRNAs expressed in the cervix that were identified in association with maternal second trimester BLLs, seven miRNAs that were identified in association with maternal patella bone Pb levels, and six miRNAs that were identified in association with maternal tibia Pb levels (see Table 8-2). In another epigenetics study in the same PROGRESS cohort, Sanchez-Guerra et al. (2019) assessed the association of blood Pb exposure during pregnancy with mitochondrial DNA (mtDNA) content, which is a sensitive marker of mitochondrial function and oxidative stress, in cord blood. Maternal blood Pb samples were obtained at three time points (second trimester n = 410, third trimester n = 356, and at delivery n = 354), and cord blood (n = 346) Pb samples were obtained at delivery. Maternal Pb levels during the second trimester (β: 0.017 [95% CI: 0.002, 0.031]) were

associated with higher mtDNA content; however, there were null associations between cord BLLs at delivery (β: 0.016 [95% CI: 0.001, 0.03]), maternal third trimester blood Pb (β: 0.015 [95% CI 0.00, 0.03]), and maternal BLLs at delivery (β: 0.013 [95% CI: −0.001, 0.027]). These epigenetic studies provide support of potential mechanistic pathways in which Pb exposure is associated with maternal health during pregnancy.

8.3.1.1.3 Epidemiologic Studies on Other Outcomes Related to Maternal Health During Pregnancy

There were several other outcomes related to maternal health during pregnancy. More specific study details, including Pb levels, study population characteristics, potential confounders, and select results from these studies are highlighted in Table 8-2. In other outcomes related to maternal health during pregnancy, Pb exposure has been associated with decreased free thyroxine (FT4) during mid-pregnancy (Kahn et al., 2014); increased thyroid peroxidase antibodies (TPOAb) during mid-pregnancy (Kahn et al., 2014); small increases in umbilical cord blood Pb and elevations in systolic blood pressure and diastolic blood pressure during labor and delivery (Wells et al., 2011); changes in Global Severity Index (GSI), depression and anxiety symptom scores (Li et al., 2017b); bone mineral density of the patella (Osorio-Yáñez et al., 2021); increased matrix metalloproteinases (MMP), regulators of uterine remodeling (Kim et al., 2022); and increased risk of preeclampsia (Gajewska et al., 2021; Wu et al., 2021). However, there were no associations between Pb exposure and reduced cortisol awakening response (Braun et al., 2014); maternal depression (Ishitsuka et al., 2020); anti-Müllerian hormone (AMH), a suggested marker of ovarian function and biological marker of female fecundity (Christensen et al., 2016); hormone levels in pregnancy (Gustin et al., 2021); or thyroid function (Corrales Vargas et al., 2022).

8.3.1.2 Toxicological Studies on Maternal Health During Pregnancy

Previous Pb ISAs and AQCDs did not report any toxicological studies that investigated the effects of Pb on maternal health during pregnancy. Despite this lack of prior studies to compare to, recent toxicological studies have reported on the effects of Pb on maternal weight gain during pregnancy (Table 8-3). Maternal weight gain is often used as an indicator of fetal growth and maternal overt toxicity. Additionally, maternal weight gain shares associations with gestational conditions in humans (Santos et al., 2019). Recent studies dosed Sprague-Dawley rats with Pb via gavage for the first 20 days of pregnancy and reported that the 160 ppm Pb treatment group exhibited reduced weight gain during pregnancy (maternal BLLs on gestational day [GD] 20 were reported to be 23.9−27.7 µg/dL) (Saleh et al., 2019; Saleh et al., 2018). Of note is that both studies by Saleh et al. (Saleh et al., 2019; Saleh et al., 2018) reported reduced brain weight of dams, indicating that overt toxicity may have contributed to the overall reduction in maternal weight. Further, the reported maternal BLLs were higher than those observed in the

following studies that investigated the same outcomes. Cory-Slechta et al. (2013) and Schneider et al. (2016) both dosed C57BL/6 mice with 100 ppm Pb via drinking water starting 2 months prior to mating and reported no effects on maternal bodyweight gain and observed much lower maternal BLLs with Cory-Slechta et al. (2013) reporting 12.12 μg/dL at weaning and Schneider et al. (2016) reporting 12.61 μg/dL on lactation day 21. Similarly, Wang et al. (2014) reported no effects in Wistar rats dosed with Pb via drinking water for various durations during pregnancy. In Wang et al. (2014) dosing from GD 1–10, GD 11–20, and GD 1–20 resulted in maternal BLLs of 26.4, 12.4, and 36.0 μg/dL, respectively, at termination of the study on GD 20. Although some of these BLLs overlap with those seen in the studies by Saleh et al. (2018) and Saleh et al. (2019) wherein suppression of maternal weight gain was observed, it is possible that the use of different strains or different dosing routes could be attributed to the observed difference in effect on maternal weight gain. Additionally, the reduction of brain weight observed in the dams used in the studies by Saleh et al. (2018) and Saleh et al. (2019) suggest that maternal overt toxicity may be responsible for the observed reduction in maternal weight gain.

8.3.1.3 Integrated Summary of Effects on Maternal Health During Pregnancy

The 2013 Pb ISA did not include epidemiologic and/or toxicological studies that evaluated the relationship between Pb exposure and maternal health during pregnancy. There were consistent null associations between Pb exposure and GDM among the recent epidemiologic studies. While the critical window for GDM is unknown, these studies had different time points during pregnancy in which Pb exposure was measured and different biomarkers of exposure (blood, serum, and erythrocyte) and the null associations persisted. A few of the studies were limited by the cross-sectional study design and the small number of GDM cases. Additionally, a few of the recent epidemiologic studies incorporated mixture methods to consider Pb exposure in conjunction with co-exposure to other metals to evaluate associations with GDM, which helps to reduce uncertainties regarding co-pollutant confounding. The limited number of epigenetic studies provide support of potential mechanistic pathways in which Pb exposure are associated with selected maternal health during pregnancy. Furthermore, there was a small body of evidence across various additional pregnancy-related endpoints in the epidemiologic literature; however, the small number limits the ability to judge coherence and consistency across these studies, although the positive associations observed demonstrate that Pb exposure could result in physiological responses that contribute to adverse pregnancy outcomes (e.g., changes in thyroid function, maternal mental health, changes in blood pressure, preeclampsia). In the recent toxicological literature, there were a limited number of studies that investigated the relationship between Pb exposure and maternal weight gain during pregnancy; however, the only studies that observed changes in maternal weight gain also reported signs of possible overt toxicity (reduced brain weight), indicating that weight gain during pregnancy may not have been a direct effect of Pb exposure. The majority of recent toxicological studies in rodents reported that maternal weight gain during pregnancy was unaffected by Pb exposure.

8.3.2 Prenatal Growth

The recent epidemiologic and toxicological studies that examined the relationship between Pb exposure and prenatal growth, which includes outcomes such as fetal growth, birth weight, body length at birth, and GA, are summarized in the text below. Study details of the recent epidemiologic studies are included in Table 8-4 and the recent toxicological studies are in Table 8-3.

8.3.2.1 Epidemiologic Studies on Prenatal Growth

The epidemiologic studies in the 2013 Pb ISA reported associations between maternal bone Pb and low birth weight and with studies of Pb air exposures and birth weight. The associations were less consistent when using maternal blood Pb or umbilical cord and placenta Pb as the exposure measurement, although some studies did demonstrate associations. The studies of Pb exposure and fetal growth were limited by their cross-sectional study design, small sample size, high air Pb concentrations (air Pb as high as 30 $\mu g/m^3$), and in some studies, the lack of control of confounders.

A large number of epidemiologic studies have been published since the 2013 Pb ISA on exposure to Pb and prenatal growth. The studies in this section focus on these prenatal growth outcomes, including birth weight; low birth weight; body length, crown-to-heel length, head circumference (HC), Ponderal Index (PI; weight/height^3), GA, SGA, and large for gestational age (LGA). Multiple cross-sectional and cohort studies have been conducted that examined the relationship between Pb exposure and prenatal growth; however, the findings from the recent epidemiologic studies are inconsistent. There are differences in study design, timing of the exposure (at different points during pregnancy, at delivery), differences in biomarkers examined for Pb (maternal blood, maternal serum, cord blood, maternal red blood cells, placental tissue), and small sample sizes in some studies. The study details, including information on study population, biomarker of exposure, and outcome, are in Table 8-4.

Several studies used cord blood to assess Pb exposure and reported null associations with birth weight (Lee et al., 2021; Govarts et al., 2020; Tatsuta et al., 2017; Wang et al., 2017b; Govarts et al., 2016; García-Esquinas et al., 2013; Xie et al., 2013), while a single study reported a reduction in birth weight (Xu et al., 2012). Among these studies, there were also inconsistent associations when examining cord blood Pb exposure and birth weight among infant sex. Tatsuta et al. (2017) evaluated the associations between cord blood Pb and birth weight between male and female infants, but the associations remained null. While there were null associations with birth weight, birth length, HC, and PI when infant sexes were analyzed together, analyses stratifying by infant sex reported associations in male infants, including increased birth weight (β: 206.50 [95% CI: 46.15, 366.86]) and decreased HC (β: −0.65 [95% CI: −1.24, −0.06]) per 1-unit increase $\log_{10}$-Pb cord blood concentration. Among female infants, there was only a reduction in PI (β: −0.16 [95% CI: −0.30, −0.02]) per 1-unit increase in the $\log_{10}$-Pb cord blood concentration (Wang et al., 2017b).

In addition to birth weight, there were several other prenatal growth outcomes in these studies that were evaluated in association with cord blood Pb; however, the associations were inconsistent. García-Esquinas et al. (2013) also reported null associations between cord blood Pb and birth length, and 1- and 5-minute Apgar scores from the 144 newborns who were a part of cross-sectional biomonitoring study of the BioMadrid Project. Xu et al. (2012) also reported decreased mean GA of 0.57 weeks (95% CI: 0.51, 0.63), with increased risk of low birth weight rate (OR: 1.61 [95% CI: 1.37, 1.90]), and increased risk of intrauterine growth retardation rate (OR: 2.12 [95% CI: 1.68, 2.69]). Xie et al. (2013) reported a negative association with birth length (β: −0.84 cm [95% CI: −1.52, −0.16]) per square root 1-μg/dL increase in cord blood Pb, but null associations with birth weight (β: −99.33 g [95% CI: −217.33, 20.67]) and HC (β: −0.36 [95% CI: −0.81, 0.03]). A single study that was conducted among 1,578 mother-infant pairs in Saudi Arabia reported no associations between cord BLLs and PI below the 10th percentile (OR: 0.66 [95% CI: 0.42, 1.05]) (Al-Saleh et al., 2014).

Maternal blood was also used to measure Pb exposure in association with prenatal growth outcomes in multiple cross-sectional studies, but the associations were inconsistent. Xie et al. (2013) reported a negative association with birth weight (β: −148.99 g [95% CI: −286.33, −11.66]) per square root 1-μg/dL increase in maternal blood Pb measured at delivery, but null associations with birth length (β: −0.46 cm [95% CI: −1.25, 0.34]) and HC (β: −0.37 cm [95% CI: −0.78, 0.19]) among 252 mother-infant pairs in a rural area located on the south coast of Laizhou Bay, China between 2010 and 2011. However, Kim et al. (2020) reported negative associations between maternal blood natural log (ln)-Pb, measured at delivery, and HC (β: −0.75 cm [95% CI: −1.17, −0.32]) and PI (β: −0.62 kg/m^3 [95% CI: −1.13, −0.11]), but there were null associations with birth weight (β: 60 g [95% CI: −15, 135]), BMI (β: −0.14 kg/m^2 [95% CI: −0.39, 0.11]), and SGA (OR: 0.69 [95% CI: 0.33, 1.46]) among participants of e-waste Recycling Exposure and Community Health (e-REACH) Study. A study by Xu et al. (2022b) reported that a one ln-unit increase in maternal BLLs, measured at delivery, was associated with increased GA (β: 0.18 weeks [95% CI: 0.05, 0.31]), decreased birth length (β: −0.39 cm [95% CI: −0.66, −0.22]), and decreased HC (β: −0.22 cm [95% CI: −0.39, −0.06]), but a null association with birth weight. There were also null associations across tertiles of maternal BLLs and low birth weight.

In addition to cord blood and maternal blood, other biomarkers such as maternal serum, cord blood serum, and placental tissue were used to assess Pb exposure with birth weight among other studies and reported inconsistent associations (Yang et al., 2020; Freire et al., 2019; Mikelson et al., 2019; Tang et al., 2016; Hu et al., 2015). A study that measured Pb in both maternal serum, measured at delivery, and cord blood serum reported null associations with birth weight for both biomarkers (Hu et al., 2015), while another study reported null associations between cord blood serum and birth weight-for-gestational-age Z-score, when modeled continuously or categorized by quintiles (Yang et al., 2020). Although there were null associations with birth weight and GA, there was a decrease in birth height and a decrease in HC per ln-Pb increase in umbilical cord serum among 103 mother-newborn pairs from an island in the East China Sea (Tang et al., 2016). When placental tissue was the biomarker of exposure for Pb, a single cross-sectional study reported null associations with birth weight, low birth weight, birth, head, GA, and SGA

(Freire et al., 2019), but another reported a decrease in birth weight of 58.3 g (95% CI: −97.9, −18.8) per ln-Pb increase in placental tissue (Mikelson et al., 2019).

The use of advanced statistical methods to evaluate the impact of co-exposure to other metals, or mixtures, helps to address uncertainties of co-pollutant confounding. To assess the associations between metal mixtures (arsenic [As], cadmium [Cd], manganese [Mn], and Pb) in umbilical cord blood and birth weight, birth length, and HC, 1,088 participants of a birth cohort in Bangladesh were assessed in a cohort study (Lee et al., 2021). There were null associations with birth weight (β: −0.04 g [95% CI: −0.19, 0.11]), birth length (β: −0.06 cm [95% CI: −0.20, 0.09]), and HC (β: 0.08 cm [95% CI: −0.06, 0.23]) in association with an IQR increase in ln-Pb cord blood concentrations, when adjusted for confounders and other metals. In addition to the multivariable regression analysis, Lee et al. (2021) also used Bayesian kernel machine regression (BKMR) to estimate the effects of co-exposure to metal mixtures. BKMR is a method that estimates the multivariable exposure-response function in a flexible and parsimonious way, conducts variable selection on the (potentially high-dimensional) vector of exposures, and allows for a grouped variable selection approach that can accommodate highly correlated exposures. In the BKMR analysis, there was an inverse association between the metal mixture overall and birth length when all four metal concentrations were ≥60th percentile and HC when all four metals were ≥55th percentile, compared to their median values, with stronger associations as the concentrations of the four metals increased. However, when estimating the difference in birth size with an IQR increase in each individual metal when the other metals were fixed at their 25th, 50th, or 75th percentiles, the associations with Pb were null.

Overall, in the multiple longitudinal birth cohort studies, there were inconsistent findings between various Pb exposure biomarkers and prenatal growth outcomes. The multiple longitudinal birth cohort studies have reported inconsistent associations. These studies collected maternal samples during different time periods during pregnancy and utilized different biomarkers to measure Pb exposure to evaluate associations with a variety of prenatal growth outcomes. In the longitudinal studies that measured Pb exposure from maternal blood, there were inconsistent patterns of association with prenatal growth outcomes, regardless of the trimester Pb exposure was measured or prenatal growth outcome (see Table 8-4). Several studies reported null associations with birth weight (Shih et al., 2021; Woods et al., 2017; Taylor et al., 2016; Bloom et al., 2015; García-Esquinas et al., 2014; Rabito et al., 2014) and birth weight Z-score (BWZ) (Daniali et al., 2023), while others reported reductions in birth weight (Goto et al., 2021; Hu et al., 2021; Rodosthenous et al., 2017; Taylor et al., 2015). Of note, Rodosthenous et al. (2017) measured Pb levels in maternal blood during the second trimester among 944 mother-infant pairs in the PROGRESS cohort in association with birth weight using both linear and quantile regression. While the linear regression reported a null association with birth weight-for-gestational-age Z-score (β: −0.06 [95% CI: −0.13, 0.003]) per $\log_2$-Pb blood level increase, the quantile regression analysis revealed larger magnitudes of the association maternal blood Pb and birth weight-for-gestational-age Z-score. The magnitude of the association was largest in the lowest (<30th) Z-score percentiles (difference in Z-score

ranged from −0.13 to −0.08). The use of quantile regression provides insights to potential sensitivity to Pb exposure for smaller infants, an association that was not detected by linear regression.

While some studies reported null associations with birth length (Daniali et al., 2023; Shih et al., 2021; Bloom et al., 2015), a single study reported a 0.20 cm decrease (95% CI: −0.30, −0.10) in birth length per 1 μg/dL increase in maternal BLL (collected during the second or third trimester) among participants of the Japan Environment and Children's Study (JECS) (Goto et al., 2021). A single study reported a reduction in HC of 0.03 cm (95% CI −0.06, −0.00) per 1 μg/dL increase of first trimester maternal blood Pb (Taylor et al., 2016), but other studies reported null associations with HC and first trimester maternal blood Pb (Daniali et al., 2023; Taylor et al., 2015), pre-pregnancy maternal and parental blood (Bloom et al., 2015), or second or third trimester maternal blood Pb (Shih et al., 2021). While there was reported decreased GA (β: −1.9 days [95% CI: −3.1, −0.5]) per IQR increase in second trimester maternal ln-Pb blood level among those in Puerto Rico Testsite for Exploring Contamination Threats (PROTECT) cohort (Ashrap et al., 2020), there were null associations with gestational and pre-pregnancy maternal and parental blood (Bloom et al., 2015) and maternal BLLs during the second or third trimester among the JECS (Goto et al., 2021); however, Goto et al. (2021) did report an increased risk of SGA (OR: 1.34 [95% CI: 1.16, 1.55]) and increased risk of low birth weight (OR: 1.34 [95% CI: 1.16, 1.55]) per 1 μg/dL increase in maternal BLL, but other studies did not report increased risk of SGA (Thomas et al., 2015) and maternal blood (collected during the first and third trimesters of pregnancy) or second trimester maternal blood (Ashrap et al., 2020). There were consistent null associations with PI and maternal blood (Shih et al., 2021; Bloom et al., 2015) and crown-to-heel length and first trimester maternal blood Pb (Taylor et al., 2016; Taylor et al., 2015).

In addition, some of the longitudinal studies considered different effect modifiers when assessing the associations between maternal BLLs and prenatal growth outcomes. Among participants in the Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) study, there were null associations between maternal blood (collected during the first and third trimesters of pregnancy) and SGA across tertiles of maternal blood Pb (Thomas et al., 2015). In addition, an exploratory analysis was conducted to examine the potential effect modification of single nucleotide polymorphisms (SNP) in GSTP1 and GSTO1 genes on the relationship of maternal blood Pb and SGA. There was a marginal interaction between maternal Pb exposure and the GSTP1 A114V SNP ($p = 0.06$), but there was no indication of effect modification by other GSTP1 and GSTO1 SNPs on the associations between maternal blood Pb and SGA. In another study in the PROTECT cohort, the modifying effect of psychosocial stress on the association between maternal blood Pb exposure and GA, BWZ, SGA, and LGA were examined in a subset of 682 pregnant women (Ashrap et al., 2021). Maternal blood samples were collected at 18 ± 2 weeks gestation and 26 ± 2 weeks gestation. Among mothers who reported "good" psychosocial status, there was decreased gestation age (β: −1.9 days [95% CI: −3.2, −0.6]); however, there were null associations with BWZ (β: 0.1 [95% CI: 0.0, 0.2]), SGA (OR: 0.86 [95% CI: 0.65, 1.14]), and LGA (OR: 0.89 [95% CI: 0.64, 1.23]). The associations for mothers who reported "poor" psychosocial status were null across the birth outcomes.

In addition to the associations between prenatal growth outcomes and Pb levels, there were sex-stratified differences. In a study by García-Esquinas et al. (2014), 97 mother-father-infants in the BioMadrid Study were used to evaluate associations between prenatal Pb exposure and fetal development from three biomarkers (maternal and paternal blood Pb at 34 weeks gestation and cord blood at delivery) with different growth metrics at birth. While there were no associations between log-Pb blood levels (maternal, paternal, or cord) and gestation age, birth weight, birth length, abdominal diameter, or cephalic diameter (CD), associations were observed when analyses were stratified by infant sex. Among female infants, there was decreased birth length of 1.06 cm (95% CI: −2.03, −0.08) and CD of −0.55 cm (95% CI: −1.03, −0.07) per two-fold increase in paternal BLLs (μg/L), but there were no associations among male infants. In the study by Shih et al. (2021), there were null associations between maternal blood log_2-Pb concentrations (collected between 6 and 32 weeks of gestation) and prenatal growth outcomes (GA, birth weight, birth length, HC, and PI). However, when stratified by infant sex, there were reductions in GA (β: −0.98 weeks [95% CI: −1.67, −0.30]), birth weight (β: −381 g [95% CI: −583, −178]), birth length (β: −1.44 cm [95% CI: −2.45, −0.42]), and HC (β: −1.10 cm [95% CI: −1.70, −0.50]), but had a null association with PI (β: −1.07 kg/m3 [95% CI: −1.56, 0.39]) among female infants, while the associations for these same outcomes were null among male infants.

There were also a limited number of studies that considered co-exposure to other pollutants. From the MIREC study, 1,857 mother-infant pairs were analyzed to examine the relationship between prenatal exposure to a mixture of endocrine-disrupting chemicals, including Pb, and birth weight using BKMR (Hu et al., 2021). Maternal blood was collected during the first trimester of pregnancy. In the adjusted model for log_2-Pb, every two-fold increase in Pb concentration was associated with a mean birth weight reduction of 82.22 g (95%: −145.46, −18.97), and when adjusted for other metals, the reduction in mean birth weight was 75.89 g (95% CI: −141.24, −10.54). In the mixtures analysis, Pb was the main contributor to the adverse effect on birth weight in the metal mixture consisting of As, Cd, mercury (Hg), Mn, and Pb. An increase in the log_2-Pb concentration from the 25th to the 75th percentile was associated with a posterior mean of −47g, meaning that there was a reduction in mean birth weight of 47 g, while holding the other components in the metal mixture constant at their median values.

In addition to maternal blood Pb, other biomarkers such as maternal erythrocytes, maternal serum, and teeth were used to assess Pb exposure with prenatal birth outcomes, including birth weight, birth length, or HC. Maternal erythrocytes from blood samples were collected during the third trimester (mean: gestational week 29) from 584 mothers in the Nutritional impact on Immunological maturation during Childhood in relation to the Environment (NICE) study in Northern Sweden (Gustin et al., 2020). Maternal erythrocytes reflect exposure over the past 1–3 months. A doubling of maternal erythrocyte Pb concentration was not associated with birth weight (β: −13 g [95% CI: −66, 41]), birth length (β: −0.080 cm [95% CI; −0.31, 0.15]), or HC (β: 0.059 cm [95% CI: −0.22, 0.34] for maternal erythrocyte Pb concentration less than the median of 14 μg/kg and β: −0.24 cm [95% CI: −0.53, 0.056] for maternal erythrocyte Pb concentration greater than median of 14 μg/kg). There was no interaction by infant sex. When mutually adjusted for other maternal metal exposure to Cd and Hg, the null associations persisted.

In a subset of the Project Viva prospective pre-birth cohort, individual and joint effects of metal mixture components on birth weight, length, HC, and GA were estimated in association with maternal erythrocyte Pb concentrations collected during early pregnancy (11.3 ± 2.8 weeks of gestation) from 1,423 mother-infant pairs (Rahman et al., 2021). In single metal model, an IQR increase in maternal erythrocyte Pb concentration was associated with a 33.9 g (95% CI: −65.3, −2.5) decrease in birth weight, but there were no associations with birth length (β: −0.10 cm [95% CI: −0.29, 0.09]), HC (β: −0.07 cm [95% CI: −0.17, 0.04]), or GA (β: 0.03 weeks [95% CI: −0.10, 0.16]). When stratified by infant sex, the associations were null for both male and female infants and birth weight, birth length, HC, and GA. Additionally, there was consistent pattern of association of decreased birth weight, birth length, and HC overall and in the infant sex-stratified analyses (see Table 8-4).

A total of 3,125 mother-infant pairs were recruited from the China-Anhui Birth Cohort Study (C-ABCS) to investigate the associations between maternal serum Pb levels the first trimester (median of 11 weeks gestation) and in the second trimester (median of 16 weeks gestation) with growth metrics (Wang et al., 2017a). Overall maternal serum Pb during pregnancy had a negative association with birth weight (β: −2.74 g [95% CI: −5.17, −0.31]), but null associations with birth length, HC, and chest circumference. When stratified by trimester, the negative association with birth weight persisted, with a reduction of 4.40 g (95% CI: −8.22, −0.58) for first trimester maternal serum Pb and a 1.64 g (95% CI: −4.80, −0.58) reduction for second trimester maternal serum Pb. There were no associations by trimester maternal serum Pb for birth length, HC, or chest circumference. In addition, there was increased risk of SGA of 1.45 (95% CI: 1.04, 2.02) for subjects with medium-Pb maternal serum (1.18–1.70 μg/dL) and increased risk of SGA of 1.69 (95% CI: 1.22, 2.34) in subjects with high-Pb maternal serum (≥1.71 μg/dL), compared to low-Pb maternal serum (<1.18 μg/dL). When stratified by infant sex, there was increased risk of SGA among female infants (OR: 1.51 [95% CI: 0.99, 2.31] for medium-Pb maternal serum and OR: 1.68 [95% CI: 1.12, 2.54] for high-Pb maternal serum), but among male infants, the associations were null. There was an increased risk of SGA with high first trimester maternal serum Pb (OR: 2.13 [95% CI: 1.24, 3.38]), but there were null associations among second trimester maternal serum Pb.

In a small cohort study, second and third trimester Pb levels were estimated from baby teeth from 145 participants in the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study (WHEALS) (Cassidy-Bushrow et al., 2019). There were no associations between tooth Pb in the second or third trimester and BWZ (β: −0.15 [95% CI: −0.35, 0.05] for second trimester and β: −0.06 [95% CI: −0.24, 0.12] for third trimester) or GA at delivery (β: 0.08 [95% CI: −0.19, 0.35] for second trimester and β: 0.14 [95% CI: −0.11, 0.39] for third trimester) in the fully adjusted models. There was no indication that there was a time effect (difference between the effect estimates in the second and third trimesters) for birth weight for Z-score (β: −0.31 [95% CI: −0.90, 0.28]) or GA at delivery (β: −0.22 [95% CI: −1.08, 0.64]). Additionally, when stratified by child's sex, there were no associations between tooth Pb in the second or third trimester and BWZ or GA at delivery.

In a study by Bui et al. (2022), effects of short-term maternal exposure to airborne Pb during pregnancy on birth weight, low birth weight, and SGA was estimated using a quasi-experimental variation in airborne Pb exposure based on the National Association for Stock Car Auto Racing (NASCAR)'s deleading of racing fuel in a difference-in-difference model in the Charlotte-Concord-Gastonia Metropolitan Statistical Area in North Carolina. After deleading of racing fuel, there was an average increase in birth weight of 102.50 g (95% CI: 45.73, 159.2), decreased probability of low birth weight of 0.0445 (95% CI: −0.0697, −0.0194), and reduction in the probability of SGA of 0.0396 (95% CI: −0.0638, −0.0155) among children born to mothers residing less than 4000 meters of the Charlotte Motor Speedway, compared with those residing greater than 10,000 meters. The difference-in-difference methodology allows for the control of time-varying confounders, removing biases from comparisons over time in the treatment group that could be the result of trends due to other causes of the outcome.

8.3.2.2 Toxicological Studies on Prenatal Growth

The 2013 Pb ISA discussed a few studies that reported reduced birth weight of offspring from Pb-treated dams (Massó-González and Antonio-García, 2009; Wang et al., 2009; Teijón et al., 2006). Recent toxicological studies consistently report no effects of Pb on birth weight (Table 8-3). Most studies began exposure of the dam prior to conception of the offspring (Zhao et al., 2021; Tartaglione et al., 2020; Rao Barkur and Bairy, 2016; Schneider et al., 2016; Barkur and Bairy, 2015; Weston et al., 2014; Cory-Slechta et al., 2013) and a few studies began exposure of the dam at the time of conception (GD 0) (Rao Barkur and Bairy, 2016; Barkur and Bairy, 2015; Barkur et al., 2011). Of note is that Teijón et al. (2006), a study discussed in the 2013 Pb ISA, elaborated that the observed reduction in litter weights born to Pb-treated dams was largely driven by the reduced size of female pups, whereas males were unaffected. In agreement, some recent studies that reported no effect of Pb on birth weight assessed weight in male pups only (Barkur and Bairy, 2015; Barkur et al., 2011). However, all other recent studies included females in birth weight analyses and reported no effects of Pb on birth weight of exposed offspring.

8.3.2.3 Integrated Summary of Effects on Prenatal Growth

The epidemiologic studies in the 2013 Pb ISA reported associations between maternal bone Pb and low birth weight and with studies of Pb air exposures and birth weight. The associations were less consistent when using maternal blood Pb or umbilical cord and placenta Pb as the exposure measurement although some studies did demonstrate associations. The studies of Pb exposure and fetal growth were limited by cross-sectional study design, small sample size, high Pb concentrations (air Pb as high as 30 $\mu g/m^3$), and in some studies, the lack of control of confounders. A recent quasi-experimental study of maternal exposure to airborne Pb during pregnancy found an increase in birth weight, decreased probability of low birth weight, and reduction in the probability of SGA after the deleading of racing fuel. However, overall, the recent epidemiologic studies reported inconsistent associations between Pb

exposure and prenatal growth outcomes, while the toxicological studies consistently reported no effects of Pb on offspring birth weight. The inconsistent findings from the recent epidemiologic studies may be due to differences in study design, timing of when the exposure was measured (e.g., during pregnancy, at delivery), biomarkers examined for Pb (e.g., maternal blood, cord blood, maternal red blood cells, maternal serum, placental tissue), difference in growth metrics assessed (e.g., birth weight, birth length, GA), and small sample sizes in some studies. While there were inconsistencies in the findings among the epidemiologic studies, the recent epidemiologic studies were able to address a few of the uncertainties in the 2013 Pb ISA. Many of the recent studies were conducted in well-designed longitudinal birth cohorts, considered the differences in effects by infant sex, and controlled for wide range of confounders, including GA (when not an outcome of interest), and maternal health factors (e.g., smoking, parity, BMI). Additionally, some epidemiologic studies controlled for other metal exposure, and other studies evaluated the associations with joint effects or as a mixture. A few toxicological studies were reviewed in the 2013 Pb ISA, all of which reported reductions in birth weight of offspring born from Pb-exposed dams. However, recent toxicological studies do not support previous studies and consistently report no effects of Pb on offspring birth weight.

8.3.3 Preterm Birth

The recent epidemiologic and toxicological studies that examined the relationship between Pb exposure and preterm birth are summarized in the text below. Study details of the recent epidemiologic studies are included in Table 8-5 and the recent toxicological studies are in Table 8-3.

8.3.3.1 Epidemiologic Studies on Preterm Birth

The epidemiologic studies reviewed in the 2013 Pb ISA reported overall inconsistent findings regarding a relationship between indicators of Pb exposure and preterm birth. However, there were a few well-conducted epidemiologic studies that reported associations between maternal blood Pb and preterm birth (Vigeh et al., 2011; Jelliffe-Pawlowski et al., 2006).Among the epidemiologic studies , there were no apparent patterns within the type of exposure measurement or Pb level. Many of these studies are limited by the small number of preterm births and their cross-sectional design (i.e., studies of umbilical cord blood may not adequately characterize BLLs earlier in pregnancy). Among the longitudinal cohort studies, the results were mixed, with some studies reporting associations between maternal blood Pb during pregnancy and preterm birth. Most studies controlled for potentially important confounders, such as maternal age and smoking.

In the recent epidemiologic studies examining the risk of preterm birth and Pb exposure, the findings were generally consistent (Table 8-5). Most notably is a quasi-experimental study employing difference-in-difference methodology. In a study by Bui et al. (2022), the effects of short-term maternal

exposure to airborne Pb during pregnancy on preterm birth was estimated using a quasi-experimental variation in airborne Pb exposure based on NASCAR's deleading of racing fuel in a difference-in-difference model in the CCG MSA in North Carolina. There was decreased probability of preterm birth of 0.295 (95% CI: −0.0572, −0.000185) among children born to mothers residing less than 4000 meters of the CMS, compared to those residing greater than 10,000 meters after deleading of racing fuel. The difference-in-difference methodology allows for the control of time-varying confounders, removing biases from comparisons over time in the treatment group that could be the result of trends due to other causes of the outcome.

In a cross-sectional study of 696 mother-infant pairs in the Study on the Environment and Reproductive Health (EMASAR) cohort in Argentina, the relationship between maternal Pb levels, which were collected 36 ± 12 hours postpartum, and preterm birth was examined (Xu et al., 2022b). Among tertiles of maternal Pb levels, there were null associations with preterm birth (OR: 1.24 [95% CI: 0.35, 4.4] in tertile 2 and OR:1.26 [95% CI: 0.32, 5.00] in tertile 3). In another study, cord blood samples were obtained from 432 infants born in an area with e-recycling (Guiyu) and 99 from an area without e-recycling (Xiamen) in China, but there was no increased risk of preterm birth (OR: 1.09 [95% CI: 0.93, 1.28]) (Xu et al., 2012). Additionally, another study used placental tissue Pb levels in association with preterm birth among 327 mother-infant pairs who were part of the Instituto de Nanociencia y Materiales de Aragón (INMA) Project in Spain and found no association with risk of preterm birth (OR: 0.40 [95% CI: 0.04, 4.70]) (Freire et al., 2019).

In a case-control study, maternal serum Pb, collected during the first or second trimester, was not associated with risk of spontaneous preterm birth (OR: 1.46 [95% CI: 0.97, 2.18]) among 147 cases and 381 controls (Yu et al., 2019). When stratified by the trimester of collection of maternal serum Pb, there was null association for spontaneous preterm birth (OR: 1.63 [95% CI: 0.91, 2.91]) with first trimester maternal serum Pb only or second trimester maternal serum Pb only (OR: 1.27 [95% CI: 0.71, 2.28]). In a nested case-control study, the association between exposure to 41 metals/metalloids, including Pb, during early pregnancy measured in maternal serum and risk of spontaneous preterm birth was investigated (Xu et al., 2022a). There were 74 cases of spontaneous preterm birth and 74 controls. In the highest quartile of maternal serum Pb levels, there was an increased risk of spontaneous preterm birth of 4.09 (95% CI: 1.31, 12.77) and there was evidence of potential exposure-response across the quartiles (p for trend: 0.017).

Tsuji et al. (2018) used data on 14,847 pregnant women who were participants of the JECS to assess the association between second and third trimester maternal blood (collected at gestational weeks 14–39) and early preterm (22 to <34 weeks) and late preterm (34 to <37 weeks). Among the quartiles of Pb exposure, there was no increased risk in early preterm birth or late preterm birth. There was also no evidence of a linear exposure-response trend among the Pb exposure quartiles in either the early preterm births (p for trend: 0.134) or late preterm (p for trend: 0.920). In another cohort study using data from the JECS, per each 0.1 μg/dL increase in maternal BLL, there was no increased risk of preterm delivery (OR: 0.90 [95% CI: 0.70, 1.16]) (Goto et al., 2021).

In a small cohort (n = 98) from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study in Shelby County, TN, Pb was measured cord blood and from maternal blood collected during the second and third trimester, at delivery (Rabito et al., 2014). Each 0.1-unit increase in maternal blood Pb in the second trimester (OR:1.66 [95%CI: 1.23, 2.23]) and third trimester (OR: 1.24 [95% CI: 1.01, 1.52]) was positively associated with preterm birth, but there was no increased risk of early-term birth (≥37 to <39 weeks) associated with maternal blood Pb in the second trimester (OR: 0.87 (95% CI: 0.63, 1.20]) and third trimester (OR: 0.88 [95% CI: 0.69, 1.13]).

In the Avon Longitudinal Study of Parents and Children, maternal blood samples were collected as early as possible in pregnancy, with a median GA of 11 weeks at the time of sampling (range 1–42 weeks, IQR 9–13 weeks) (Taylor et al., 2015). There was increased risk of preterm delivery (OR: 2.00 [95% CI: 1.35, 3.00]) for maternal BLLs ≥5 µg/dL. Li et al. (2017a) investigated the associations between maternal serum Pb levels and risk of preterm birth in a population-based birth cohort (n = 3,125), part of the China-Anhui Birth Cohort. Maternal serum Pb levels were categorized into tertiles: low-Pb (<1.18 µg/dL), medium-Pb (1.18−1.70 µg/dL), and high-Pb (≥1.71 µg/dL). There was an increased risk of preterm birth in the medium-Pb tertile (OR: 2.33 [95% CI: 1.49, 3.65]) and high-Pb tertile (OR: 3.09 [95% CI: 2.01, 4.76]).

In a study by Ashrap et al. (2020), individual and mixture effects of metals and metalloids on preterm birth among 731 pregnant women in the PROTECT cohort were examined. Maternal blood was collected at 16–20 and 24–28 weeks gestation. There was an increased risk of preterm birth (OR: 1.63 [95% CI: 1.17, 2.28]) and spontaneous preterm birth (OR: 1.53 [95% CI: 1.00, 2.35]) per IQR increase in maternal blood Pb in the individual pollutant model. The mixture pollutant models and elastic net regularization identified Pb and zinc as the most important predictors of preterm birth, while BKMR method identified Pb, zinc, and Mn as most predictive of preterm birth. In another study in the PROTECT cohort, the modifying effect of psychosocial stress on the association between Pb and overall preterm birth (<37 completed weeks of gestation) and spontaneous preterm birth (<37 completed weeks of gestation defined as presentation of premature rupture of the membranes, spontaneous preterm labor, or both) (Ashrap et al., 2021). There was an increased risk of overall preterm birth among mothers who reported "good" psychosocial status (OR: 1.72 [95% CI: 1.14, 2.58]), but null association among mothers who reported "poor" psychosocial status (OR: 1.43 [95% CI: 0.69, 2.97]). There were null associations among mothers who reported "good" psychosocial status and "poor" psychosocial status and spontaneous preterm birth (OR: 1.56 [95% CI: 0.93, 2.6] and OR: 1.22 [95% CI: 0.42,3.56], respectively).

8.3.3.2 Toxicological Studies on Preterm Birth

Both the 2013 Pb ISA and the 2006 Pb AQCD did not describe any studies that reported on the effects of Pb on preterm birth in animals. Only one recent study was found that reports on gestation duration (Betharia and Maher, 2012). Betharia and Maher (2012) reported no effect of Pb on gestation

term when Sprague-Dawley rats were dosed from GD 0 to postnatal day (PND) 20. BLLs were measured in offspring and reported to be 9.03 µg/dL on PND 2, 0.976 µg/dL on PND 25, 0.0318 µg/dL on PND 60.

8.3.3.3 Integrated Summary of Effects on Preterm Birth

In summary, there were inconsistencies in the recent epidemiologic studies examining the relationship between Pb exposure and risk of preterm birth, similar to the 2013 Pb ISA. There was no apparent pattern associated with any biomarker of Pb exposure. Several of the recent epidemiologic studies were conducted in well-designed, longitudinal birth cohorts, and controlled for wide range of confounders, including GA, other metals, and maternal health factors (e.g., smoking, parity, BMI). Overall, among the epidemiologic studies, there was a pattern of elevated risk of preterm birth observed across several studies from multiple geographic locations, including a quasi-experimental study. Among these studies, there were still some uncertainties in the timing of the exposure (e.g., during pregnancy, at delivery), and biomarkers examined for Pb (e.g., maternal blood, cord blood, maternal red blood cells, maternal serum, placental tissue). There were no toxicological studies that investigated the effects of Pb on preterm birth in the 2013 Pb ISA and the 2006 Pb AQCD, and recent toxicological data are sparse with only a single PECOS-relevant study available, which reported no effects of Pb on gestation duration, making it difficult for toxicological data to support epidemiologic evidence.

8.3.4 Birth Defects

The recent epidemiologic and toxicological studies that examined the relationship between Pb exposure and birth defects are summarized in the text below. Study details of the recent epidemiologic studies are included in Table 8-6 and the recent toxicological studies are in Table 8-3.

8.3.4.1 Epidemiologic Studies on Birth Defects

In the 2013 Pb ISA, there were only a few studies available for review evaluating associations between Pb exposure and birth defects, specifically NTDs. These studies did not report associations between Pb exposure and NTDs. These studies were limited by the timing of Pb measurements, whether taken at delivery or postnatally, and the lack of potential confounders.

A few recent epidemiologic studies examined the relationship between Pb levels and birth defects. Several studies evaluated the association between NTDs in different biomarkers (placental tissue, umbilical cord tissue, and maternal serum) (Liu et al., 2021; Tian et al., 2021; Jin et al., 2013). Recent studies that measured Pb exposure from placental tissue or umbilical cord tissue reported no increased risk for NTDs overall or by subtype (Liu et al., 2021; Jin et al., 2013) (see Table 8-6 for details). However, in a case-control study which evaluated the single and joint effects of 10 metals measured in

maternal serum during pregnancy, there was increased risk for NTDs (Tian et al., 2021). In the single pollutant model, there was increased risk of NTD of 2.05 (95% CI: 1.05, 4.02) in the second tertile and 3.51 (95% CI: 1.76, 6.98) in the third tertile, relative to the lowest tertile of maternal serum Pb levels, indicating an exposure-response relationship (p for trend: <0.001). There was also increased risk by NTD subtype. There was increased risk of spina bifida of 2.16 (95% CI: 1.00, 4.88) in the second tertile and 5.16 (95% CI: 2.24, 11.87) in the third tertile, relative to the lowest tertile of maternal serum Pb levels, with an indication of an exposure-response relationship (p for trend: 0.022). For anencephaly, there was increased risk of 2.97 (95% CI: 1.09, 8.12) in the second tertile and 5.54 (95% CI: 1.89, 16.19) in the third tertile, relative to the lowest tertile of maternal serum Pb levels, with an indication of an exposure-response (p for trend: 0.002). Among female infants, there was increased risk of NTD of 6.45 (95% CI: 2.20, 18.95) in the highest tertile, relative to the lowest tertile of maternal serum Pb levels, with exposure-response relationship (p for trend: 0.001). Among male infants, there was increased risk of NTD of 2.16 (95% CI: 1.03, 4.59), and an indication of an exposure-response relationship (p for trend: 0.048).

Pi et al. (2018) investigated the associations between placental Pb concentrations and the risk of orofacial cleft (OFC) defects among 103 cases and 206 controls in northern China. With increasing tertiles of placenta Pb concentrations (p for trend <0.001), there was increased odds of orofacial defects of 3.88 (95% CI: 1.78, 8.42) for those in the second (57.5–96.8 ng/g dry weight) tertile of placenta Pb exposure and 5.17 (95% CI: 2.37, 11.29) for those in the highest (≥96.8 ng/g dry weight) tertile of placenta Pb exposure, compared to the lowest (<57.5 ng/g dry weight). When restricting to those with higher than the median placenta Pb concentration (≥77.2 ng/g), there was increased risk of 3.08 (95% CI: 1.74, 5.47) of OFC defects among 71 cases and 84 controls. However, in a nested case-control study among a subset of participants in the JECS, Takeuchi et al. (2022) did not find increased risk of cleft lip and palate (n = 192 cases and n = 1,920 matched controls) and second trimester maternal blood Pb concentrations (OR: 1.10 [95% CI: 0.55, 2.21]), which controlled for co-exposure to three other metals (Hg, Cd, and Mn) in the multivariate model.

In another study of the JECS, maternal serum Pb samples were collected during mid- and late gestation and were evaluated in association with congenital abdominal malformations (Miyashita et al., 2021). There were 139 cases and 89,134 controls. There were null associations across the quartiles of maternal serum Pb concentrations and any abdominal malformations, with no exposure-response relationship across quartiles (p for trend: 0.233). The null associations persisted for the subtypes of congenital abdominal malformations, but there was an inverse exposure-response relationship observed across the quartiles of maternal serum Pb and omphalocele (p for trend: 0.033).

A single study explored the associations between umbilical cord serum Pb levels and congenital heart disease (CHD) birth defects among 97 case and 201 controls (Liu et al., 2018). In the highest umbilical serum Pb group (≥8.26 ng/mL), the odds of CHD were 1.67 (95% CI: 0.88, 3.17) compared to the those in the lowest umbilical serum Pb group (<6.69 ng/mL). The odds by CHD subtypes were near null, (CIs include 1) (see Table 8-6).

8.3.4.2 Toxicological Studies on Birth Defects

The 2013 Pb ISA did not report any toxicological studies that investigated the effects of Pb on birth defects. The 2006 Pb AQCD described studies that reported Pb-induced birth defects; however, these findings were confounded by maternal toxicity (Dey et al., 2001; Ronis et al., 1996; Flora and Tandon, 1987). Two recent studies published since the 2013 Pb ISA have investigated Pb-induced birth defects in offspring in rodents (Table 8-3). Both studies dosed Wistar rats with 0.2% Pb in the drinking water for varying duration, including dosing starting 30 days prior to gestation and ending the day prior to mating, dosing from GD 0 to PND 21, and dosing from GD 0 to 21 (Rao Barkur and Bairy, 2016; Barkur and Bairy, 2015). Offspring BLLs measured on PND 22 varied between 3.02–3.03 μg/dL for animals from dams dosed prior to gestation, 5.30–5.51 μg/dL for animals from dams dosed during gestation, and 31.6–32.0 μg/dL for animals from dams dosed from the beginning of gestation to lactation day 21. No maternal toxicity was apparent in any of the recent studies, suggesting that the contrast found between the lack of malformations observed in these recent publications and the reported malformations described in the 2006 Pb AQCD may be attributed to a lack of maternal toxicity due to the use of lower doses in more recent studies.

8.3.4.3 Integrated Summary of Effects on Birth Defects

The studies reviewed in the 2013 Pb ISA did not report associations between Pb exposure and NTDs. Among the recent epidemiologic studies, there were inconsistent associations with Pb exposure and NTDs, congenital heart defects, and OFC defects overall. While the associations were generally null for NTDs and CHDs, there was a pattern of positive associations with OFC defects. The inconsistencies in these findings are limited by the different birth defects of interest, the small sample sizes given the rare outcome, timing of Pb exposure (different measurements to estimate exposure during pregnancy), differences in the biomarker tested, and the confounders considered in the analyses. The recent epidemiologic studies controlled for a wide range of potential confounders; however, which was a limitation from the 2013 Pb ISA. Further, some studies considered co-exposure to other metals and differences by infant sex. Some previous toxicological studies reported that Pb exposure resulted in birth defects in offspring, but it was noted that these studies often used doses so high that maternal toxicity occurred as well. Recent toxicological studies report no effects of Pb on birth defects in offspring and also do not report that maternal toxicity occurred, further supporting that maternal toxicity may have been involved with the birth defects observed in previous studies.

8.3.5 Spontaneous Abortion and Pregnancy Loss and Fetal and Infant Mortality

The 2013 Pb ISA concluded that the toxicological and epidemiologic data provided inconsistent findings for the role of Pb in spontaneous abortions, while there were no available epidemiologic or toxicological studies on the relationship between Pb levels and infant mortality. The recent epidemiologic and toxicological studies examining the relationship between Pb exposure and spontaneous abortion, pregnancy loss, and fetal and infant mortality are summarized in the text below. Study details of the recent epidemiologic studies are included in Table 8-7 and the recent toxicological studies are in Table 8-3.

8.3.5.1 Epidemiologic Studies on Spontaneous Abortion and Pregnancy Loss and Fetal and Infant Mortality

In the 2013 Pb ISA, there was a limited number of epidemiologic studies that examined Pb exposure and spontaneous abortion or pregnancy loss with inconsistent findings. Studies that examine spontaneous abortion or pregnancy loss are difficult to conduct, as many spontaneous abortions or pregnancy losses occur during the first trimester. Women may miscarry before being enrolled in a study and/or women may not have known they were pregnant when they miscarried, further limiting the ability to detect subtle effects, especially if higher Pb exposures do lead to increased risk of early spontaneous abortions or pregnancy loss. In addition, some studies are limited by their retrospective examination of current Pb biomarker levels in relation to previous miscarriages. The epidemiologic studies reviewed in the 2013 Pb ISA had limited sample sizes and little control for potential confounding factors, with some studies including no potential confounders in their analyses. There were no epidemiologic studies of Pb exposure and fetal and infant mortality reviewed in the 2013 Pb ISA and there were no recent PECOS-relevant epidemiologic studies of Pb exposure and fetal and infant mortality.

There were only a few recent epidemiologic studies that evaluated Pb exposure and spontaneous abortion and pregnancy loss. There were inconsistent findings among the studies and no apparent pattern of association by biomarker of Pb exposure. In a recent study, cord blood samples were obtained from 432 infants born in an area with e-recycling (Guiyu) and 99 from an area without e-recycling (Xiamen) in China (Xu et al., 2012). There was an increased risk of 4.20 (95% CI: 3.40, 5.18) of stillbirth rate with cord BLLs comparing infants from the area with e-recycling (Guiyu) compared to infants from the area without e-recycling (Xiamen). In a recent cohort study, couples (n = 344) were prospectively followed to explore the relationship between blood Pb concentrations at enrollment and with pregnancy followed to estimate the risk of incident of pregnancy loss (Louis et al., 2017). Each participant's blood Pb concentration and time to pregnancy loss was modeled individually and as a couple. In the individual partner models, there was no increased risk of pregnancy loss for female partner blood Pb (hazard ratio [HR]: 1.01 [95% CI: 0.82, 1.25]) or male partner blood Pb (HR: 0.95 [95% CI: 0.77, 1.17]). In the couple-based model, the associations were unchanged (female partner HR: 1.01 [95% CI: 0.80, 1.28] and

male partner HR: 0.96 [95% CI: 0.77, 1.22]). Among a cohort of 166 women in Iran, there was no increased risk (OR: 1.08 [95% CI: 0.98, 1.20]) of spontaneous abortion with maternal BLLs in early pregnancy (Vigeh et al., 2021). In another prospective cohort among women seeking treatment at a fertility clinic in Turkey, blood Pb concentrations were assessed in association with ongoing pregnancy (Tolunay et al., 2016). The study participants were categorized into patients with ongoing pregnancy (n = 20) and patients who experienced assisted reproductive technology (ART) failure, miscarriage, or biochemical pregnancy (n = 81). There was a 2.2% lower risk (relative risk [RR]: 0.978 [95% CI: 0.957, 0.999]) for ongoing pregnancy for each 1 μg/dL higher blood Pb concentration. Among a cohort of 1,184 women undergoing assisted reproductive therapy in China, associations between maternal serum Pb concentrations and spontaneous abortion before gestational week 12 were evaluated (Li et al., 2022). There was an increased risk of 1.39 (95% CI: 1.02, 1.91) of spontaneous abortion before gestational week 12 with increasing maternal Pb serum levels. When categorized into tertiles, the associations between maternal Pb serum levels and spontaneous abortion before gestational week 12 were null.

8.3.5.2 Toxicological Studies on Spontaneous Abortion and Pregnancy Loss and Fetal and Infant Mortality

The 2013 Pb ISA did not report any toxicological studies that investigated the effects of Pb on offspring mortality at any stage of development. Some studies that investigated the effects of Pb on offspring mortality were summarized in the 2006 Pb AQCD. Overall, these studies found that gestational exposure increased pregnancy loss and implantation loss (BLLs >32 μg/dL) (Pinon-Lataillade et al., 1995; Singh et al., 1993; Piasek and Kostial, 1991; Lögdberg et al., 1987). Some recent studies have also investigated the effects of Pb exposure on offspring mortality (Table 8-3). However, recent studies reported that Pb did not have effects on measures of pre- or postnatal mortality, including litter size. Rodent studies that dosed prior to and during gestation reported no increase in stillbirth or decrease in number of pups born to treated dams (Saleh et al., 2018; Rao Barkur and Bairy, 2016; Barkur and Bairy, 2015; Weston et al., 2014; Cory-Slechta et al., 2013; Betharia and Maher, 2012). BLLs, sources (e.g., BLLs from dams or BLLs from offspring), and times of measurement were variable between these studies (0.0318–27.7 μg/dL; GD 20–PND 60), but in general, BLLs in recent studies were lower than those reported in previous studies. The contrast in the effects of Pb exposure on offspring mortality observed between previous studies and recent studies may be attributed to the lower BLLs achieved in recent studies compared to the higher BLLs in previous studies.

Postnatal offspring mortality was also investigated in some rodent studies, and some studies reported on measures of offspring mortality that included postnatal death and survival until certain timepoints after birth (e.g., weaning). These studies also did not report any effects of Pb exposure on postnatal survival. Most studies utilized dosing paradigms that dosed before or during gestation (Barkur and Bairy, 2015; Betharia and Maher, 2012) and reported BLLs at different times postnatally (PND 2–60; 0.0318 μg/dL–5.30 μg/dL) with BLLs tending to be lower in time points with the longest amount of time

since cessation of exposure. Some studies utilized a dosing paradigm that exclusively exposed animals postnatally (Barkur and Bairy, 2015; Graham et al., 2011). In agreement, these studies also reported no effects of offspring mortality during postnatal time points (PND 4–29; BLLs 3.27–26.65 μg/dL).

8.3.5.3 Integrated Summary of Effects on Spontaneous Abortion and Pregnancy Loss and Fetal and Infant Mortality

The 2013 Pb ISA reported inconsistent findings from the epidemiologic studies on Pb exposure and spontaneous abortion and pregnancy loss. The findings from recent epidemiologic studies on Pb exposure and spontaneous abortion and pregnancy loss were also inconsistent. A single study reported increased risk of stillbirth with cord blood Pb. While recent cohort studies among healthy participants did not find increased risk of pregnancy loss or spontaneous abortion, women seeking treatment from a fertility clinic had increased risk of spontaneous abortion before gestational week 12 or decreased risk of an on-going pregnancy. The women seeking fertility treatment that were recruited as participants may be different from those in the general population, limiting the generalizability of the results as the study populations may not be representative of the general population as they have already been diagnosed and are seeking treatment for fertility issues. However, early pregnancy loss is more likely to be ascertained from women seeking treatment at fertility clinics. Previous toxicological studies reported increased rates of pregnancy loss and implantation loss in animals dosed with Pb during gestation. This contrasts with more recent literature which did not report any effect of Pb on pre- or postnatal offspring mortality. Although not always consistent, BLLs were generally lower in recent toxicological literature when compared to previous literature, possibly explaining the observed contrast in results.

8.3.6 Placental Function

In the 2013 Pb ISA, there were no epidemiologic or toxicological studies available that evaluated Pb concentrations and associations with placenta function. Recent epidemiologic and toxicological studies evaluating the association between Pb exposure and placental function are limited. The epidemiologic studies were cross-sectional studies. Study details for the recent epidemiologic studies are included in Table 8-8 and the toxicological studies are included in Table 8-3.

8.3.6.1 Epidemiologic Studies on Placental Function

In the 2013 Pb ISA, there were no epidemiologic studies available that evaluated Pb concentrations and associations with placenta function. In recent cross-sectional epidemiologic studies, there were different markers of placental function evaluated. One marker of placental function that was evaluated was placental thickness, which can restrict intrauterine fetal growth (Al-Saleh et al., 2014). Maternal BLLs measured at delivery were found to be associated with the risk of placental thickness

below the 10th percentile (OR: 1.64 [95% CI: 1.12, 2.41]). In another study, using a cross-section from the JECS, the relationship between maternal blood Pb collected during the second trimester and placental previa and placenta accreta among 16,019 women was examined (Tsuji et al., 2019). Placenta previa is a condition in which the placenta is attached to the lower uterine segment and completely or partially covers the internal cervix, and when chorionic villi abnormally invade to myometrium, placenta accreta occurs (Tsuji et al., 2019). There was increased odds of placenta previa in the second quartile (4.80–5.95 ng/g) of maternal blood Pb (OR: 2.59 [95% CI:1.40, 4.80]), but null associations the third quartile (5.96–7.44 ng/g) maternal blood Pb (OR: 1.32 [95% CI: 0.66, 2.64]) and fourth quartile (≥7.45 ng/g) maternal blood Pb (OR: 1.34 [95% CI: 0.67, 2.67]). There were null associations for placenta accreta across the blood Pb quartiles (Table 8-8).

8.3.6.2 Toxicological Studies on Placental Function

The 2013 Pb ISA reported a single study that investigated the effects of Pb exposure on placental function. Wang et al. (2009) reported decreased placental weight in Wistar rats along with dose-dependent increasing pathology of cytoarchitecture and cytoplasmic organelles. Focusing on different gestational periods, this study exposed dams to 0.025% Pb via drinking water from either GD 1–10, GD 11–20, or GD 1–20 (maternal BLLs on GD 20 were 26.3, 12.4 μg/dL, and 36.0 μg/dL, respectively). Some recent studies have reported on similar placental outcomes (Table 8-3). Wang et al. (2014) also dosed using the same dosing paradigm (dosing during GD 1–10, GD 11–20, or GD 1–20 via drinking water) and reported that placentae collected from pregnant Wistar rats on GD 20 showed similar dose-dependent decreases in weight and histopathological abnormalities such as vascular congestion, trophoblast degeneration, chorionic villi interstitial edema, irregularity of trophoblast cells in the labyrinth and trophospongium, degeneration of trophoblast cells, and chorionic villi vacuolization (maternal Pb levels on GD 20 were reported to be between 12.4–36.0 μg/dL and varied by dosing window). Two other studies that dosed pregnant Sprague-Dawley rats via gavage from GD 0–20 and similarly reported reduced placental weights (maternal blood Pb on GD 20 was 23.9–27.7 μg/dL) (Saleh et al., 2019; Saleh et al., 2018). Of note is that both of these recent studies by Saleh et al. (Saleh et al., 2019; Saleh et al., 2018) also reported reduced brain weights in dams which is indicative of overt toxicity. Thus, it is possible the altered placental weight could be attributed to overt toxicity experienced by the dams.

8.3.6.3 Integrated Summary of Effects on Placental Function

There were no epidemiologic studies available that evaluated Pb concentrations and associations with placenta function in the 2013 Pb ISA. The recent epidemiologic studies reviewed that assessed the relationship of Pb exposure and placental are limited. The differences in the different markers of placental function make it difficult to judge coherence and consistency across these studies, but these positive associations are an indication that exposure to Pb may result in effects on placental function during

pregnancy. Previous toxicological data on the effects of Pb on placental weight are limited to a single study which reported decreased placental weight and histological alterations. Recent studies also reported that dams dosed with Pb had reduced placental weight, but of note is that these studies also reported reduced brain weight in dams, suggesting that overt toxicity may have occurred and could be related to the observed reductions in placental weight.

8.3.7 Other Pregnancy and Birth Outcomes

There were several recent studies that evaluated associations between Pb exposure and other pregnancy and birth outcomes in the epidemiologic and toxicological literature. More specific study details for the epidemiologic studies, including Pb levels, study population characteristics, potential confounders, and select results from these studies are highlighted in Table 8-9. Specific study details for the toxicological studies are provided in Table 8-3.

8.3.7.1 Epidemiologic Studies on Other Pregnancy and Birth Outcomes

There were several recent studies with other outcomes related to pregnancy and birth. More specific study details, including Pb levels, study population characteristics, potential confounders, and select results from these studies are highlighted in Table 8-9. In studies of other pregnancy and birth outcomes, maternal Pb blood concentrations were associated with high levels of leptin, a fetal marker of metabolic function (Ashley-Martin et al., 2015a); and cord blood Pb concentrations were negatively associated with cord blood relative telomere length (rTL) (Herlin et al., 2019). However, there were null associations in several other studies evaluating Pb exposure and outcomes related to pregnancy and birth. There was a null association between maternal serum Pb levels and nuchal translucency, which is the subcutaneous space in the fetal neck and is visible with ultrasound imaging in the first trimester (Liao et al., 2015). Increased nuchal translucency thickness in the first trimester has been reported to be a risk factor for chromosomal abnormalities, genetic syndromes, congenital heart defects, structural abnormalities, intrauterine infection, neurodevelopmental delay, and fetal demise (Liao et al., 2015). There was null associations between maternal blood Pb concentrations and thymic stromal lymphopoietin (TSLP) and interleukin-33 (IL-33), which are biomarkers of fetal immune system (Ashley-Martin et al., 2015b); maternal blood Pb concentrations and elevated cord blood concentrations of immunoglobulin E (IgE) (Ashley-Martin et al., 2015b); and maternal blood Pb and markers of fetal metabolic function (low leptin, low adiponectin, and high adiponectin) (Ashley-Martin et al., 2015b). Additionally, there were inconsistent associations between maternal BLLs during pregnancy and secondary sex ratio. Among participants in the ALSPAC in the United Kingdom, Taylor et al. (2014) reported no associations among quintiles of maternal Pb levels during the first trimester of pregnancy and secondary sex ratio (odds of having a male child). Among the participants of the Longitudinal Investigation of Fertility and the Environment (LIFE) cohort, there were associations with secondary sex ratio (ratio of live male to female

births, reflecting a male excess) and both maternal and parental blood samples were measured for Pb at baseline (before pregnancy) (Bloom et al., 2015). However, Tatsuta et al. (2022b) reported increased odds of male births (secondary sex ratio) of 1.279 (95% CI: 1.224, 1.336) in the highest quintile of maternal blood Pb among a subset of participants in the JECS.

8.3.7.2 Toxicological Studies on Other Pregnancy and Birth Outcomes

The 2013 Pb ISA summarized a single study reporting on other birth outcomes such as sex ratio. Dumitrescu et al. (2008a) reported an increased female:male ratio in offspring born to Wistar rats that were dosed with 100 or 150 ppb of Pb in the drinking water starting 3 months prior to mating and continuing until birth. This study did not report on BLLs in dams or offspring, resulting in more challenges when comparing this study to more recently published studies (Table 8-3). Weston et al. (2014) was the only recent study to report an effect of Pb exposure on the sex ratio of pups born to exposed dams. In agreement with Dumitrescu et al. (2008a), Weston et al. (2014) reported that Long-Evans rats dosed starting 76 days prior to mating and continuing through birth gave birth to female skewed litters when compared to control. However, it is worth noting that in Weston et al. (2014) control litters had unusually high numbers of males that resulted in a 1.5 male:female ratio of pups born, whereas Pb-treated litters had a more even distribution that resulted in a ratio closer to 1:1 (BLLs were 14.6 and 15.7 μg/dL in female and male pups, respectively, on PNDs 5–6). Other recent studies contrast with these studies and report no effects on sex ratio in Pb-treated females. One study using a dosing paradigm similar to the two studies above (exposure beginning 2 months prior to dosing and continuing through birth) reported no effects of Pb on sex ratio (BLLs 12.12 μg/dL in dams at weaning) in C57BL/6 mice (Cory-Slechta et al., 2013). Similarly, Tartaglione et al. (2020) dosed Wistar rats from 4 weeks prior to mating through birth and reported no changes in sex ratio (BLLs 25.5 μg/dL on PND 23 in pups). Additional studies in rats dosed females from the beginning of pregnancy through birth and also reported no changes in sex ratio (BLLs 6.68–9.03 μg/dL in pups taken at ages PND 2 and PND 28 in (Betharia and Maher, 2012) and (Baranowska-Bosiacka et al., 2013), respectively). With the only recent study reporting alterations in sex ratio also reporting unusual sex ratios in the control group, the effects of Pb exposure on sex ratio is equivocal.

8.3.7.3 Integrated Summary of Effects on Other Pregnancy and Birth Outcomes

There was a small body of recent epidemiologic studies across various other pregnancy and birth outcomes; however, the small number of studies limits the ability to judge coherence and consistency across these studies, although the associations reported demonstrate that Pb exposure could result in physiological responses that contribute to adverse pregnancy and birth outcomes, such as markers of fetal metabolic function, fetal immune system biomarkers, and rTL. Toxicological evidence regarding other pregnancy and birth outcomes are equivocal. While the 2013 Pb ISA reported a study that found that Pb

exposure led to female-skewed litters, a few recent studies reported no effects of Pb on the ratio of male to female pups born to Pb-exposed dams.

8.4 Effects on Development

The 2013 Pb ISA (U.S. EPA, 2013) concluded that the collective body of evidence integrated across epidemiologic and toxicological studies, based on the findings of delayed pubertal onset among males and females, was sufficient to conclude that there is a causal relationship between Pb exposure and developmental effects. The current epidemiologic and toxicological studies continue to support associations between Pb exposure and developmental effects, particularly the delayed onset of puberty in both males and females. This section does not cover associations between Pb exposure and neurodevelopmental outcomes, which are discussed in detail in Appendix 3 Nervous System Effects. The recent epidemiologic and toxicological studies of Pb exposure and effects on development are detailed in the following sections. The developmental endpoints in subsequent sections are based on postnatal growth, bodyweight, and stature; puberty among females; and puberty among males.

8.4.1 Effects on Postnatal Growth

The recent epidemiologic and toxicological studies that examine the relationship between Pb exposure and postnatal growth are detailed below. More specific study details for the epidemiologic studies, including Pb levels, study population characteristics, potential confounders, and select results from these studies are highlighted in Table 8-10. Specific study details for the toxicological studies are provided in Table 8-11.

8.4.1.1 Epidemiologic Studies on Postnatal Growth

The 2013 Pb ISA found inconsistent results between Pb exposure and postnatal growth. Longitudinal epidemiologic studies had inconsistent findings regarding the association between Pb levels and postnatal growth. There were further inconsistencies in the findings of the cross-sectional studies evaluated. While multiple cross-sectional studies reported an association between Pb levels and impaired growth, several other cross-sectional studies did not report associations between Pb and growth. The inconsistencies across the studies may be due to study design and differences in the timing of exposure to Pb (e.g., prenatal, at delivery, or postnatal). However, the longitudinal studies were controlled for multiple potential confounders, such as age and parity.

There were multiple recent epidemiologic studies that evaluated the relationship between Pb exposure and postnatal growth. Overall, there were negative associations between Pb exposure and

specific postnatal growth outcomes among the cross-sectional studies. However, among cohort studies, there were some inconsistencies in the associations of Pb exposure and different postnatal growth outcomes. These inconsistencies in the cohort studies may be due to differences in the timing of when Pb exposure was measured, the biomarker of Pb exposure, and the timing of the outcome.

Among the other cross-sectional studies of Pb exposure and postnatal growth, there were consistent negative associations. In a National Health and Nutrition Examination Survey (NHANES) (2013–2016) analysis of 6–11-year-old children (n = 1,634), there were negative associations between an IQR difference in blood Pb concentrations (median: 0.5 μg/dL) and standing height (β: −3.116 cm [95% CI: −5.03, −1.202]), waist circumference (WC; β: −5.742 cm [95% CI: −8.769, −2.715]), upper arm length (β: −1.068 cm [95% CI: −0.625, −0.512]), and BMI (β: −2.092 kg/m^2 [95% CI: −3.227, −0.957]) (Signes-Pastor et al., 2021). Among male participants, the negative associations persisted with postnatal growth outcomes. Among female participants, there were negative associations with BMI, WC, and upper arm length, but null associations with standing height. Similarly, in a study of primary school children aged 7–11 years in China, there were negative associations with concurrently measured BLLs (median: 2.61 μg/dL) and height (β: −3.21 cm [95% CI: −4.24, −2.17]), weight (β: −1.96 kg [95% CI: −3.11, 0.82]), bust circumference (β: −2.77 cm [95% CI: −3.79, −1.76]), and waistline (β: −3.65 cm [95% CI: −4.78, 2.52]); however, there was a null associations with BMI (β: 0.20 kg/m^2 [95% CI: −0.65, 0.25]) (Kuang et al., 2020).

When standardizing postnatal growth metrics by Z-score, the associations with Pb exposure were mixed, even with all median BLLs across studies less than 5 μg/dL (range: 0.663–4.6 μg/dL). In a cross-sectional study, among children ≤6 years of age (n = 1,678) in China, there were negative associations between children's $\log_{10}$-BLLs and weight for age Z-score (WAZ) (β: −0.33 [95% CI: −0.56, −0.11]) and height-for-age Z-score (HAZ) (β: −0.38 [95% CI: −0.63, −0.14]), but null associations with BMI-for-age Z-score (BMIZ) (Zhou et al., 2020). When the BLLs were grouped by tertiles, the children in the highest tertile (>5 μg/dL) had lower WAZ (β: −0.42 [95% CI: −0.62, −0.23]), lower HAZ (β: −0.36 [95% CI: −0.58, −0.15]), and lower BMIZ (β: −0.29 [95% CI: −0.50, −0.07]) than those in the lowest tertile (<2.5 μg/dL). The patterns of association held when stratified by child's sex (see Table 8-10). Among children ranging in age from 8 to 23 months in South Korea, BLLs were associated with post-birth weight gain (WAZ-BWZ, or the difference of the WAZ at the time of the study and BWZs) (β: −0.238 [−0.391, −0.085], standard error [SE]: 0.078) and current HC for age Z-scores (HCAZs; β: −0.213 [−0.366, −0.06], SE:0.078) (Choi et al., 2017). However, among participants in the Canadian MIREC Child Development Plus Study, there were no associations reported between blood Pb measured at 2 and 5 years of age and HAZ, WAZ, or BMIZ overall or when stratified by child's sex (Ashley-Martin et al., 2019).

Multiple cohort studies examined the relationship between Pb exposure at different time periods (prenatally and/or at different time periods during childhood) with growth metrics, mainly height and weight. Among the cohort studies that measured Pb in cord blood, there were inconsistent associations. While a study among children in Krakow, Poland found no associations with change in mean height over

a 9-year follow-up period (Jedrychowski et al., 2015), a study in the Children's Health and Environmental Chemicals in Korea (CHECK) study, reported positive associations with Z-scores for weight and BMI at 24 months of age (weight β: 0.717 [95% CI: 0.195, 1.239] and BMI β: 0.695 [95% CI: 0.077, 1.313], respectively) (Kim et al., 2017). However, there were no associations between cord blood Pb and the Z-scores of the child's weight, height, or BMI at any other time point (see Table 8-10 for details). When stratified by children's sex, cord blood Pb was positively associated with an increase of birth height (β: 0.017 [95% CI: 0.003, 0.031]) and a decrease of PI at birth (β: −0.055 [95% CI: −0.103, −0.006]) in boys, but not in girls.

Among participants (n = 1,150) in the Mothers' and Children's Environmental Health (MOCEH) study in South Korea, maternal BLLs at delivery were negatively associated with Z-scores of weight for age (β: −0.33 [95% CI: −0.53, −0.13]) and length for age (β: −0.30 [95% CI −0.53, −0.08]) at 24 months, meaning that a 1-μg/dL increase in late pregnancy Pb levels decreased weight and length at 24 months by 0.33 kg and 0.30 cm, respectively (Hong et al., 2014). However, there were no associations between maternal BLLs in early pregnancy (before 20 weeks gestation) and cord blood Pb with weight and length (Table 8-10).

Several cohort studies conducted in Mexico measured Pb exposure during pregnancy in maternal blood, cord blood, and maternal bone and various postnatal growth outcomes. Renzetti et al. (2017) investigated how Pb exposure during pregnancy is associated with children's growth outcomes, including height, weight, BMI, and percentage body fat, measured between ages 4–6 years old in a Mexico City pregnancy cohort (PROGRESS). Maternal blood Pb was measured during the second and third trimester of pregnancy, as well as at delivery. Cord blood was measured at delivery. Bone Pb levels in the tibia and patella were also assessed in mothers as a long-term biomarker 1 month postpartum. There were negative associations between maternal third trimester BLLs and height-for-age (β: −0.10 [95% CI: −0.19, −0.01]) and weight for age (β: −0.11 [95% CI: −0.22, −0.003]), but there were no associations between any other marker of Pb exposure (maternal second trimester blood, cord blood Pb, maternal blood at delivery) and height-for-age, weight for age, BMI, or percentage of body fat (see Table 8-10). In the Early Life Exposure in Mexico to Environmental Toxicants (ELEMENT) project, Liu et al. (2019a) assessed Pb exposure in maternal bone (as a proxy for cumulative fetal exposure) at 1 month postpartum and also in blood samples from children annually from 1 to 4 years in association with BMIZ, WC, sum of skinfolds, and body fat percentage in 248 children aged 8–16 years. Maternal patella Pb levels were associated with lower child BMIZ (β: −0.02 [95% CI: −0.03, −0.01]), WC (β: −0.12 cm [95% CI: −0.22, −0.03]), sum of skinfolds (β: −0.29 mm [95% CI: −0.50, −0.08]), and body fat percentage (β: −0.09% [95% CI: −0.17, −0.01]). However, there were no associations detected from the postnatal exposure period (blood samples in children). In another study, children born between 1994 and 2005 in Mexico City had Pb exposure measured in maternal patella Pb concentrations, a marker of prenatal period exposure, and from infant and childhood measured in blood at birth to 24 months and 30–48 months (Afeiche et al., 2012). Among infants with BLL exceeding the median (4.5 μg/dL), there was a decrease in height of 0.84 cm (95% CI: −1.43, −0.26) compared to children with a level below the median. There were no associations between

prenatal Pb or childhood Pb and height and there were no associations with BMI at any time point (prenatal, infancy, or childhood). In cohort of Mexican children aged 6–8 years old, growth (height, HAZ, and knee height) were assessed in association with BLLs at baseline, after 6 months, and 12 months (Kerr et al., 2019). Additionally, as BLLs may differ by the aminolevulinic acid dehydratase (ALAD) genotype, the authors compared children with the $ALAD_{1–2/2–2}$ genotype to children with the $ALAD_{1–1}$ genotype. There were negative associations with height (β: −0.11 cm [95% CI: −0.18, −0.04]), knee height (β: −0.04 cm [95% CI: −0.07, −0.02]), and HAZ (β: −0.02 cm [95% CI: −0.03, −0.01]). Children with $ALAD_{1–1}$ had decreased height, knee height, and HAZ, while children with the $ALAD_{1–2/2–2}$ had reduced knee height and HAZ, but not height. There were no associations between BLLs and growth at 6- or 12-month follow-up reported, irrespective of ALAD genotype. This epigenetic study proposes a potential mechanistic pathway of BLLs differing by genotypes and the associations with growth metrics during child developmental periods.

There were several studies that explored the associations between Pb exposure and postnatal growth specifically by sex. In a study by Burns et al. (2017), associations of BLLs were assessed with longitudinal age-adjusted height (HAZ) and BMI (BMIZ) among male participants in the Russian Children's Study. Over 10 years of follow-up, after covariate adjustment, boys with higher (≥5 μg/dL) BLLs compared with lower BLLs were shorter (adjusted mean difference in HAZ: −0.43 [95% CI −0.60, −0.25]), translating to a 2.5 cm lower height at age 18 years. The decrement in height for boys with higher BLLs was most pronounced at 12 to 15 years of age (interaction p: 0.03). However, boys with higher BLLs were leaner (adjusted mean difference in BMIZ: −0.22 [95% CI: −0.45, 0.01]). Deierlein et al. (2019) used data from the Breast Cancer and the Environment Research Program to investigate associations of childhood blood Pb concentrations and anthropometric measurements among a multi-site, multiethnic cohort of girls (n = 683). Blood Pb concentrations were collected before 10 years of age and height, BMI, WC, percent body fat was measured between 7–14 years of age. There were decreases in height (range: −2.0 to −1.5 cm), BMI (range: −0.9 to −0.7 kg/m^2), WC (range: −3.0 to −2.2 cm), percent body fat (range: −2.9 to −1.7%) among girls ages 7 through 14 with BLLs of ≥1 μg/dL compared to <1 μg/dL (Table 8-10).

There were a limited number of studies that examined stunting with exposure to Pb in children. A single cross-sectional study in a subset of participants in the Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development (MAL-ED) study in Bangladesh reported increased odds of stunting (OR: 1.78 [95% CI: 1.07, 2.99]) and being underweight (OR: 1.63 [95% CI: 1.02, 2.61]) with elevated (≥5 μg/dL) BLLs, but not wasting (OR: 1.18 [95% CI: 0.64, 2.19]) (Raihan et al., 2018). In a cohort study among rural Bangladeshi children, Pb exposure was assessed from umbilical cord blood at birth and blood Pb at 20–40 months of age with stunting (Gleason et al., 2016). The odds of stunting at 20–40 months was 1.12 (95% CI: 1.02, 1.22) per each 1 μg/dL increase in childhood BLL; however, there was no association was found between cord BLL and risk of stunting (OR: 0.97 [95% CI: 0.94–1.00]).

8.4.1.2 Toxicological Studies on Postnatal Growth

The 2013 Pb ISA summarized several current studies and several from the 2006 Pb AQCD that reported on the effects of Pb on offspring bodyweight and size. The reported effects were fairly consistent, and nearly all studies reported reductions in bodyweight of offspring exposed to Pb during developmental periods. Gestational exposure to Pb proved to be sufficient to reduce offspring bodyweight and body length in rodent studies (Massó-González and Antonio-García, 2009; Wang et al., 2009; Teijón et al., 2006; Ronis et al., 2001; Ronis et al., 1998a; Ronis et al., 1998c; Ronis et al., 1996). The only study in the 2013 Pb ISA that did not report a reduction in bodyweight was Leasure et al. (2008), which reported that bodyweight increased at 1 year of age in male C57BL/6 offspring that were dosed starting prior to conception and ending on PND 10.

Many recent publications have also reported on the effects of Pb-induced changes in bodyweight of offspring (Table 8-11). In contrast with the 2013 Pb ISA, only some studies reported that Pb exposure affected offspring bodyweight. One study that dosed Sprague-Dawley rat pups with 1 or 10 mg/kg/d directly via gavage from PND 4 to 28 reported that bodyweight was decreased in male offspring in both groups on PND 26 (BLLs 3.27–12.5 µg/dL on PND 29) (Graham et al., 2011). Another study dosed Wistar rat dams via drinking water (30 mg/L Pb) from birth until weaning, at which point offspring were weaned onto the same dosage of Pb in their drinking water as their dam until outcome assessment (de Figueiredo et al., 2014). In agreement with Graham et al. (2011), this study by de Figueiredo et al. (2014) reported reductions in bodyweight of male Wistar rat offspring on PND 60 that were exposed from conception through PND 60, although female offspring were not evaluated (BLLs 7.2 µg/dL on PND 60). Similarly, one study exposed CD-1 mice offspring to Pb via dam drinking water (27 or 109 ppm Pb) from PND 1 to 21 and reported reductions in body weight of pups on PNDs 11, 15, and 19 (BLLs 19.57–29.16 µg /dL on PND 18) (Duan et al., 2017). In contrast, one study conducted in Sprague-Dawley rats that were exposed from GD 0 to PND 21 via the dam's drinking water (10 µg/mL Pb) reported increased bodyweight in offspring on PND 1 and increased bodyweights in females only on PND 49 and 56 (BLLs 9.03 µg/dL on PND 2, 0.976 µg/dL on PND 25, 0.0318 µg/dL on PND 60 in pups) (Betharia and Maher, 2012).

Contrasting these recent studies and previous studies discussed in the 2013 Pb ISA are several studies that reported no effects of Pb exposure on bodyweight in offspring. Studies in both mice and rats utilizing dosing paradigms that begin exposure prior to conception (Albores-Garcia et al., 2021; Zhao et al., 2021; Sobolewski et al., 2020; Rao Barkur and Bairy, 2016; Barkur and Bairy, 2015) reported no effects of Pb exposure on bodyweight at any time point measured (BLLs ranged between 0.4–15.7 µg/dL across various time points and studies). Similar null findings were reported in other rodent studies utilizing other exposure windows including gestational (Rao Barkur and Bairy, 2016; Barkur and Bairy, 2015), lactation (Rao Barkur and Bairy, 2016; Barkur and Bairy, 2015; Basgen and Sobin, 2014), and a combination thereof (Basha and Reddy, 2015; Barkur et al., 2011) (BLLs ranged between 2.74–26.86 µg/dL).

8.4.1.3 Integrated Summary of Effects on Postnatal Growth

Overall, among the recent epidemiologic studies, there were negative associations between Pb exposure and specific postnatal growth outcomes among the cross-sectional studies. However, among cohort studies, there were some inconsistencies in the associations of Pb exposure and different postnatal growth outcomes. These inconsistencies in the cohort studies may be the result of the differences in the timing of Pb exposure measurement (prenatally or postnatally) and the biomarker to measure Pb exposure (maternal blood, maternal bone, cord blood). Additionally, there was limited evidence that there are potential differences in the associations between Pb exposure and growth metrics between males and females. There is also limited evidence of potential epigenetic effects of BLLs differing by genotypes and the associations with growth metrics during child developmental periods. While cross-sectional studies are limited by the concurrent measurement of Pb and postnatal growth outcomes, there were several well-designed cohort studies that support the associations of Pb exposure and decreased growth. These studies accounted for a wide range of potential confounders, including co-exposure to other metals; however, some studies did not consider prenatal growth (birth weight, birth length) or maternal characteristics (height, weight, BMI, smoking), which could potentially influence postnatal growth. While there was a small body of literature examining the associations between stunting and exposure to Pb, there was consistent increased odds in stunting with Pb exposure. Previous toxicological studies tended to report reductions in postnatal weight of offspring exposed to Pb; however, recent literature is inconsistent. Some studies reported reductions of offspring weight following exposure to Pb in prenatal or early postnatal life, while others report no effects of Pb on postnatal weight in offspring. Discerning reasons for the observed inconsistencies is difficult because studies still reported results that contrasted with other studies that used similar dosing windows, doses, and animal species.

8.4.2 Effects on Puberty among Females

The recent epidemiologic and toxicological studies examining the relationship between Pb exposure and effects on puberty among females are summarized in the text below. Study details of the recent epidemiologic studies are included in Table 8-12.

8.4.2.1 Epidemiologic Studies on Puberty among Females

The epidemiologic studies reviewed in the 2013 Pb ISA found consistent associations between higher concurrent blood Pb and delayed pubertal development in females. The association persisted in populations with mean and/or median concurrent BLLs of 1.2–9.5 μg/dL. While most of the studies had large sample sizes and controlled for potential confounders, they were cross-sectional study designs, so there are some uncertainties regarding temporality between Pb exposure and pubertal onset; additionally,

these studies were not able to separate out the influence of past Pb exposure, including prenatal exposures, from more recent exposures.

The recent epidemiologic studies assessing the associations between blood Pb and onset of puberty among females used different markers of puberty. A single cross-sectional study of NHANES (2011–2012) data evaluated the associations between blood Pb concentration and circulating serum total testosterone levels in 6–19-year-old children and adolescents (Yao et al., 2019). Testosterone is a principal sex hormone needed for normal physiologic processes during all lifestages and for females, testosterone is of crucial importance for bone density and necessary for normal ovarian and sexual function, libido, energy, and cardiovascular and cognitive functions (Yao et al., 2019). While there were no associations between blood Pb and testosterone in female children (6–11 years), serum testosterone levels were 14.85% greater (95% CI: 0.83%, 30.81%) in female adolescents (12–19 years) in the lowest quartile of BLLs (≤0.35 μg/dL) than those in the highest quartile (>0.63 μg/dL) in the fully adjusted model. For both female children and adolescents, there were no significant trends with increasing quartiles of exposure (p for trend 0.63 and 0.08, respectively).

In a cross-sectional study in Poland, two different groups of adolescent girls aged 7–16 years (n = 436 in 1995 and n = 361 in 2007) were assessed for effects of Pb on the age at attaining menarche (Sławińska et al., 2012). While the associations between blood Pb and menarche from either group of girls were null (1995 OR: 0.70 [95% CI: 0.27, 1.85] and 2007 OR: 0.31 [95% CI: 0.09, 1.06]), the patterns of association between these two times periods suggest delayed menarche. In another cross-sectional study among school-age girls (n = 490) in Poland, there was a pattern of decreased odds between blood Pb and age at menarche, whether controlled for BMI (OR: 0.54 [95% CI: 0.26, 1.13]), percentage of body fat (OR: 0.52 [95% CI: 0.25, 1.08]), or sum of skinfolds (OR: 0.53 [95% CI: 0.26, 1.10]) (Gomula et al., 2022). While these cross-sectional studies reported imprecise associations, the pattern of association is important to note.

Three successive, cross-sectional Flemish Environment and Health Studies (FLEHS I, FLEHS II, and FLEHS III) were conducted among adolescents (aged 14–15 years old) in Belgium between 2002–2015 (De Craemer et al., 2017). Female puberty markers of age at menarche, breast development, and pubic hair development were evaluated in relation to blood Pb exposure. There was a consistent pattern of delayed age at menarche across the three study cohorts (FLEHS I OR: 0.039 [95% CI: −0.072, 0.15]; FLEHS II OR: 0.257 [95% CI: 0.091, 0.424]; FLEHS III OR: 0.126 [95% CI: −0.021, 0.273]). The associations between blood Pb and breast development were inconsistent, but there was indication of delayed development among FLEHS I participants (OR: 0.798 [95% CI: 0.653, 0.969]). There were no associations between blood Pb and development of pubic hair among adolescent females across the three study cohorts.

Multiple cohort studies examined the associations between Pb exposure and puberty in females. These studies used different biomarkers of exposure and different markers of puberty (Liu et al., 2019b; Jansen et al., 2018; Nkomo et al., 2018). Cord BLLs and BLLs at age 13 were evaluated in association

with puberty progression (development of pubic hair and development of breasts) among 684 females in the Birth to Twenty Plus (BT20+) birth cohort in South Africa (Nkomo et al., 2018). In females with elevated BLLs (≥5 µg/dL) at age 13, there was lower level of breast development (RR: 0.45 [95% CI: 0.29, 0.68]) and slower progression of pubic hair development (RR: 0.46 [95% CI: 0.27, 0.77]), but there were no associations between cord blood Pb and pubic hair or breast development at age 13. In a cohort of Mexican children, cumulative blood Pb from 1–4 years old was associated with delayed breast development (OR: 0.96 [95% CI: 0.92, 0.99]) and delayed pubic hair development (OR: 0.95 [95% CI: 0.92, 0.99]), but maternal patella Pb and maternal tibia Pb were not associated with either breast or pubic hair development in girls between 9–18 years old (n = 283) (Liu et al., 2019b). Additionally, the highest tertile of maternal patella Pb and the second tertile of cumulative blood Pb from 1–4 years of age was associated with delayed menarche. In a subset of the ELEMENT project cohort (n = 200), maternal blood was measured during each trimester of pregnancy and daughters (mean age at follow-up assessment 13.8 ± 2.0 years) were asked about the occurrence of their first menstrual cycle (Jansen et al., 2018). Only second trimester maternal BLLs were associated with later age at menarche (HR: 0.59 [95% CI: 0.28, 0.90]).

8.4.2.2 Toxicological Studies on Puberty among Females

There were no recent animal toxicological studies on the effects of Pb on puberty in females. The 2013 Pb ISA reported that one research group Iavicoli et al. (Iavicoli et al., 2006; Iavicoli et al., 2004) observed that mouse offspring exposed to Pb prior to birth and through puberty (BLLs 0.7–13 µg/dL) resulted in a dose-dependent delay in multiple markers of sexual maturation (e.g., vaginal opening, age at first estrus). The latter study by this group utilized a multigenerational dosing paradigm in which they observed delays of pubertal onset in the F_2 generation similar to those seen in the F_1. The 2013 Pb ISA also summarized a study in which Fisher 344 rats were dosed daily via gavage (12 mg/mL Pb) starting 30 days prior to breeding through weaning of the offspring (PND 23), resulting in delayed age at vaginal opening in the offspring (BLLs of dams just prior to breeding averaged 39.8 µg/dL) (Pine et al., 2006). Of particular interest is that the observed delay in vaginal opening was attenuated in offspring that received IGF-1 injections starting on PND 28 until vaginal opening was observed, demonstrating that IGF-1 is a critical element to Pb-induced pubertal onset delays. Reports of delayed puberty due to Pb exposure in the 2013 Pb ISA are consistent with studies in the 2006 Pb AQCD which observed delays in puberty in female Fisher 344 and Sprague-Dawley rats exposed to Pb during gestation and/or lactation (Dearth et al., 2004; Dearth et al., 2002; Ronis et al., 1998c; Ronis et al., 1996).

8.4.2.3 Integrated Summary of Effects on Puberty among Females

There were several markers of puberty among females that were assessed for associations with Pb exposures in the recent epidemiologic studies. Multiple cross-sectional studies and a single cohort study

reported an association between blood Pb and delayed menarche among females, with relevant BLLs (Gomula et al., 2022; Jansen et al., 2018; De Craemer et al., 2017; Sławińska et al., 2012). While these cross-sectional studies reported imprecise associations, the pattern of association is important to note. There was also indication of slower breast development, but the studies assessing breast development were limited (Nkomo et al., 2018; De Craemer et al., 2017). Additionally, there were a limited number of studies that evaluated the development of pubic hair, but these results were inconsistent (Liu et al., 2019b; Nkomo et al., 2018; De Craemer et al., 2017). A single study among NHANES participants reported increased serum total testosterone levels in female adolescents. The recent epidemiologic studies assessing the associations between Pb exposure and puberty among females were limited by the timing of the exposure to Pb and biomarker of exposure (blood, maternal bone, cord blood). However, these studies consider a wide range of confounders, including height, weight, and BMI, and the associations reported demonstrate that Pb exposure could result in physiological responses that contribute to changes in puberty in females.

No recent PECOS-relevant toxicological studies investigated the effects of Pb on puberty. However, studies from the 2013 Pb ISA and the 2006 Pb AQCD provide toxicological evidence that indicates that Pb delays onset of puberty in female rodents. Several studies report delays in pubertal markers such as vaginal opening and first estrus. Of note is that one study, Pine et al. (2006) reported that the observed delay in vaginal opening in Pb-treated animals was attenuated when Pb treated animals were supplemented with IGF-1 starting on PND 28. This strongly suggests that the mechanism through which Pb induces delays pubertal onset in females is dependent on IGF-1 disruption.

8.4.3 Effects on Puberty among Males

The recent epidemiologic and toxicological studies examining the relationship between Pb exposure and effects on puberty among males are summarized in the text below. Study details of the recent epidemiologic studies are included in Table 8-12.

8.4.3.1 Epidemiologic Studies on Puberty among Males

The epidemiologic studies reviewed in the 2013 Pb ISA demonstrated an inverse relationship of Pb on pubertal development among males at low blood Pb (mean and/or median BLLs of 3.0 to 9.5 μg/dL). The studies were mostly cross-sectional, but the findings from these studies were supported by those from a prospective longitudinal study (Williams et al., 2010). Boys with higher (≥5 μg/dL) BLLs at ages 8–9 years old had 24% to 31% reduction of pubertal onset based on testicular volume (TV), genitalia staging, and pubic hair staging (Williams et al., 2010). While temporality of effects is difficult to establish due to the nature of the cross-sectional study design, the larger studies controlled for potential

confounders, with a few studies considering the inclusion of dietary factors, but did not control for other metal exposures that may impact the associations.

In an NHANES (2011–2012) analysis, concurrent BLLs and serum total testosterone levels were measured in 6–19-year-old children and adolescents (Yao et al., 2019). Testosterone is a principal sex hormone needed for the normal physiologic processes during all life stages. In males, testosterone is essential for the development and maintenance of secondary sexual traits, and can also influence bone mass, muscle strength, mood, and intellectual capacity. When comparing the highest quartile of blood Pb to the lowest, there was no association between serum testosterone levels in either male children (β: −13.09% [95% CI: −34.45%, 15.22%]) or male adolescents (β: 6.32% [95% CI: −14.62%, 32.4%]). Among three successive, cross-sectional Flemish Environment and Health Studies (FLEHS I, FLEHS II and FLEHS III) of adolescents in Belgium between 2002–2015, blood Pb was negatively associated with free estradiol (fE2; OR: 0.908 [95% CI: 0.839, 0.983]) and free testosterone (OR: 0.909 [95% CI: 0.828, 0.997]) in FLEHS II, but not in FLEHS I (De Craemer et al., 2017). The associations between blood Pb and estradiol (E2), testosterone, sex hormone binding globulin (SHBG), luteinizing hormone (LH), and follicle stimulating hormone (FSH) were generally null (see Table 8-12). In addition to sex hormones, De Craemer et al. (2017) also evaluated the associations between blood Pb and genital development and pubic hair development among male adolescents. Across the three cross-sectional studies, there was decreased odds of delayed onset of genital development (FLEHS I OR: 0.843 [95% CI: 0.717, 0.99]; FLEHS II OR: 0.697 [95% CI: 0.462, 0.998]; FLEHS III OR: 0.621 [95% CI: 0.388, 0.967]) and pubic hair development (FLEHS I OR: 0.808 [95% CI: 0.686, 0.949]; FLEHS II OR: 0.849 [95% CI: 0.563, 1.365]; FLEHS III OR: 0.515 [95% CI: 0.327, 0.774]).

In the BT20+ birth cohort in South Africa, cord BLLs and blood levels at age 13 were evaluated in association to puberty progression pubic hair development and genital development in 732 males (Nkomo et al., 2018). In males, elevated cord BLLs (≥5 μg/dL) was associated with slower pubic hair development (RR: 0.28 [95% CI: 0.11, 0.74]). There were no associations between cord blood Pb and genital development or BLLs at age 13 with pubic hair development or genital development. Similarly, there were no associations between maternal patella Pb, maternal tibia Pb, and cumulative blood Pb from 1–4 years old and pubertal development (genitalia, pubic hair, and TV) in boys (Liu et al., 2019b).

However, in a longitudinal cohort of boys from the Russian Children's Study, higher BLLs (≥5 μg/dL) measured at age 8–9 years old (baseline) had pubertal onset 7.7–8.4 months later, on average, than those with lower BLLs (<5 μg/dL) (Williams et al., 2019). Boys with higher BLLs at baseline had later adjusted mean age at sexual maturity, with 4.2–5.1 months later attainment compared to boys with lower BLLs. There was a shift in mean age for age at pubertal onset for stage 2 genitalia (G2) of 8.40 months (95% CI: 3.70, 13.10), 8.12 months (95% CI: 3.46, 12.78) for stage 2 pubic hair (P2), and 7.68 months (95% CI: 3.46, 11.90) for TV >3 mL. There was a shift in mean age for age at sexual maturity for stage 5 genitalia (G5) of 4.20 months (95% CI: 0.56, 7.84) and 5.14 months (95% CI: 1.70, 8.58) for TV ≥20 mL, but a null association for stage 5 pubic hair (4.23 months [95% CI: −0.31, 8.77]).

Furthermore, there was no shift in the mean age for duration of pubertal progression for genitalia (G2 to G5), pubic hair (P2 to P5), or TV (>3 mL to ≥20 mL). In a mediation analysis, growth measurements at age 11 were included to better understand what portion of the shift in mean age at sexual maturity was attributable to the effect of BLL on growth. The association of peripubertal BLL with height Z-score (HTZ) at age 11 accounted for 34%–53% of the total effect of BLLs on age at maturity, while BMI Z-score at age 11 only accounted for 6%–23%. In another Russian Children's Study, Fleisch et al. (2013) longitudinally measured serum insulin-like growth factor (IGF-1) to assess the association with childhood BLLs. BLLs were measured at baseline only and IGF-1 levels were only measured during the follow-up periods. Boys were enrolled between the ages of 8–9 years and were prospectively followed, with IGF-1 measurements obtained at two-year follow-up (ages 10–11 years) and at four-year follow-up (ages 12–13 years). The overall mean IGF-1 concentration was 29.2 ng/mL lower (95% CI: −43.8, −14.5) for boys with high BLLs at age 8–9 years (≥5 μg/dL [max is 31 μg/dL]) versus those with lower baseline BLLs (<5 μg/dL) in adolescence among boys.

8.4.3.2 Toxicological Studies on Puberty among Males

There were no recent toxicological studies on the effects of Pb on puberty in males, as was also the case at the time of the 2013 Pb ISA. The 2006 Pb AQCD reported that one study found that prenatal exposure to Pb delayed sexual maturation in a dose-dependent manner in male rats (Ronis et al., 1998c). Specifically, Ronis et al. (1998c) reported that prostate weight (used in this study as a marker of sexual maturation) was reduced in male rat offspring treated with Pb from GD 5 through sacrifice.

8.4.3.3 Integrated Summary of Effects on Puberty among Males

The epidemiologic studies reviewed in the 2013 Pb ISA demonstrated an inverse relationship of Pb on pubertal development among males at low blood Pb (mean and/or median BLLs of 3.0 to 9.5 μg/dL). Overall, the recent epidemiologic studies assessing the associations between Pb exposure and different markers of puberty (hormone levels, pubic hair development, genital development, TV) among males reported more inconsistent findings at low BLLs. Additionally, there were differences in the timing of exposure to Pb and different biomarkers of Pb exposure (maternal blood, maternal bone, cord blood, or concurrent blood). The recent epidemiologic studies were able to consider a wide range of confounders, including height, weight, and BMI, and some studies were conducted among established longitudinal cohorts. No recent toxicological studies reported on the effects of Pb on male puberty. Similarly, the 2013 Pb ISA reported no studies investigating Pb and male puberty. One study reported by the 2006 Pb AQCD investigated the effects of Pb on puberty using prostate weight as a marker of sexual maturity in male rats exposed to Pb starting on GD 5. Treatment with Pb resulted in reductions in prostate weight around the time of puberty, possibly indicating that Pb delayed the onset of sexual maturation in Pb-treated animals when compared to control.

8.4.4 Other Developmental Effects

There were several recent studies that evaluated associations between Pb exposure and other developmental effects in the epidemiologic and toxicological literature. Study details of the recent epidemiologic studies are included in Table 8-13 and the recent toxicological studies are in Table 8-11.

8.4.4.1 Epidemiologic Studies on Other Developmental Effects

There were several recent studies with other outcomes related to developmental effects. In studies of other related to developmental effects, there was a negative association with child blood Pb and mitochondrial DNA copy number (Alegría-Torres et al., 2020); positive associations with maternal Pb exposure and diurnal cortisol rhythms in infants (Tamayo y Ortiz et al., 2016); and lower salivary sialic acid levels (a metric for oral anti-inflammatory potential which may increase the risk of dental caries) (Hou et al., 2020), but no associations between tooth Pb levels (second trimester, third trimester, or postnatal) and alpha diversity metrics (bacterial or fungal), indicators of gut microbiota (Sitarik et al., 2020) or child blood Pb and telomere length (Alegría-Torres et al., 2020).

8.4.4.2 Toxicological Studies on Other Developmental Effects

The 2013 Pb ISA and the 2006 Pb AQCD did not report any studies that investigated the effects of Pb exposure on developmental milestones. However, some recent studies have investigated these outcomes (Table 8-11). One study dosed Wistar dams via drinking water (0.2% Pb) either prior to conception, during gestation only, during lactation only, or during both gestation and lactation and reported that only exposure during both gestation and lactation elicited impacts on developmental milestones (Rao Barkur and Bairy, 2016). Specifically, the age at eye opening was reduced. However, although this exposure paradigm was the only one that produced effects on age at eye opening, it was also the only paradigm that resulted in BLLs higher than 30 µg/dL and reported a BLL of 31.59 µg/dL in pups on PND 22. Rao Barkur and Bairy (2016) also investigated other developmental milestones such as pinna detachment and tooth eruption but reported no Pb-induced changes in either of these outcomes. An additional study investigated the effects of Pb on similar outcomes including eye opening, eye slit formation, fur development, tooth eruption, and pinna detachment, but reported no effects when Wistar dams were dosed via drinking water (0.2% Pb) from GD 6 to 21 (BLLs 11.2 µg/dL in pups on PND 21) (Basha and Reddy, 2015).

8.4.4.3 Integrated Summary of Other Developmental Effects

The recent epidemiologic studies have the potential to provide initial support of potential mechanistic pathways for diurnal cortisol rhythms, lower salivary sialic acid levels, and DNA oxidative

stress damage from Pb exposure among children during developmental periods. However, the small number of studies limits the ability to judge coherence and consistency across the outcomes evaluated in these studies, although the associations with diurnal cortisol rhythms, lower salivary sialic acid levels, and decrease in mitochondrial DNA copy number indicate that Pb exposure could result in physiological responses that may contribute to adverse developmental effects. Recent toxicological studies on other developmental effects of Pb largely pertain to the effects of Pb on developmental milestones of offspring. Of the few toxicological studies available, no effects of Pb on developmental milestones were reported with the only exception being a reduction at the age of eye opening, but this treatment group had BLLs higher than 30 μg/dL.

8.5 Effects on Female Reproductive Function

The 2013 Pb ISA concluded that the relationship observed with female reproductive outcomes, such as fertility and hormone levels in some epidemiologic and toxicological studies was sufficient evidence to conclude a suggestive causal relationship between Pb exposure and female reproductive function. Epidemiologic studies provided information on different exposure periods and support the conclusion that Pb possibly affects at least some aspects of female reproductive function. However, toxicological studies were less supportive for suggesting a causal relationship between Pb exposure and female reproductive function. This may primarily be due to a lack of variety in female reproductive endpoints investigated by studies identified in the literature. The only outcomes reported by PECOS-relevant toxicological studies include litter size, number of litters, and maternal body weight. Subsequently, no evidence was available for outcomes such as cyclicity, female hormones, sex organ histopathology (including ovarian follicular counts), or female fertility indicators (e.g., latency to pregnancy, implantation counts, conception rate). Additionally, the available toxicological evidence was inconclusive, and the only studies that reported effects on female reproductive outcomes also reported Pb-induced reductions in brain weight, indicating the possibility that animals were experiencing overt toxicity from Pb (Saleh et al., 2019; Saleh et al., 2018). The recent epidemiologic and toxicological studies of Pb exposure and female reproductive function are detailed in the following sections.

8.5.1 Effects on Hormone Levels and Menstrual/Estrous Cycle

The recent epidemiologic and toxicological studies examining the relationship between Pb exposure and hormone levels and menstrual/estrous cycle are summarized in the text below. Study details of the recent epidemiologic studies are included in Table 8-14 and the recent toxicological studies are in Table 8-15.

8.5.1.1 Epidemiologic Studies on Hormone Levels and Menstrual/Estrous Cycle

The epidemiologic studies reviewed in the 2013 Pb ISA reported associations between concurrent/closely timed BLLs and hormone levels in female adults. However, while there were changes in hormone levels, there were inconsistencies in the hormones that were evaluated across the different studies. A limitation of some the epidemiologic studies evaluated was the cross-sectional design, which leaves uncertainty regarding Pb exposure magnitude, timing, duration, and frequency that contributed to the observed associations. Additionally, the covariates included in statistical models as potential confounders varied among studies, which could contribute to between study heterogeneity. Another limitation of the epidemiologic studies is that not all of the studies investigated important confounders, such as other metal exposures or smoking. The recent epidemiologic studies are divided into studies on hormone levels and studies on menstrual/estrous cycle. The recent epidemiologic studies on hormone levels in the following section are specific to hormones related to reproductive function and recent epidemiologic studies on other hormones are described in Section 9.4.2 in the Other Health Effects Appendix.

8.5.1.1.1 Epidemiologic Studies on Hormone Levels in Females

There were a few cross-sectional studies that evaluated the associations between Pb exposure and different hormones in females (Lee et al., 2019; Chen et al., 2016; Krieg and Feng, 2011). These studies used population-based surveys to evaluate associations between blood Pb and hormones and found consistent positive associations with FSH in post-menopausal women. In an NHANES (1999–2002) analysis, Krieg and Feng (2011) evaluated serum FSH and LH. Serum FSH slope increased per every $\log_{10}$-blood Pb increase in the post-menopausal women (β: 26.38 [95% CI: 13.39, 39.38]), women who had both ovaries removed (β: 27.71 [95% CI: 1.64, 53.78]), and pre-menopausal women (β: 11.97 [95% CI: 3.27, 20.66]), but serum FSH was not associated with BLLs in pregnant women, women who were menstruating, or women who were taking birth control pills. Serum LH slope increased per every $\log_{10}$-blood Pb increase in the post-menopausal women (β: 11.63 [95% CI: 4.40, 18.86]) and women who had both ovaries removed (β: 20.59 [95% CI: 2.14, 39.04]), but serum LH was not associated with BLLs in the pregnant women, women who were menstruating, women who were taking birth control pills, and pre-menopausal women. In another cross-sectional, population-based survey in China, Chen et al. (2016) examined the associations between blood Pb and total testosterone (tT), E2, and SHBG, in addition to LH and FSH in postmenopausal women (age >55 years). When comparing the highest quartile of blood Pb (>5.98 μg/dL) to the lowest (<2.70 μg/dL), there were positive associations with BLLs and SHBG (β: 0.048, SE: 0.016, $p < 0.01$), FSH (β: 0.046, SE: 0.016, $p < 0.01$), and LH (β: 0.037, SE: 0.016, $p < 0.05$). There were null associations between BLLs and tT or E2. Across the quartiles of blood Pb, there were also positive trends observed with SHBG (p for trend: 0.002), FSH (p for trend: 0.001), and LH (p for trend: 0.026), suggesting a potential linear exposure response between blood Pb and these hormones. In a study of the Korea National Health and Nutrition Examination Survey (KNHANES) (2012–2014), blood

Pb and serum FSH levels were assessed in postmenopausal women (aged 50 or older) (Lee et al., 2019). Serum FSH levels were positively associated with increasing blood log-Pb (β: 2.929 [95% CI: 0.480, 5.377]).

8.5.1.1.2 Epidemiologic Studies on Menstrual/Estrous Cycle

There were no available epidemiologic studies in the 2013 Pb ISA that evaluated Pb exposure with menopause. There are a limited number of studies that examined the relationship between Pb exposure and menopause, and these recent studies reported consistent positive associations. A recent cross-sectional study, NHANES (1999–2010) data was used to examine the associations between blood Pb and menopause among women aged 45–55 years (age range where menopause is likely to occur) (Mendola et al., 2013). In the overall study sample (NHANES 1999–2010), with increasing quartiles of blood Pb, there were increasing odds of menopause. Comparing the lowest BLLs (<1.0 μg/dL), the odds for Q2 through Q4 were 1.7 (95% CI: 1.0, 2.8), 2.1 (95% CI: 1.2, 3.6), and 4.3 (2.6, 7.2), respectively. When adjusting for bone measurements (either bone alkaline phosphatase or femoral neck bone density), the associations were similar. In a subset (n = 434) of the Nurse's Health Study, the associations between bone Pb levels and age at menopause were explored (Eum et al., 2014). Compared with women in the lowest tertile of tibia Pb (<6.5 μg/g), those in the highest tertile (>13 μg/g) were 1.21 years younger at menopause on average (95% CI: −2.08, −0.35; p for trend: 0.006). Women in the highest tertile of tibia Pb had an increased odds of 5.30 (95% CI: 1.42, 19.78; p for trend: 0.006) for early menopause (menopause before age 45) compared with women in the lowest tertile. The associations with early menopause were null across tertiles for patella Pb and BLLs.

8.5.1.2 Toxicological Studies on Hormone Levels and Menstrual/Estrous Cycle

There are no recent animal toxicological studies on the effects of Pb on the menstrual/estrous cycle. The 2013 Pb ISA did not report any studies that investigated the effects of Pb on the menstrual/estrous cycle, however some studies were summarized in the 2006 Pb AQCD. Specifically, studies conducted in non-human primates found that Pb exposure increased menstrual cycle variability, reduced days of menstrual flow, increased cycle length, and reduced progesterone (Franks et al., 1989; Laughlin et al., 1987). However, another study with a lower BLL than the previous studies (<40 μg/dL versus 44–89 μg/dL) did not report an effect on the menstrual cycle in a non-human primate species (Foster et al., 1992). Impacts of Pb on estrous cyclicity were examined in two rat studies that both utilized multiple dosing paradigms to assess the varying impacts Pb exposure may have during different developmental periods. Specifically, one study used the following exposure windows: gestation only, lactation only, gestation and lactation, postnatal (from birth and continued past weaning), and continuous (from the beginning of gestation continued past weaning) (Ronis et al., 1998a). This study reported that offspring in the postnatal and continuous exposure groups had fewer females who were regularly cycling.

The other study was conducted by the same research group and utilized the following dosing windows: post-pubertal (PND 60 to PND 74), pre-pubertal (PND 24 to PND 74), and in utero (GD 5 to PND 85) (Ronis et al., 1996). Rats in the pre-pubertal and in utero exposure paradigm groups experienced estrous cyclicity disruption. While this study seems to indicate that pre-pubertal periods are more sensitive to chemical insult, the previous study by Ronis et al. (1998a) suggests that normal cyclicity is recoverable after cessation of exposure. However, it is worth noting that in both of these studies the BLLs were very high, with a range of 63.2–264 μg/dL for treatment groups that displayed treatment-related effects.

There are no recent animal toxicological studies on the effects of Pb on reproductive hormones. The 2013 Pb ISA reported on a few studies that investigated the effects of Pb on reproductive hormones, but none on cyclicity. Rodent studies reported that gestational and lactational exposure decreased circulating levels of progesterone and E2 (Pillai et al., 2010; Nampoothiri and Gupta, 2008). Dumitrescu et al. (2008b) reported similar findings in adult female Wistar rats that were exposed to Pb for 6 months via drinking water. Dumitrescu et al. (2008b) reported reductions in E2, progesterone, and FSH and increases in LH and testosterone. The 2006 Pb AQCD reports findings from some toxicological studies that show effects of Pb on hormones and cyclicity. Reductions in progesterone were observed in a study wherein monkeys had BLLs of 25 to 30 μg/dL, but no such reductions in progesterone were observed in monkeys with even lower BLLs (10 to 15 μg/dL) (Foster et al., 1996).

8.5.1.3 Integrated Summary of Effects on Hormone Levels and Menstrual/Estrous Cycle

The recent cross-sectional, population-based survey epidemiologic studies found consistent positive associations between blood Pb and FSH in women who were post-menopausal. While these studies are limited by their study design, the studies were conducted in well-established population-based surveys. These studies considered a range of confounders, including controlling for BMI and smoking, even co-exposure to other metals. The recent studies examining the relationship between menopause and Pb exposure found consistent positive associations. The results from concurrent exposure of blood Pb with menopause were supported by the results from a longitudinal cohort that examines bone Pb, a cumulative biomarker of Pb exposure, and menopause, both the difference in age at menopause and risk of early menopause. No recent PECOS-relevant toxicological studies reported on the effects of Pb on hormone levels in females or menstrual or estrous cyclicity. However, previous toxicological evidence suggests that Pb may disrupt reproductive hormones and menstrual and estrous cyclicity in females. Two toxicological studies in rats reported disruptions in estrous cyclicity, and two toxicological studies based in non-human primates reported alterations to different menstrual cycle aspects (e.g., length of cycle, length of menstruation) and reproductive hormone levels. Additional rodent studies reported effects of Pb on circulating reproductive hormone levels, including sex steroid hormones (progesterone, testosterone, and E2) and gonadotropin hormones (LH and FSH).

8.5.2 Effects on Female Fertility

Multiple epidemiologic and toxicological studies have examined the relationship between Pb and female fertility. These studies are summarized in the text below. Study details of the recent epidemiologic studies are included in Table 8-14 and the recent toxicological studies are in Table 8-15.

8.5.2.1 Epidemiologic Studies on Female Fertility

The epidemiologic studies reviewed in the 2013 Pb ISA examined a variety of fertility-related endpoints. Although some studies demonstrated an association between higher Pb biomarker levels and fertility/pregnancy, the results are inconsistent across studies. One limitation in most of these studies is that the participants were women seeking help for fertility problems. The participants were not samples of the general population and therefore cannot be generalized to all women of childbearing age. This may also have introduced substantial selection bias into the study.

The recent epidemiologic studies also evaluated different outcomes to measure fertility. In an NHANES (2013–2014 and 2015–2016) study, Lee et al. (2020) assessed whether BLLs were associated with self-reported infertility by comparing BLLs of infertile women (n = 42) to pregnant women (n = 82). There was increased risk of 2.60 (95% CI: 1.05, 6.41) per two-fold increase in BLLs of infertility. When BLLs were categorized into tertiles, risk of infertility was more pronounced (OR: 5.40 [95% CI: 1.47, 19.78] in tertile 2 (0.41–0.62 μg/dL) and OR: 5.62 [95% CI: 1.13, 27.90] in tertile 3 (0.63–5.37 μg/dL), respectively). In the LIFE Study, a cohort of couples were followed prospectively to assess persistent environmental chemicals and human fecundity (Louis et al., 2012). BLLs in both the female and male partners were collected at baseline. Female BLLs were not associated with increased time to pregnancy in the female exposure model (OR: 0.97 [95% CI: 0.85, 1.11]) or the couple exposure model (OR: 1.06 [95% CI: 0.91, 1.24]). However, there was decreased odds, or longer time to pregnancy, for male BLLs in both the male exposure model (OR: 0.85 [95% CI: 0.73, 0.98]) and the couple exposure model (OR: 0.82 [95% CI: 0.68, 0.97]).

In a cross-sectional study among infertile women in Taiwan, Lai et al. (2017) examined the associations between BLLs and diagnosis of endometriosis, which can cause infertility. Increasing tertiles of BLLs was associated with higher odds of endometriosis (OR: 2.59 [95% CI: 1.11, 6.06] for T3 compared to T1). In a cohort study, among couples undergoing the first in vitro fertilization (IVF) cycle, maternal Pb levels were assessed with pregnancy outcomes (Li et al., 2022). Pb levels in serum were collected before oocyte retrieval. With increasing maternal serum Pb levels, there was a reduction in successful implantation (OR: 0.85 [95% CI: 0.77, 0.94]) and clinical pregnancy (OR: 0.95 [95% CI: 0.91, 0.99]). Additionally, when maternal serum Pb was categorized into tertiles, there was a lower rate of successful implantation (OR: 0.58 [95% CI: 0.40, 0.85]) in the highest Pb tertile, compared to the lowest Pb tertile. Among tertiles of Pb serum levels, the associations were null for clinical pregnancy. Furthermore, there was a negative association with maternal serum Pb and high-quality embryo rate (β:

−0.14 [95% CI: −0.32, −0.04]), but there were null associations with all other embryo quality indicators (Table 8-14). In a cohort of 195 couples undergoing IVF, Pb was measured in serum and follicular fluid from the female partner and semen from the male partner in association with six IVF outcomes (Zhou et al., 2021a). There were no associations between serum or follicular fluid Pb levels and any IVF outcomes—normal fertilization, good embryo, blastocyst formation, high-quality blastocyst, pregnancy, or live birth.

8.5.2.2 Toxicological Studies on Female Fertility

The 2013 Pb ISA reported some studies that investigated the effects of Pb on female fertility. A handful of these studies reported that exposure to Pb reduced litter sizes in exposed female rats (Dumitrescu et al., 2008a; Teijón et al., 2006) and mice (Iavicoli et al., 2006). Contrasting this is a study that found no changes in fertility rate or litter size in female rats treated prior to mating through pregnancy (Nampoothiri and Gupta, 2008). Recent studies corroborate the findings of Nampoothiri and Gupta (2008) and do not demonstrate any effects of Pb on female fertility in terms of litter size or number of litters produced by dosed dams in mice (Schneider et al., 2016; Cory-Slechta et al., 2013) or rats (Rao Barkur and Bairy, 2016; Barkur and Bairy, 2015; Weston et al., 2014; Betharia and Maher, 2012). Among these recent studies, a variety of dosing paradigms were utilized, including exposure during preconception, lactation, gestation, and combinations thereof (BLLs ranged between 3.02–26.86 µg/dL in pups on PND 2–22). The contrast in effects on litter size between studies that do and do not report effects of Pb on litter size is perplexing, and the inconsistencies of BLL measurements (e.g., some measured Pb levels in offspring, some measured in dams, some studies did not report BLLs at all) between studies further exacerbates the difficulty of reconciling these contrasts. However, some plausible explanations for these differences exist and primarily involve differences in study design. Studies that reported reductions in litter size due to Pb exposure tended to either use higher doses (Teijón et al., 2006), longer dosing durations (Iavicoli et al., 2006), or dosed sires in addition to dosing dams (Dumitrescu et al., 2008a) when compared to studies that did not report reductions in litter sizes.

8.5.2.3 Integrated Summary of Effects on Female Fertility

Among the recent epidemiologic studies, there were inconsistent associations between Pb exposure and female fertility. In studies among participants in the general population, there was an increased risk of self-reported infertility and longer time to pregnancy. However, among studies with women who were either seeking help at a fertility clinic or reported infertility, the associations were inconsistent. Because the study participants included only a small sample of women who were either seeking help at a fertility clinic or reported infertility, there may be selection bias and limits the generalizability of the results as study participants have already been diagnosed and are seeking treatment for fertility issues. Further, pregnancy outcomes, such as successful implantation, are more likely to be

ascertained from women seeking treatment at fertility clinics. Additionally, the recent epidemiologic studies were limited by the concurrently measured exposure and outcome, different biomarkers of exposure (e.g., blood, serum, and follicular fluid), and a small number of participants. However, these studies did include adjustment for potential confounders, including age, BMI, and partner exposure. Previous toxicological evidence reported inconsistent effects of Pb on fertility in females. All recent toxicological studies reported that female fertility was not affected by Pb exposure, even when a variety of dosing paradigms were used.

8.5.3 Effects on Morphology and Histology of Female Sex Organs (Ovaries, Uterus, Fallopian Tubes/Oviducts, Cervix, Vagina, and Mammary Glands)

Recent epidemiologic and toxicological studies evaluating the association between Pb exposure and morphology or histology of female sex organs (ovaries, uterus, fallopian tubes/oviducts, cervix, vagina, and/or mammary glands) are limited. Study details for the single cross-sectional epidemiologic study are included in Table 8-14 and the toxicological studies are included in Table 8-15.

8.5.3.1 Epidemiologic Studies of Morphology and Histology of Female Sex Organs (Ovaries, Uterus, Fallopian Tubes/Oviducts, Cervix, Vagina, and Mammary Glands)

In the 2013 Pb ISA, there were no epidemiologic studies available that evaluated Pb concentrations and associations with morphology or histology of female sex organs (ovaries, uterus, fallopian tubes/oviducts, cervix, vagina, and/or mammary glands). A recent cross-sectional study examined the association between BLLs and rate of uterine fibroids and uterine fibroid volume (Ye et al., 2017). Among 288 (46 with fibroids and 242 without) pre-menopausal women included in the study, there were null associations between blood Pb and the presence of uterine fibroids (OR: 1.39 [95% CI: 0.75. 2.56]) and volume of the largest fibroids (β: 0.12 [95% CI: −2.26, 2.51]). When blood Pb was categorized into quartiles, the association with volume of uterine fibroids remained null. While the associations between blood Pb and rate of uterine fibroids and uterine fibroid volume were generally null, the women with uterine fibroids had higher geometric mean BLLs than women without fibroids (1.43 μg/dL versus 1.35 μg/dL, respectively).

8.5.3.2 Toxicological Studies of Morphology and Histology of Female Sex Organs (Ovaries, Uterus, Fallopian Tubes/Oviducts, Cervix, Vagina, and Mammary Glands)

There are no recent animal toxicological studies on the effects of Pb on morphology or histology of female sex organs. The 2013 Pb ISA discussed a single study that reported Pb exposure increased

membrane fluidity in granulosa cells in Charles Foster rats that were dosed via intraperitoneal injections for 15 days (Nampoothiri and Gupta, 2006). The 2006 Pb AQCD also reported that exposure to Pb during early pregnancy caused structural changes in the uterine epithelium in mice (Nilsson et al., 1991; Wide and Nilsson, 1979).

8.5.3.3 Integrated Summary of Morphology and Histology of Female Sex Organs (Ovaries, Uterus, Fallopian Tubes/Oviducts, Cervix, Vagina, and Mammary Glands)

There was a single recent epidemiologic study evaluating associations between Pb exposure and uterine fibroids. Although this was a small cross-sectional study, it was able to control for a large range of confounders. The results from this single study are limited by the small sample size and concurrent measurements of blood Pb and fibroids. Toxicological evidence regarding Pb exposure and female sex organs is scarce. No recent PECOS-relevant toxicological studies were available. Previous studies discussed in the 2013 Pb ISA and the 2006 Pb AQCD were scarce and reported few effects of Pb on female sex organ morphology or histology.

8.6 Effects on Male Reproductive Function

The 2013 Pb ISA concluded that there was toxicological evidence with supporting epidemiologic evidence to conclude that a causal relationship exists between Pb exposure and effects on male reproductive function. The key evidence was provided by toxicological studies in rodents, non-human primates, and rabbits showing detrimental effects on semen quality, sperm, and fecundity/fertility with supporting evidence in epidemiologic studies of associations between Pb exposure and detrimental effects on sperm. Recently published research has continued to support an association between Pb and sperm/semen production, quality, and function. Studies of Pb and male reproductive function are described in the sections below.

8.6.1 Effects on Sperm/Semen Production, Quality, and Function

Multiple epidemiologic and toxicological studies have examined the relationship between Pb and sperm and semen production, quality, and function. These studies are summarized in the text below. Study details of the recent epidemiologic studies are included in Table 8-16 and the recent toxicological studies are in Table 8-17. The majority of the recent epidemiologic studies are cross-sectional with concurrent measurements of Pb levels in biological samples and sperm-related outcomes. Recent toxicological studies use a variety of dosing paradigms, and those that dose for longer periods of time

(>30 days) or during a developmental window most often reported effects of Pb exposure on aspects of sperm and semen quality.

8.6.1.1 Epidemiologic Studies on Sperm/Semen Production, Quality, and Function

The 2013 Pb ISA epidemiologic studies of Pb exposure and sperm and semen production, quality, and function were cross-sectional, mostly in occupational cohorts, with concurrent measurements of Pb levels in biological samples and sperm-related outcomes. The multiple epidemiologic studies in occupational cohorts had mean BLLs over 40 µg/dL for individuals occupationally exposed to Pb. The occupational studies also had limited consideration for potential confounding factors, such as other workplace exposures, which may impact the associations. The epidemiologic studies of men attending fertility clinics may be subject to selection bias, and the results may not be generalizable. Additionally, these studies reported imprecise estimates, did not control for other potential confounders such as other metals, and had small sample sizes.

Several recent cross-sectional studies have explored the relationship between Pb exposure and sperm and semen production, quality, and function. These studies were all conducted in males attending fertility clinics and reported inconsistent associations for various metrics of sperm/semen production, quality, and function. There were other cross-sectional studies that also examined associations with sperm and semen production, quality, and function using different and Pb measured in semen, seminal fluid, and seminal plasma, but these findings were more inconsistent.

Among the cross-sectional studies that evaluated associations with blood Pb, there was lower normal sperm morphology with increasing BLLs (Shi et al., 2021; Sukhn et al., 2018; Li et al., 2015). Additionally, Li et al. (2015) reported increased odds of lower semen quality, sperm concentration, numbers of sperm, total motility sperm, and progressive motility sperm with increasing BLLs, whereas Sukhn et al. (2018) reported null associations with sperm volume, concentration, total count, progressive motility, viability, and World Health Organization (WHO) morphology, and Shi et al. (2021) reported null associations between blood Pb and semen parameters of semen volume, sperm concentration, total sperm count, sperm motility, total motile sperm count, sperm vitality, DNA fragmentation index, and percentage of acrosome reacted sperm (see Table 8-16). Furthermore, there were differences in BLLs between men categorized as having low-quality semen and those classified as having normal or high-quality semen (Sukhn et al., 2018; Li et al., 2015). Li et al. (2015) reported mean blood Pb for men in the low-quality semen group was 3.43 µg/dL and 2.38 µg/dL for those in the high-quality semen group, and Sukhn et al. (2018) reported the mean blood Pb for low-quality semen group of 5.198 µg/dL and 3.575 µg/dL for the normal-quality semen group.

Other cross-sectional studies examined the relationship between Pb measured in seminal fluid and metrics of sperm/semen production, quality, and function, but the associations were inconsistent (Jia et al., 2022; Sukhn et al., 2018; Pant et al., 2014). Pant et al. (2014) measured Pb in semen and metrics of

sperm/semen production, quality, and function, and reported associations of higher Pb levels in sperm with decreased sperm motility (β: −2.43% [95% CI: −4.87%, −0.001%]), decreased sperm concentration (β: 1.97 10^6/mL [95% CI: −3.16, −0.33]), increased tail length (β: 3.79 [95% CI: 0.56, 7.02]), increased percent DNA in tail (β: 1.31 [95% CI: 0.17, 3.74]), and increased tail movement (β: 1.20 [95% CI: 0.23, 2.16]). However, Sukhn et al. (2018) assessed sperm characteristic relationships with seminal fluid Pb and reported increased odds of below-reference sperm viability and WHO morphology with higher seminal fluid Pb, but null associations with volume, concentration, total count, and progressive motility. Jia et al. (2022) reported no associations between seminal plasma Pb concentrations and semen parameters (semen volume, sperm concentration, total sperm number, progressive motility, and normal morphological rate).

A recent cohort study examined the associations between peripubertal blood Pb, collected at enrollment, and parameters of sperm and semen production, quality, and function for 223 participants in the Russian Children's Study, with the semen sample collected 10 years after enrollment (Williams et al., 2022). There were null associations between peripubertal blood Pb and sperm parameters (sperm concentration, total count, progressive motility, and total progressive motile sperm count, or probability of having low semen quality based on sperm count/motility), whether blood Pb was modeled continuously, categorized as tertiles, or categorized as low (<5 μg/dL) blood Pb versus high (≥5 μg/dL) blood Pb (see Table 8-16).

8.6.1.2 Toxicological Studies on Sperm/Semen Production, Quality, and Function

The 2013 Pb ISA summarized several toxicological studies that investigated the effects of Pb exposure on sperm-related outcomes. Utilizing a variety of dosing paradigms and animal models, previously published studies have demonstrated that Pb exposure reduced sperm counts, reduced numbers of viable sperm, reduced motility, and increased morphological abnormalities (Pillai et al., 2012; Anjum et al., 2011; Allouche et al., 2009; Oliveira et al., 2009; Salawu et al., 2009; Shan et al., 2009; Tapisso et al., 2009; Massanyi et al., 2007; Piao et al., 2007; Wang et al., 2006). Results from recently published studies tend to suggest that Pb exposure impacts sperm and semen parameters (Table 8-17). All available studies that reported outcomes on sperm and semen parameters were conducted in mice. Only one study utilized a developmental exposure paradigm and dosed lactating CD-1 mice from PND 0 to 21 which resulted in reduced numbers of sperm at PND 70 in male offspring in the highest dose group (BLLs 19.1 μg/dL) (Wang et al., 2013a). Other studies that directly exposed male mice after weaning also reported Pb-induced sperm alterations including increased incidence of abnormal morphology, reduced density, and reduced viability (BLLs 9.4–11.92 μg/dL) (Zhang et al., 2021; Xie et al., 2020; Godínez-Solís et al., 2019). However, some studies also reported no Pb-induced effects on sperm motility, concentration, count, or viability (BLLs 9.4–11.8 μg/dL) (Pavlova et al., 2021; Godínez-Solís et al., 2019). It is worth noting that while Pavlova et al. (2021) reported no Pb-induced effects on sperm count, Pb-treated animals had sperm counts 25% lower than those of control mice, but this effect failed to reach statistical significance ($p = 0.146$). In terms of patterns in the reported data, studies that utilized long-term

exposure (>30 days) or dosed during developmental periods tended to report effects of Pb on sperm or semen parameters, and Pavlova et al. (2021) was the only study to use short-term exposure during adulthood and also was the only study to report no effects at all on any sperm or semen parameters.

8.6.1.3 Integrated Summary of Effects on Sperm/Semen Production, Quality, and Function

Among the recent epidemiologic studies that evaluated associations between Pb exposure (measured in blood, semen, seminal fluid, or seminal plasma) and effects on sperm/semen production, quality, and function, there were inconsistent findings, which was similar to the conclusion in the 2013 Pb ISA. More consistent associations were observed for blood Pb with decreased sperm/semen production, quality, and function than for Pb measured in semen, seminal fluid, or plasma; however, there are limitations in the recent epidemiologic studies. All the cross-sectional studies were conducted in males attending fertility clinics, which may have resulted in selection bias and limits the generalizability of the results. Further, the small sample size from these cross-sectional studies also reduces the statistical power to determine the precision of the associations. With concurrent measurement of Pb exposure with outcomes related to sperm/semen production, quality, and function, temporality cannot be established. Lastly, the use of different biomarkers (e.g., blood, semen, seminal fluid, or seminal plasma) to measure Pb exposure and the different metrics of sperm/semen production, quality, and function limits the ability to judge coherence and consistency across studies. Despite these limitations, it is important to note that a wide variety of potential confounders were controlled for, including hormone levels, which could potentially impact sperm/semen production, quality, and function. Previous and recent toxicological studies generally reported that Pb alters some aspect of sperm or semen quality, such as sperm density, motility, morphology, and viability, especially those studies that employed dosing during developmental periods or for periods 30 days or longer. All recent toxicological evidence was produced from mouse strains, but previous toxicological studies report similar effects in other species such as rats and rabbits.

8.6.2 Effects on Hormone Levels in Males

The epidemiologic and toxicological studies reviewed in the 2013 Pb ISA reported inconsistent results regarding changes in hormone levels in men and associations with Pb exposure. The results from the 2013 Pb ISA were similar to the findings from the 2006 Pb AQCD. Recent epidemiologic and toxicological studies are reported below. Epidemiologic studies were mostly cross-sectional with blood Pb measured concurrently with hormone levels. Study details for the epidemiologic studies, including BLLs, study population characteristics, potential confounder, and select results, are in Table 8-16. Previous toxicological evidence regarding the effect of Pb on hormones in males is somewhat inconsistent, but most studies reported impacts of Pb on hormone levels. Recent toxicological studies are extremely limited, but support previous toxicological studies reported in the 2013 Pb ISA that observed

Pb-induced effects on hormones in males. Study details for the recent toxicological studies are in Table 8-17.

8.6.2.1 Epidemiologic Studies on Hormone Levels in Males

In the 2013 Pb ISA, there were a few epidemiologic studies that evaluated hormone levels in males in association with Pb exposure. The findings of these studies were inconsistent. The epidemiologic studies were limited by their sample populations, often occupational cohorts or men recruited from fertility clinics, which may not be representative of the general populations and limits the generalizability of the results. More specifically, the occupational cohorts may have other metal exposures that were not considered and may confound the associations, while studies conducted with subjects from fertility clinics are subject to selection bias. While these studies included important confounders such as smoking, other factors, such as exposure to other metals, were often absent. The cross-sectional study design of some of the epidemiologic studies reviewed makes it difficult for temporality of effects to be established. Additionally, most of the epidemiologic studies examined concurrent Pb exposure and hormone levels, which may not reflect changes resulting from long-term exposures.

The recent epidemiologic studies on hormone levels detailed in this section are specific to hormones related to reproductive function and recent epidemiologic studies on other hormones are described in Section 9.4.2 in the Other Health Effects Appendix.

There are a few recent epidemiologic cross-sectional studies that evaluated the associations between hormone levels in males and Pb exposure. There were consistent positive associations between blood Pb and testosterone among these studies. One NHANES analysis combined three consecutive cycles of NHANES (1999–2000, 2001–2002, and 2003–2004) to investigate the associations between blood Pb and various sex hormones: testosterone, free testosterone, E2, fE2, androstenedione glucuronide, and SHBG among men over 20 years old (Kresovich et al., 2015). Comparing the highest quartile of blood Pb exposure (>3.20 μg/dL) to the lowest (≤1.40 μg/dL), testosterone was positively associated with blood Pb (β: 0.79, SE: 0.22) and there was an indication of exposure-response (p for trend: 0.0026). There were null associations between blood Pb and all other sex hormones. In another NHANES (2011–2012) study, blood Pb and serum testosterone were measured in men of reproductive age (18–55 years old) (Lewis and Meeker, 2015). Of the 484 men included in the analysis, there was a 6.65% (95% CI: 2.09%, 11.41%) change in the serum testosterone concentration associated with a doubling (100% increase) in blood Pb concentration. Chen et al. (2016) also reported positive associations between concurrent testosterone and blood Pb concentrations. Utilizing data from a population-based survey, the Survey on the Prevalence in East China for Metabolic Diseases and Risk Factors (SPECT)-China, 2,286 men were included in the analysis to investigate the relationship between quartiles of BLLs and multiple reproductive hormones – tT, SHBG, E2, LH, and FSH. When comparing the highest quartile of blood Pb (>6.249 μg/dL) to the lowest (<2.90 μg/dL), there were positive associations with BLLs and tT (β: 0.033,

SE: 0.010, p < 0.01), SHBG (β: 0.038, SE: 0.012, p < 0.01), FSH (β: 0.030, SE: 0.015, p < 0.05), and LH (β: 0.028, SE: 0.013, p < 0.05), but null associations with E2 (β: −0.003, SE: 0.017). Across the quartiles of blood Pb, there were also positive trends observed with tT (p for trend: 0.012), SHBG (p for trend <0.001), FSH (p for trend <0.001), and LH (p for trend <0.001), suggesting a potential linear concentration response.

While there were consistent positive associations between blood Pb and serum testosterone in the cross-sectional studies, a single cohort study reported null associations. Among a subset of participants (n = 453) in the Russian Children's Study, there were no associations between peripubertal BLLs and hormones levels (testosterone, LH, or FSH) measured between 8–19 years of age, whether blood Pb was modeled continuously or categorized (<5 μg/dL versus ≥5 μg/dL) (Williams et al., 2022).

8.6.2.2 Toxicological Studies on Hormone Levels in Males

The 2013 Pb ISA discussed several studies that reported on the effects of Pb on hormone levels in males. All studies were conducted in rats, and all directly dosed the tested animals save for one that exposed gestating and lactating dams and measured hormones in offspring. Dosing durations varied from 21 days to 24 weeks, and most studies reported reductions in testosterone (Pillai et al., 2012; Anjum et al., 2011; Biswas and Ghosh, 2006; Rubio et al., 2006). One study observed increased testosterone (Allouche et al., 2009) and another reported reductions in LH and FSH (Biswas and Ghosh, 2006). However, not all studies observed effects on male hormones due to Pb exposure. One study observed no change in testosterone (Salawu et al., 2009) and another reported no change in FSH and LH levels despite reporting increased testosterone levels (Allouche et al., 2009). Only one recent PECOS-relevant toxicological study was published that investigated the effects of Pb exposure on hormones in males (Table 8-17). This study dosed nursing CD-1 mice from PND 0 to 21 and reported reduced serum testosterone at weaning and PND 70 and reduced testicular testosterone at weaning in offspring in the highest dose group (19.1 μg/dL) (Wang et al., 2013a).

8.6.2.3 Integrated Summary of Effects on Hormone Levels in Males

The recent cross-sectional epidemiologic studies reported consistent associations between blood Pb and testosterone; however, a single cohort study reported no associations. Of note, the recent cross-sectional studies were in adult men, whereas the single cohort study was in male adolescents. Additionally, the study by Chen et al. (2016) provides further support of a positive association with SHBG, FSH, and LH and blood Pb. The positive trends among quartiles of blood Pb and testosterone, SHBG, FSH, and LH provide insight on the possible concentration-response relationship. These studies have robust sample sizes drawn from population-based surveys and controlled for a number of confounders, including smoking, but the temporality of effects is difficult to establish due to the nature of

cross-sectional study design. Recent toxicological evidence regarding the effects of Pb on hormones in males is extremely limited, but in agreement with most studies summarized in the 2013 Pb ISA which report effects of Pb on hormones in males.

8.6.3 Effects on Male Fertility

The recent epidemiologic and toxicological studies examining the relationship between Pb exposure and male fertility are summarized in the text below. The epidemiologic studies on Pb exposure and male fertility are limited. Previous epidemiologic studies were conducted among men seeking help at fertility clinics. Study details of the recent epidemiologic studies are in Table 8-16. Previous and recent toxicological evidence regarding the effect of Pb on male fertility is scarce, but generally reports reduced fertility in males exposed to Pb. Study details of the recent toxicological studies are in Table 8-17.

8.6.3.1 Epidemiologic Studies on Male Fertility

The epidemiologic studies included in the 2013 Pb ISA that assessed associations between Pb exposure and male fertility reported inconsistent findings. The few studies available for review were conducted with cases that included men seeking help at fertility clinics, resulting in limited generalizability of the studies because the study populations are not representative of the general population. Additionally, by recruiting men who were seeking help at fertility clinics, there could be selection bias, as their fertility status is already known and those seeking help at fertility clinics may be different from men who have fertility issues who may be unaware of their condition and not seeking help at a fertility clinic. Another study was conducted among occupationally exposed men, which may result in differential exposures compared to the general population. Furthermore, another study did not control for potential confounders.

There were a limited number of recent epidemiologic studies that examined associations between Pb and male fertility. In the LIFE Study, a cohort of couples were followed prospectively to assess persistent environmental chemicals and human fecundity (Louis et al., 2012). BLLs in both female and male partners were collected at baseline. While female blood Pb was not associated with increased time to pregnancy, there was decreased odds, or increased time to pregnancy, for male BLLs in both the male exposure model (OR: 0.85 [95% CI: 0.73, 0.99]) and the couple exposure model (OR: 0.82 [95% CI: 0.68, 0.97]). In a cohort of 195 couples undergoing IVF, Pb was measured in blood serum and follicular fluid from the female partner and semen from the male partner in association with six IVF outcomes (Zhou et al., 2021a). There was a positive association between Pb in seminal plasma and the possibility of obtaining a good embryo (RR: 1.86 [95% CI: 1.05, 3.11]), but the associations were null across all other IVF outcomes (normal fertilization, blastocyst formation, high-quality blastocyst, pregnancy, or live birth).

8.6.3.2 Toxicological Studies on Male Fertility

Only a few studies on the effects of Pb on male fertility were summarized in the 2013 Pb ISA. These studies reported that Pb-exposed males produced smaller litters and fewer implantations and fetuses per dam (Anjum et al., 2011; Sainath et al., 2011). Only a single recent study investigated fertility outcomes in males exposed to Pb (Table 8-17). This study exposed ICR-CD-1 mice from PND 91 to 136 via drinking water and reported that sperm from treated mice had reduced fertilization capacity, resulting in fewer fertilized oocytes in vitro (9.4 μg/dL) (Godínez-Solís et al., 2019).

8.6.3.3 Integrated Summary of Male Fertility

Similar to the 2013 Pb ISA, there were only a few epidemiologic studies evaluating associations between Pb exposure and male fertility and the findings were inconsistent. The results from these studies are limited by the small sample size and the study population was recruited from a fertility clinic, which may have resulted in selection bias and limits generalizability as the study population has already been diagnosed and are seeking treatment for fertility issues. Further, male fertility related to pregnancy outcomes, such as successful implantation and normal fertilization, are more likely to be ascertained from couples seeking treatment at fertility clinics. Additionally, different biomarkers were used to assess Pb exposure, as well as different metrics of male fertility across the studies. In terms of toxicological evidence, previous and recent studies are few in number. However, all report a reduction of male fertility in Pb-treated animals using outcomes such as litter size, implantations, and fertilized oocytes.

8.6.4 Effects on Morphology and Histology of Male Sex Organs

The toxicological studies in the 2013 Pb ISA supported historical findings that showed an association between Pb exposure and changes in the sex organs as well as germ cells. There were no epidemiologic studies available for review for the 2013 Pb ISA that examined the relationship between Pb exposure and morphology or histology of male sex organs. The current epidemiologic and toxicological studies examining the relationship between Pb exposure and effects on morphology and histology of male sex organs are summarized in the text below with study details in Table 8-16 and Table 8-17, respectively.

8.6.4.1 Epidemiologic Studies of Morphology and Histology of Male Sex Organs

In the 2013 Pb ISA, there were no epidemiologic studies available that evaluated Pb concentrations and associations with morphology or histology of male sex organs. A recent cohort study evaluated the associations between prenatal metal exposure and reproductive development in boys at 2–3 years (Huang et al., 2020). Serum concentrations of multiple metals, including Pb, were obtained from

mothers in the Guangxi Birth Cohort Study throughout pregnancy, while reproductive development was measured as TV and anogenital distance (AGD), categorized as anopenile distance (AGDap) and anoscrotal distance (AGDas), in 2–3-year-old male children. When maternal serum Pb levels were categorized by quartiles, infants in the highest quartile (serum Pb >1.23 µg/L) had, on average, a 0.064 mL (95% CI: −0.124, −0.004) smaller TV, 0.060 cm (95% CI: −0.110, −0.011) shorter AGDap, and 0.115 cm (95% CI: −0.190, −0.039) shorter AGDas than infants in the lowest quartile (serum Pb ≤ 0.54 µg/L).

8.6.4.2 Toxicological Studies of Morphology and Histology of Male Sex Organs

This section is divided into the two main outcomes for the male sex organs: changes in weight of male sex organs and changes in histology/morphology of male sex organs. The 2013 Pb ISA summarized several studies that investigated the effects of Pb exposure on male sex organ weights. Several studies reported decreases in weights of organs such as the testis, epididymides, vas deferens, seminal vesicles, and prostate (Anjum et al., 2011; Pillai et al., 2010; Dong et al., 2009; Salawu et al., 2009; Biswas and Ghosh, 2006; Rubio et al., 2006). The direction of effect was consistent, and any effects observed were only decreases in organ weights. However, the 2013 Pb ISA noted that there were many other studies that did not report effects on male reproductive organ weights even when using similar doses as those studies that did observe effects, indicating that the impact of Pb on reproductive organ weights is somewhat inconsistent. Recent studies have also investigated the effects of Pb exposure on male sex organ weight (Table 8-17). Wang et al. (2013a) reported that dosing male CD-1 mouse pups via their dams' drinking water from PND 0 to 21 led to reduced absolute weight of testes in both treatment groups at weaning and reduced relative testis weight in the highest treatment group at weaning (BLLs 19.1–21.2 µg/dL on PND 22 and 3.24–4.40 µg/dL on PND 70). However, they observed no effect on the weight of the prostate, seminal vesicle, or epididymides at weaning and no effects on relative weights of any reproductive organ on PND 70. Similarly, another study reported that dosing Sprague-Dawley rats from GD −10 to PND 183 had reduced absolute and relative testis weights (BLLs 18.6 µg/dL) (Wang et al., 2013b). However, some studies reported that Pb did not alter the weights of testes or epididymides in ICR mice (BLLs 6.02–21.66 µg/dL) (Pavlova et al., 2021; Satapathy and Panda, 2017).

The 2013 Pb ISA reported on studies that investigated the effects of Pb on the histopathology of male sex organs in rodents exposed to Pb. One of the most common outcomes was alterations of seminiferous tubule pathology, such as reduced length of some spermatogenic cycle stages within seminiferous tubules, tubule damage, and tubule atrophy (El Shafai et al., 2011; Shan et al., 2009; Massanyi et al., 2007; Rubio et al., 2006; Wang et al., 2006). A few recent Pb studies have also reported Pb-induced histopathological changes in male sex organs (Table 8-17). All recent studies were conducted in mice, and exposure paradigms used between recent studies varied from developmental to exposure only during adulthood. One study in CD-1 mice that utilized developmental exposure (dosing dams from lactational day 0 to 21) reported that Leydig cell numbers in the testes were reduced in the highest dose

group at weaning and layers of spermatogenic cells within the seminiferous tubules were decreased in both dose groups at weaning and PND 70 (BLLs at weaning 19.1–21.1 µg/dL; BLLs at PND 70 3.24–5.09 µg/dL) (Wang et al., 2013a). Some studies that dosed mice for 90 days following weaning reported histopathological disruptions to the epididymal epithelial cells (BLLs 6.02–11.8 µg/dL) (Xie et al., 2020) and that spermatogenic cells within seminiferous tubules were reduced in number (BLLs at 11.92 µg/dL) (Zhang et al., 2021). Lastly, a study that dosed mice from PND 60 to 74 reported that the epithelium of the seminiferous tubules was disorganized, the luminal region contained undifferentiated germ cells, and some tubules had decreased diameter and germ cell number and displayed incomplete spermatogenesis (BLLs 21.7 µg/dL) (Pavlova et al., 2021).

A few previous and recent studies concurrently investigated the effects of Pb on male sex organ weight and histopathology, and effects within studies were coherent (Rubio et al., 2006; Wang et al., 2013a; Pavlova et al., 2021). Both Rubio et al., 2006 and Wang et al., 2013a reported reductions in male sex organs as well as histopathological alterations, while Pavlova et al., 2021 reported no effects of Pb on sex organ weight or histopathology.

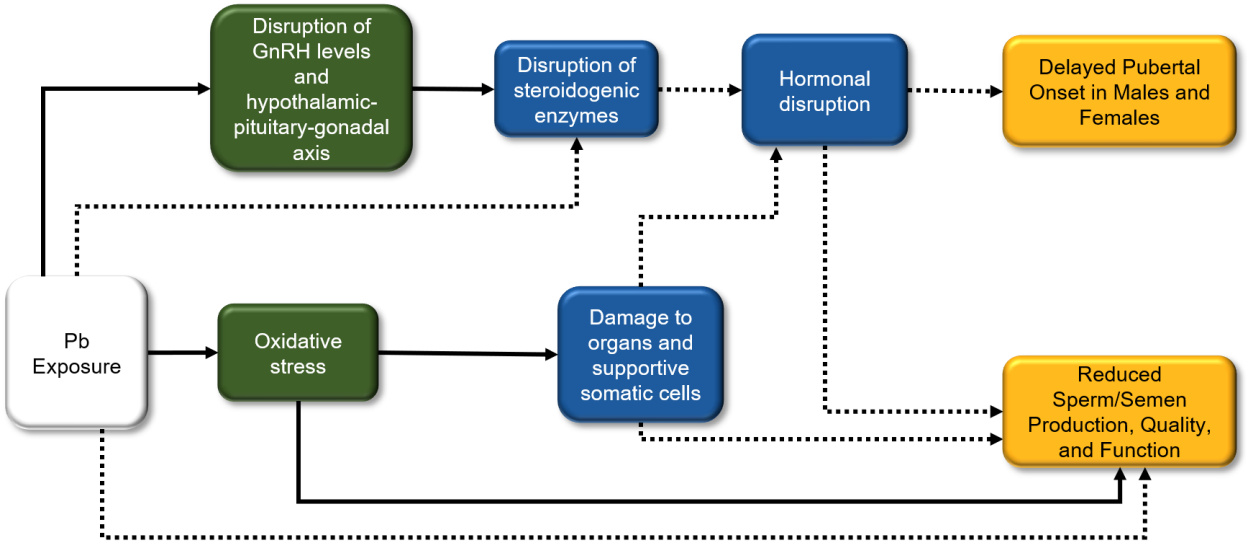
8.6.4.3 Integrated Summary of Morphology and Histology of Male Sex Organs

In the 2013 Pb ISA, there were no epidemiologic studies available that evaluated Pb concentrations and associations with morphology or histology of male sex organs. A recent cohort study reported decreased TV, shorter AGD, shorter anopenile distance, and shorter anoscrotal distance in 2–3-year-old male children. While it is difficult to judge coherence and consistency from the findings of a single study, this well-designed longitudinal cohort study does provide limited evidence of changes in morphology and histology of male sex organs. Previous and recent toxicological studies are consistent in reporting that Pb affects different aspects of sex organ histopathology. The most consistent effects appear to be disruptions of histopathology of seminiferous tubules within the testes. However, there exists a data gap regarding the effects of Pb on histopathology of other male sex organs such as the prostate, epididymides, and seminal vesicles.

8.7 Biological Plausibility

This section describes the biological pathways that may underlie some reproductive and developmental health effects from exposure to Pb. Figure 8-1 graphically depicts the proposed pathways as a continuum of pathophysiological responses—connected by arrows—that may ultimately lead to the observed delayed onset in both males and females and reduced sperm/semen production, quality, and function. This discussion of how exposure to Pb may lead to these reproductive and/or developmental events also provides biological plausibility for the epidemiologic results reported previously in this

Appendix. In addition, most studies cited in this subsection are discussed in greater detail earlier in this Appendix.



GnRH = gonadotropin-releasing hormone; Pb = lead.
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 or a genetic knockout model used in an experimental study involving Pb exposure. 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 (gray, 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.

Figure 8-1 Potential biological pathways for reproductive and developmental effects following exposure to Pb.

8.7.1 Pubertal Onset

When considering the available health evidence, plausible pathways connecting Pb exposure to two health endpoints reported in epidemiologic and toxicological studies are proposed in Figure 8-1. The first endpoint addressed in the figure above is delayed pubertal onset due to Pb exposure. Several previous epidemiologic and toxicological studies that reported delays in pubertal onset in females (Gollenberg et al., 2010; Naicker et al., 2010; Dumitrescu et al., 2008a; Iavicoli et al., 2006; Denham et al., 2005; Selevan et al., 2003; Wu et al., 2003) and males (Williams et al., 2010; Hauser et al., 2008) were summarized in the 2013 Pb ISA and several toxicological studies were summarized the 2006 Pb AQCD (Pine et al., 2006; Dearth et al., 2004; Iavicoli et al., 2004; Dearth et al., 2002; Ronis et al., 1998a, 1996). Some toxicological studies from the 2006 Pb AQCD also reported delays in pubertal onset in males (Ronis et al., 1998c; Sokol et al., 1985). While no recent PECOS-relevant toxicological studies that investigated the effects of Pb on pubertal onset were available, several recent epidemiologic studies

reported associations between Pb exposure and delayed onset of puberty in males (Williams et al., 2019; Nkomo et al., 2018; De Craemer et al., 2017) and females (Gomula et al., 2022; Jansen et al., 2018; Nkomo et al., 2018; De Craemer et al., 2017; Sławińska et al., 2012). The proposed biologically plausible pathway through which Pb induces delays in pubertal onset begins with the Pb-induced disruption of the gonadotropin-releasing hormone (GnRH) levels which may occur through reduction of circulating IGF-1 levels. GnRH is a key hormone in the hypothalamic-pituitary-gonadal axis and hormonal signaling pathways related to reproduction and pubertal onset. A recent epidemiologic study found negative associations between BLLs at 8–9 years of age and IGF-1 in boys 2 and 4 years later (Fleisch et al., 2013) and toxicological studies have reported reduced IGF-1 levels and IGF-1R expression in the brains of animals exposed to Pb (Li et al., 2016; Li et al., 2014; Dearth et al., 2002; Ronis et al., 1998b). IGF-1 is known to act on GnRH neurons and affect GnRH secretion (Dees et al., 2021; Daftary and Gore, 2005), which is responsible for the release of LH and FSH from the anterior pituitary, resulting in stimulation of the gonads to begin producing sex steroid hormones and mature oocytes and spermatozoa. One toxicological study conducted in female Fisher 344 rats found that Pb-induced delays of pubertal onset could be reversed by supplementation with IGF-1 (Pine et al., 2006). This study reported that supplementation with IGF-1 also restored GnRH and LH levels in Pb-exposed rats, demonstrating that IGF-1 disruption is a key component in delays in the onset of puberty mediated by Pb at BLLs at/above 35 μg/dL.

Pb has also been shown in some in vitro studies to directly alter steroidogenic enzyme expression (e.g., steroidogenic acute regulatory protein, 3β-hydroxysteroid dehydrogenase, and aromatase) and levels of sex steroid hormones important for proper sexual maturation, including progesterone, E2, and testosterone (Huang and Liu, 2004; Srivastava et al., 2004; Taupeau et al., 2003; Huang et al., 2002; Thoreux-Manlay et al., 1995). Additionally, although not all studies report relationships between Pb and hormone levels, some epidemiologic studies have reported associations and some toxicological studies have demonstrated effects of Pb exposure on steroidogenic enzymes and sex steroid hormones (Pollack et al., 2011; Tomoum et al., 2010; Dumitrescu et al., 2008b; Nampoothiri and Gupta, 2008; Telišman et al., 2007; Rubio et al., 2006; Sokol et al., 1985). Pb-induced disruptions of the hypothalamic-pituitary-gonadal axis, steroidogenic enzymes, and their sex steroid products are plausible explanations for the observed delays in pubertal onset reported in epidemiologic and toxicological studies.

8.7.2 Male Reproductive Function

The other health outcome proposed in Figure 8-1 is male reproductive function. Recent epidemiologic studies have reported that Pb exposure is associated with reductions in a variety of semen parameters, including sperm motility, sperm concentration, and normal sperm morphology (Shi et al., 2021; Sukhn et al., 2018; Li et al., 2015; Pant et al., 2014). These findings are generally consistent with the epidemiologic evidence presented in the 2013 Pb ISA (U.S. EPA, 2013). Further, toxicological studies provide supporting evidence that Pb negatively impacts male reproductive function (see Section 8.6.1)

(Anjum et al., 2011; Sainath et al., 2011). Figure 8-1 shows a plausible biological pathway through which Pb may act to reduce reproductive function in males.

The 2013 Pb ISA concluded that the evidence indicates a causal relationship between Pb exposure and reduced quality of sperm, and that this relationship was likely mediated through the generation of reactive oxygen species (ROS), leading to cellular damage (U.S. EPA, 2013). Specifically, the 2013 Pb ISA summarized one study that reported Pb-induced increases in oxidative stress markers and reductions in antioxidant enzyme levels in testicular plasma of rats (Salawu et al., 2009). In addition, several studies in the 2013 Pb ISA reported attenuation of Pb-induced reductions in sperm count, motility, and viability when animals were co-administered substances with known antioxidant properties (Salawu et al., 2009; Shan et al., 2009; Madhavi et al., 2007; Rubio et al., 2006; Wang et al., 2006). Further supporting the proposed pathway through which oxidative stress mediates Pb-induced effects are additional studies that report that Pb exposure dysregulates antioxidant enzymes, leading to oxidative stress and DNA damage in the affected tissues (Lopes et al., 2016; Kägi and Vallee, 1960; Ommati et al., In Press). Recent studies also support the proposed pathway and report an attenuation of Pb-induced effects on aspects of male reproductive function (e.g., subfecundity, reduced sperm count) in animals supplemented with antioxidants (Zhang et al., 2021; Abdelhamid et al., 2020; Alotaibi et al., 2020; Naderi et al., 2020; Udefa et al., 2020; Abdrabou et al., 2019; Hassan et al., 2019; Ommati et al., 2019; BaSalamah et al., 2018; Hasanein et al., 2018; Mabrouk, 2018; El Shafai et al., 2011; Leiva et al., 2011; Sainath et al., 2011; Ommati et al., In Press). Although many studies report negative effects of Pb on supporting somatic cells that have key functions in the spermatogenic cycle (e.g., Leydig cells, Sertoli cells), Pb may also have negative effects directly on sperm cells. Direct contact of Pb with sperm cells has been documented by multiple studies (Jia et al., 2022; Sukhn et al., 2018; Pant et al., 2014). One recent study reported that incubating sperm from healthy adult men for 4 hours with 30 µg/mL or 8 hours with either 15 or 30 µg/mL Pb increased DNA fragmentation, possibly due to oxidative stress and Pb binding to DNA phosphate residues, disrupting the process of chromatin condensation (Gomes et al., 2015). In another study, 4 hours of incubation of semen samples from healthy adult men with Pb reduced intracellular levels of cyclic adenosine monophosphate (cAMP) (10, 50, and 100 µM) and Ca^{2+} (2.5, 10, 50, and 100 µM), both of which are important in regulating sperm cell function (He et al., 2016). In support of this alternative mechanism of action is one non-PECOS relevant study (due to use of i.p. injection route) that reported an attenuation of Pb-induced effects on reproduction in Pb-injected male mice that were supplemented with $CaCl_2$ (Golshan Iranpour and Kheiri, 2016). Disruption of intracellular levels of key components such as cAMP and Ca^{2+} is another way in which Pb can directly affect sperm health and function outside of oxidative stress.

In summary, pathways are suggested by which Pb exposure can delay pubertal onset and reduce sperm/semen production, quality, and function. Studies indicate that Pb exposure likely impacts the hypothalamic-pituitary-gonadal axis in both males and females, leading to disruption of the onset of puberty, a developmental period with increasing regard for its sensitivity to insult due to the vulnerability of the various endocrinological events for which it is known. In addition, Pb exposure alters multiple

aspects of male reproductive function. The production of adequate quantities of viable sperm is essential for proper male fertility and reproduction. Pb exposure hampers this by negatively impacting both the sperm cell and the supportive somatic cells that play key roles in the spermatogenic cycle through increased oxidative stress and disruption of other important intracellular functions.

8.8 Summary and Causality Determination

The 2013 Pb ISA (U.S. EPA, 2013) made four causality determinations for Pb exposure and (1) effects on pregnancy and birth outcomes; (2) effects on development; (3) effects on female reproductive function; and (4) effects on male reproductive function. The 2013 Pb ISA concluded that the evidence is suggestive of a causal relationship between Pb exposure and effects on birth outcomes; a causal relationship between Pb exposure and effects on development, based on the findings of delayed pubertal onset among males and females; suggestive of a causal relationship between Pb exposure and effects on female reproductive function; and a causal relationship between Pb exposure and effects on male reproductive function. The following sections detail the causality determinations based on the recent epidemiologic and toxicological studies.

8.8.1 Summary of Effects on Pregnancy and Birth Outcomes

The 2013 Pb ISA concluded that based on the mix of inconsistent results of studies on various birth outcomes and some associations observed in epidemiologic studies of preterm birth and low birth weight/fetal growth, the evidence was suggestive of a causal relationship between Pb exposure and birth outcomes. Some associations were observed between Pb and low birth weight in epidemiologic studies that used postpartum maternal bone Pb or air Pb concentrations. Although associations were less consistent for low birth weight with maternal blood Pb measured, during pregnancy or at delivery, or with Pb measured in the umbilical cord and placenta (maternal blood Pb or umbilical cord and placenta Pb were the biomarkers most commonly used in studies of low birth weight), some negative associations between Pb biomarker levels and low birth weight or other measures of fetal growth were observed. The effects of Pb exposure during gestation in animal toxicological studies included mixed findings, but most studies reported reductions in birth weight of pups or birth weight of litters when dams were treated with Pb. Thus, although evidence available was mixed, some associations observed in epidemiologic studies of preterm birth and low birth weight or fetal growth provided suggestive evidence of a causal relationship between Pb exposure and birth outcomes.

Compared to the evidence assessed in the 2013 Pb ISA, the evidence for associations between Pb exposure and birth outcomes in the 2024 Pb ISA is notably stronger due to a recent quasi-experimental study demonstrating decreased probability of preterm birth, decreased probability of low birth weight, decreased probability of SGA, and increased birth weight (Bui et al., 2022). Overall, among the recent

epidemiologic studies, there was a pattern of elevated risk of preterm birth observed across several studies from multiple geographic locations. Additionally, the recent epidemiologic studies of preterm birth included populations for which mean/median maternal blood Pb values were below 10 μg/dL and controlled for wide range of confounders, including GA, other metals, and maternal health factors (e.g., smoking, parity, BMI). There remain uncertainties regarding the critical window for the timing of the exposure (e.g., during pregnancy, at delivery), biomarkers examined for Pb (e.g., maternal blood, cord blood, maternal red blood cells, maternal serum, placental tissue), and evaluation of co-pollutants among the epidemiologic literature with limited supportive evidence in the toxicological literature. While there were no epidemiologic or toxicological studies examining Pb exposure and maternal health outcomes in the 2013 Pb ISA, recent epidemiologic and toxicological studies reported inconsistent results regarding maternal health outcomes and different maternal health outcomes were evaluated between the epidemiologic and toxicological studies. Among the epidemiologic studies, there were consistent null associations between maternal blood (blood, serum, and erythrocytes) Pb levels and GDM in studies that reported mean/median blood Pb below 10 μg/dL. Although some recent epidemiologic studies investigated various pregnancy-related endpoints, the small number of studies limits the ability to judge coherence and consistency across these studies. Among the few toxicological studies that investigated maternal health, the only outcome reported was maternal weight gain during pregnancy. Most studies reported no effects of Pb on maternal weight gain during pregnancy, and the few that reported reductions in maternal weight gain also reported reductions in dam brain weight, a marker often indicative of overt toxicity. This suggests that the observed reduction in maternal weight gain during pregnancy reported in these studies may not be directly due to Pb exposure and may have been influenced by overt toxicity experienced by the dams.

The recent epidemiologic and toxicological studies of birth outcomes reported inconsistent findings overall. Among the recent epidemiologic studies of prenatal growth and Pb exposure, the findings were inconsistent, and no effects on birth weight were reported in the recent toxicological studies. The inconsistencies in the recent epidemiologic studies of prenatal growth and Pb exposure may be due to differences in study design, the timing of the exposure, differences in biomarkers of exposure, and the wide variation in prenatal growth outcomes assessed (birth weight, birth length, HC, GA). A few studies were further limited by small sample size, which may cause imprecision in the measures of association. Recent toxicological studies did not report any effects of Pb exposure on birth weight. Of note is a previous study discussed in the 2013 Pb ISA that reported reduced litter weights at birth were driven by reduced weights in female pups. No recent studies performed separate analyses of birth weight for male and female pups, or they did not assess female pup weights at all. This suggests that the observed lack of effects in recent literature could be due to a lack of sensitivity.

The recent epidemiologic studies of Pb exposure and birth defects, specifically NTDs, CHDs, OFC defects and abdominal congenital malformations, reported inconsistent associations. While the associations were generally null for Pb exposure (measured in placental tissue, umbilical tissue, maternal blood serum, and umbilical cord serum) and NTDs, CHDs, and abdominal congenital malformations,

there were positive associations with OFC defects when Pb was measured in placental tissue or maternal blood. The small number of studies limits the ability to judge consistency and coherence across studies of different birth defects (e.g., NTDs, CHDs, OFC defects, and abdominal congenital malformations), timing of Pb exposure (e.g., second trimester, third trimester, and at delivery), differences in biomarkers (e.g., placental tissue, umbilical tissue, maternal blood serum, and umbilical cord serum, maternal blood), and confounders considered in the analyses. Additionally, the relatively small sample sizes in some studies reduce the statistical power to determine the precision of the associations. Recent toxicological studies report no effects of Pb on birth defects in offspring. This contrasts with some previously reviewed studies that reported defects in offspring of Pb-exposed dams. However, dams in these previous studies also experienced overt toxicity due to the high Pb doses used, which did not occur in recent toxicological studies, suggesting that maternal toxicity may have been involved with the birth defects observed in previous studies.

There were only a few recent epidemiologic studies that evaluated Pb exposure and spontaneous abortion and pregnancy loss. Studies that examine spontaneous abortion are difficult to conduct as many spontaneous abortions or pregnancy losses occur during the first trimester. Women may miscarry before being enrolled in a study and/or women may not have known they were pregnant when they miscarried, thus limiting the ability of a study to detect subtle effects (e.g., if higher Pb exposures lead to increased risk of early spontaneous abortions). In the recent epidemiologic studies, some of the studies assessing spontaneous abortion and/or pregnancy loss were among women who were undergoing treatment at fertility clinics. Detection of spontaneous abortion and/or pregnancy loss is more likely to be ascertained in such clinics, but this study design approach may result in selection bias and limited generalizability of the results because the study populations are not representative of the general population as they have already been diagnosed and are seeking treatment for infertility. In the recent toxicological studies, there were no reported effects of Pb exposure on pre- or postnatal offspring mortality. Although not always consistently so, BLLs were generally lower in recent toxicological literature when compared to previous literature, possibly explaining the observed contrast in results.

There were no epidemiologic studies available that evaluated Pb concentrations and associations with placental function in the 2013 Pb ISA. There were a limited number of recent epidemiologic studies in this area. These cross-sectional studies provide insight into associations between concurrent Pb exposure and placental function, but are limited by their cross-sectional design, making it difficult to establish the temporality of the effects or the critical window of exposure to Pb that might result in changes in the placenta during pregnancy. Further, there were only a small number of cases, which may result in imprecise associations. While previous toxicological evidence included decreased placental weight and histological alterations, these findings were limited to a single study. Recent toxicological studies reported that dams dosed with Pb had reduced placental weight, but some of these studies also reported reduced brain weight in dams, suggesting that overt toxicity may have occurred and could be related to the observed reductions in placental weight.

There were also a number of recent epidemiologic studies that evaluated other outcomes related to maternal health during pregnancy such as biomarkers of fetal immune system, fetal marker for metabolic function, and rTL, but the small number limits the ability to judge the coherence and consistency across these studies. The only additional pregnancy outcome investigated in recent toxicological literature was sex ratio of offspring born to Pb-treated dams. Although most toxicological studies reported no effects of Pb on sex ratio, a single study reported that Pb produced female-skewed litters when compared to control. It is worth noting, however, that the non-Pb-exposed groups were male-skewed and had male:female offspring ratios of 1.4–1.5, whereas Pb-treated groups had male:female ratios of 1 to 1.

In summary, the collective evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and effects on pregnancy and birth outcomes. This determination is largely driven by a recent quasi-experimental study that reported Pb-related changes in birth weight and probability of low birth weight, preterm birth, and small for gestational age, in addition to other studies demonstrating effects between Pb exposure and preterm birth (Table 8-1). Additionally, there were a few high-quality epidemiologic studies that reported associations with relevant BLLs and prenatal growth, birth defects, spontaneous abortion and pregnancy loss, and placental function, but the findings overall were inconsistent. There is uncertainty related to exposure patterns resulting in likely higher past Pb exposures, especially among maternal Pb levels. Additional uncertainties are related to biomarkers of exposure (maternal blood, maternal serum, maternal bone, maternal erythrocytes, cord blood, cord blood serum, placental tissue), the critical window of exposure, and co-pollutants confounding. Of note, the cohorts in the recent epidemiologic literature would generally be expected to have had appreciable past exposures to Pb; however, the extent to which adult BLLs in these cohorts reflect the higher exposure histories is unknown as is the extent to which these past Pb exposures (magnitude, duration, frequency) may or may not elicit effects on pregnancy and birth outcomes. The recent evidence from the toxicological studies mostly reported no effects of Pb across pregnancy and birth outcomes. This may be due to the exclusion of toxicological studies with BLLs greater than 30 μg/dL, indicating the possibility that most pregnancy and birth outcomes are only affected in laboratory animals at levels higher than most environmentally relevant Pb exposure levels.

8.8.2 Summary of Effects on Development

The 2013 Pb ISA concluded that the collective body of evidence integrated across epidemiologic and toxicological studies, based on the findings of delayed pubertal onset among males and females, was sufficient to conclude that there is a causal relationship between Pb exposure and developmental effects. Multiple epidemiologic studies of Pb and puberty in the 2013 Pb ISA showed associations between concurrent BLLs and delayed pubertal onset for girls and boys. In cross-sectional epidemiologic studies of girls (ages 6–18 years) with mean and/or median concurrent BLLs from 1.2 to 9.5 μg/dL, consistent associations with delayed pubertal onset (measured by age at menarche, pubic hair development, and

breast development) were observed. In boys (ages 8–15 years), fewer epidemiologic studies were conducted but associations between BLLs and delayed puberty were observed, including associations among boys in a longitudinal study. These associations were consistently observed in populations with mean or median BLLs of 3.0 to 9.5 μg/dL. Potential confounders considered in the epidemiologic studies of both boys and girls that performed regression analyses varied. Most studies controlled for age and BMI. Other variables, such as measures of diet, socioeconomic status (SES), and race/ethnicity, were included in some of the studies. Adjustment for nutritional factors was done less often and this could be an important confounder. A study using a cohort of girls from NHANES controlled for various dietary factors as well as other potential confounders and reported an association between increased concurrent BLLs and delayed pubertal onset (Selevan et al., 2003). A limitation across most of the epidemiologic studies of BLLs and delayed puberty was the cross-sectional design, which does not allow for an understanding of temporality. There was uncertainty with regard to the exposure frequency, timing, duration, and level that contributed to the associations observed in these studies. Additionally, the toxicological studies reviewed in the 2013 Pb ISA indicated that delayed pubertal onset may be one of the more sensitive developmental effects of Pb exposure with effects observed after gestational exposures leading to BLLs in the female pup of 1.3–13 μg/dL (Iavicoli et al., 2006; Iavicoli et al., 2004). An additional study reviewed in the 2013 Pb ISA reported increases in age at vaginal opening in Wistar rats that were dosed prior to conception and in utero, but BLLs were not reported (Dumitrescu et al., 2008a). These results are supported by studies reviewed in the 2006 Pb AQCD that reported delays in pubertal onset in female rats and mice as measured by age at vaginal opening and age at first estrus (Pine et al., 2006; Dearth et al., 2004; Dearth et al., 2002; Ronis et al., 1998a; Ronis et al., 1998c; Ronis et al., 1996). BLL varied greatly between studies with some reporting effects occurring in dose groups with levels below 30 μg/dL (Dearth et al., 2004; Dearth et al., 2002), while others only report effects in groups with BLLs higher than 30 μg/dL (Ronis et al., 1998a; Ronis et al., 1998c; Ronis et al., 1996). A key study reviewed in the 2006 Pb AQCD, Pine et al. (2006) reported increased age at vaginal opening in Fisher 344 rats that was attenuated by supplementation of IGF-1. However, Pine et al. (2006) only reported BLLs of dams (39.8 μg/dL), making it difficult to determine what BLLs in the offspring may have been achieved to elicit such effects on puberty. Toxicological studies have also reported delayed male sexual maturity as measured by sex organ weight, among other outcomes, seeing significant decrements at BLLs of 20–34 μg/dL (Ronis et al., 1998c; Sokol et al., 1985). Thus, the 2013 Pb ISA concluded that the data from the toxicological literature and from epidemiologic studies demonstrated puberty onset in both males and females was delayed with Pb exposure.

In the 2013 Pb ISA, findings from epidemiologic studies of the effect of Pb on postnatal growth were inconsistent. Findings from the toxicological literature of the effect of Pb exposure on postnatal growth summarized in the 2013 Pb ISA and the 2006 Pb AQCD were fairly consistent, and most studies showed decreases in body weight of Pb-exposed offspring at postnatal time points, while one study reported an increase in body weight at 1 year of age in male offspring only.

The 2013 Pb ISA summarized some toxicological evidence that demonstrated the effect of Pb on other developmental outcomes, including impairment of retinal development, effects on the lens of the eye, and alterations in the developing hematopoietic, hepatic systems and teeth. No studies that investigated more classic toxicological developmental milestones (e.g., eye slit formation, eye opening, pinna detachment) were reported in the 2013 Pb ISA.

In the recent epidemiologic and toxicological literature, the relationships between Pb exposure and puberty onset in both females and males, as well as postnatal growth, were reviewed. While there were no recent PECOS-relevant toxicological studies in puberty in either females or males, the recent epidemiologic studies reported consistent patterns of association between blood Pb exposure and delayed age of menarche (Gomula et al., 2022; Jansen et al., 2018; De Craemer et al., 2017; Sławińska et al., 2012) and some indication of slower breast development (Nkomo et al., 2018; De Craemer et al., 2017) in females, which is similar to the findings from the epidemiologic studies reviewed in the 2013 Pb ISA. However, the associations between Pb exposure and male pubertal onset were inconsistent among the cross-sectional studies. The differences in markers of puberty in males (hormone levels, pubic hair development, genital development, TV) may explain the inconsistencies in findings across recent studies. While the studies assessing Pb exposure and female and male puberty were limited by differences in the timing of exposure to Pb or Pb biomarker (blood, maternal bone, cord blood), these studies consider a wide range of confounders, including height, weight, and BMI.

The recent toxicological and epidemiologic studies that evaluated the relationship between Pb exposure and postnatal growth were inconsistent. The majority of recent toxicological studies did not report changes in postnatal growth due to Pb exposure (Zhao et al., 2021; Xie et al., 2020; Rao Barkur and Bairy, 2016; Basha and Reddy, 2015; Basgen and Sobin, 2014). However, some recent toxicological studies reported decreases (Duan et al., 2017; de Figueiredo et al., 2014; Graham et al., 2011) and increases (Betharia and Maher, 2012) in body weight of offspring due to Pb exposure. Among epidemiologic studies that evaluated the associations between blood Pb and postnatal growth in children (older than 4 years) there were more consistent patterns of associations of decreased height and weight (Signes-Pastor et al., 2021; Kuang et al., 2020; Zhou et al., 2020; Deierlein et al., 2019; Kerr et al., 2019; Choi et al., 2017). Overall, there were negative associations between Pb exposure and specific postnatal growth outcomes among the cross-sectional studies. However, among cohort studies, there were some inconsistencies in the associations of Pb exposure and different postnatal growth outcomes. These inconsistencies in the cohort studies may be due to differences in the timing of when Pb exposure was measured, the biomarker of Pb exposure (maternal blood, maternal bone, cord blood, infant blood, childhood blood), and the timing of the outcome. The current inconsistent findings of exposure to Pb and postnatal growth are similar to those reported in the 2013 Pb ISA.

There was a small body of epidemiologic studies across various other developmental effects; however, the small number of studies limits the ability to judge coherence and consistency across these studies, although the associations reported demonstrate that Pb exposure could result in physiological

responses that contribute to adverse developmental effects, including changes to diurnal cortisol rhythms, lower salivary sialic acid levels, and oxidative stress damage to DNA from Pb exposure among children during developmental periods. Recent studies that investigate other developmental outcomes such as developmental milestones are scarce. Some toxicological studies investigated developmental milestones in rodents (e.g., pinna detachment, eye slit formation, eye opening, tooth eruption, and fur development), but no effects of Pb exposure were reported on any of these milestones in groups with PECOS-relevant BLLs.

In summary, the collective evidence is sufficient to conclude a *causal relationship* exists between Pb exposure and effects on development. The key evidence is outlined in Table 8-1. While there were no recent PECOS-relevant toxicological studies that investigated the impacts of Pb on puberty in either females or males, previous toxicological evidence demonstrated that Pb exposure consistently delayed pubertal onset in female rodents. Of note is one key previous toxicological study (Pine et al., 2006) which demonstrated that delayed pubertal onset in female rats developmentally exposed to Pb could be completely attenuated by supplementation with IGF-1. Further, the recent epidemiologic studies reported consistent patterns of associations between blood Pb exposure and delayed age of menarche and some indication of slower breast development in females, which is similar to the findings from the epidemiologic studies reviewed in the 2013 Pb ISA. The few recent cohort studies of male pubertal onset found consistent associations between Pb exposure and delayed onset. Recent cross-sectional studies reported inconsistent results, possibly due to differences in the markers of puberty examined (hormone levels, pubic hair development, genital development, TV). Though the effects of Pb exposure on postnatal growth were inconsistent overall, there was some evidence from toxicological studies indicating reduced body weight of offspring and from epidemiologic studies reporting associations between blood Pb and decreased height and weight in children. The cohorts in the recent epidemiologic literature would generally be expected to have had appreciable past exposures to Pb; however, the extent to which adult BLLs in these cohorts reflect the higher exposure histories is unknown, as is the extent to which these past Pb exposures (magnitude, duration, frequency) may or may not elicit developmental effects such as decreased postnatal growth or disrupted puberty. Toxicological evidence supports biologically plausible pathways of how Pb exposure exerts its effects on pubertal onset (Li et al., 2016; Li et al., 2014; Pine et al., 2006; Dearth et al., 2002; Ronis et al., 1998b), including studies suggesting that Pb may impact pubertal onset via dysregulation of IGF-1 resulting in a cascade of effects that alters levels of hormones important during the pubertal period.

8.8.3 Summary of Effects on Female Reproductive Function

The 2013 Pb ISA concluded that the available evidence was suggestive of a causal relationship between Pb exposure and female reproductive function. Epidemiologic and toxicological studies of reproductive function among females investigated whether Pb biomarker levels were associated with hormone levels, fertility, menstrual/estrous cycle changes, and altered morphology or histology of female

reproductive organs. Two previous toxicological studies conducted in non-human primates reported disrupted menstrual cyclicity and reduced progesterone, although another non-human primate study with lower BLLs than the other studies (<40 μg/dL versus 44–89 μg/dL) reported no effects on menstrual cyclicity. Some previous toxicological studies in rodents also demonstrated impacts of Pb exposure on estrous cyclicity, but of note is the high BLLs in treated animals (63.2–264 μg/dL). Some of the epidemiologic studies reviewed in the 2013 Pb ISA reported associations with concurrent BLLs and altered hormone levels in adults, but results varied among studies, possibly due to the different hormones examined and the different timing in menstrual and lifecycles. There was some evidence of a potential relationship between Pb exposure and female fertility, but findings were mixed. The majority of the epidemiologic studies were cross-sectional and adjustment for potential confounders varied from study to study, with some potentially important confounders, such as BMI, not included in all studies. Further, most of the epidemiologic studies on female reproductive function reviewed in the 2013 Pb ISA had small sample sizes and were generally conducted in women attending infertility clinics. Previous toxicological studies reported inconsistent effects of Pb on female fertility outcomes in rodents (reduced litter size, reduced number of litters produced), while all recent toxicological studies reported no effects of Pb exposure on female fertility outcomes. Studies that reported impacts of Pb on female fertility outcomes tended to use higher doses, longer dosing durations, and/or concurrently exposed sires in addition to dams, which may explain the observed contrast between studies. Although epidemiologic and toxicological studies provide information on different exposure periods, both types of studies, including some high-quality epidemiologic and toxicological studies, supported the conclusion that Pb may affect some aspects of female reproductive function.

There were no recent PECOS-relevant toxicological studies of the effects of Pb exposure on hormone levels in females or menstrual/estrous cyclicity; however, there were several recent epidemiologic studies. The recent epidemiologic studies examining the relationship between Pb exposure and hormone levels reported consistent positive associations between blood Pb and FSH and LH in women who were post-menopausal. While these studies were limited by their cross-sectional study design, the studies were conducted in well-established population-based surveys. These studies considered a range of confounders, including controlling for BMI, smoking, and co-exposure with Cd, but not all studies adjusted for some potential important confounders such as age at menarche, pregnancy history, oral contraceptive use, and female hormone use, such as IVF or hormone therapy. Additionally, the recent studies examining the relationship between menopause and Pb exposure found consistent positive associations of early risk of menopause. The results from a study of concurrent exposure of blood Pb with menopause were supported by the results from a longitudinal cohort that reported that bone Pb, a cumulative biomarker of Pb exposure, was associated with difference in age at menopause and risk of early menopause.

Among the recent epidemiologic studies, there were inconsistent associations between Pb exposure and female fertility. In studies among participants in the general population, there was an increased risk of self-reported infertility and longer time to pregnancy (Lee et al., 2020; Louis et al.,

2012). However, among studies with women who were either seeking help at a fertility clinic or reported infertility the associations were inconsistent. Because the study participants included only a small sample of women who were either seeking help at a fertility clinic or self-reported infertility, selection bias may exist and limits the generalizability of the results. Additionally, these studies were limited by the concurrently measured exposure and outcome, different biomarkers of exposure (blood, serum, and follicular fluid), and a small number of participants. These studies did include adjustment for potential confounders, including age, BMI, and partner exposure. The recent toxicological studies in female fertility did not observe alterations in the number of litters or the litter size in Pb-exposed dams that began dosing prior to conception.

There was only a single recent epidemiologic study evaluating the association between Pb exposure and morphology or histology of female sex organs (ovaries, uterus, fallopian tubes/oviducts, cervix, vagina, and/or mammary glands) and no recent PECOS-relevant toxicological studies. The results from the single epidemiologic study reported null associations between blood Pb and rate of uterine fibroids and uterine fibroid volume, but women with uterine fibroids had higher geometric mean BLLs than women without fibroids (1.43 μg/dL versus 1.35 μg/dL, respectively).

In summary, the collective body of evidence is sufficient to conclude that there is *likely to be a causal relationship* between Pb exposure and female reproductive function. The strongest line of evidence is from recent epidemiologic studies examining the relationship between Pb exposure and effects on hormone levels and menstrual/estrous cyclicity (Table 8-1). Positive associations from a longitudinal cohort between bone Pb, a biomarker of cumulative Pb exposure, and both earlier age at menopause and risk of early menopause were supported by results from a cross-sectional NHANES study of concurrent exposure of blood Pb with earlier age at menopause. Additionally, recent epidemiologic studies found consistent positive associations between blood Pb and FSH and LH in women who were post-menopausal. While these studies are limited by their cross-sectional study design, the studies were conducted in well-established population-based surveys. These studies considered a range of confounders, even co-exposure to other metals, but not all studies adjusted for some potential important confounders such as age at menarche, pregnancy history, oral contraceptive use, and female hormone use, such as IVF or hormone therapy. While there were no recent PECOS-relevant toxicological studies that examined the effects of Pb on hormone levels in females or menstrual or estrous cyclicity, previous toxicological evidence suggests that Pb may disrupt reproductive hormones and menstrual and estrous cyclicity in females. Two toxicological studies in rats reported disruptions in estrous cyclicity, and two toxicological studies based in non-human primates reported alterations to different menstrual cycle aspects (e.g., length of cycle, length of menstruation) and reproductive hormone levels. Additional rodent studies reported effects of Pb on circulating reproductive hormone levels, including sex steroid hormones (progesterone, testosterone, and E2) and gonadotropin hormones (LH and FSH).

8.8.4 Summary of Effects on Male Reproductive Function

The 2013 Pb ISA concluded that there was sufficient evidence to support a causal relationship between Pb exposures and male reproductive function. This determination was based on toxicological evidence of sperm/semen production, quality, and function with supporting evidence in the epidemiologic studies, in addition to evidence supportive for a mode of action. Previous toxicological studies with relevant Pb exposure routes reported effects on rodent sperm quality and sperm production rate (BLL range: 34–37 µg/dL) (Sokol and Berman, 1991; Sokol et al., 1985), sperm DNA damage (BLL of 19 and 22 µg/dL) (Nava-Hernández et al., 2009), and histological or ultrastructural damage to the male reproductive organs in studies from rodents (BLL of 5.1 µg/dL) (El Shafai et al., 2011) and non-human primates (BLL of 43 µg/dL) (Cullen et al., 1993). These effects were found in animals exposed to Pb during peripuberty or adulthood for 1 week to 3 months. The toxicological studies reported that Pb exposure decreased reproductive organ weight and caused histological changes in the testes and germ cells. Subfecundity (decreased number of pups born/litter) was reported in unexposed females mated to Pb-exposed males. Also, sperm from Pb-exposed rats (BLLs: 33 to 46 µg/dL) used for IVF of eggs harvested from unexposed females yielded lower rates of fertilization (Sokol et al., 1994). Supporting evidence was provided by decrements in sperm quality from rabbits administered Pb subcutaneously (BLLs of 25 µg/dL) (Moorman et al., 1998).

The 2013 Pb ISA reported detrimental effects of Pb on sperm observed in epidemiologic studies with concurrent BLLs of 25 µg/dL and greater among men occupationally exposed (Hsu et al., 2009; Kasperczyk et al., 2008; Naha and Manna, 2007; Naha and Chowdhury, 2006). Findings of these epidemiologic studies are limited due to these high exposure levels among the occupational cohorts and the lack of consideration for potential confounding factors, including occupational exposures other than Pb. Studies among men with lower Pb levels were limited to infertility clinic studies, which may produce a biased sample and findings that lack generalizability. However, a well-conducted epidemiologic study that enrolled men going to a clinic for either infertility issues or to make a semen donation and controlled for other metals and smoking reported a positive association of blood Pb with various detrimental effects in sperm (Telišman et al., 2007). The median concurrent BLL in this study was 4.92 µg/dL (range: 1.13–14.91). A similar study also reported possible associations between concurrent blood Pb and various semen parameters, but the results were extremely imprecise (large confidence intervals [CIs]), making it difficult to draw conclusions (Meeker et al., 2008).

The epidemiologic and toxicological studies in the 2013 Pb ISA reported inconsistent results regarding hormone aberrations associated with Pb exposure. Due to the complexity of the reproductive system, uncertainty exists as to whether Pb exerts its toxic effects on the reproductive system by affecting the responsiveness of the hypothalamic-pituitary-gonadal axis by suppressing circulating hormone levels or by some other pathway. Inconsistent findings were also apparent among epidemiologic studies of fertility among men.

Toxicological studies from the 2013 Pb ISA suggested that oxidative stress was a major contributor to the effects of Pb exposure on the male reproductive system, providing mode of action support. The effects of ROS may involve interference with cellular defense systems leading to increased lipid peroxidation and free radical attack on lipids, proteins, and DNA. Several studies showed that Pb induced germ cell injury (as evidenced by aberrant germ cell structure and function) and increased generation of ROS within the male sex organs. Co-administration of Pb with various antioxidant compounds either eliminated Pb-induced injury or greatly attenuated its effects. In addition, many studies that observed increased oxidative stress also observed increased apoptosis, which is likely a critical underlying mechanism in Pb-induced germ cell dysfunction.

Recent epidemiologic and toxicological studies examined Pb exposure and male reproductive function, including sperm/semen production, quality, and function; hormone levels; fertility; and morphology and histology of male sex organs. Among the studies that evaluated the relationship of Pb exposure and sperm/semen production and quality, there was consistent evidence of effects when the exposure metric was blood Pb. In the recent epidemiologic studies, there were consistent associations of decreased sperm/semen production and quality with increased blood Pb, but there were inconsistent associations when Pb was measured in seminal fluid or seminal plasma. The majority of the epidemiologic studies that evaluated the associations of Pb and sperm/semen production and quality were cross-sectional studies conducted in males attending fertility clinics, limiting the generalizability of the results. The studies were further limited by concurrent measurement of exposure and outcome, different biomarkers of Pb, different seminal parameters, exposure circumstances (historical exposure, magnitude, duration, timing, and frequency), and small sample sizes. Despite these limitations, it is important to note that a wide variety of potential confounders were considered, including controlling for hormone levels. The recent toxicological studies support the findings from the epidemiologic studies. Among the recent toxicological studies, the majority reported that Pb exposure negatively impacted sperm/semen production and quality, although these studies were limited to a single species, and no recent toxicological studies reported on the effects of Pb on sperm or semen parameters in any other laboratory animal species.

There were a limited number of recent epidemiologic and toxicological studies that examined the relationship between Pb and hormones in males. While recent epidemiologic and toxicological studies reported changes in hormone levels among males, the direction of the observed relationships differed across disciplines. Specifically, the epidemiologic studies reported Pb-associated increases in testosterone, whereas the toxicological studies reported a reduction in testosterone following exposure to Pb. Additionally, recent cross-sectional epidemiologic studies reported inconsistent associations between blood Pb and other sex hormones. One study reported positive associations between blood Pb and SHBG, FSH, and LH, as well as positive trends among quartiles of blood Pb, suggestive of a potential exposure-response relationship. In contrast, an NHANES study reported null associations between blood Pb and E2, fE2, androstenedione glucuronide, and SHBG. Recent toxicological evidence regarding the effects of Pb on male sex hormones is limited to a single study that reported that exposure through the dam's milk

from birth to weaning (PND 21) in CD-1 mice was sufficient to reduce testosterone in the serum at weaning and on PND 70.

The recent epidemiologic and toxicological studies of Pb exposure and male fertility were limited. In the recent epidemiologic studies, male fertility was measured by IVF outcomes. There were inconsistent associations with Pb exposure and male fertility, with one study reporting blood Pb was associated with longer time to pregnancy, but another reported a positive association between Pb in seminal plasma and the possibility of obtaining a viable embryo. Differences in Pb biomarkers and difference in outcomes might explain the inconsistencies of the associations among these studies. The males in these studies were also recruited from fertility clinics, which might have resulted in selection bias and limits the generalizability of the results. A single recent toxicological study reported that sperm from Pb-exposed mice had reduced fertilization capacity, resulting in fewer fertilized oocytes in vitro.

There were a limited number of studies of Pb exposure and morphology or histology of male sex organs. There was only a single recent epidemiologic study that reported decreased TV, shorter anopenile distance, and shorter anoscrotal distance with maternal serum Pb exposure. Among the recent toxicological studies, Pb exposure resulted in effects in the morphology or histology of male sex organs. Alterations in testis weight were inconsistent with some studies reporting Pb-induced decreases in testis weight and some reporting that testis weight was unaffected by Pb treatment. However, of the studies that reported on this outcome, only those that dosed prior to weaning reported that Pb treatment reduced testis weight, suggesting that this outcome may be more sensitive to developmental exposures. Few studies investigated the effects of Pb on accessory sex organ weight in males, and of the few studies available, no effects of Pb were reported on weight of the prostate, seminal vesicles, or epididymides. Testicular histopathology was consistently altered by Pb exposure, often resulting in visible changes to the seminiferous tubules and surrounding tissue. Toxicological studies also reported Pb-induced changes in cellular structures in the epididymides.

In summary, the collective body of evidence is sufficient to conclude a *causal relationship* exists between Pb exposure and male reproductive function. There is coherent evidence across the epidemiologic and toxicological studies of detrimental effects of Pb exposure on male reproductive function (Table 8-1). The strongest evidence of effects of Pb on male reproductive function is seen in the consistency of the reported effects of Pb on sperm and semen parameters in both toxicological and epidemiologic studies. However, the recent epidemiologic and toxicological studies suggest that Pb exposure may also result in alterations in testosterone levels, fertility, and changes in morphology or histology of male sex organs. Epidemiologic studies consistently report associations between Pb measured in blood and decreased sperm/semen production and quality, and toxicological studies consistently report Pb-induced reductions of a variety of semen parameters such as sperm density, motility, viability, and normal sperm morphology. There are biological plausible pathways through which Pb exposure may alter sperm/semen production and quality. Specifically, Pb exposure has been shown to cause oxidative stress, which can damage the supportive somatic cells in the testis (Leydig cells and

Sertoli cells) as well as damage the sperm cells directly. Supportive somatic cells are responsible for producing sex steroid hormones and regulating spermatogenesis, and disruption of either of these functions can impact the quality and quantity of the sperm produced.

Table 8-1 Summary of evidence contributing to causality determinations for Pb exposure and reproductive and developmental effects

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
Effects on Pregnancy and Birth Outcomes – Likely to be Causal			
A few high-quality epidemiologic studies of Pb levels and preterm birth demonstrate associations	Evidence in a single quasi-experimental study and some high-quality epidemiologic studies demonstrates associations with preterm birth. There is uncertainty related to exposure patterns resulting in likely higher past Pb exposure, especially among maternal Pb levels.	Bui et al. (2022) Jelliffe-Pawlowski et al. (2006) Vigeh et al. (2011) See Section 8.3	Maternal BLLs: >10 µg/dL
A few high-quality epidemiologic studies show associations with relevant BLLs, but findings are overall inconsistent	Inconsistent findings for studies for maternal health outcomes, prenatal growth, birth defects, spontaneous abortion and pregnancy loss, and placental function. There is uncertainty related to exposure patterns resulting in likely higher past Pb exposure, especially among maternal Pb levels. Additional uncertainties regarding biomarker of exposure (maternal blood, maternal serum, maternal bone, maternal erythrocytes, cord blood, cord blood serum, placental tissue) and the critical window of exposure.	See Section 8.3	Maternal BLLs: 0.32–6.7 µg/dL Cord blood Pb: 0.37–10.78 µg/dL
Inconsistent toxicological evidence	Previous studies report reduced BW, but recent studies report few impacts of Pb on BW, abortion, still birth, maternal weight gain, birth defects, or placental weight and histology.	See Section 8.3	Placental weight altered at BLLs as low as 12.42 µg/dL
Effects on Development – Causal			
Delayed Puberty Onset			
Consistent associations with relevant BLLs in high-quality epidemiologic studies	Consistent evidence in multiple cross-sectional and longitudinal epidemiologic studies for females and males. Most of these studies have large sample sizes	See Section 8.4.2.1 and Section 8.4.3.1	Female Puberty BLLs: 0.65–6.57 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
	and controlled for potential confounding by covariates such as age and BMI.		Male Puberty BLLs: 0.66–6.5
Consistent toxicological evidence with relevant Pb exposures	Consistent toxicological evidence from multiple laboratories of delayed male and female puberty onset with Pb exposure via diet, drinking water, or oral gavage in rodents	Pine et al. (2006) Iavicoli et al. (2006) Dumitrescu et al. (2008a) Ronis et al. (1998a) Ronis et al. (1998c) Dearth et al. (2002) Dearth et al. (2004) Ronis et al. (1996) Iavicoli et al. (2004) Sokol et al. (1985)	Markers of pubertal onset reduced in animals with BLLs as low as 12.7 µg/dL
Evidence clearly describes biological plausibility	Toxicological evidence supports hypothalamic-pituitary-gonadal axis dysfunction and changes in IGF-1 contributing to Pb-induced delay in puberty onset.	Pine et al. (2006) Dearth et al. (2002)	Pine et al. (2006) reported dam BLLs to be 39.8 µg/dL at the time of mating; Dearth et al. (2002) reported dam BLLs to be 25.4 µg/dL at weaning
Postnatal Growth			
Available epidemiologic evidence is inconsistent	Multiple studies, mostly cross-sectional, for children of varying ages have reported inconsistent results for the association between BLLs and various measures of growth. There is uncertainty related to exposure patterns resulting in likely higher past Pb exposure, especially among maternal Pb levels. Additional uncertainties regarding biomarkers of exposure (maternal blood, maternal serum, maternal bone, maternal erythrocytes, cord blood, cord blood serum, placental tissue) and the critical window of exposure.	See Section 8.4.1.1	Maternal BLLs: 0.5–10.1 µg/dL Cord blood Pb: 0.91–3.1 µg/dL
Available toxicological evidence is inconsistent	There are inconsistent findings in the toxicological literature on Pb exposure and postnatal growth.	See Section 8.4.1.2	BLLs ranged from 0.0318–29.16 µg/dL

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
Effects on Female Reproductive Function – Likely to be Causal			
A few high-quality epidemiologic studies of Pb levels and hormones demonstrate associations	Evidence in some high-quality cross-sectional epidemiologic studies demonstrates associations with hormone levels but results are mixed based on the hormone examined. There is uncertainty related to exposure patterns resulting in likely higher past Pb exposure.	Krieg and Feng (2011) Chen et al. (2016) Lee et al. (2019)	BLLs: 1.6–4.1 µg/dL
A few high-quality epidemiologic studies of Pb levels and menopause demonstrate associations	Evidence in some high-quality epidemiologic studies demonstrates associations with menopause. There is uncertainty related to exposure patterns resulting in likely higher past Pb exposure.	Mendola et al. (2013) Eum et al. (2014)	BLLs: 1.21–3.0 µg/dL Bone Pb Tibia: 10 µg/g Patella: 12 µg/g
Available epidemiologic studies of Pb levels and fertility are inconsistent	Epidemiologic studies of this association are limited by the small sample sizes included in those studies. In addition, most of the study populations were drawn from women undergoing IVF and/or attending infertility clinics. There is uncertainty related to exposure patterns resulting in likely higher past Pb exposure.	See Section 8.5.2.1	BLLs: 0.50–2.13 µg/dL
Available toxicological evidence is inconsistent.	Recent toxicological evidence is scarce and reports no effects of Pb on litter size and number of litters in exposed dams. Previous evidence reports inflammation, decreased ovarian antioxidant capacity, altered ovarian steroidogenesis.	See Section 8.5 See Section 4.8.4 from U.S. EPA (2013)	BLLs ranged from 7.72–12.61 µg/dL in dams in recent literature
Effects on Male Reproductive Function – Causal			
Sperm/Semen Production, Quality, and Function			
High-quality and consistent toxicological evidence with relevant Pb exposures to rule out chance, bias, and confounding with reasonable confidence.	Decreased sperm counts, decreased sperm production rate, dose-dependent suppression of spermatogenesis in rodents with drinking water Pb exposure.	See Section 4.8.3.1 from U.S. EPA (2013) See Section 8.6.1	BLL after adult drinking water exposure for 30 d: 34 µg/dL BLL after peripubertal or adult drinking water exposure for 30 d: 35 and 37 µg/dL.

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
	Ultrastructural and histological damage to non-human primate testis and seminiferous tubules		Maximum BLLs after daily oral Pb exposure (gelatin capsule) during infancy, post infancy, or over a lifetime (up to 10 yr): 32 to 36 µg/dL
	Histologic damage to rodent seminiferous tubules including spermatids and developing sperm.		BLL after adult exposure (oral gavage) for 3 mo: 5.31 µg/dL
	Ultrastructural abnormalities to rat spermatogenesis.		BLL after i.p. injection for 16 d: 7.4 µg/dL
	Direct effects on rodent sperm DNA after drinking water Pb exposure.		BLL after adult exposure for 13 wk: 19 and 22 µg/dL
	Sperm from Pb exposed rats used for IVF of eggs harvested from unexposed females yielded lower rates of fertilization.		BLL after adult exposure for 14–60 d: 33–46 µg/dL
	Semen and sperm quality in rabbits with subcutaneous Pb treatment; ultrastructural damage to spermatids with i.p. injection of Pb.		BLL after adult exposure for 15 wk: 16–24 µg/dL
Available epidemiologic evidence is inconsistent	The few epidemiologic studies examining this outcome generally have small samples sizes and are drawn from men attending infertility clinics. There is uncertainty related to exposure patterns resulting in likely higher past Pb exposure and biomarker of exposure (blood, semen, seminal plasma, seminal fluid).	See Section 8.6.1.1	BLLs: 2.18–3.26 µg/dL
Available toxicological evidence consistently reports alterations of sperm and semen parameters	Consistent reductions of sperm with normal morphology, sperm density, and sperm viability.	See Section 8.6.1	BLLs ranged from 5.09–11.8 µg/dL at time of outcome assessment

Rationale for Causality Determination[a]	Key Evidence[b]	Key References[b]	Pb Biomarker Levels Associated with Effects[c]
Hormone Levels			
A few high-quality epidemiologic studies of Pb levels and hormones demonstrate associations	Evidence in some high-quality cross-sectional epidemiologic studies demonstrates associations with testosterone levels and adult males, but inconsistent associations with other hormones. A longitudinal study among male adolescents reported null associations with hormone levels.	See Section 8.6.2.1	Concurrent BLLs: 1.0–4.4 µg/dL
Available toxicological evidence is inconsistent	Evidence for testosterone is inconsistent across studies and few studies are available for other male sex hormones.	See Section 8.6.2 See Section 4.8.3.2 from U.S. EPA (2013)	Recent study reported effects at BLLs of 5.09 and 19.1 µg/dL at time of outcome assessment
Fertility			
Lack of large, well-conducted epidemiologic studies but overall inconsistent evidence	The few epidemiologic studies examining this outcome generally have small samples sizes and are drawn from men attending infertility clinics. There is uncertainty related to exposure patterns resulting in likely higher past Pb exposure and biomarker of exposure (blood, semen).	See Section 8.6.3.1	BLLs: 1.03–1.27 µg/dL
Limited toxicological evidence	Few toxicological studies investigate male fertility, but most report reductions in fertility outcomes such as fertilized oocytes in recent literature and number of offspring per litter in previous studies	See Section 8.6.3 See Section 4.8.3.3 from U.S. EPA (2013)	Recent study reported effects at BLLs of 9.4 µg/dL

BLL = blood lead level; BMI = body mass index; BW = birth weight; d = day(s); IGF-1 = insulin-like growth factor 1; IVF = in vitro fertilization; mo = month(s); Pb = lead; wk = week(s); 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.

8.9 Evidence Inventories – Data Tables to Summarize Study Details

Table 8-2 Epidemiologic studies of exposure to Pb and maternal health outcomes

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Gestational Diabetes Mellitus					
Shapiro et al. (2015) Canada 2008–2011 Cohort	MIREC n: 1274 Women at least 18 yr of age during the first trimester of pregnancy (6 to <14 wk gestation) with singleton, live births	Blood Maternal blood was measured by ICP-MS Age at Measurement: Maternal age during first trimester of pregnancy Geometric mean: Normal glucose: 0.6 µg/dL IGT cases: 0.6 µg/dL GDM cases: 0.6 µg/dL Quartiles (µg/dL): Q1: 0.2–0.4 Q2: 0.5–0.6 Q3: 0.6–0.9 Q4: 0.9–4.1	Maternal health during pregnancy: GDM IGT and GDM were assessed by chart review based on the results of a 50-g glucose challenge test and 75 or 100-g OGTT Age at outcome: Maternal age at IGT or GDM diagnosis during pregnancy	Logistic regression models were adjusted for maternal age, race, pre-pregnancy BMI, and education	OR (95% CI): GDM vs. normal glucose Q1: Reference Q2: 0.8 (0.3, 1.9) Q3: 0.6 (0.2, 1.6) Q4: 1.1 (0.5, 2.6) p for trend: 0.87 IGT vs. normal glucose Q1: Reference Q2: 0.8 (0.4, 1.8) Q3: 0.6 (0.2, 1.3) Q4: 0.9 (0.4, 2.1) p for trend: 0.62 GDM or IGT vs. normal glucose Q1: Reference Q2: 0.8 (0.4, 1.5) Q3: 0.6 (0.3, 1.1) Q4: 1.0 (0.6, 1.8) p for trend: 0.76

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Soomro et al. (2019) Poitiers and Nancy France February 2003 to January 2006 Cohort	Etude des Déterminants pré et post natals du développement de la santé de l'Enfant study n: 623 Pregnant women between 24 and 28 wk of gestation	Blood Maternal blood measured by EAAS with Zeeman background correction Age at Measurement: Maternal age at 24–28 wk gestation Geometric mean[c]: 1.62 µg/dL Median[c]: 1.7 µg/dL 75th[c]: 2.2 µg/dL 95th[c]: 3.8 µg/dL Max[c]: 8.0 µg/dL	Maternal health during pregnancy: GDM At 24–28 wk, maternal blood glucose concentrations were measured 1 hr after a 50 g glucose challenge. The GDM was diagnosed by using the OGTT when there were >2 blood glucose concentrations greater than the following cut points: fasting = 95 mg/dL, at 1 hr = 180 mg/dL, at 2 hr = 155 mg/dL, and at 3 hr = 140 mg/dL Age at outcome: Maternal age at 24–28 wk gestation	Multiple logistic regression models were adjusted for maternal smoking, maternal age, maternal BMI, maternal education level, pregnancy-induced hypertension, and number of siblings	OR (95% CI): GDM vs. normal glucose: 1.318 (0.895, 1.94) IGT vs. normal glucose: 0.853 (0.676, 1.077) GDM or IGT vs. normal glucose: 0.86 (0.682, 1.084)
Oguri et al. (2019) Japan January 2011 to March 2014 Cohort	JECS n: 16,955 Pregnant women from 15 Regional Centers throughout Japan who had single pregnancies, did not have a history of diabetes, or receive insulin treatment, and hypoglycemic agents during pregnancy; did not use steroids during pregnancy	Blood Maternal blood was measured by ICP-MS Age at Measurement: Maternal age at 22 to 28 wk of gestation Geometric mean non-GDM: 6.05 ng/g GDM: 6.13 ng/g Max: 70.9 ng/g Quartiles (ng/g): Q1: ≤5.00 Q2: 5.1–10.0	Maternal health during pregnancy: GDM Pregnant women were diagnosed with GDM if the results of a 75 g, 2 hr OGTT exceeded: fasting = 92 mg/dL (5.1 mmol/L); 1 hr = 180 mg/dL (10.0 mmol/L); and 2 hr = 153 mg/dL (8.5 mmol/L) Age at outcome: maternal age at diagnosis of GDM	Logistic regression models adjusted for maternal age at birth, pre-pregnancy BMI, pregnancy-induced hypertension, and pack-years in the nulliparous models and maternal age at birth, pre-pregnancy BMI, history of GDM, pregnancy-induced hypertension, and pack-years in the parous models; Model 1 was a multi-pollutant model with both Cd and Pb; Model 3 was a single pollutant model of Pb	OR (95% CI): Model 1: Nulliparous: Q1: Reference Q2: 1.22 (0.75, 1.97) Q3: 1.60 (0.72, 3.55) Q4: 2.51 (0.72, 8.72) Parous: Q1: Reference Q2: 0.88 (0.65, 1.20) Q3: 0.79 (0.41, 1.41) Q4: 0.31 (0.04, 2.29) Model 3:

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Q3: 10.1–15.0 Q4: ≥15.1			Nulliparous: Q1: Reference Q2: 1.19 (0.74, 1.91) Q3: 1.55 (0.70, 3.42) Q4: 2.42 (0.70, 8.40) Parous: Q1: Reference Q2: 0.89 (0.66, 1.20) Q3: 0.75 (0.41, 1.39) Q4: 0.30 (0.04, 2.23)
Wang et al. (2019) Taiyuan China 2012–2016 Case-control	n: 776 cases and 776 controls Women aged 18 yr or older with GA of 20 wk or more and without mental illness were eligible for the study. Women who had stillbirths or birth defects, who had multiple births, who did not donate blood samples, or who had gestational weeks less than 29 wk were excluded	Blood Maternal blood was measured by ICP-MS Age at Measurement: Mean maternal age for GDM: 31.00 yr Mean maternal age for non-GDM: 30.97 yr Median[c]: 2.7968 µg/dL 75th[c]: 3.5981 µg/dL Tertiles (µg/dL): Low: <2.254 Middle: 2.254–3.323 High: ≥3.323	Maternal health during pregnancy: GDM GDM diagnosis was based on a 75 g OGTT during gestational weeks 24 and 28. Women who met one or more of the following criteria were diagnosed with GDM: (1) fasting blood glucose was more than 5.1 mmol/L, (2) 1 hr blood glucose >10.0 mmol/L, or (3) 2 hr blood glucose >8.5 mmol/L Age at outcome: maternal age at gestational weeks 24–28	Logistic regression models adjusted for pre-pregnancy BMI, gestational weight gain, physical activity, parity, family history of diabetes, and month of conception; the multi-pollutant model was also adjusted for nickel, As, Cd, antimony, thallium, Hg, and Pb	OR (95% CI): Single Pollutant Pb Model: Low: Reference Middle: 1.04 (0.81, 1.35) High: 1.01 (00.78, 1.30) p for trend: 0.963 Multi-pollutant Model: Low: Reference Middle: 1.06 (0.80, 1.41) High: 110 (0.80, 1.51) p for trend: 0.622
Zhou et al. (2021b) China	n: 8169 Pregnant women of GA in the first trimester (<14 wk) and singleton	Blood Maternal (serum) analyzed by polarography method	Maternal health during pregnancy: GDM GDM was diagnosed by the 75 g OGTT according to	Logistic regression analyses: Model 1 adjusted for maternal age, parity, first trimester BMI, history of spontaneous abortion, history of ectopic	OR (95% CI) Model 1: T1: Reference T2: 1.05 (0.90, 1.21)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
January 2017–December 2018 Cohort	pregnancy with no diabetes prior to pregnancy were recruited from their first prenatal visit to the Southern Medical University Affiliated Foshan Women and Children's Hospital.	Age at measurement: maternal mean age: 30.14 yr Median[2c]: 2.53 µg/dL 75th[c]: 4.00 µg/dL Tertiles (µg/dL): T1: ≤1.96 T2: 1.961–3.41 T3: ≥3.411	the International Association for Diabetes in Pregnancy Study Group's criteria. Age at outcome: maternal mean age: 30.14 yr	pregnancy, family history of diabetes, family history of hypertension; Model 2 adjusted for Model 1 plus other five (Mn, copper, calcium, zinc, and magnesium) metals	T3: 0.89 (0.76, 1.03) Model 2: T1: Reference T2: 1.05 (0.90, 1.22) T3: 0.89 (0.76, 1.04)
Zheng et al. (2021) Boston, Massachusetts United States 1999–2002 Cohort	Project Viva n: 1311 Pregnant women participating in Project Viva were included in this study; women were those of singleton gestation, able to answer questions in English, and GA <22 wk at recruitment.	Blood Maternal blood (erythrocyte) measured in the first trimester measured by ICP-MS Age at measurement: maternal age during first trimester mean (SD): 32.3 (4.6) yr Median: 17.6 ng/g 75th: 23.6 ng/g	Maternal health during pregnancy: gestational glucose Glucose tolerance test 26–28 wk gestation, as measured by non-fasting 50 g oral glucose challenge test. Age at outcome: maternal age at 26–28 wk gestation mean (SD): 32.3 (4.6) yr	BKMR models adjusted for maternal age, self-identified race/ethnicity, pre-pregnancy BMI, GDM in prior pregnancy, smoking, maternal education, diabetes status of biological mother, and gestational week at blood collection for metals measurements	Difference in mid-gestational glucose concentration (mg/dL) associated with IQR changes of Pb exposure, with all other metals fixed at their medians (95% credible interval)[b]: −0.5 (−1.6, −0.6)
Tatsuta et al. (2022a) Japan 2011–2014 Cohort	JECS n: 78,964 Women who delivered a live infant with singleton pregnancy. Women were excluded if there was a missed blood sample, missed	Blood Maternal blood measured by ICP-MS Age at measurement: Maternal age at second or third trimester; non-GDM	Maternal health during pregnancy: GDM GDM diagnosed by OGTT in second or third trimester overt GDM diagnosed prior to OGTT was excluded. Age at outcome: maternal	Logistic regression adjusted for pre-pregnancy BMI, age at blood collection, smoking/drinking habits during pregnancy, history of GDM, history of delivering a macrosomia, regional center, fish intake	OR (95% CI): Q1: Reference Q2: 1.026 (0.872, 1.206) Q3: 0.968 (0.821, 1.141) Q4: 1.007 (0.854, 1.187) Q5: 0.974 (0.824, 1.151)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	diagnosis of GDM, missing HbA1c data, HbA1c ≥6.5% at <24 gestational weeks, or a history of type 1 or type 2 diabetes.	mean age 31.0 yr; GDM mean age 33.3 yr Median: 5.9 ng/g 95th: 10.6 ng/g	age at second or third trimester; non-GDM mean age 31.0 yr; GDM mean age 33.3 yr	and co-exposure to Cd, Mn, and Se	
Epigenetic Effects During Pregnancy					
Sanders et al. (2015) Mexico City Mexico 2007–2011 Cohort	PROGRESS birth cohort n: 60 This study was conducted on a sub-cohort of 60 Mexican women aged 18–40 yr participating in the PROGRESS birth cohort in Mexico City, and who consented to a cervical swab during mid-pregnancy (16–19 wk gestation) for miRNA, thereby participating in the PROGRESS Cervix Study.	Blood and bone Maternal blood was measured with a dynamic reaction cell ICP-MS. Maternal bone was measured with spot-source ^{109}Cd K-XRF instrument within 1 mo of delivery Age at Measurement: Maternal age at exposure sampling (mean 27.9 yr with a range of 18–40) Mean: Blood: 2.85 µg/dL Patella[d]: 4.16 Tibia[d]: 1.45 Max: Blood: 9.38 µg/dL Patella3: 20.90 Tibia3: 19.45	Maternal health during pregnancy: altered miRNA expression in the cervix Cervical cells were collected in a method similar to a standard Pap smear protocol, where a cotton swab was used to collect cells from the endocervix. Total RNA was extracted using the Exiqon miRCURY kit. MiRNAs were quantified by using a NanoPhotometer P-300. MiRNA expression was assessed using the NanoString nCounter system. Age at outcome: Maternal age at assessment (mean 27.9 yr with a range of 18–40)	Multivariable linear regression models were adjusted for maternal age, education, smoke exposure in the home, and parity	β (95% CI)[b], interpreted as % expression change Blood, per 10-fold increase in Pb: hsa-miR-297: 84.0 (15.7, 192.8) hsa-miR-188: 48.5 (7.9, 1.04.2) Bone Pb, per 1-unit increase in Pb: Patella: hsa-miR-320e: −4.7 (−7.3, −1.4) hsa-miR-22–3p: −4.7 (−8.6, −0.7) hsa-miR-93–5p: −6.7 (−12.3, −0.7) hsa-miR-769–5p: −5.4 (−9.9, −0.7) hsa-miR-297: 2.1 (0.0, 4.2) hsa-miR-425–5p: −6.7 (−12.3, 0.0) hsa-miR-361–3p: 2.8 (0.0, 5.7) Tibia:

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					hsa-miR-575: −4.1 (−6.7, −1.4) hsa-miR-4286: −8.6 (−13.5, −3.4) hsa-miR-15a-5p: 7.2 (1.4, 14.1) hsa-miR-142–3p: 5.7 (0.7, 11.7) hsa-miR-193b-3p: −7.3 (−12.9, −0.7) hsa-miR-494: −4.1 (−8.0, 0.0)
Sanchez-Guerra et al. (2019) Mexico City, Mexico December 2007–July 2011 Cohort	PROGRESS Study n: 410 mother-infant pairs Participants who were <20 wk gestation; maternal age of ≥18 yr and without medical history of heart or kidney disease) who underwent clinical examinations at different hospitals from Mexican Social Security System	Blood Maternal blood (collected at second and third trimester and delivery) and umbilical cord blood were measured by ICP-QQQ Age at measurement: maternal age at measurement (mean age 27.22 yr) Mean second trimester: 3.79 µg/dL; third trimester: 3.90 µg/dL; at delivery: 4.16 µg/dL; cord blood: 3.50 µg/dL 75th second trimester: 4.51 µg/dL; third trimester: 4.73 µg/dL; at delivery: 5.28 µg/dL; cord blood: 4.45 µg/dL	Maternal health during pregnancy: altered cord blood mtDNA content Venous cord blood measured the relative mtDNA content through mitochondrial-to-nuclear DNA ratio in cord blood Age at outcome: Maternal age at delivery (Mean age 27.22 yr)	Multivariate linear regression models were adjusted for sex, mother's age, mother's BMI, SES, smoke exposure, $PM_{2.5}$ levels, GA, platelets and leucocytes in cord blood, C-section, PROM, preeclampsia, and date of visit	β (95% CI) Maternal blood Second trimester: 0.017 (0.002, 0.031) Third trimester: 0.015 (0.00, 0.03) At delivery: 0.013 (−0.001, 0.027) Cord blood At delivery: 0.016 (0.001, 0.03)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Other Outcomes Related to Maternal Health During Pregnancy					
Kahn et al. (2014) Mitrovoca and Pristina, Kosovo May 1985 and December 1986 Cohort	Yugoslavia Prospective Study of Environmental Lead Exposure n: 291 Women in their second trimester of pregnancy were invited to participate in a study of pregnancy outcomes at their first prenatal visit to government clinics located at the centers of two towns in Kosovo. Women with singleton births, between 18 and 44 wk of gestation, had no major central nervous system defects, no chromosomal abnormalities, and residing <10 km from clinic	Blood Maternal blood (serum) collected at mid-pregnancy (no method reported) Age at Measurement: Pristina Mean: 26.6 yr; Mitrovica Mean: 26.7 yr Mean: Pristina: 5.57 µg/dL; Mitrovica: 20 µg/dL Max: Pristina: 18.60 µg/dL; Mitrovica: 41.30 µg/dL	Maternal health during pregnancy: thyroid function during pregnancy Maternal thyroid function during pregnancy was assessed using fT4, TSH, and TPOAb. fT4 and TPOAb were measured by a radioimmunoassay procedure, and TSH was measured using an immunoradiometric assay procedure. Age at outcome: Pristina Mean: 26.6 yr; Mitrovica Mean: 26.7 yr	Multiple linear regression analysis: fT4 models adjusted for height, ethnicity, BMI, fetal GA, maternal education, adults per room; TSH models: hemoglobin, ethnicity, BMI, fetal GA, maternal age; TPOAb models (continuous and dichotomous): ethnicity, fetal GA, maternal age, adults per room	β (95% CI)[b] fT4: −0.074 (−0.10, −0.046) TSH: 0.026 (−0.065, 0.12) TPOAb: 0.31 (0.17, 0.46) OR (95% CI)[b] TPOAb: 2.41 (1.53, 3.82), comparing ≥10 IU/mL vs. <10 IU/mL
Wells et al. (2011) Baltimore, MD United States November 2004 and March 2005 Cohort	Baltimore Tracking Health Related to Environmental Exposures Study n: 285 Singleton births with cord blood available, with complete covariates data	Blood UCB was measured by ICP-MS Age at Measurement: Maternal age at delivery (range: 14–43, mean: 26) Geometric mean: 0.66 µg/dL 75th: 0.96 µg/dL Max: 6.47 µg/dL	Maternal health during pregnancy: blood pressure in late pregnancy Hospital personnel measured maternal blood pressure at admission for labor and delivery and continuously during hospitalization. Three pairs of blood pressure measurements from each mother were recorded: SBP and DBP at admission, the	Multivariable linear regression models were adjusted for maternal age, maternal race, neighborhood median household income, prima parity, smoking during pregnancy, pre-pregnancy BMI, and anemia	β (95% CI), as change in blood pressure (mmHg) Admission SBP: Q1: Referent Q2 2.89 (−2.16, 7.94) Q3: 1.05 (−4.04, 6.14) Q4: 6.87 (1.51, 12.21) p for trend: 0.033 Admission DBP: Q1: Referent

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
			maximum SBP and corresponding DBP, and the minimum SBP and corresponding DBP. Age at outcome: maternal age at delivery (range: 14–43, mean: 26)		Q2: 0.00 (−3.95, 3.96) Q3: 0.81 (−3.17, 4.80) Q4: 4.40 (0.21, 8.59) p for trend: 0.036 Maximum SBP: Q1: Referent Q2: 2.47 (−3.08, 8.02) Q3: −1.76 (−7.36, 3.85) Q4: 7.72 (1.83, 13.60) p for trend: 0.055 Maximum DBP: Q1: Referent Q2: 3.93 (−2.86, 10.72) Q3: −0.42 (−7.27, 6.43) Q4: 8.33 (1.14, 15.53) p for trend: 0.086
Li et al. (2017b) Shanghai China 2010 Cohort	N: 1,485 Pregnant women during late pregnancy (28–36 gestational weeks)	Blood Maternal blood was measured by background corrected GFAAS collected gestational week 28–36 Age at measurement: 13–42 yr old Geometric mean: 3.99 µg/dL Max: 14.84 µg/dL	Maternal health during pregnancy: maternal stress Maternal life event stress and emotional stress were assessed using the LESPW and SCL-90-R, respectively. Age at outcome: 13–42 yr old	Generalized additive models were adjusted for maternal age, ethnicity, maternal education, family monthly income, years living in Shanghai	β (95% CI)[b] Log-blood Pb GSI: 0.01 (−0.05, 0.07) Depression: 0.03 (−0.05, 0.10) Anxiety: 0.01 (−0.06, 0.08) Log-blood Pb ≤0.41 µg/dL GSI: 0.22 (0.05, 0.40) Depression: 0.34 (0.12, 0.56) Anxiety: 0.01 (−0.06, 0.08) Log-blood Pb >0.41 µg/dL

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					GSI: −0.07 (−0.16, 0.01) Depression: −0.09 (−0.19, 0.02) Anxiety: −0.08 (−0.18, 0.02)
Osorio-Yáñez et al. (2021) Mexico 2007–2011 Cohort	PROGRESS n: 668 Women enrolled during second trimester of pregnancy, were ≥18 yr of age, lived in Mexico City for the following 3 yr	Blood and bone Maternal blood was measured by ICP-QQQ; bone Pb measured by K-XRF and obtained two estimated for patella and tibia (one for each leg), which were measured 26–55 d postpartum Age at measurement: Median (SD): 27 (5.5) yr Median Blood – 2nd Trimester: 2.80 µg/dL Blood – 3rd Trimester: 2.99 µg/dL Bone, tibia: 2.84 µg/g Bone, patella: 3.49 µg/g Max: Blood: 2nd Trimester: 20.70 µg/dL 3rd Trimester: 28.25 µg/dL Tibia: 30.1 µg/g Patella: 43.2 µg/g	Maternal health during pregnancy: bone remodeling Bone speed of sound measured at the second and third trimesters of pregnancy at the distal radius and medium phalange using QUS. Age at outcome: Median (SD): 27 (5.5) yr	Linear models adjusted for maternal age, SES, parity, BMI, and GA at the time of Z-score measurement; linear mixed model adjusted for maternal age, SES, parity, BMI, and GA at the time of QUS measurement; models with blood were mutually adjusted for other (Cd and As) metals	β (95% CI)[b] Bone (radius) QUS Z-score at 2nd Trimester Blood (µg/dL): −0.06 (−0.18, 0.07) Tibia (µg/g bone mineral): 0.002 (−0.07, 0.07) Patella (µg/g bone mineral): −0.08 (−0.15, −0.01) Bone (radius) QUS Z-score at 3rd Trimester Blood (µg/dL): −0.03 (−0.16, 0.10) Tibia: 0.017 (−0.05, 0.09) Patella: −0.03 (−0.10, 0.05) Bone (radius) QUS Z-score during pregnancy Blood (µg/dL): −0.04 (−0.13, 0.04) Tibia (µg/g bone mineral): 0.006 (−0.04, 0.06) Patella (µg/g bone mineral): −0.06 (−0.10, −0.01)
Kim et al. (2022)	PROTECT n: 617	Blood	Maternal health during pregnancy: MMP	Linear mixed effects models adjusted for maternal age, education,	B (95% CI)[b] as percent change in MMP per IQR increase in blood Pb

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Puerto Rico and United States 2010 Cohort	Pregnant women in the first trimester or early second trimester of pregnancy that resided in the Northern Karst aquifer region, known for a large number of Superfund and other hazardous waste sites.	Maternal blood, collected at up to two study visits (median 18- and 26-wk gestation), was measured by ICP-MS Age at measurement: Mean (SD) age at enrollment: 26.9 (5.5) yr Median: Enrollment: 0.32 ng/mL Follow up:0.32 ng/mL 75th: Enrollment: 0.42 ng/mL Follow up: 0.43 ng/mL Max: Enrollment: 2.18 ng/mL Follow-up: 1.51 ng/mL	Expression levels of MMP1, MMP2, and MMP9 measured using customized Luminex assay from Invitrogen Age at outcome: Mean (SD) age at enrollment: 26.9 (5.5) yr	exposure to second-hand tobacco smoke, and pre-pregnancy BMI	MMP1: 23.6 (12.9, 35.2) MMP2: 5.89 (2.23, 9.67) MMP9: −3.31 (−8.12, 1.75) Females: MMP1: 16.3 (5.74, 28.0) MMP2: 5.48 (1.50, 9.62) MMP9: −1.89 (−7.35, 3.90) Males: MMP1: 10.5 (1.15, 20.6) MMP2: 2.24 (−1.25, 5.86) MMP9: −5.14 (−9.85, −0.17)
Gajewska et al. (2021) Poland 2018–2020 Case-control	n: 146 (66 with preeclampsia) Healthy pregnant women and healthy non-pregnant women visiting the Independent Public Clinical Hospital No 4 in Lublin for a stay in the hospital or routine testing.	Blood Maternal blood was measured by ICP-MS Age at measurement: Mean: 29.16 yr Median: 28 yr Range: 18–47 yr All Participants: Mean (SD): 2.63 (1.34) µg/dL Median: 2.6 µg/dL Preeclampsia Participants:	Maternal health during pregnancy: preeclampsia Diagnosis of preeclampsia was based on the definition from the American College of Obstetrics and Gynecologists. Age at outcome: Mean: 29.16 yr Median: 28 yr Range: 18–47 yr	Logistic regression adjusted by the pregnant woman's age, place of resident (urban/rural), GA, multiplicity of pregnancy, and number of previous pregnancies	OR (95% CI)[b]: 2.65 (1.2, 5.86)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Mean (SD) 3.36 (1.23) Median: 3.49 µg/dL Max: All Participants: 6.1 µg/dL Preeclampsia Participants: 6.1 µg/dL			
Wu et al. (2021) China, Foshan, Guangdong Province August 2019–November 2019 (participants followed from 8–12 wk of pregnancy to birth) Cohort	n: 2174 Pregnant women that were registered, checkup, and delivering in the Foshan Chancheng Central Hospital were included in the study.	Blood Maternal blood, collected between 12 and 27 (±6) wk of pregnancy and before date of diagnosed preeclampsia, was measured by AAS Age at measurement: Mean age at delivery (SD): 29.04 (4.25) yr Median: 3.60 µg/dL Quartiles (µg/dL): Q1: 2.00–2.90 Q2: 3.00–3.60 Q3: 3.70–4.40 Q4: 4.50–7.90	Maternal health during pregnancy: preeclampsia Preeclampsia was based on electronic medical records. Preeclampsia was defined as newly diagnosed hypertension and proteinuria occurring after 20 wk of gestation. Hypertension was defined as systolic ≥140 mmHg or DBP ≥90 mmHg, 2 occasions, 4 hr apart in a previously normotensive woman. Proteinuria was defined as ≥300 mg/24-hr urine collections, or protein/creatinine ≥0.3, or dipstick reading ≥1 Age at outcome: maternal age after 28 wk gestation	Logistic regression models were adjusted for age at delivery, pre-pregnancy BMI, parity, method of conception (natural conception, ART conception), and education level; logistic	OR (95% CI) Dose-effect analysis of the relationship between BLLs and the risk of preeclampsia Linear regression model[b]: 1.43 (1.17, 1.74) BLLs ≤4.2 µg/dL[b]: 0.79 (0.50, 1.24) BLLs >4.2 µg/dL[b]: 2.05 (1.50–2.81) Preeclampsia: Continuous model[b]: 1.43 (1.17, 1.74) Q1: Reference Q2: 1.48 (0.64, 3.39) Q3: 0.85 (0.33, 2.20) Q4: 2.38 (1.13, 5.03) p for trend: 0.02 Mild Preeclampsia: Continuous model[b]: 1.62 (1.27, 2.06) Q1: Reference Q2: 2.63 (0.81, 8.63) Q3: 1.33 (0.35, 5.06) Q4: 4.26 (1.41, 12.89)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					p for trend: 0.01 Severe Preeclampsia: Continuous model[b]: 1.10 (0.72, 1.68) Q1: Reference Q2: 0.69 (0.19, 2.49) Q3: 0.51 (0.13, 2.05) Q4: 1.12 (0.38, 3.27) p for trend: 0.78
Braun et al. (2014) Mexico City, Mexico July 2007 and February 2011 Cohort	n: 1054 Participants for this study were enrolled from an ongoing prospective birth cohort in Mexico City. Pregnant women receiving health insurance and prenatal care through the Mexican Social Security System were invited to participate in the study. To be eligible for participation in the study, women had to be <20 wk gestation, ≥18 yr old, free of heart or kidney disease, have access to a telephone, plan to reside in Mexico City for the next 3 yr, not use steroids (including glucocorticoids) or anti-epilepsy drugs, and not consume alcohol on a daily basis.	Blood and bone Maternal blood was measured by GFAAS during the second trimester. Maternal bone was measured by K-XRF instrument ~1 mo postpartum Age at measurement: ≥18 yr old Mean: blood: 3.7 µg/dL tibia: 2.7 µg/g patella: 4.6 µg/g Blood Pb Quintiles Q1: 0–<1.8 µg/dL Q2: 1.8–<2.4 µg/dL Q3: 2.4–<3.4 µg/dL Q4: 3.4–<5.1 µg/dL Q5: ≥5.1 µg/dL	Maternal health during pregnancy: hypothalamic-pituitary-adrenal axis function measured from salivary cortisol concentrations Between 14 and 35 wk of gestation (mean [SD]: 19.7 [2.4] wk), pregnant women provided five saliva samples each day over 2 consecutive days during the week or weekend. Women were instructed to provide samples using the passive drool technique upon awakening, 45 min after waking, 4 hr after waking, 10 hr after waking, and at bedtime. Saliva samples were assayed in the same batch in duplicate for cortisol using a chemiluminescence assay with sensitivity of ~0.16 ng/ml.	Linear mixed models with random intercepts for day and participant were adjusted for maternal age, marital status, years of education, parity, and smoking status (never, former, and current), BMI, and stress or depressive symptoms	β (95% CI), as % difference in cortisol area under the curve nmol-hr Blood Pb Quintiles Q1: Reference Q2: 8 (−1, 18) Q3: 9 (0, 19) Q4: 8 (−1, 18) Q5: 2 (−6, 12) Tibia Pb Quintiles: Q1: Reference Q2: −5 (−14, 5) Q3: 2 (−8, 13) Q4: 0 (−10, 10) Q5: 6 (−4, 18) Patella Pb Quintiles: Q1: Reference Q2: 1 (−8, 12) Q3: −6 (−14, 4) Q4: 12 (1, 24)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Tibia Pb Quintiles Q1: <2 µg/g Q2: 2–<4.3 µg/g Q3: 4.3–<6.7 µg/g Q4: 6.7–<11.1 µg/g Q5: ≥11.1 µg/g Patella Pb Quintiles Q1: <2 µg/g Q2: 2–<4.5 µg/g Q3: 4.5–<7.8 µg/g Q4: 7.8–<12.7 µg/g Q5: >12.7–43.2 µg/g	Age at outcome: maternal age at the time of outcome measurement		Q5: 4 (−6, 16)
Ishitsuka et al. (2020) Japan January 2011 – March 204 Cohort	JECS n: 17,267 Pregnant women from 15 Regional Centers throughout Japan who had single pregnancies, did not have a history of diabetes, or receive insulin treatment, and hypoglycemic agents during pregnancy; did not use steroids during pregnancy	Blood Maternal blood was measured by ICP-MS Age at measurement: maternal age at 27 wk of gestation (mean age: 31 ± 5 yr) Geometric mean: 0.58 µg/dL Quintiles (µg/dL): Q1: 0.143–0.433 Q2: 0.444–0.523 Q3: 0.524–0.616 Q4: 0.617–0.7533 Q5: 0.754–6.752	Maternal health during pregnancy: maternal depression Psychological symptoms during middle or late pregnancy were assessed using the K6. Age at outcome: maternal age at 27 wk of gestation (mean age: 31 ± 5 yr)	Multivariable logistic regression models adjusted for age, parity, marital status, education, employment status, household income, and smoking and alcohol status	OR (95% CI) Pb per one-unit increase K6 ≥13: 1.00 (0.76, 1.32) K6 ≥5: 0.98 (0.88, 1.09) K6 ≥13: Q1: Reference Q2: 0.94 (0.69, 1.27) Q3: 0.97 (0.71, 1.31) Q4: 0.92 (0.68, 1.25) Q5: 0.87 (0.64, 1.19) K6 ≥5: Q1: Reference Q2: 1.03 (0.92, 1.16) Q3: 1.07 (0.95, 1.19) Q4: 0.98 (0.87, 1.10) Q5: 1.01 (0.90, 1.13)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Christensen et al. (2016) Ukraine and Greenland 2002–2004 Cross-sectional	Climate Change, Environmental Contaminants, and Reproductive Health n: 117 Women at least 18 yr old and born in the country of the study.	Blood Maternal blood was measured by ICP-MS Age at measurement: ≥18 Mean[c]: 1.74 µg/dL Median[c]: 1.457 µg/dL Tertiles[c] (µg/dL): T1: 0.544–1.013 T2: 1.013–1.902 T3: 1.902–14.088	Maternal health during pregnancy: AMH Concentrations of AMH were assessed by the Immunotech enzyme immunoassay AMH/Müllerian-inhibiting substance assay from serum. Age at outcome: ≥18	General linear models were adjusted for GA, maternal age, research site, parity, fish intake, BMI, ever smoker and pelvic diseases and infections	β (95% CI)[b] per one-unit ln-Pb increase: −0.0423 (−0.4989, 0.4144)
Gustin et al. (2021) Sweden, Norrbotten county Enrollment: 2015–2018, follow-up through 29 gestational weeks Cohort	NICE n: 544 Pregnant women visiting their local maternity clinics who were residents of southern or eastern Norrbotten count and planned to give birth at Sunderby Hospital. Only first pregnancies and singleton births included. Those with thyroid dysfunction were excluded.	Blood Maternal blood (erythrocyte) was measured by ICP-MS Age at measurement: Median: 30 yr Median: 11 µg/kg 95th: 27 µg/kg	Maternal health during pregnancy: hormone Levels (fT4, tT4, fT3, tT3, TSH, fT4:tT4, fT3:tT3, fT3:fT4) Plasma samples from gestational week 29 analyzed via electrochemiluminescence immunoassays	Multivariate linear regression models adjusted for parity, maternal education, maternal pre-pregnancy smoking	β (95% CI)[b] fT4 (pmol/L): 0.014 (−0.21, 0.18) tT4 (nmol/L): 0.90 (−1.5, 3.3) fT3 (pmol/L): 0.036 (−0.018, 0.090) tT3 (nmol/L): 0.038 (−0.015, 0.091) TSH (mIU/L): −0.023 (−0.13, 0.087) fT4:tT4: −0.001 (−0.002, 0.001) fT3:tT3: −0.009 (−0.031, 0.014) fT3:fT4: 0.004 (−0.003, 0.011)
Corrales Vargas et al. (2022)	n: 344	Blood Maternal blood measured by ICP-MS	Maternal health during pregnancy: thyroid function TSH, fT4, and fT3	Linear regression models adjusted for age, GA, cotinine detection, pre-pregnancy BMI, and	β (95% CI) for % change in 1st measurement of outcomes per 10% increase in blood Pb (µg/L) at enrollment

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Matina County, Limon Coast Rica 2010–2011 Cohort		Age at measurement: Maternal age at collection (recruited <33 wk gestation with 2nd blood sample 10 wk later) Median: 0.666 µg/dL 75th: 0.908 µg/dL 90th: 1.211 µg/dL Max: 3.43 µg/dL	measured in serum using electrochemiluminescence	severe vomiting during pregnancy	TSH (mIU/L): −2.3 (−16.15, 11.55) fT4 (pmol/L): 0.99 (−0.11, 2.09) fT3 (pmol/L): −0.21 (−0.52, 0.10) β (95% CI) for % change in 2nd measurement of outcomes per 10% increase in blood Pb (µg/L) at enrollment, excluding outliers: TSH (mIU/L): −0.08 (−0.22, 0.07) fT4 (pmol/L): 1.96 (0.66, 3.25) fT3 (pmol/L): 0.24 (−0.13, 0.61)

AAS = atomic absorption spectrometry; AMH = anti-Müllerian hormone; ART = assisted reproductive technology; BKMR = Bayesian kernel machine regression; BMI = body mass index; Cd = cadmium; CI = confidence interval; d = day(s); DBP = diastolic blood pressure; EAAS = electrothermal atomic absorption spectrometry; fT3 = free triiodothyronine; fT3:fT4 = ratio of free triiodothyronine to free thyroxine; fT3:tT3 = ratio of free triiodothyronine to total triiodothyronine; fT4 = free thyroxine; fT4:tT4 = ratio of free thyroxine to total thyroxine; GDM = gestational diabetes mellitus; GFAAS = graphite furnace atomic absorption spectrometry; GSI = Global Severity Index; hr = hour(s); ICP-MS = inductively coupled plasma mass spectrometry; ICP-QQQ = inductively coupled plasma triple quad; IGT = impaired glucose tolerance; IQR = interquartile range; JECS = Japan Environment and Children's Study; K6 = Kessler Psychological Distress Scale; K-XRF = K-shell X-ray fluorescence; LESPW = Life Event Scale for Pregnant Women; MIREC = Maternal-Infant Research on Environmental Chemicals; miRNA = micro RNA; min = minute(s); MMP = matrix metalloproteinases; mo = month(s); mtDNA = mitochondrial DNA; NICE = Nutritional impact on Immunological maturation during Childhood in relation to the Environment; OGTT = oral glucose tolerance test; OR = odds ratio; $PM_{2.5}$ = fine particulate matter; PROGRESS = Programming Research in Obesity, Growth, Environment and Social Stressors; PROM = premature rupture of membranes; PROTECT = Puerto Rico Test site for Exploring Contamination Threats; Q = quartile; QUS = quantitative ultrasound; SBP = systolic blood pressure; SCL-90-R = Symptom-Checklist-90-Revised; SD = standard deviation; Se = selenium; SES = socioeconomic status; TPOAb = thyroid peroxidase antibodies; TSH = thyroid-stimulating hormone; tT3 = total triiodothyronine; tT4 = total thyroxine; UCB = umbilical cord blood; wk = week(s); yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. 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.

[b]Effect estimates unable to be standardized.

[c]Pb measurements were converted from µg/L to µg/dL.

[d]No units provided.

Table 8-3 Animal toxicological studies of Pb exposure and pregnancy and birth outcomes

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Saleh et al. (2018)	**Rat (Sprague-Dawley)** Control (vehicle), F, n = 8 dams 160 ppm Pb, F, n = 8 dams 320 ppm Pb, F, n = 8 dams	GD 1 to 20	Dams were dosed via oral gavage. Authors report a significant decrease in brain weight occurred, indicating potential overt toxicity.	Dams (GD 20): 5.1 µg/dL for control 27.7 µg/dL for 160 ppm Pb 41.5 µg/dL for 320 ppm Pb	Abortion, Placental Weight
Saleh et al. (2019)	**Rat (Sprague-Dawley)** Control (vehicle), F, n = 8 dams 160 ppm Pb, F, n = 8 dams 320 ppm Pb, F, n = 8 dams	GD 1 to 20	Dams were dosed via oral gavage. Authors report a significant decrease in brain weight occurred, indicating potential overt toxicity.	Dams (GD 20): 5.26 µg/dL for control 23.9 µg/dL for 160 ppm Pb 42.9 µg/dL for 320 ppm Pb	Placental Weight
Cory-Slechta et al. (2013)	**Mouse (C57BL/6)** Control (untreated), M/F, n = 16–29 (8–17/8–12) pups 100 ppm Pb, M/F, n = 16–29 (8–17/8–12) pups	GD −61 to PND 365	Dams were dosed via drinking water starting 2 mo prior to mating. Offspring were continued on the same exposure as their dams until the end of the experiment at 12 mo of age. Sample sizes are only available for "Final" group sizes for males and females in Table 1.	Dams at weaning (PND 24): 0.22 µg/dL for control 12.12 µg/dL for 100 ppm Pb	BW, Sex Ratio
Schneider et al. (2016)	**Mouse (C57BL/6)** Control (untreated), F, n = NR 100 ppm Pb, F, n = NR	GD −61 to PND 21	Dams were dosed via drinking water starting 2 mo prior to mating through lactation (weaning assumed to be PND 21). Dams were also treated to a non-stress or prenatal stress	Dams at weaning (assumed PND 21): 0.22 µg/dL for control 12.61 µg/dL for 100 ppm Pb Pups (PND 5–6): 0.37 µg/dL for control 10.2 µg/dL for 100 ppm Pb	BW

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
			condition. Only data from dams in the non-stress condition were used.		
Wang et al. (2014)	**Rat (Wistar)** Control (untreated), F, n = 17 dams 0.25% Pb GD 1–10, F, n = 16 dams 0.25% Pb GD 11–20, F, n = 15 dams 0.25% Pb GD 1–20, F, n = 15 dams	GD 1–10, or GD 11–20, or GD 1–20	Dams were dosed via drinking water during different windows of pregnancy. Assumed termination of study on GD 20.	Dams (assumed GD 20): 0.828 µg/dL for control 26.29 µg/dL for 0.25% Pb GD 1–10 12.4 µg/dL for 0.25% Pb GD 11–20 36.02 µg/dL for 0.25% Pb GD 1–20	Placenta Histopathology, Placental Weight
Weston et al. (2014)	**Rat (Long-Evans)** Dams Control (untreated), F, n = 20 50 ppm Pb, F, n = 19 Pups Control (untreated), M/F, n = 12.4 (7/5.4 average number of male and female pups per litter in control) 50 ppm Pb, M/F, n = 7.4 (6.3/1.1 average number of male and female pups per litter in Pb non−stress group)	GD −76 to PND 21	Dams were dosed via drinking water starting 2–3 mo prior to breeding. Exposure ended at weaning (PND 21).	Dams (PND 21): 0.500 µg/dL for control 7.72 µg/dL for 50 ppm Pb Pups (PND 5–6): 0.603 µg/dL for control males 0.690 µg/dL for control females 15.7 µg/dL for 50 ppm Pb males 14.6 µg/dL for 50 ppm Pb females	BW, Sex Ratio
Rao Barkur and Bairy (2016)	**Rat (Wistar)**	GD −30 to GD −1; GD 0 to GD 21; PND 1 to	Dams were dosed via drinking water for varying amounts of time: Pregestation Only (1 mo prior	Pups (PND 22): 0.19 µg/dL for control	Stillborn Pups, BW

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
	Control (untreated), F, n = 6 dams 0.2% Pb Pregestation Only, n = 6 dams 0.2% Pb Gestation Only, n = 6 dams 0.2% Pb Lactation Only, n = 6 dams 0.2% Pb Gestation and Lactation, F, n = 6 dams	PND 21; GD 0 to PND 21	to conception), Gestation Only (21 d), Lactation Only (21 d), and Gestation and Lactation (42 d).	3.03 µg/dL for 0.2% Pb in Pregestation Only group 5.51 µg/dL for 0.2% Pb in Gestation Only group 26.86 µg/dL for 0.2% Pb in Lactation Only group 31.59 µg/dL for 0.2% Pb in Gestation and Lactation group	
Barkur and Bairy (2015)	**Rat (Wistar)** Control (untreated), F, n = 6 dams 0.2% Pb Pregestation Only, F, n = 6 dams 0.2% Pb Gestation Only, F, n = 6 dams 0.2% Pb Lactation Only, F, n = 6 dams 0.2% Pb Gestation and Lactation, F, n = 6 dams	GD −30 to GD −1; GD 0 to GD 21; PND 0 to PND 21; GD 0 to PND 21	Dams were dosed via drinking water for varying amounts of time: Pregestation Only (1 mo prior to conception), Gestation Only (21 d), Lactation Only (21 d), and Gestation and Lactation (42 d).	Pups (PND 22): 0.18 µg/dL for control 3.02 µg/dL for 0.2% Pb in Pregestation Only group 5.30 µg/dL for 0.2% Pb Gestation Only group 26.7 µg/dL for 0.2% Pb in Lactation Only group 32.0 µg/dL for 0.2% Pb in Gestation and Lactation group	Stillborn Pups, BW
Tartaglione et al. (2020)	**Rat (Wistar)** Control, M/F, n = NR 50 mg/L Pb, M/F, n = NR	GD −28 to PND 23	Dams were dosed via drinking water starting 4 wk prior to mating until weaning (PND 23).	Pups (PND 23): 0.700 µg/dL for 0 mg/L Pb 25.5 µg/dL for 50 mg/L Pb	BW, Sex Ratio

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Zhao et al. (2021)	**Rat (Sprague-Dawley)** Control (untreated), F, n = 6 dams 109 ppm Pb, F, n = 6 dams	GD −14 to PND 10	Dams were dosed via drinking water starting 2 wk prior to mating and continued until PND 10.	Pups: PND 0 0.87 µg/dL for control 48.2 µg/dL for 109 ppm Pb PND 10 0.87 µg/dL for control 11.5 µg/dL for 109 ppm Pb PND 21 0.87 µg/dL for control 2.81 µg/dL for 109 ppm Pb PND 30 0.87 µg/dL for control 1.20 µg/dL for 109 ppm Pb	BW
Barkur et al. (2011)	**Rat (Wistar)** Control (untreated), F, n = 6 dams 0.2% Pb GD 0 to PND 21, F, n = 6 dams	GD 0 to PND 21	Dams were dosed via drinking water throughout gestation until weaning (PND 21). Only male pups were examined.	Pups: PND 22 0.266 µg/dL for control 31.2 µg/dL for 0.2% Pb PND 120 0.234 µg/dL for control 0.468 µg/dL for 0.2% Pb	BW
Betharia and Maher (2012)	**Rat (Sprague-Dawley)** Control (untreated), M/F, n = 36–48 (18–24/18–24) pups 10 µg/mL Pb, M/F, n = 36–48 (18–24/18–24) pups	GD 0 to PND 20	Dams were dosed via drinking water throughout pregnancy until weaning (PND 20).	Pups: PND 2 0.188 µg/dL for control 9.03 µg/dL for 10 µg/mL Pb PND 25:	Stillborn Pups, Sex Ratio

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
				0.088 µg/dL for control 0.976 µg/dL for 10 µg/mL Pb PND 60: 0.0244 µg/dL for control 0.0318 µg/dL for 10 µg/mL Pb	
Graham et al. (2011)	**Rat (Sprague-Dawley)** Control (vehicle), M/F, n = 14–16 (7–8/7–8) 1 mg/kg Pb, M/F, n = 14–16 (7–8/7–8) 10 mg/kg Pb, M/F, n = 14–16 (7–8/78)	PND 4 to 28	Offspring were dosed via oral gavage every other day from PND 4 until PND 28.	PND 29: 0.267 µg/dL for 0 mg/kg 3.27 µg/dL for 1 mg/kg 12.5 µg/dL for 10 mg/kg	Offspring Mortality
Baranowska-Bosiacka et al. (2013)	**Rat (Wistar)** Control (untreated), F, n = 3 dams 0.1% Pb, F, n = 3 dams Control, M/F, n = 36 (17/19) pups 0.1% Pb, M/F, n = 36 (18/18) pups	GD 1 to PND 21	Dams were dosed via drinking water throughout pregnancy until weaning (PND 21).	Pups (PND 28): 0.93 µg/dL for control 6.86 µg/dL for 0.1% Pb	Sex Ratio

BLL = blood lead level; BW = birth weight; d = day(s); F = female; GD = gestational day; M = male; mo = month(s); NR = not reported; Pb = lead; PND = postnatal day; wk = week(s).

Table 8-4 Epidemiologic studies of Pb exposure and prenatal growth

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Xie et al. (2013) Shandong Province China September 2010 and December 2011 Cohort	n: 252 Pregnant women aged 18 yr or older, planning to deliver at the Binhai hospital, and more than 3 yr of residence in the Laizhou Bay; exclusion criteria included diagnoses of gestational or preexisting diabetes, hypertension, HIV, or AIDS; GA <28 wk; known occupational exposure to heavy metals; with history of participation in an assisted reproduction program; difficulties with communication; and infants with severe neonatal illnesses	Blood and cord blood Maternal blood and UCB were measured by GFAAS. Age at Measurement: at delivery (within 3 d before delivery) Mean (SD): Maternal: 3.53 (1.51) µg/dL UCB: 2.92 (1.58) µg/dL Median: Maternal: 3.20 µg/dL UCB: 2.52 µg/dL 75th: Maternal: 4.18 µg/dL UCB: 3.95 µg/dL Max: Maternal: 11.91 µg/dL UCB: 10.60 µg/dL	Prenatal growth: BW, BL, HC BW, BL, and HC were measured by several trained midwives within 1 hr after birth Age at outcome: birth	Multiple linear regression models were adjusted for infant sex, maternal education, maternal age, GA, pre-pregnancy BMI, parity, and weight gain during pregnancy	β (95% CI)[b] Maternal blood: BW (g): −148.99 (−286.33, −11.66) BL (cm): −0.46 (−1.25, 0.34) HC (cm): −0.37 (−0.78, 0.19) UCB: BW (g): −99.33 (−217.33, 20.67) BL (cm): −0.84 (−1.52, −0.16) HC (cm): −0.36 (−0.81, 0.03)
García-Esquinas et al. (2013) Madrid Spain October 2003 to May 2004 Cohort	BioMadrid Project n: 112 Father-pregnant woman-newborn trios residing in two areas of the Madrid Autonomous Region, a municipal district in the city of Madrid (urban area) and a second zone lying in the Greater Madrid	Blood and cord blood Blood collected from both parents during pregnancy and UCB was collected at delivery and measured by AAS Age at measurement: maternal age: ≥15; birth Geometric mean (95% CI)[c]:	Prenatal growth: BW, length, 1- and 5-min Apgar scores Anthropometric data were measured once, before breastfeeding started. Apgar score was measured on a scale from 1 to 10, at 1 and 5 min after delivery. Infants were evaluated on a scale of	Multivariable linear regression models were adjusted for newborn's sex, GA, maternal age, maternal cigarette smoking and sampling season	β (95% CI)[b] UCB: BW (g): 123 (−37.9, 284) BL (cm): 0.52 (−0.39, 1.44) 1-min Apgar score: 0.67 (−0.19, 1.16) 5-min Apgar score: 0.29 (−0.04, 0.54)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	Metropolitan Belt (metropolitan area); women were required to be aged over 15 yr, to be expecting a single pregnancy, and to intend to deliver their babies at the public hospital assigned to them, lived in the study area for more than a year, and did not have a blood transfusion in the previous year	Maternal blood: 1.98 (1.816, 2.162) µg/dL Paternal blood: 3.30 (3.048, 3.564) µg/dL UCB: 1.409 (1.277, 1.555) µg/dL Median[c]: Maternal blood: 1.898 µg/dL Paternal blood: 3.324 µg/dL UCB: 1.380 µg/dL 75th[c]: Maternal blood: 2.721 µg/dL Paternal blood: 4.321 µg/dL UCB: 1.911 µg/dL	0 to 2 according to five categories (skin color, muscle tone, reflexes, respiratory effort, and heart rate), and the points from each category added together to determine the total score. Age at outcome: birth		
Govarts et al. (2016) 5 provinces of Flanders, Belgium August 2008–July 2009 Cohort	Flemish human environmental health survey (FLEHS II) n: 248 Women with uncomplicated live-born singleton pregnancies, living in Flanders for at least 10 yr, ability to fill in a Dutch questionnaire, and giving birth in one out of ten randomly selected maternities	Cord blood UCB was measured by HR-ICP-MS Age at Measurement: birth Geometric mean[c]: 0.864 µg/dL 75th[c]: 1.138 µg/dL	Prenatal growth: BW BW was obtained from the medical records Age at outcome: birth	Linear regression models were adjusted for GA, child's sex, smoking of the mother during pregnancy, parity, and maternal pre-pregnancy BMI	β (95% CI)[b] for an increase of Z-score of UCB Pb IQR increase: −37.14 g (−93.64, 19.36)
Tatsuta et al. (2017) Tohoku Japan 2000–2003	Tohoku Study of Child Development n: 489 Singleton pregnancy, Japanese as the first language, neonates	Cord blood UCB was measured by ICP-MS	Prenatal growth: BW BW was obtained from medical records	Multiple regression models were adjusted for GA, parity, BMI before pregnancy, smoking/drinking habits	β (p-value)[b] All infants: −0.011 g (0.784) Male infants: 0.023 g (0.692)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cohort	born at term (36–42 wk of gestation) with BW of more than 2400 g, and no congenital anomalies or diseases	Age at Measurement: birth Median: 1.0 µg/dL Male infants: 1.0 µg/dL Female infants: 1.0 µg/dL 95th: 1.7 µg/dL Male infants: 1.7 µg/dL Female infants: 1.7 µg/dL	Age at outcome: birth	during pregnancy, and fish/seafood intake	Female infants: −0.039 g (0.513)
Wang et al. (2017b) Shanghai China September 2008 and October 2009 Cohort	n: 1,009 mother-infant pairs Singleton pregnant women who had lived in Shanghai for at least 2 yr, were aged 18 yr or older, and were delivering at the selected hospitals were recruited. Pregnant women were excluded if they had chronic diseases before pregnancy, pregnancy complications, or a history of occupational heavy metal exposure. Infants who had severe disorders or congenital malformations at birth were also excluded.	Cord blood UCB measured by GFAAS Age at Measurement: birth Geometric mean: 4.07 µg/dL (95% CI: 3.98, 4.17)	Prenatal growth: BW, BL, HC, and the PI Neonatal anthropometry, including BW, BL, and HC, was performed by trained delivery room staff with standardized equipment, and the results were recorded. PI was calculated Age at outcome: birth	Multiple linear regression models; models for BW, HC, and PI were adjusted for maternal age, GA, maternal BMI before delivery, parity, sex of baby, monthly household income per capita, mode of delivery; models for BL were maternal age, GA, maternal BMI before delivery, parity, sex of baby, monthly household income per capita; all models for female infants and BL model for male infants were adjusted for maternal age, GA, maternal BMI before delivery, parity, monthly household income per capita; models for male infants for BW, HC, and PI were adjusted for maternal age, GA, maternal BMI before delivery, parity, monthly household income	β (95% CI)[b] All Infants BW (g): 50.68 (−69.53, 170.88) BL (cm): 0.36 (−0.13, 0.86) HC (cm): −0.39 cm (−0.80, 0.02) PI (g/cm^3): −0.03 (−0.12, 0.07) Female Infants BW (g): −139.15 (−317.89, 39.59) BL (cm): 0.32 (−0.38, 1.03) HC (cm): −0.13 (−0.71, 0.44) PI (g/cm^3): −0.16 (−0.30, −0.02) Male Infants BW (g): 206.50 g (46.15, 366.86) BL (cm): 0.35 (−0.35, 1.05) HC (cm): −0.65 (−1.24, −0.06)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
				per capita, mode of delivery	PI (g/cm^3): 0.09 (−0.04, 0.21)
Govarts et al. (2020) Belgium FLEHS I: 2002–2004; FLEHS II: 2008–2009; FLEHS III: 2013–2014; 3xG: 2010–2015 Cohort	FLEHS I, II and III and a regional birth cohort (3xG) n: 1,579 mother-newborn pairs: FLEHS I n = 957, II n = 224, III n = 273, and 3xG n = 125 Inclusion criteria were to be able to fill out a Dutch questionnaire and to live at least 5 yr in the selected study areas (FLEHS I), at least 10 yr in Flanders (FLEHS II), at least 5 yr in Flanders (FLEHS III), or living in the recruitment area (3xG). Live-born singleton births	Cord blood UCB measured by HR-ICP-MS Age at Measurement: birth Median[c]: FLEHS I: 1.42 µg/dL FLEHS II: 0.83 µg/dL FLEHS III: 0.61 µg/dL 3xG: 0.61 µg/dL pooled: 0.97 µg/dL 75th[c]: FLEHS I: 2.41 µg/dL FLEHS II: 1.13 µg/dL FLEHS III: 0.87 µg/dL 3xG: 0.72 µg/dL pooled: 1.78 µg/dL	Prenatal growth: BW BW was recorded shortly after delivery Age at outcome: birth	Multiple linear regression models were adjusted for other exposures, GA (linear and quadratic terms), sex of the newborn, maternal age at delivery, maternal pre-pregnancy BMI, parity, smoking during pregnancy and cohort	β (95% CI)[b], interpreted as the change in mean BW per interquartile fold change (the fold change of the 75th percentile over the 25th percentile in exposure) in ln-Pb: 16.98 g (−13.14, 47.11) per 2.94 interquartile fold change in ln-Pb
Lee et al. (2021) Sirajdikhan and Pabna Sadar regions Bangladesh 2008–2011 Cohort	Dhaka Community Hospital Trust n: 1088	Cord blood UCB measured by acid digestion and ICP-MS Age at measurement: birth Geometric mean (Geometric SD): 3.18 (2.35) µg/dL Median: 3.07 µg/dL	Prenatal growth: BW, BL, HC Trained staff measured anthropometer at birth; GA estimated using ≤16-wk ultrasound. Age at outcome: birth	Linear models adjusted for maternal age, maternal BMI at enrollment, child sex, GA, household income, second-hand smoke, site daily tea (heavy metals) and cord blood As, Cd, Mn concentrations	β (95% CI)[b], per IQR increase in ln-cord blood Pb: Birth Z-scores BW (g): −0.04 (−0.19, 0.11) BL (cm): −0.06 (−0.20, 0.09) HC (cm): 0.08 (−0.06, 0.23) Untransformed birth size measurements

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		75th: 6.04 µg/dL Max: 83.5 µg/dL			BW (g): −20.68 (−78.43, 37.08) BL (cm): −0.23 (−0.61, 0.15) HC (cm): 0.08 (−0.10, 0.25)
Xu et al. (2012) Guiyu and Xiamen China 2001–2008 Cohort	n: 531 (n = 432 from Guiyu and n = 99 from Xiamen) Women who gave birth in Guiyu or non-urban area of Xiamen between 2001 and 2008	Cord blood UCB measured by GFAAS Age at Measurement: birth Median: Guiyu: 10.78 µg/dL Xiamen: 2.25 µg/dL Max: Guiyu: 47.46 µg/dL Xiamen: 7.22 µg/dL	Prenatal growth: BW, LBW rate, IUGR rate, GA Obtained from birth records; LBW was defined as <2500 g Age at outcome: birth	Multiple linear and logistic regression models were adjusted for maternal age and infant sex	β (95% CI)[b] Mean BW (g): −91 (−180, −75) Mean GA (wk): 0.57 (0.51, 0.63) OR (95% CI)[b] LBW: 1.61 (1.37, 1.90) IUGR: 2.12 (1.68, 2.69)
Al-Saleh et al. (2014) Al-Kharj Saudi Arabia 2005–2006 Cohort	n: 1,578 Women aged 16–50 yr who delivered in Al-Kharj hospital, Saudi Arabia	Cord blood UCB measured by AAS Age at Measurement: maternal age 16–50; birth Mean (SD): UCB: 2.551 (2.592) µg/dL Median: UCB: 2.057 µg/dL 75th: UCB: 2.689 µg/dL Max: UCB: 56.511 µg/dL	Prenatal growth: PI PI was calculated as BW (kilograms) divided by birth height (m) cubed Age at outcome: birth	Logistic regression model was adjusted for maternal age, parity, mother's third trimester BMI, urinary cotinine, geographical distribution of current dwelling, newborn mother's highest education, total family income, and GA	OR (95% CI)[b]: 0.766 (0.502, 1.167)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Kim et al. (2020) Guiyu and Haojiang China Cross-sectional	e-REACH Study n: 314 Women 18 yr or older with a singleton pregnancy, had lived in their respective town for the duration of their pregnancy, and consented to participate in the study. Women were excluded if they had a multiple pregnancy, used assistive reproductive technology to become pregnant, had a history of psychiatric or thyroid disorders, or lived outside of their respective town for a cumulative of 3 mo or more during their pregnancy	Blood Maternal blood, collected at delivery, was measured by GFAAS Age at Measurement: ≥18 (age at delivery) Geometric mean: Guiyu: 6.7 µg/dL Haojiang: 3.8 µg/dL Max: Guiyu: 27 µg/dL Haojiang: 16 µg/dL	Prenatal growth: BW, HC, GA, newborn BMI, PI GA was calculated based on the LMP and the date of delivery. Newborn BMI and PI were calculated using the recorded BW and BL. Age at outcome: ≥18 (age at delivery)	Multiple linear and logistic regression models were adjusted for maternal age, maternal education, maternal occupation, maternal BMI, gravidity, ETS, and neonate sex	β (95% CI)[b], interpreted as the difference in BW, HC, BMI, or PI, per 1-unit increase ln-Pb maternal blood BW (g): 60 (−15, 135) HC (cm): −0.75 (−1.17, −0.32) BMI (kg/m^2): −0.14 (−0.39, 0.11) PI (kg/m3): −0.62 (−1.13, −0.11) OR (95% CI)[b] SGA: 0.69 (0.33, 1.46)
Xu et al. (2022b) Ushuaia (South, higher income) and Salta (North, lower income) Argentina 2011–2012 Cross-sectional	EMASAR n: 696 Women who either were about to deliver or had given birth within the last 48 hr at one of the two hospitals. Women had to be above 18 yr of age.	Blood Maternal blood measured by ICP-MS Age at measurement: birth Median[c]: Overall: 1.34 µg/dL Ushuaia: 0.98 µg/dL Salta 1.50 µg/dL	Prenatal growth: GA, BW, BL, HC, LBW Medical records were used to obtain measures at birth. Age at outcome: birth	Linear models adjusted for maternal age, pre-pregnancy BMI, parity, smoking, and education	β (95% CI): BW (g): −47.23 (−94.46, 0.004) BL (cm): −0.439 (−0.658, −0.219) HC (cm): −0.223 (−0.385, −0.061) GA (wk): 0.18 (0.05, 0.309) OR (95%CI) LBW: T1: Reference T2: 0.59 (0.10, 3.55)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Geometric mean[c]: Overall: 1.393 µg/dL Ushuaia: 1.01 µg/dL Salta 1.58 µg/dL 75th[c]: Overall: 1.851 µg/dL Ushuaia: 1.30 µg/dL Salta: 2.09 µg/dL			T3: 0.53 (0.09, 3.16)
Hu et al. (2015) Beijing, Lanzhou, Taiyuan, Xiamen China June-August 2011 Cohort	n: 81 Mother-infant pairs that were enrolled from 4 hospitals in 4 cities in China	Blood and cord blood Maternal blood (serum) and UCB (serum) were measured by ICP-MS Age at Measurement: median maternal age: 28.5 yr (range: 18–44); at birth Median: Maternal: 23.1 ng/g UCB: 22.0 ng/g 75th: Maternal: 33.2 ng/g UCB: 33.7 ng/g	Prenatal growth: BW BW was obtained from the medical delivery records Age at outcome: birth	Multivariate linear regression models were adjusted for infant gender, maternal age, gestational week, and maternal BMI	β (95% CI)[b] Maternal serum Pb: −1.7 g (−9.1, 5.6) UCB serum Pb: −1.5 g (−5.2, 8.2)
Yang et al. (2020) Wuhan China 2014–2015	Births at Women and Children Medical and Healthcare Center of Wuhan n: 734 The participants were	Cord blood UCB (serum) was measured by ICP-MS Age at Measurement: birth	Prenatal growth: BW (BWGA Z-score) Midwives immediately measured BW after delivery and was standardized for	Generalized linear regression models adjusted for maternal age, annual household income levels, pre-pregnancy BMI, parity, passive smoking during pregnancy,	β (95% CI)[b], per unit increase in ln-Pb UCB serum Continuous: 0.01 (−0.002, 0.05) Quartiles:

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cohort	enrolled at their first antenatal examination (<gestational 16 wk). The inclusion criteria were (1) residence in Wuhan city; (2) with a single gestation; (3) willing to take the following prenatal care during pregnancy and give birth at the study hospital; (4) willing to complete questionnaires and provide blood samples from the umbilical cord at delivery.	Geometric mean: 1.65 µg/L Median: 2.71 µg/L 75th: 4.29 µg/L Quartiles[d] Q1: <25th percentile Q2: 25th–50th percentile Q3: 50th–75th percentile Q4: >75th percentile	gestational weeks to construct BWZ. Age at outcome: birth	maternal weight gain during pregnancy, fetal sex	Q1: Reference Q2: 0.11 (−0.09, 0.30) Q3: −0.05 (−0.24, 0.14) Q4: 0.05 (−0.14, 0.24) p for trend: 0.84
Tang et al. (2016) Shengsi Island, Hangzhou China July 2011 to May 2012 Cohort	n: 103 Eligible pregnant women included those planning to deliver at the only hospital, without apparent clinical symptoms, without any maternal history of illness, and no poor habits such as drug use. Eligible infants were singleton births and had no congenital diseases.	Cord blood UCB (serum) measured by ICP-MS Age at Measurement: birth Mean (SD)[c]: 12.841 (28.646) µg/dL Median[c]: 7.620 µg/dL 75th[c]: 11.580 µg/dL Tertiles (µg/dL)[c]: T1: <5.633 T2: 5.633–9.197 T3: >9.197	Prenatal growth: BW, length (height), and HC and GA All of these infant anthropometric measurements were collected at birth by professional healthcare workers. GA was obtained using the reported date of the LMP and delivery date. Age at outcome: birth	Multivariable linear regression models were adjusted for maternal BMI, maternal age, education level, newborn gender, number of abortions, parity, and pregnancy weight gain	β (95% CI)[b] BW (g): −0.019 (−0.045, 0.006) BL (cm): 0.29 (−0.50, −0.09) HC (cm): −0.22 (−0.44, −0.00) GA (wk): −0.21 (−0.44, 0.03) BW, in g: T1: Reference T2: −0.15 (−0.41, 0.11) T3: −0.05 (−0.30, 0.21) BL, in cm: T1: Reference T2: −0.13 (−0.39, 0.13) T3: −0.15 (−0.40, 0.11)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					HC, in cm: T1: Reference T2: −0.31 (−0.59, −0.02) T3: −0.13 (−0.40, 0.14) GA, in wk: T1: Reference T2: −0.23 (−0.50, 0.05) T3: −0.20 (−0.49, 0.08)
Freire et al. (2019) Spain 2000–2008 Cohort	Environment and Childhood (INMA) Project n: 327 Pregnant women of general population resident in each study area [Ribera d'Ebre, Menorca, Granada, Valencia, Sabadell, Asturias and Gipuzkoa] and their children. Criteria for inclusion of the mothers were: (i) to be resident in one of the study areas, (ii) to be at least 16 yr old, (iii) to have a singleton pregnancy, (iv) to not have followed any program of assisted reproduction, (v) to wish to deliver in the reference hospital and (vi) to have no	Other: Placenta Placenta (including maternal and fetal sides as well as central and peripheral parts) measured with GFAAS using AAS with Zeeman background correction Age at Measurement: birth Median: <6.5 ng/g (LOD) 75th: <6.5 ng/g (LOD)	Prenatal growth: BW, length, HC, LBW, GA, and SGA Neonatal anthropometric measurements were obtained by the attending midwife or nurse; GA was calculated as the number of weeks from the self-reported LMP to the end of pregnancy; LBW was defined by a BW of less than 2500 g at term, newborns were defined as SGA when below the 10th percentile of the expected weight according to the Spanish BW curve adjusted for GA and sex	Linear models or logistic regression models were adjusted for adjusted for cohort (random effect), newborn sex, and co-exposure to other metals (As, Hg, Cd, Mn, Cr); BW and LBW models were additionally adjusted for GA, maternal smoking during pregnancy, maternal working during pregnancy, and pre-pregnancy BMI; BL models were additionally adjusted for GA and maternal smoking during pregnancy; HC models were additionally adjusted for GA, maternal smoking during pregnancy, pre-pregnancy BMI, and cesarean delivery; GA models were additionally adjusted for maternal education level; SGA models were additionally adjusted for father's	β (95% CI)[b] BW (g): 54.57 (−70.84, 180.0) BL (cm): −0.26 (−0.97, 0.44) HC (cm): −0.10 (−0.57, 0.36) GA (wk): −0.11 (−0.57, 0.36) OR (95% CI)[b] LBW: 2.94 (0.38, 28.34) SGA: 1.69 (0.53, 8.82)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	communication problems		Age at outcome: birth	education and maternal working during pregnancy	
Mikelson et al. (2019) Chattanooga, TN United States Cohort	n: 374 Singleton births of HIV and hepatitis negative mothers over 18 yr of age, with GA greater than 34 wk, and infants with no major morphological or chromosomal abnormalities	Other: Placenta Placenta tissue measured by ICP-MS Age at Measurement: birth Mean (SD): 37.97 (270.5) µg/kg Median: 12.03 µg/kg 75th: 23.23 µg/kg Max: 5073 µg/kg	Prenatal growth: BW Obtained at birth records Age at outcome: birth	Multivariable regression models adjusted maternal pre-pregnancy BMI, maternal age, GA, race, infant sex, and smoking while pregnant	β (95% CI)[b]: −58.3 g (−97.9, −18.8) β (95% CI)[b], as estimated change in BW from 25th to 75th percentile: −72.7 g (−122, −23.4)
Bloom et al. (2015) Michigan (4 counties) and Texas (12 counties) United States 2005–2009 Cohort	LIFE n: 235 Potential participants were identified, using fishing license registries or a commercially available direct marketing data base, from 12 counties in Texas and four in Michigan, respectively, with presumed exposure to persistent organic pollutants. Inclusion criteria comprised a committed heterosexual relationship, women aged 18–40 yr (men >18), English or Spanish speaker, no use of an injectable	Blood Maternal and paternal blood, collected before pregnancy (baseline), were measured by ICP-MS Age at Measurement: >18, maternal mean age: 29.75 (SD: 3.73) yr and paternal mean age: 31.52 (SD:4.57) yr Mean (SD): Maternal: 0.71 (0.30) µg/dL Paternal: 1.13 (0.63) µg/dL Median: Maternal: 0.66 µg/dL Paternal: 0.98 µg/dL Max:	Prenatal growth: GA, BW, BL, HC, PI, and secondary sex ratio Women were followed until delivery when they completed and returned birth announcements that captured date and sex of birth, weight and length, and HC. Secondary sex ratio is the ratio of live male to female births, reflecting a male excess. Age at outcome: birth	Multiple regression models for continuous outcomes: effect of maternal exposure adjusted for paternal exposure, maternal age, difference in maternal and paternal age, and maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine (mg/dL); effect of paternal exposure adjusted for maternal exposure, paternal age, difference in maternal and paternal age, and maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine (mg/dL)	β (95% CI): GA, in days Maternal Exposure: T1: Reference T2: 0.43 (−0.48, 1.35) T3: 0.14 (−0.81, 1.09) p for trend: 0.671 Paternal Exposure: T1: Reference T2: 0.19 (−0.70, 1.08) T3: 0.61 (−0.31, 1.53) p for trend: 0.416 BW, in kg Maternal Exposure: T1: Reference T2: 81.80 (−79.94, 2238.55)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	contraceptive within 12 mo, and a menstrual cycle length of 21–42 d.	Maternal: 2.23 µg/dL Paternal: 6.43 µg/dL Tertiles (µg/dL): Maternal Blood Pb T1: <0.55 (<33rd percentile) T2: 0.55–0.73 (33rd to 67th percentile) T3: >0.73 (>67th percentile) Paternal Blood Pb T1: <0.84 (<33rd percentile) T2: 0.84–1.16 (33rd to 67th percentile) T3: >1.16 (>67th percentile)			T3: −34.885 (−197.76, 128.06) p for trend: 0.202 Paternal Exposure: T1: Reference T2: 20.46 (−134.17, 175.09) T3: 62.91 (−94.73, 220.55) p for trend: 0.882 BL, in cm Maternal Exposure: T1: Reference T2: 0.43 (−0.48, 1.35) T3: 0.14 (−0.81, 1.09) p for trend: 0.671 Paternal Exposure: T1: Reference T2: 0.19 (−0.70, 1.08) T3: 0.61 (−0.31, 1.53) p for trend: 0.416 HC, in cm Maternal Exposure: T1: Reference T2: 0.03 (−0.68, 0.74) T3: −0.33 (−1.07, 0.41) p for trend: 0.132 Paternal Exposure: T1: Reference T2: 0.12 (−0.57, 0.80) T3: −0.03 (−0.72, 0.67) p for trend: 0.971

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					PI, in kg/cm^3 Maternal Exposure: T1: Reference T2: 0.82 (−7.66, 9.31) T3: −4.26 (−13.16, 4.64) p for trend: 0.321 Paternal Exposure: T1: Reference T2: −0.22 (−8.50, 8.05) T3: −5.19 (−13.71, 3.33) p for trend: 0.150
Rabito et al. (2014) Shelby County, Tennessee United States 2008–2011 Cohort	CANDLE study n: 98 Healthy pregnant woman between the ages of 16 and 40 yr, carrying a single fetus with the intent to deliver the fetus, residence within Shelby County, Tennessee, and having the intent to deliver at one of three area-based hospitals	Blood and cord blood Maternal blood and UCB were measured by ICP-MS Age at Measurement: Maternal age at collection (second or third trimester or delivery) (median: 29.50 yr); birth Median: Second trimester: 0.43 µg/dL Third trimester: 0.43 µg/dL At delivery: 0.50 µg/dL Cord blood: 0.37 µg/dL Geometric mean (SD): Second trimester: 0.42 (0.20) µg/dL	Prenatal growth: BW BW was obtained from medical records Age at outcome: birth	Linear regression models were adjusted for gravidity, marital status, and GA (in weeks)	β (95% CI)[b], per 0.1-unit increase in second trimester maternal blood Pb: −43.21 g (−88.6, 2.18)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Third trimester: 0.45 (0.28) µg/dL At delivery: 0.50 (0.35) µg/dL Cord blood: 0.37 (0.32) µg/dL Max: Second trimester: 1.22 µg/dL Third trimester: 2.10 µg/dL At delivery: 2.47 µg/dL Cord blood: 1.80 µg/dL			
Shih et al. (2021) United States January 2009–September 2010 Cohort	Initial Vanguard Study of the National Children's Study n: 125 (68 males, 57 females) Mother-infant pairs enrolled in the National Children's Study.	Blood Maternal blood was measured using dynamic reaction cell ICP-MS. Age at measurement: Maternal age at 6–32 wk of gestation Median: Overall: 0.34 µg/dL Male infants: 0.35 µg/dL Female infants: 0.33 µg/dL Max: Overall: 2.86 µg/dL Male infants: 2.86 µg/dL Female infants: 0.85 µg/dL	Prenatal growth: BL, HC, BW, GA, and PI Birth outcomes measured during physical examination of infants at birth; BL (cm) and HC (cm) were measured twice, and the average of the two readings was used. For those without measures at birth, medical records were extracted by the National Children's Study. GA and BW were obtained from medical records. Age at outcome: birth	Linear regression models adjusted for maternal age, race/ethnicity, education, income, smoking status during pregnancy, number of prior livebirths, continuous BMI, and infant sex	β (95% CI)[b], as expected change for birth outcomes GA (wk) Overall: −0.558 (−2.297, 1.181) Males: 1.084 (−0.855, 3.024) Females: −4.335 (−7.365, −1.305) BW (g) Overall: −403.593 (−916.671, 109.485) Males: 141.814 (−431.7, 715.329) Females: −1685.349 (−2581.105, −789.592) BL (cm) Overall: −0.343 (−2.92, 2.233) Males: 2.211 (−0.667, 5.089)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Females: −6.37 (−10.86, −1.88) HC (cm) Overall: −1.245 (−2.769, 0.279) Males: 0.292 (−1.397, 1.981) Females: −4.866 (−7.52, −2.212) PI (kg/m^3) Overall: −3.134 (−6.698, 0.429) Males: −2.377 (−6.486, 1.731) Females: −4.733 (−11.191, 1.725)
Woods et al. (2017) Cincinnati, Ohio United States 2003–2006 Cohort	HOME Study n: 272 Women were recruited between 13 and 19 wk of pregnancy from prenatal clinics and were >18 yr old, <19 wk gestation at the time of enrollment, and living in a residence built before 1987	Blood Maternal blood was measured by sensitive and specific liquid or gas chromatography mass spectrometry Age at measurement: maternal age at 16–26 wk gestation Geometric mean (geometric SD): 0.7 (1.4) µg/dL Median: 0.7 µg/dL 75th: 0.8 µg/dL	Prenatal growth: BW BW was abstracted from birth records Age at outcome: birth	Bayesian hierarchical linear models were adjusted for maternal race, age at delivery, infant sex, maternal education, tobacco exposure, household annual income, employment, maternal insurance status, marital status, pre-natal vitamin use, and maternal BMI; sensitivity analysis included GA	Posterior mean (95% credible interval)[b], as the difference in BW per 10-fold increase in maternal blood Pb: −44.8 g (−110, 21.7)
Taylor et al. (2016) Bristol, UK	ALSPAC n: 4,190	Blood	Prenatal growth: BW, HC, crown-to-heel length	Multivariable fractional polynomials and modeled adjusted for maternal	β (95% CI)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
April 1991–December 1992 Cohort	All pregnant women in the former Avon Health Authority with an expected delivery date between April 1,1991, and December 31, 1992, were eligible for the study; 14,541 pregnant women were initially enrolled, resulting in a cohort of 14,062 live births	Maternal blood was measured by ICP-MS Age at measurement: maternal age at measurement (median GA of sampling: 11 wk) Median: 3.40 µg/dL 75th: 4.33 µg/dL Max: 19.41 µg/dL	HC and CHL were measured by trained study staff where the mother gave permission or if these data were missing, the values were extracted from the medical records by trained study staff. BW was derived from obstetric data and from central birth notification data: where values disagreed by <100 g then the lowest value was accepted; if the values disagreed by >100 g then the value was coded as missing. Age at outcome: birth	educational attainment, smoking, GA (centered at 40 wk), maternal height and pre-pregnancy weight, and sex of the infant	BW (g): −9.93 (−20.27, 0.41) HC (cm): −0.03 (−0.06, 0.00) CHL (cm): −0.05 (−0.10, 0.00)
García-Esquinas et al. (2014) Madrid Spain October 2003–May 2004 Cohort	BioMadrid Project n: 97 Women were required to be aged over 15 yr, to be expecting a single pregnancy, intend to deliver their babies at the public hospital assigned to them, lived in the study area (Madrid Autonomous Region) for more than a year, and did not have	Blood and cord blood Blood, from both parents, and UCB measured by AAS with a transversely heated graphite atomizer furnace assembly and longitudinal Zeeman-effect background correction Age at measurement: maternal and paternal age at median gestational week was 33.9 (IQR 31.6–35.7) and at birth	Prenatal growth: GA, BW, BL, AD, or CD GA, BW, BL, AD, or CD was collected at delivery Age at outcome: birth	Multivariable linear regression models were adjusted for sampling maternal age, maternal tobacco smoke, area (metropolitan/urban), and in non-stratified models, newborn's sex	β (95% CI)[b], as mean difference per two-fold increase in BLL Maternal blood Pb BW (g): 62.4 (−73.1, 197.8) BL (cm): 0.17 (−0.56, 0.91) AD (cm): 0.31 (−0.52, 1.15) CD (cm): 0.15 (−0.21, 0.51) GA (wk): 0.02 (−0.44, 0.47) Paternal blood Pb BW (g): −110.8 (−235.6, 6.0)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	a blood transfusion in the previous year	Geometric mean[c]: Maternal: 1.83 µg/dL Paternal: 3.17 µg/dL UCB: 0.45 µg/dL			BL (cm): −0.44 (−1.12, 0.23) AD (cm): −0.81 (−1.64, −0.00) CD (cm): −0.32 (−0.65, 0.00) GA (wk): −0.17 (−0.59, 0.26) UCB Pb BW (g): 80.0 (−36.8, 196.6) BL (cm): 0.30 (−0.33, 0.93) AD (cm): 0.56 (−0.12, 1.24) CD (cm): −0.16 (−0.47, 0.15) GA (wk): −0.04 (−0.44, 0.35) Male Infants Maternal blood Pb BW (g): 62.6 (−145.2, 270.4) BL (cm): 0.29 (−0.83, 1.41) AD (cm): 1.10 (−0.25, 2.45) CD (cm): −0.16 (−0.47, 0.15) GA (wk): 0.11 (−0.58, 0.81) Paternal blood Pb BW (g): −93.5 (−269.6, 82.5) BL (cm): 0.13 (−0.81, 1.06) AD (cm): −0.64 (−1.89, 0.61)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					CD (cm): −0.11 (−0.57, 0.35) GA (wk): 0.06 (−0.53, 0.65) UCB Pb BW (g): 80.0 (−66.0, 226.0) BL (cm): 0.66 (−0.11, 1.44) AD: 0.76 cm (−0.16, 1.67) CD: −0.11 cm (−0.37, 0.39) GA: 0.06 wk (−0.53, 0.65) Female Infants Maternal blood Pb BW (g): 62.2 (−128.0, 252.4) BL (cm): 0.08 (−0.95, 1.10) AD (cm): −0.21 (−1.30, 0.88) CD (cm): −0.05 (−0.55, 0.46) GA (wk): −0.06 (−0.70, 0.57) Paternal blood Pb BW (g): −129.4 (−312.3, 53.4) BL (cm): −1.06 (−2.03, −0.08) AD (cm): −1.94 cm (−2.06, 0.18) CD (cm): −0.55 (−1.03, −0.07) GA (wk): −0.41 (−1.02, 0.21)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					UCB Pb BW (g): 80.0 (−115.7, 275.7) BL (cm): −0.37 (−1.41, 0.67) AD (cm): 0.31 (−0.73, 1.35) CD (cm): −0.47 (−0.98, 0.05) GA (wk): −0.13 (−0.79, 0.65)
Daniali et al. (2023) Isfahan, Iran 2019–2020 Cohort	Prospective Epidemiologic Research Studies in Iran – Isfahan Center n: 263 Pregnant Iranian women who have lived in Isfahan for at least 1 yr, and did not have any history of infertility, those in the first trimester of pregnancy, and those who intended to give birth in hospitals of Isfahan city. All participants with major risks of SGA and IUGR such as serious medical complications (hypertension or diabetes or kidney disease), cerclage until 24 wk of pregnancy,	Blood Maternal blood was measured by ICP-MS Age at measurement: maternal age at first trimester (mean maternal age 29.94 yr) Geometric mean ± SD: 2.534 ± 0.205 µg/dL Median: 2.786 µg/dL 25th: 1.741 µg/dL 75th: 4.01 µg/dL	Prenatal growth: BW, HC, BL Standardized neonatal anthropometric measurements were obtained by trained midwives using calibrated instruments. Age at outcome: birth	Infant sex, and maternal age, BMI at enrollment (12−14 wk gestation), income, secondhand smoke exposure, parity, and education.	B (95%CI) BW (g): −0.057 (−0.099, −0.014) BL (cm): 0.01 (−0.034, 0.054) HC (cm): −0.036 (−0.076, 0.004)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	history of stillbirth or preterm labor, multiple pregnancies, or abnormal sonographic evidence were excluded from the study.				
Taylor et al. (2015) Bristol UK April 1991–December 1992 Cohort	ALSPAC n: 4,285 All pregnant women in the former Avon Health Authority with an expected delivery date between April 1, 1991, and December 31, 1992, were eligible for the study	Blood Maternal blood was measured by ICP-MS Age at measurement: maternal age at measurement (median GA of sampling: 11 wk) Mean (SD): 3.67 (1.47) µg/dL Geometric mean: 3.43 µg/dL Median: 3.42 µg/dL Max: 19.14 µg/dL	Prenatal growth: BW, HC, CHL, and LBW BW, HC, and CHL were measured by trained staff or extracted from medical records; LBW was <2500 g Age at outcome: birth	Linear regression models were adjusted for maternal height, maternal pre-pregnancy weight, maternal educational attainment, parity, number of cigarettes per day, sex of baby, GA at delivery or death; logistic regression models for LBW were adjusted for maternal height, maternal pre-pregnancy weight, maternal educational attainment, parity, number of cigarettes per day, sex of baby and GA at delivery or death	β (95% CI) BW (g): −1.62 (−2.909, −0.331) HC (cm): −0.005 (−0.043, 0.033) CHL (cm): −0.006 (−0.013, 0.001) OR (95% CI) LBW: 1.37 (0.86, 2.18)
Hu et al. (2021) Canada 2008–2011 Cohort	MIREC n: 1857 Women from the MIREC cohort who delivered singleton live births, had complete sociodemographic information, and provided biological samples during the first trimester of the pregnancy.	Blood Maternal blood was measured by ICP-MS Age at Measurement: Maternal age during first trimester Geometric mean[c]: 0.62 µg/dL	Prenatal growth: BW Infant BW (g) abstracted from medical records and examined continuously. Age at outcome: birth	Maternal age, race, education, pre-pregnancy BMI, smoking status, parity, infant sex, cubic-spline GA; multi-pollutant model was also adjusted for As, Cd, Hg, and Mn	β (95% CI), as two-fold increase in Pb blood Single pollutant model: −82.22 g (−145.46, −18.97) Multi-pollutant model: −75.89 g (−141.24, −10.54)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Median[c]: 0.60 µg/dL 75th[c]: 0.85 µg/dL			
Goto et al. (2021) Japan January 2011–March 2014 Cohort	JECS n: 16,423 Pregnant women living in the study area and understanding of the Japanese language. Participants were excluded: if they did not meet the Pb measurement quality control criteria (n = 2,002); if mothers who: were lost to follow-up; had severe maternal conditions preceding pregnancy, such as chronic hypertension, pregestational diabetes or cardiac disease, during pregnancy; or had pregnancies ending in abortions or stillbirths (n = 1,209); if infants had chromosomal or major congenital anomalies (n = 263) or multiple births (n = 283)	Blood Maternal blood was measured by ICP-MS Age at measurement: maternal age at second or third trimester (mean age at delivery: 31 ± 5.0 yr) Mean: 0.69 µg/dL Median: 0.63 µg/dL 75th: 0.78 µg/dL Max: 7.4 µg/dL	Prenatal growth: BW, SGA, and LBW BW was the primary outcome. Anthropometric data were measured by trained delivery room staff. Gestational dating was performed from the first accurate ultrasound examination during the first trimester. SGA was defined as a BW below the 10th percentile of the national BWs reported in the Japanese standard growth chart, which also considers GA, infant sex, and maternal parity. LBW was defined as a BW below 2500 g, regardless of GA. Age at outcome: birth	Multivariable linear regression models were adjusted for maternal age at birth, BMI before pregnancy, weight gain during pregnancy, maternal educational background, a history of preterm birth, alcohol consumption during pregnancy, smoking habit during pregnancy, and parity	β (95% CI), per 0.1 µg/dL increase in maternal blood Pb BW (g): −54 (−74.5, −33.5) HC (cm): −0.10 (−0.05, −0.15) BL (cm): −0.20 (−0.30, −0.10) GA (days): 0.20 d (−0.35, 0.75) β (95% CI), per doubling increment in maternal blood Pb BW (g): −86.595 (−112.16, −61.03) HC (cm): −0.152 (−0.25, −0.054) BL (cm): −0.326 (−0.468, −0.185) GA (days): 0.087 (−0.566, 0.74) OR (95% CI), per 0.1 µg/dL increase in maternal BLL SGA: 1.34 (1.16, 1.55) LBW: 1.34 (1.16, 1.55) OR (95% CI), per doubling increment in maternal blood Pb SGA: 1.952 (1.526, 2.498) LBW: 1.34 (1.16, 1.55)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Rodosthenous et al. (2017) Mexico City Mexico 2007–2011 Cohort	PROGRESS n: 944 Inclusion criteria: singleton pregnancy, GA <20 wk, maternal age of >18 yr, expectation to live in Mexico City for the following 3 yr, and have access to a telephone; exclusion criteria: chronic medical conditions such as heart or kidney disease; use of steroids or anti-epilepsy drugs; drug addiction; and daily consumption of alcoholic beverages due to its association with adverse fetal outcomes	Blood Maternal blood measured by ICP-QQQ Age at measurement: maternal age at ~20 wk gestation Mean (SD): 3.7 (2.7) µg/dL Quartile Mean (SD) (µg/dL): Q1: 1.4 (0.3) Q2: 2.4 (0.2) Q3: 3.6 (0.5) Q4: 7.3 (2.8) Median: 2.8 µg/dL 75th: 4.5 µg/dL Max: 22.9 µg/dL Quartiles (µg/dL) Q1: <1.93 Q2: 1.93–2.79 Q3: 2.80–4.53 Q4: >4.53	Prenatal growth: BWGA, SGA Infants with a BWGA Z-score <10th percentile as SGA Age at outcome: birth	Multivariable linear regression models were adjusted for maternal age, BMI, SES, hemoglobin levels, and infant sex Quantile regression models were adjusted for maternal age, BMI, SES, hemoglobin levels, and infant sex Multivariable logistic regression models were adjusted for maternal age, BMI, SES, hemoglobin levels, and infant sex	β (95% CI)[b], as difference in BWGA Z-score per $\log_2$ increase in maternal BLL: −0.06 (−0.013, 0.03) β (95% CI)[b], as the BWGA Z-score per $\log_2$ increase in maternal BLL QL 0.05: −0.08 (−0.19, 0.03) QL 0.10: −0.13 (−0.25, −0.004) QL 0.15: −0.11 (−0.22, −0.002) QL 0.20: −0.12 (−0.20, −0.03) QL 0.25: −0.10 (−0.19, −0.02) QL 0.30: −0.11 (−0.18, −0.04) QL 0.35: −0.04 (−0.12, 0.04) QL 0.40: −0.06 (−0.14, 0.03) QL 0.45: −0.05 (−0.13, 0.04) QL 0.50: −0.07 (−0.16, 0.01) QL 0.55: −0.07 (−0.16, 0.01) QL 0.60: −0.07 (−0.15, 0.01) QL 0.65: −0.04 (−0.12, 0.04) QL 0.70: −0.04 (−0.12, 0.03)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					QL 0.75: −0.01 (−0.08, 0.06) QL 0.80: −0.02 (−0.1, 0.06) QL 0.85: −0.06 (−0.16, 0.04) QL 0.90: −0.06 (−0.16, 0.02) QL 0.95: −0.02 (−0.13, 0.09) OR (95% CI) for SGA: Q1: Reference Q2: 1.30 (0.79, 2.15) Q3: 1.15 (0.92, 1.45) Q4: 1.09 (1.00, 1.18) p for trend: 0.06
Ashrap et al. (2020) Puerto Rico 2010–2017 Cohort	PROTECT n: 731 Participants were recruited at approximately 14 ± 2 wk of gestation at seven prenatal clinics and hospitals throughout Northern Puerto Rico and followed until birth; maternal age between 18 and 40 yr; residence inside of the Northern Karst aquifer region; disuse of oral contraceptives within the 3 mo prior to pregnancy; disuse of IVF to become	Blood Maternal blood was measured by ICP-MS Age at measurement: 18–40 (collection between 18 and 26 wk of gestation) Geometric mean (SD): Preterm births: 0.39 (1.6) µg/dL Term births: 0.32 (1.5) µg/dL Median: Preterm births: 0.36 µg/dL Term births: 0.32 µg/dL	Prenatal growth: GA, SGA, LGA, BWZ All the birth outcome data were extracted from medical records. GA was calculated; BWZ was defined as the number of SDs by which a BW is above or below the mean; SGA births were defined as below the 10th percentile of BWZs; LGA births were defined as above the 90th percentile of BWZs	Logistic regression models were adjusted for maternal age, maternal education level, pre-pregnancy BMI, and exposure to second-hand smoking	β (95% CI)[b], per change per IQR increase in maternal blood ln-Pb GA (days): −1.8 (−3.1, −0.5) Tertiles[d]: GA (days): T1: Reference T2: −0.2 (−2.9, 2.4) T3: −2.9 (−5.5, −0.2) BWZ: T1: Reference T2: −0.12 (−0.32, 0.07) T3: 0.09 (−0.11, 0.29)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	pregnant; and free of any major medical or obstetrical complications, including pre-existing diabetes. Each woman participated in a total of up to three study visits (18 ± 2 wk, 22 ± 2 wk, and 26 ± 2 wk of gestation).		Age at outcome: birth		OR (95% CI)[b], per change per IQR increase in maternal blood ln-Pb SGA: 0.91 (0.69, 1.2) Tertiles[d]: SGA T1: Reference T2: 1.58 (0.88, 2.83) T3: 0.62 (0.30, 1.26) LGA T1: Reference T2: 1.13 (0.63, 2.03) T3: 0.74 (0.40, 1.40)
Thomas et al. (2015) Canada 2008–2011 Cohort	MIREC Study n: 1,835 Pregnant women were recruited in the first trimester of pregnancy from 10 study sites across Canada. Exclusion criteria included: inability to communicate and consent in either French or English, >14 wk gestation at the time of recruitment, <18 yr of age, diagnosed with a fetal anomaly or a history of major chronic disease. Excluded from the analysis were: 18 women who withdrew	Blood Maternal blood, collected during the first and third trimesters of pregnancy, was measured by ICP-MS Age at Measurement: Maternal age at first and third trimesters Median: 0.59 µg/dL 75th: 0.81 µg/dL Max: 4.04 µg/dL Tertiles (µg/dL): T1: <0.52 T2: 0.52–1.04 T3: >1.04	Prenatal growth: SGA SGA births were identified as those weighing less than the 10th percentile for a reference population based on the same completed week of gestation and infant sex Age at outcome: birth	Log binomial multivariate regression models estimated RR and adjusted for smoking and parity	RR (95% CI): T1: Reference T2: 1.33 (0.88, 1.99) T3: 1.19 (0.65, 2.18) RR (95% CI) for GSTP1 A114V CC Pb ≤0.08 µg/dL: Reference Pb >0.08 µg/dL: 0.90 (0.57, 1.41) TC + tT Pb ≤0.08 µg/dL: Reference Pb >0.08 µg/dL: 2.25 (0.95, 5.16) p for interaction: 0.06

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	during the study, 51 women who gave birth to multiples, 9 stillbirths, 32 spontaneous abortions, 13 therapeutic abortions, 28 with no metal exposure data, and 15 with no infant sex, weight, or GA recorded				RR (95% CI) for GSTP1 I105V AA Pb ≤0.08 µg/dL: Reference Pb >0.08 µg/dL: 1.22 (0.69, 2.15) AG + GG Pb ≤0.08 µg/dL: Reference Pb >0.08 µg/dL: 0.95 (0.54, 1.66) p for interaction: 0.53 RR (95% CI) for GSTO1 A104A CC Pb ≤0.08 µg/dL: Reference Pb >0.08 µg/dL: 0.94 (0.52, 1.69) CA + AA Pb ≤0.08 µg/dL: Reference Pb >0.08 µg/dL: 1.20 (0.70, 2.06) p for interaction: 0.54
Ashrap et al. (2021) Puerto Rico 2011–2017 Cohort	PROTECT n = 682 Participants were recruited at approximately 14 ± 2 wk of gestation at seven prenatal clinics and hospitals throughout Northern Puerto Rico and	Blood Maternal blood was measured by ICP-MS Age at measurement: 18–40 (collection between 18 and 26 wk of gestation)	Prenatal growth: GA, BWZ, small for gestation, large for gestation Birth outcomes were extracted from medical records. Psychosocial status was evaluated using four questionnaires	Linear and logistic regression models were adjusted for maternal age, maternal education, pre-pregnancy BMI, second-hard smoke exposure	β (95% CI)[b], per IQR increase in in maternal blood ln-Pb GA, change in days Good Psychosocial Status: −1.9 (−3.2, −0.6) Poor Psychosocial Status: −1.3 (−4.0, 1.5) BWZ, change in Z-score

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	followed until birth; maternal age between 18 and 40 yr; residence inside of the Northern Karst aquifer region; disuse of oral contraceptives within the 3 mo prior to pregnancy; disuse of IVF to become pregnant; and free of any major medical or obstetrical complications, including pre-existing diabetes. Each woman participated in a total of up to three study visits (18 ± 2 wk, 22 ± 2 wk, and 26 ± 2 wk of gestation)	Geometric mean: 3.1 µg/dL Median: 3.1 µg/dL 75th: 4.1 µg/dL 95th: 6.5 µg/dL Max: 15.1 µg/dL	Age at outcome: birth		Good Psychosocial Status: 0.1 (0.0, 0.2) Poor Psychosocial Status: −0.1 (−0.3, 0.2) OR (95% CI)[b], per IQR increase in in maternal blood ln-Pb SGA Good Psychosocial Status 0.86 (0.65, 1.14) Poor Psychosocial Status: 1.49 (0.67, 3.33) LGA Good Psychosocial Status 0.89 (0.64, 1.23) Poor Psychosocial Status: 1.10 (0.57, 2.10)
Gustin et al. (2020) Norrbotten County Sweden 2015–2018 Cohort	NICE n: 589 The cohort was established in the catchment area of Sunderby hospital in Norrbotten county, Sweden. At the routine ultrasound in gestational week 17–18, parents who were interested in participation were given more information and an informed consent to sign at home and send back. To be included in the study, families had	Blood Maternal blood (erythrocyte) was measured by ICP-MS Age at measurement: Maternal age at gestational week 24–36 (mean: 31 yr, range 19–45 yr) Mean: 14 µg/kg Median: 11 µg/kg Max: 148 µg/kg	Prenatal growth: BW, BL, and HC Information on the infants' weight (g), length (cm), and HC (cm) at birth was collected from the hospital records at Sunderby hospital. Age at outcome: birth	Multivariable-adjusted linear and spline regression models were adjusted for maternal age, early-pregnancy BMI, parity, education, pre-pregnancy smoking, pre-pregnancy snuff or non-smoking tobacco use, pre-pregnancy alcohol consumption, and marital/cohabitant status; infant sex and GA at birth (in days); models were also mutually adjusted for other maternal metals (Cd and Hg)	β (95% CI)[b]: BW (g): −13 (−66, 41) p for interaction with infant sex: 0.88 BL (cm): −0.080 (−0.31, 0.15) p for interaction with infant sex: 0.43 HC (cm): Less than median: 0.059 (−0.22, 0.34) p for interaction with infant sex: 0.84 Greater than median: −0.24 (−0.53, 0.056)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	to be residents in Norrbotten county and be able to communicate in written and spoken Swedish.				p for interaction with infant sex: 0.23 Mutually adjusted for other maternal metals BW (g): −0.0091 (−0.077, 0.058) BL (cm): −0.0078 (−0.079, 0.064) HC (cm): Less than median: 0.018 (−0.058, 0.094) Greater than median: −0.050 (−0.13, 0.0026)
Rahman et al. (2021) Massachusetts United States 1999–2002 Cohort	Project Viva n: 1391 Women were recruited at prenatal care visits at eight urban and suburban practices of a multi-specialty group practice in eastern Massachusetts. Exclusion criteria included multiple gestation, inability to answer questions in English, GA ≥22 wk at recruitment and plans to move away from the study area before delivery.	Blood Maternal blood (erythrocyte) was measured by ICP-MS. Age at measurement: maternal age at collection (mean 11.3 ± 2.8 wk gestation); mean maternal age (SD): 32.3 (4.7) yr Geometric mean: 17.99 ng/g Median: 17.7 ng/g 75th: 23.6 ng/g	Prenatal growth: BW, BL, HC, GA GA from reported last menstrual period, BW, BL, and HC from medical records Age at outcome: birth	Multivariable linear regression models were adjusted for maternal age, education, pre-pregnancy BMI, parity, smoking status, race/ethnicity, household income, infant sex, and GA at delivery (except when GA is an outcome)	β (95% CI)[b], per IQR (10.1 ng/g) increase: BW (g): Full Cohort: −33.9 (−65.3, −2.5) Males: −32.5 (−77.4, 12.5) Females: −34.6 (−77.2, 8.1) BL (cm): Full Cohort: −0.10 (−0.29, −0.09) Males: −0.08 (−0.35, 0.19) Females: −0.13 (−0.39, 0.13) HC (cm) Full Cohort: −0.07 (−0.17, 0.04) Males: −0.14 (−0.29, 0.02)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Females: 0.00 (−0.15, 0.15) GA (wk) Full Cohort: 0.03 (−0.10, 0.16) Males: 0.12 (−0.07, 0.30) Females: −0.04 (−0.22, 0.14) (95% CI)[b], per IQR (10.1 ng/g) increase, when As, Cd, Mn, Zn, and Hg were fixed at the 25th percentile: BW (g): Full Cohort: −0.05 (−0.11, 0.02) Males: −0.03 (−0.12, 0.06) Females: −0.06 (−0.14, 0.02) BL (cm): Full Cohort: −0.06 (−0.14, 0.03) Males: −0.04 (−0.16, 0.07) Females: −0.04 (−0.14, 0.07) HC (cm) Full Cohort: −0.08 (−0.18, 0.02) Males: −0.08 (−0.26, 0.09) Females: −0.04 (−0.14, 0.07)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					GA (wk) Full Cohort: 0.02 (−0.06, 0.10) Males: 0.05 (−0.06, 0.16) Females: −0.01 (−0.12, 0.100) β (95% CI)[b], per IQR (10.1 ng/g) increase, when As, Cd, Mn, Zn, and Hg were fixed at the 50th percentile: BW (g): Full Cohort: −0.04 (−0.10, 0.01) Males: −0.03 (−0.11, 0.05) Females: −0.05 (−0.13, 0.02) BL (cm): Full Cohort: −0.05 (−0.13, 0.04) Males: −0.04 (−0.15, 0.07) Females: −0.03 (−0.14, 0.07) HC (cm) Full Cohort: −0.06 (−0.15, 0.03) Males: −0.06 (−0.21, 0.09) Females: −0.03 (−0.14, 0.07) GA (wk)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Full Cohort: 0.01 (−0.06, 0.08) Males: 0.04 (−0.06, 0.14) Females: −0.02 (−0.12, 0.08) β (95% CI)[b], per IQR (10.1 ng/g) increase, when As, Cd, Mn, Zn, and Hg were fixed at the 75th percentile: BW (g): Full Cohort: −0.04 (−0.11, 0.02) Males: −0.03 (−0.12, 0.06) Females: −0.05 (−0.13, 0.03) BL (cm): Full Cohort: −0.04 (−0.12, 0.05) Males: −0.04 (−0.15, 0.08) Females: −0.03 (−0.14, 0.08) HC (cm) Full Cohort: −0.03 (−0.13, 0.08) Males: −0.05 (−0.22, 0.13) Females: −0.03 (−0.14, 0.08) GA (wk) Full Cohort: −0.01 (−0.09, 0.07)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Males: 0.03 (−0.08, 0.14) Females: −0.03 (−0.14, 0.08)
Wang et al. (2017a) China 2009 Cohort	C-ABCS n: 3,125 Pregnant women with singleton, live births	Blood Maternal blood (serum) was detected by GFAAS Age at measurement: maternal age at collection (first trimester, median: 11 wk) and second trimester (median: 16 wk) (mean age: 27.5 yr) Mean: Overall: 1.50 µg/dL First trimester: 1.52 µg/dL Second trimester: 1.49 µg/dL Median: Overall: 1.43 µg/dL First trimester: 1.43 µg/dL Second trimester: 1.43 µg/dL Max: Overall: 5.46 µg/dL First trimester: 5.16 µg/dL Second trimester: 5.46 µg/dL Tertiles (µg/dL): Low: <1.18 Medium: 1.18–1.70	Prenatal growth: SGA, BW, BL, HC, and CC SGA was defined as live-born infants with BW below 10th percentile for the babies of the same GA according to a global reference; BW, BL, HC, and CC were measured at birth Age at outcome: birth	Multivariate linear and logistic regression models were adjusted for pre-pregnancy BMI, maternal age, gravidity, monthly income, parity, and time of serum collection	β (95% CI)[b] Maternal serum during pregnancy BW (g): −2.74 (−5.17, −0.31) BL (cm): −0.013 (−0.026, 0.001) HC (cm): −0.008 (−0.019, 0.004) CC (cm): −0.008 (−0.018, −0.002) First trimester maternal serum BW: −4.40 g (−8.22, −0.58) BL: −0.022 cm (−0.048, 0.005) HC: −0.007 cm (−0.022, 0.007) CC: −0.015 cm (−0.030, <0) Second trimester maternal serum BW (g): −1.64 (−4.80, −0.58) BL (cm): −0.006 (−0.020, 0.009) HC (cm): −0.008 (−0.024, 0.008) CC (cm): −0.002 (−0.016, −0.011) OR (95% CI)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		High: ≥1.71			SGA All Infants Low: Reference Medium: 1.45 (1.04, 2.02) High: 1.69 (1.22, 2.34) Males Low: Reference Medium: 1.44 (0.83, 2.50) High: 1.75 (1.03, 2.99) Females Low: Reference Medium: 1.51 (0.99, 2.31) High: 1.68 (1.12, 2.54) First trimester maternal serum Low: Reference Medium: 1.19 (0.65, 2.19) High: 2.13 (1.24, 3.38) Second trimester maternal serum Low: Reference Medium: 1.57 (1.05, 2.34) High: 1.48 (0.98, 2.21)
Cassidy-Bushrow et al. (2019) Wayne County, MI United States September 2003 and December 2007 (December 2011 and January 2015)	WHEALS n: 145 Pregnant women were in their second trimester or later, were aged 21–49 yr, and were living in a predefined geographic area in Wayne and Oakland counties that	Teeth Teeth, representing second and third trimester exposure, measured by LA-ICP-MS Mean (SD)[6]: Second trimester: 0.04 (0.03) µg/g	Prenatal growth: BWZ and GA BWZ and GA obtained from prenatal and birth records Age at outcome: birth	Linear regression models adjusted for batch, tooth attrition, tooth type, race, urban, ETS, anemic, maternal age, and year house built; the effect of time is the difference in effect estimates from the second and third trimesters	β (95% CI)[b]: BWZ Second trimester: −0.15 (−0.35, 0.05) Third trimester: −0.06 (−0.24, 0.12) Effect of Time: −0.31 (−0.90, 0.28)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cohort	included the city of Detroit as well as the suburban areas immediately surrounding the city	Third trimester: 0.05 (0.04) µg/g			Boys Second trimester: −0.20 (−0.47, 0.07) Third trimester: −0.04 (−0.31, 0.23) Girls Second trimester: −0.12 (−0.39, 0.15) Third trimester: −0.06 (−0.33, 0.21) GA (wk) Second trimester: 0.08 (−0.19, 0.35) Third trimester: 0.14 (−0.11, 0.39) Effect of time: −0.22 (−1.08, 0.64) Boys Second trimester: 0.08 (−0.41, 0.57) Third trimester: 0.01 (−0.44, 0.46) Girls Second trimester: 0.12 (−0.21, 0.45) Third trimester: 0.27 (−0.06, 0.60)
Bui et al. (2022) North Carolina	CCG MSA n: 147,673 live births in the CCG MSA;	Births where the mother's residential address was within 4,000 meters of CMS	Prenatal growth: BW, LBW, and SGA	Difference-in-difference models were used to compare birth outcomes in	β (95% CI)[b], as estimated average treatment effect of treatment group

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
United States 2004–2009 Quasi-experimental	Treatment group n: 1,138; Control group n: 13,398 Exogenous variation in Pb exposure resulting from NASCAR's deleading of racing fuel in 2007 was used as a quasi-experiment. CMS, located in the CCG, was the only NASCAR racetrack in North Carolina that held races every year during our sample period. Races occurred bi-annually, in October and May, ensuring that all full and near full-term births in the sample were prenatally exposed via the mother to *at least* one NASCAR event.	were classified as the treatment group, while the control group consists of births where the mother's residential address is in the CCG but is at least 10,000m from the racetrack centroid	BW was the newborn's weight, in grams. LBW was defined as BW <2500 g. SGA was defined as BW below the tenth percentile for clinical GA. Age at outcome: birth	a non-randomized treatment group before and after deleading to those in the control group. Models were adjusted for mother's age, education, race, and smoking behavior; father's age, education, and race; infant's birth order and sex; as well as proximity to a TRI facility or airport, median household income, and age of housing stock; a set of census tract, month, and year indicator variables were also included	BW (g) All births Any exposure: 102. 5 (45.73, 152.2) Trimester 1: 418.6 (205.1, 632.1) Trimester 2: 47.68 (−40.01, 135.4) Trimester 3: 262 (97.01, 427.1) Full-term births Any exposure: 24.08 (−15.14, 63.29) Trimester 1: 104.7 (−54.65, 264) Trimester 2: 44.16 (−36.35, 124.7) Trimester 3: 80.19 (−30.44, 190.8) LBW All births Any exposure: −0.045 (−0.07, −0.019) Trimester 1: −0.062 (−0.178, 0.054) Trimester 2: −0.022 (−0.061, 0.017) Trimester 3: −0.158 (−0.314, −0.001) Full-term births Any exposure: 0.001 (−0.014, 0.016)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Trimester 1: 0.05 (−0.038, 0.138) Trimester 2: −0.035 (−0.054, −0.016) Trimester 3: −0.006 (−0.07, 0.057) SGA All births Any exposure: −0.04 (−0.064, −0.016) Trimester 1: −0.042 (−0.242, 0.158) Trimester 2: −0.058 (−0.118. 0.002) Trimester 3: −0.038 (−0.122, 0.045) Full-term births Any exposure: −0.028 (−0.051, −0.004) Trimester 1: −0.053 (−0.274, 0.168) Trimester 2: −0.049 (−0.103, 0.004) Trimester 3: 0.022 (−0.081, 0.125)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]

AAS = atomic absorption spectrometry; AD = abdominal diameter; ALSPAC = Avon Longitudinal Study of Parents and Children; As = arsenic; BL = birth length; BMI = body mass index; BW = birth weight; BWGA = birth weight-for-gestational age; BWZ = birth weight Z-score; C-ABCS = China-Anhui Birth Cohort Study; CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CC = chest circumference; CCG = Charlotte-Concord-Gastonia; Cd = cadmium; CD = cephalic diameter; CHL = crown-heel length; CMS = Charlotte Motor Speedway; Cr = chromium; d = day(s); EMASAR = Study on the Environment and Reproductive Health; e-REACH = e-waste Recycling Exposure and Community Health; ETS = environmental tobacco smoke; FLEHS = Flemish Environment and Health Study; GA = gestational age; GFAAS = graphite furnace atomic absorption spectrometry; HC = head circumference; Hg = mercury; HOME = Health Outcomes and Measures of the Environment; hr = hour(s); HR-ICP-MS = high resolution inductively coupled plasma mass spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; ICP-QQQ = inductively coupled plasma triple quad; INMA = Instituto de Nanociencia y Materiales de Aragón; IQR = interquartile range; IUGR = intrauterine growth restriction; IVF = in vitro fertilization; LA-ICP-MS = laser ablation-inductively coupled plasma-mass spectrometry; LBW = low birth weight; LGA = large for gestational age; LIFE = Longitudinal Investigation of Fertility and the Environment; LMP = last menstrual period or last missed period; ln = natural log; LOD = limit of detection; MIREC = Maternal-Infant Research on Environmental Chemicals; min = minute(s); Mn = manganese; mo = month(s); MSA = Metropolitan Statistical Area; NICE = Nutritional impact on Immunological maturation during Childhood in relation to the Environment; OR = odds ratio; PI = Ponderal Index; PROGRESS = Programming Research in Obesity, Growth Environment and Social Stress; PROTECT = Puerto Rico Test site for Exploring Contamination Threats; QL = lower quartile; RR = relative risk; SD = standard deviation; SES = socioeconomic status; SGA = small for gestational age; TRI = Toxics Release Inventory; UCB = umbilical cord blood; WHEALS = Wayne County Health, Environment, Allergy and Asthma Longitudinal Study; wk = week(s); yr = year(s).

[a]Effect estimates are standardized to a 1 μg/dL increase in blood Pb or a 10 μg/g increase in bone Pb, unless otherwise noted. 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.

[b]Effect estimates unable to be standardized.

[c]Pb measurements were converted from μg/L to μg/dL.

[d]No cut points provided for the categorizations.

Table 8-5 Epidemiologic studies of Pb exposure and preterm birth

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Xu et al. (2012) Guiyu and Xiamen China 2001–2008 Cohort	n: 531 (n = 432 from Guiyu and n = 99 from Xiamen) Women who gave birth in Guiyu or non-urban area of Xiamen between 2001 and 2008	Cord blood UCB measured by GFAAS Age at measurement: birth Median: Guiyu: 10.78 µg/dL Xiamen: 2.25 µg/dL Max: Guiyu: 47.46 µg/dL Xiamen: 7.22 µg/dL	Preterm birth rate Preterm birth was defined as birth <37 wk gestation Age at outcome: birth	Multiple logistic regression models were adjusted for maternal age and infant sex	OR (95% CI)[b]: 1.09 (0.93, 1.28)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Xu et al. (2022b) Argentina 2011–2012 Cross-sectional	EMASAR n: 696 Women who either were about to deliver or had given birth within the last 48 hr at one of the two hospitals. Women had to be above 18 yr of age.	Blood Maternal blood measured by ICP-MS Age at measurement: birth Median[c]: Overall: 1.34 µg/dL Ushuaia: 0.98 µg/dL Salta 1.50 µg/dL Geometric mean[c]: Overall: 1.393 µg/dL Ushuaia: 1.01 µg/dL Salta 1.58 µg/dL 75th[c]: Overall: 1.851 µg/dL Ushuaia: 1.30 µg/dL Salta: 2.09 µg/dL	Preterm birth Medical records were used to obtain measures at birth. Age at outcome: birth	Logistic models adjusted for maternal age, pre-pregnancy BMI, parity, smoking, education, and LBW	OR (95%CI) T1: Reference T2: 1.24 (0.35, 4.40) T3: 1.26 (0.32, 5.00)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Freire et al. (2019) Spain 2000–2008 Cross-sectional	INMA Project n: 327 Pregnant women of general population resident in each study area [Ribera d'Ebre, Menorca, Granada, Valencia, Sabadell, Asturias and Gipuzkoa] and their children. Criteria for inclusion of the mothers were: (1) to be resident in one of the study areas, (2) to be at least 16 yr old, (3) to have a singleton pregnancy, (4) to not have followed any program of assisted reproduction, (5) to wish to deliver in the reference hospital and (6) to have no communication problems	Other: Placenta Placenta (including maternal and fetal sides as well as central and peripheral parts) measured by GFAAS with Zeeman background correction Age at measurement: birth Median: <6.5 ng/g (LOD) 75th: <6.5 ng/g (LOD)	Preterm delivery Preterm birth was defined as live birth before 37 wk of pregnancy, Age at outcome: birth	Logistic regression models were adjusted for cohort (random effect), newborn sex, co-exposure to other metals (As, Hg, Cd, Mn, Cr), and maternal education level	OR (95% CI)[b]: 0.40 (0.04, 4.70)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Yu et al. (2019) Shanxi Province China December 2009–December 2013 Case-control	n: 528 Women with prenatal examination at ≤22 gestational weeks, ≥18 yr old, and living in the local counties for ≥1 yr	Blood Maternal blood (serum) was measured by ICP-MS Age at measurement: maternal age at first trimester (≤12 wk gestation) or second trimester (13–28 wk) Median[d] Overall: 0.0482 µg/dL First trimester: 0.0489 µg/dL Second trimester: 0.0476 µg/dL 75th[d]: Overall: 0.0751 µg/dL First trimester: 0.0783 µg/dL Second trimester: 0.0735 µg/dL	Spontaneous preterm birth Spontaneous preterm birth is defined as a live birth at <37 wk GA without iatrogenic causes, including spontaneous preterm labor with intact membranes and PROM Age at outcome: birth	Unconditional logistic regression models were adjusted for maternal age, BMI, education, occupation, residence, gravidity, parity, spontaneous abortion history, folic acid use, drug use, passive smoking, and child gender	OR (95% CI)[b] Overall: 1.46 (0.97, 2.18) First trimester: 1.63 (0.91, 2.91) Second trimester: 1.27 (0.71, 2.28)
Xu et al. (2022a) Pingding, Shouyang, and Taigu Counties Shanxi Province China December 2009–December 2013 Case-Control	n: 148 (74 cases, 74 controls) Pregnant women were recruited if over 18 yr old, living locally for at least 1 yr, seeking first prenatal visit at or before 22 gestational weeks, and seeking to manage birth/pregnancy at Maternal and Child Health Hospitals of study counties.	Blood Maternal blood (serum) measured by ICP-MS Age at measurement: maternal age during 4–22 gestational week Median[d]: 0.049 µg/dL 75th[d]: 0.078 µg/dL	Spontaneous preterm birth Information about spontaneous preterm birth was collected from pregnancy health records at the hospitals Age at outcome: birth	Unconditional logistic regression with adjustment for age, BMI, education, occupation, residence, gravidity, parity, spontaneous abortion history, folic acid use, medication use, passive smoking, infant sex, fasting blood collection, and sampling time.	OR (95% CI): Q1: Reference Q2: 1.63 (0.53, 5.04) Q3: 1.81 (0.60, 5.52) Q4: 4.09 (1.31, 12.77) p for trend: 0.017

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Tsuji et al. (2018) Japan January 2011 and March 2014 Cohort	JECS n: 14,847 Women who delivered live birth infant with singleton pregnancies without missing exposure or covariate data	Blood Maternal blood measured by ICP-MS Age at measurement: Maternal age at gestational weeks 14–39 (mean maternal age 31.4 yr) Median: 5.96 ng/g 75th: 7.44 ng/g Quartiles (ng/g) Q1: ≤4.49 Q2: 4.80–5.95 Q3: 5.96–7.43 Q4: ≥7.44	Preterm birth Preterm births were divided into early (<34 wk) and late preterm births (34 to <37 wk) Age at outcome: birth	Multivariable logistic regression analysis adjusted for age, pre-pregnancy BMI, smoking, smoking habits of partner, drinking habits, gravidity, parity, the number of cesarean sections, uterine infection, household income, educational levels, and sex of infant	OR (95% CI) Early preterm Q1: Reference Q2: 0.66 (0.37, 1.20) Q3: 0.80 (0.46, 1.41) Q4: 1.22 (0.74, 2.02) p for trend: 0.134 Late preterm Q1: Reference Q2: 0.99 (0.78, 1.26) Q3: 0.98 (0.77, 1.25) Q4: 0.92 (0.72, 1.18) p for trend: 0.920

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Goto et al. (2021) Japan January 2011 to March 2014 Cohort	JECS n: 15,540 First, data from participants who withdrew from the study or did not meet the Pb measurement quality control criteria were excluded (n = 2,002). Second, data from mothers who: were lost to follow-up; had severe maternal conditions preceding pregnancy, such as chronic hypertension, pregestational diabetes or cardiac disease, during pregnancy; or had pregnancies ending in abortions or stillbirths (n = 1,209) was excluded. Third, data from infants with chromosomal or major congenital anomalies (n = 263) or multiple births (n = 283) was excluded.	Blood Maternal blood measured by ICP-MS Age at measurement: Maternal age at second or third trimester (mean age at delivery: 31 ± 5.0 yr) Mean: 0.69 µg/dL Median: 0.63 µg/dL 75th: 0.78 µg/dL Max: 7.4 µg/dL	Preterm birth (<37 gestational weeks) risk Preterm birth was defined as a GA of less than 37 completed wk. Age at outcome: birth	Multivariable linear regression models were adjusted for maternal age at birth, BMI before pregnancy, weight gain during pregnancy, maternal educational background, a history of preterm birth, alcohol consumption during pregnancy, smoking habit during pregnancy, and parity	OR (95% CI), per 0.1 µg/dL increase in maternal blood Pb: 0.90 (0.70, 1.16) OR (95% CI), per doubling increment in maternal blood Pb: 0.978 (0.689, 1.39)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Rabito et al. (2014) Shelby County, Tennessee United States 2008–2011 Cohort	CANDLE study n: 98 Healthy pregnant woman between the ages of 16 and 40 yr, carrying a single fetus with the intent to deliver the fetus, residence within Shelby County, Tennessee, and having the intent to deliver at one of three area-based hospitals	Blood and cord blood Maternal blood, collected at second and third trimester and at delivery, and cord blood, collected at deliver, were measured by ICP-MS Age at measurement: Maternal age at collection (median: 29.50 yr) Median: Second trimester: 0.43 µg/dL Third trimester: 0.43 µg/dL At delivery: 0.50 µg/dL Cord blood: 0.37 µg/dL Geometric mean (SD): Second trimester: 0.42 (0.20) µg/dL Third trimester: 0.45 (0.28) µg/dL At delivery: 0.50 (0.35) µg/dL Cord blood: 0.37 (0.32) µg/dL Max: Second trimester: 1.22 µg/dL Third trimester: 2.10 µg/dL At delivery: 2.47 µg/dL Cord blood: 1.80 µg/dL	Preterm birth Preterm birth (<37 wk), early term birth (37–39 wk), or full-term birth (≥39 wk) based on GA, which was determined by expected due data and LMP Age at outcome: birth	Logistic regression models were adjusted for marital status, maternal education level, and maternal income	OR (95% CI)[b], per 0.1-unit increase in maternal blood Pb Preterm birth Second trimester: 1.66 (1.23, 2.23) Third trimester: 1.24 (1.01, 1.52) Early term birth Second trimester: 0.87 (0.63, 1.20) Third trimester: 0.88 (0.69, 1.13)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Taylor et al. (2015) Bristol UK April 1991-December 1992 Cohort	ALSPAC n: 4,285 All pregnant women in the former Avon Health Authority with an expected delivery date between April 1, 1991, and December 31, 1992, were eligible for the study	Blood Maternal blood measured by ICP-MS, collected as early as possible in pregnancy (median GA of sampling: 11 wk) Age at measurement: Maternal age at measurement Mean (SD): 3.67 (1.47) µg/dL Geometric mean: 3.43 µg/dL Median: 3.42 µg/dL Max: 19.14 µg/dL	Preterm delivery Preterm delivery was less than 37 wk of gestation Age at outcome: birth	Logistic regression models for preterm birth were adjusted for maternal height, maternal pre-pregnancy weight, maternal educational attainment, parity, number of cigarettes per day, sex of baby	OR (95% CI)[b]: 2.00 (1.35, 3.00)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Li et al. (2017a) China January 1 to December 31, 2009 Cohort	C-ABCS n: 3,125 Mother-and-singleton-offspring pairs from Hefei City who provided informed consent, did not drink alcohol or smoke cigarettes during pregnancy, did not have mental disorders, did not have pregnancy-induced hypertension, preeclampsia, gestational diabetes, heart disease, thyroid-related disease, a history of ≥3 previous miscarriages, or plans to leave location before delivery	Blood Maternal blood (serum) measured by GFAAS coupled with a deuterium-lamp background correction system, collected in the first and second trimesters (median time for serum collection: 14 gestational weeks; range from 4 to 27 gestational week) Mean: 1.50 µg/dL Max: 5.46 µg/dL Tertiles: low-Pb: <1.18 µg/dL medium-Pb: 1.18–1.70 µg/dL high-Pb: ≥1.71 µg/dL	Preterm birth Gestational week was calculated using mother's last menstrual period. Preterm birth was defined as a live birth at less than 37 completed gestational weeks and preterm birth can be further sub-divided into early preterm birth (<32 gestational weeks), moderate preterm birth (32 to <34 gestational weeks) and late preterm birth, 34 to <37 gestational weeks) Age at outcome: birth	Multiple logistic regression models estimated the association between maternal serum Pb level and risk of preterm birth, adjusted for maternal age, pre-pregnancy BMI, monthly income, gravidity, and parity	OR (95% CI): Low-Pb: Reference Medium-Pb: 2.33 (1.49, 3.65) High-Pb: 3.09 (2.01, 4.76)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Ashrap et al. (2020) Puerto Rico 2010–2017 Cohort	PROTECT n: 731 Participants were recruited at approximately 14 ± 2 wk of gestation at seven prenatal clinics and hospitals throughout Northern Puerto Rico and followed until birth; maternal age between 18 and 40 yr; residence inside of the Northern Karst aquifer region; disuse of oral contraceptives within the 3 mo prior to pregnancy; disuse of IVF to become pregnant; and free of any major medical or obstetrical complications, including pre-existing diabetes. Each woman participated in a total of up to three study visits (18 ± 2 wk, 22 ± 2 wk, and 26 ± 2 wk of gestation)	Blood Maternal blood was measured by ICP-MS Age at measurement: 18–40 (collection between 18 and 26 wk of gestation) Geometric mean (SD): Preterm births: 0.39 (1.6) µg/dL Term births: 0.32 (1.5) µg/dL Median: Preterm births: 0.36 µg/dL Term births: 0.32 µg/dL	Preterm birth (overall and spontaneous preterm birth) All the birth outcome data were extracted from medical records. Preterm birth was defined as <37 completed weeks of gestation with further classification of spontaneous preterm birth (presentation of premature rupture of the membranes, spontaneous preterm labor, or both) and non-spontaneous preterm birth (preterm births with preeclampsia or with both artificial membrane rupture and induced labor) Age at outcome: birth	Logistic regression models were adjusted for maternal age, maternal education level, pre-pregnancy BMI, and exposure to second-hand smoking	OR (95% CI)[b], per IQR increase in maternal blood ln-Pb Preterm birth Overall: 1.63 (1.17, 2.28) Spontaneous: 1.53 (1.00, 2.35) Tertiles[e]: Overall preterm birth: T1: Reference T2: 1.27 (0.65, 2.47) T3: 1.93 (1.02, 3.62) Spontaneous preterm birth: T1: Reference T2: 0.69 (0.29, 1.66) T3: 1.50 (0.71, 3.18)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Ashrap et al. (2021) Puerto Rico 2011–2017 Cohort	PROTECT n = 682 Participants were recruited at approximately 14 ± 2 wk of gestation at seven prenatal clinics and hospitals throughout Northern Puerto Rico and followed until birth; maternal age between 18 and 40 yr; residence inside of the Northern Karst aquifer region; disuse of oral contraceptives within the 3 mo prior to pregnancy; disuse of IVF to become pregnant; and free of any major medical or obstetrical complications, including pre-existing diabetes. Each woman participated in a total of up to three study visits (18 ± 2 wk, 22 ± 2 wk, and 26 ± 2 wk of gestation)	Blood Maternal blood was measured by ICP-MS Age at measurement: 18–40 (collection between 18 and 26 wk of gestation) Geometric mean: 3.1 µg/dL Median: 3.1 µg/dL 75th: 4.1 µg/dL 95th: 6.5 µg/dL Max: 15.1 µg/dL	Preterm birth (overall and spontaneous preterm birth) Birth outcomes were extracted from medical records. Psychosocial status was evaluated using four questionnaires Age at outcome: birth	Logistic regression models were adjusted for maternal age, maternal education, pre-pregnancy BMI, and exposure to secondhand smoking	OR (95% CI)[b], per IQR increase in in maternal blood ln-Pb Preterm birth: Good Psychosocial Status: 1.72 (1.14, 2.58) Poor Psychosocial Status: 1.43 (0.69, 2.97) Spontaneous preterm birth: Good Psychosocial Status: 1.56 (0.93, 2.60) Poor Psychosocial Status: 1.22 (0.42, 3.56)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Bui et al. (2022) North Carolina United States 2004–2009 Quasi-experimental	CCG MSA n: 147,673 live births in the CCG MSA; Treatment group n: 1,138; Control group n: 13,398 Exogenous variation in Pb exposure resulting from NASCAR's deleading of racing fuel in 2007 was used as a quasi-experiment. CMS, located in the CCG, was the only NASCAR racetrack in North Carolina that held races every year during our sample period. Races occurred bi-annually, in October and May, ensuring that all full and near full-term births in the sample were prenatally exposed via the mother to *at least* one NASCAR event.	Births where the mother's residential address was within 4,000 meters of CMS were classified as the treatment group, while the control group consists of births where the mother's residential address is in the CCG but is at least 10,000m from the racetrack centroid	Preterm birth Preterm birth was defined as clinical GA <37 wk. Age at outcome: birth	Difference-in-difference models were used to compare birth outcomes in a non-randomized treatment group before and after NASCAR deleading to those in the control group. Models were adjusted for mother's age, education, race, and smoking behavior; father's age, education, and race; infant's birth order and sex; as well as proximity to a TRI facility or airport, median household income, and age of housing stock; a set of census tract, month, and year indicator variables were also included	β (95% CI)[b], as estimated average treatment effect of treatment group All births Any exposure: −0.03 (−0.057, −0.002) Trimester 1: −0.247 (−0.438, −0.057) Trimester 2: 0.019 (−0.042, 0.079) Trimester 3: −0.163 (−0.277, −0.049)

ALSPAC = Avon Longitudinal Study of Parents and Children; As = arsenic; BMI = body mass index; C-ABCS = China-Anhui Birth Cohort Study; CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CCG = Charlotte-Concord-Gastonia; Cd = cadmium; CMS = Charlotte Motor Speedway; Cr = chromium; EMASAR = Study on the Environment and Reproductive Health; GA = gestational age; GFAAS = graphite furnace atomic absorption spectrometry; hr = hour(s); Hg = mercury; ICP-MS = inductively coupled plasma mass spectrometry; INMA = Instituto de Nanociencia y Materiales de Aragón; IVF = in vitro fertilization; LBW = low birth weight; LMP = last menstrual period or last missed period; LOD = limit of detection; mo = month(s); MSA = Metropolitan Statistical Area; OR = odds ratio; PROM = premature rupture of membranes; PROTECT = Puerto Rico Test site for Exploring Contamination Threats; SD = standard deviation; TRI = Toxics Release Inventory; UCB = umbilical cord blood; wk = week(s); yr = year(s).

[a]Effect estimates are standardized to a 1 μg/dL increase in blood Pb or a 10 μg/g increase in bone Pb, unless otherwise noted. 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.

[b]Effects estimates unable to be standardized.

[c]Pb measurements were converted from μg/L to μg/dL.

[d]Pb measurements were converted from ng/mL to μg/dL.

[e]No cut points provided for the categorizations.

Table 8-6 Epidemiologic studies of Pb exposure and birth defects

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Jin et al. (2013) Shanxi Province China October 2002 – onward Case-control	n: 210: 80 controls, 50 any NTD case; 36 cases of anencephaly; and 44 cases of spina bifida Once a fetus with an NTD was identified as a case, a healthy newborn without congenital malformations was selected as a control. The control was of the same sex as the case and had a mother residing in the same county as that of the case. In this study, we randomly selected 36 cases of newborns with anencephaly and 44 cases of newborns with spina bifida as case groups and 50 healthy term newborns as a control group.	Other: Placenta Placental tissue, collected at delivery or pregnancy termination, was measured with ICP-MS Age at Measurement: delivery or pregnancy termination Mean (SD) Controls: 22.38 (16.35) ng/g; NTD cases: 23.30 (22.42) ng/g; Anencephaly cases: 19.30 (15) ng/g Spina bifida cases: 23.04 (20.03) ng/g Median Controls: 16.9 ng/g NTD cases: 17.59 ng/g Anencephaly cases: 10.96 ng/g Spina bifida cases: 17.38 ng/g 75th: Controls: 28.83 ng/g NTD cases: 28.15 ng/g Anencephaly cases: 28.86 ng/g Spina bifida cases: 28.86 ng/g	Birth defects: NTDs Trained local health workers made primary diagnoses by physical examination of the fetal/newborn body for any pregnancy outcomes and filled in a reporting form for each case. Three pediatricians independently reviewed the case report forms and photographs before assigning the final diagnostic codes Age at outcome: birth or pregnancy termination	No attempt was made to adjust for confounding factors in our analyses of Pb because no differences in their placental concentrations were present between cases and controls.	OR (95% CI)[b]: Any NTD: 1.14 (0.56, 2.30) Anencephaly: 1.08 (0.46, 2.56) Spina bifida: 1.19 (0.53, 2.67)
Liu et al. (2021)	n: 332	Other: Umbilical cord tissue	Birth defects: NTDs	Multivariate logistic regression model	OR (95% CI)b: 1.23 (0.78, 1.94)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Shanxi, China 2004–2016 Case-control	Fetuses from elective pregnancy terminations and newborns from the Shanxi Province in China. Cases were defined as those with NTD, and controls were healthy newborns matched by maternal residence and date of last menstruation.	Umbilical cord tissue measured by ICP-MS Age at measurement: At delivery or elective termination Median: 26.18 ng/g 75th: 48.58 ng/g Max: 225.572 ng/g Categorization: Low exposure (<1.10 ng/g) High exposure (>=1.10 ng/g)	NTD cases were diagnosed by fetal ultrasound scan or physical examination at birth or pregnancy termination. Age at outcome: birth or pregnancy termination	adjusted for folic acid supplementation	
Tian et al. (2021) Shanxi province, China 2003–2016 Case control	n: 750 Participants were recruited from six counties or cities in the Shanxi province of northern China.	Blood Maternal blood (serum) was measured by ICP-MS Age at measurement: Maternal age at collection Median[c]: Controls: 0.087 µg/dL Case: 0.115 µg/dL 75th[c]: Controls: 0.197 µg/dL Cases: 0.268 µg/dL	Birth defects: NTDs Diagnoses of malformation are made by local health workers through physical examination of the newborns or electively terminated fetuses, in combination with fetal ultrasound scans. Age at outcome: birth or pregnancy termination	Multilevel mixed effects logistic regression model adjusted for maternal age, maternal BMI, education, gestational weeks, sex of the fetus, periconceptional folic acid use, maternal flu, or fever.	OR (95% CI): Tertiles[d] NTDs Lowest: Reference Medium: 2.05 (1.05, 4.02) Highest: 3.51 (1.76, 6.98) p for trend: <0.001 Spina bifida Lowest: Reference Medium: 2.16 (1.00, 4.88) Highest: 5.16 (2.24, 11.87) p for trend: 0.022 Anencephaly Lowest: Reference

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Medium: 2.97 (1.09, 8.12) Highest: 5.54 (1.89, 16.19) p for trend: 0.002 Female Infants NTDs Lowest: Reference Medium: 2.63 (0.99, 7.24) Highest: 6.45 (2.20, 18.95) p for trend: 0.001 Male Infants NTDs Lowest: Reference Medium: 2.11 (1.02, 4.34) Highest: 2.16 (1.03, 4.59) p for trend: 0.048
Pi et al. (2018) Shanxi Province (Pingding, Xiyang, Taigu, and Zezhou) China 2005–2007 Case-control	n: 103 cases and 206 controls Newborns or terminated fetuses with any major external structural defects, including OFCs, NTDs, congenital hydrocephalus, limb defects were recruited from five rural counties in Shanxi Province	Other: Placenta Placental tissue, collected immediately after delivery, was measured by ICP-MS Age at Measurement: birth Mean (SD) Controls 72.6 (34.8) ng/g Case: 130.9 (95.7) ng/g Median Controls: 67.9 ng/g Cases: 96.1 ng/g 75th Controls: 98.1 ng/g Cases: 176.4 ng/g	Birth defects: OFCs Diagnoses of newborns/fetuses with major birth defects were done through physical examination or prenatal ultrasound examination by county healthcare workers. Once a newborn/fetus with a major birth defect was identified as a case, a healthy newborn with no congenital malformation was selected as a control to match the case by residence of the mother (the same	Binary logistic regression adjusted for occupation, newborn sex, gestational weeks, previous history of birth defects, maternal flu or fever, and passive smoking during the periconceptional period	OR (95% CI) Orofacial defects: T1: Reference T2: 3.88 (1.78, 8.42) T3: 5.17 (2.37, 11.29) p for trend: <0.001

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Tertiles (ng/g): T1: <57.5 T2: 57.5–96.8 T3: ≥96.8	county), date of the LMP (±4 wk), and newborn sex. Age at outcome: at diagnosis		
Takeuchi et al. (2022) Japan 2011–2014 Case-control	JECS n:192 cases, 1920 matched controls Pregnant women living in the study area and understanding of the Japanese language. Participants were excluded if they had missing data (heavy metal data, matching variables, and/or both). Covariates for matching were maternal age, psychological stress measured by the K6 score, gestational weeks of blood sampling during second trimester, folic acid intake estimated from a food-frequency questionnaire, alcohol intake (self-reported), smoking (self-reported), education level, BMI before pregnancy, diabetes before pregnancy, intake of supplements (self-reported), and regional center	Blood Maternal blood measured by ICP-MS Age at measurement: Maternal age at collection (second trimester) Median[e] Cohort: 0.585 µg/dL Cases: 0.584 µg/dL Controls: 0.575 µg/dL 75th[e] Cohort: 0.73 µg/dL Cases: 0.72 µg/dL Controls: 0.71 µg/dL	Birth defects: Cleft palate and cleft lip (isolated) Validated medical records were used to identify isolated cleft lip and palate.	Conditional logistic regression adjusted for sex and concentrations of Hg, Cd and Mn	OR (95% CI), per 0.1 µg/dL increase in maternal blood Pb: 1.10 (0.55, 2.21)
Miyashita et al. (2021)	JECS. N: 89,273	Blood	Birth defects: Abdominal congenital malformations	Multivariate logistic regression models were adjusted for maternal age, smoking habit,	OR (95% CI) Abdominal congenital malformations

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Japan January 2011–March 2014 Cohort	Pregnant women and their newborns recruited for the JECS. Singleton, live births were included.	Maternal blood (serum) measured by ICP-MS. Age at measurement: maternal age at collection (mid-late pregnancy) Median Cohort: 5.84 ng/g Controls: 5.85 ng/g Cases: 5.53 75th Cohort: 7.32 ng/g Controls: 7.32 ng/g Cases: 7.00 ng/g Max Cohort: 110 ng/g Quartiles (ng/g): Q1: <4.7 Q2: 4.7–<5.84 Q3: 5.84–<7.32 Q4: ≥7.32	Abdominal congenital malformations (including omphalocele, gastroschisis, esophageal atresia with/without fistula, duodenal atresia, intestinal atresia, anorectal atresia, diaphragmic hernia) were identified from birth records or records 1 mo post birth Age at outcome: birth to month post birth	drinking habit, paternal smoking habit, birth year of child, sex of child	Q1: Reference Q2: 1.19 (0.76, 1.84) Q3: 0.77 (0.47, 1.26) Q4: 0.85 (0.52, 1.38) p for trend: 0.233 Diaphragmic hernia Q1: Reference Q2: 1.24 (0.51, 2.99) Q3: 0.89 (0.34, 2.31) Q4: 0.81 (0.30, 2.20) p for trend: 0.543 Omphalocele Q1: Reference Q2: 0.72 (0.29, 1.81) Q3: 0.35 (0.11, 1.12) Q4: 0.35 (0.11, 1.13) p for trend: 0.033 Gastroschisis Q1: Reference Q2: 1 Q3: 1.00 (0.14, 7.09) Q4: 2.63 (0.50, 13.70) p for trend: 0.212 Esophageal atresia with/without fistula Q1: Reference Q2: 0.49 (0.04, 5.43) Q3: 0.95 (0.13, 6.80) Q4: 1.88 (0.33, 10.50) p for trend: 0.346 Duodenal atresia/stenosis Q1: Reference Q2: 0.25 (0.03, 2.27) Q3: 0.50 (0.09, 2.75)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Q4: 0.99 (0.24, 4.06) p for trend: 0.910 Intestinal atresia/stenosis Q1: Reference Q2: 1.40 (0.31, 6.29) Q3: 1.06 (0.21, 5.27) Q4: 1.12 (0.22, 5.64) p for trend: 0.989 Anorectal atresia/stenosis Q1: Reference Q2: 1.65 (0.74, 3.67) Q3: 0.57 (0.19, 1.68) Q4: 0.62 (0.21, 1.83) p for trend: 0.158
Liu et al. (2018) China February 2010–October 2011 Case-control	n: 97 cases with CHDs and 201 controls without any abnormalities Eligible fetuses with cardiac defects diagnosed during prenatal examination were recruited as the case group. For each case, one pregnant control without any fetal malformation was selected in the same hospital with a gestation age within 2 wk of the case fetus. Cases and controls with GAs from 14 to 40 wk were selected for this study after the following exclusion criteria were applied: (1) multiple pregnancies; (2) CHD family history; (3) fetus diagnosed with a chromosomal abnormality or hereditary syndrome; (4) fetus with	Cord blood UCB (serum) was measured by ICP-MS Age at Measurement: birth Median[c] Cases: 0.791 µg/dL Controls: 0.740 µg/dL 75th[c] Case: 0.922 µg/dL Controls: 0.877 µg/dL Tertiles (µg/dL): Low: <0.696 Medium: 0.696−0.826 High: ≥0.826	Birth defects: CHDs Cardiac defects diagnosed during prenatal examination were recruited as the case group. Age at outcome: age at diagnosis	Logistic regression models were adjusted for maternal age, maternal pre-pregnancy BMI, maternal education level, folic acid supplement, and parental smoking	OR (95% CI) CHD, Overall Low: Reference Medium: 1.46 (0.77, 2.77) High: 1.67 (0.88, 3.17) Septal Defects Low: Reference Medium: 1.20 (0.57, 2.52) High: 1.61 (0.78, 3.32) Conotruncal Defects Low: Reference Medium: 1.35 (0.60, 3.06) High: 1.47 (0.65, 3.34) Right-sided Outflow Tract Deformity Low: Reference

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	extra cardiac malformations; (5) uncompleted questionnaire for some reason. CHD cases were classified into six subtypes based on the anatomic lesion: (i) septal defects, (ii) conotruncal defects, (iii) left sided outflow tract deformity, (iv) right-sided outflow tract deformity, (v) anomalous pulmonary venous return, and (vi) other cardiac structural abnormalities.				Medium: 0.92 (0.37, 2.26) High: 1.21 (0.50, 2.94) Left-sided Outflow Tract Deformity Low: Reference Medium: 2.29 (0.62, 8.41) High: 1.32 (0.29, 5.91) Anomalous Pulmonary Venous Return Low: Reference Medium: 1.71 (0.37, 7.83) High: 1.49 (0.30, 7.44) Other Cardiac Structural Abnormalities Low: Reference Medium: 1.10 (0.36, 3.40) High: 1.41 (0.47, 4.22)

BMI = body mass index; Cd = cadmium; CHD = congenital heart diseases/defects; GA = gestational age; Hg = mercury; ICP-MS = inductively coupled plasma mass spectrometry; K6 = Kessler Psychological Distress Scale; LMP = last menstrual period or last missed period; Mn = manganese; mo = month(s); NTD = neural tube defect; OFC = orofacial cleft; OR = odds ratio; SD = standard deviation; UCB = umbilical cord blood; wk = week(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. 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.

[b]Effects estimates unable to be standardized.

[c]Pb measurements were converted from ng/mL to µg/dL.

[d]No cut points provided for the categorizations.

[e]Pb measurements were converted from µg/L to µg/dL.

Table 8-7 Epidemiologic studies of Pb exposure and fetal and infant mortality and spontaneous abortion and pregnancy loss

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Xu et al. (2012) Guiyu and Xiamen China 2001–2008 Cross-sectional	n: 531 (n = 432 from Guiyu and n = 99 from Xiamen) Women who gave birth in Guiyu or non-urban area of Xiamen between 2001 and 2008	Cord blood UCB measured by GFAAS Age at Measurement: birth Median: Guiyu: 10.78 µg/dL Xiamen: 2.25 µg/dL Max: Guiyu: 47.46 µg/dL Xiamen: 7.22 µg/dL	Stillbirth rate Stillbirth was defined as fetal death before complete expulsion or extraction from the mother at >20 wk of gestation Age at outcome: birth	Multiple logistic regression models were adjusted for maternal age and infant sex	OR (95% CI)[b]: 4.20 (3.40, 5.18)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Louis et al. (2017) Michigan and Texas United States 2005–2009 Cohort	LIFE Study n: 344 Female partners aged 18–40 and male partners aged ≥18 yr who were in a committed relationship; no physician diagnosis of infertility/sterility; off contraception <2 mo; and an ability to communicate in English or Spanish. Female partners also had to have menstrual cycles ranging between 21 and 42 d as required by the fertility monitor and without the use of injectable hormonal contraceptives in the past year given the uncertain timing for ovulation return	Blood Blood from female and male partners was measured by ICP-MS Age at Measurement: 18–40 for females and ≥18 for males Median Females: 0.66 µg/dL Males: 1.00 µg/dL 75th: Females: 0.82 µg/dL Males: 1.37 µg/dL	Pregnancy loss Pregnancy was prospectively captured by women's use of the Clearblue® digital home pregnancy test, which is sensitive in detecting 25 mIU/mL of hCG and accurately used by women. Depending upon timing of loss, it was detected by conversion to a negative pregnancy test, clinical confirmation, or return of menses. Age at outcome: 18–40 yr	Cox proportional hazard models; individual partner model adjusted for age, BMI, history of prior loss conditional on gravidity, average number of daily alcoholic drinks consumed, and cigarettes smoked during the preconception and early pregnancy windows for females and preconception for males; couples based model adjusted for each partner's metal concentration, age, difference in couples' ages, BMI, average number of daily alcoholic drinks consumed and cigarettes smoked during the preconception and early pregnancy window for females and preconception for males, and history of prior loss conditional on gravidity	HR (95% CI)[b] Individual partner model Female partner: 1.01 (0.82, 1.25) Male partner: 0.95 (0.77, 1.17) Couple based model Female partner: 1.01 (0.80, 1.28) Male partner: 0.96 (0.77, 1.22)
Vigeh et al. (2021) Tehran Iran March 2016–October 2017 Cohort	Tehran Environment and Neurodevelopmental Disorder n: 166 (spontaneous abortion n: 25 and ongoing pregnancy n: 141) Pregnant women with GA of 10–16 wk and of Iranian nationality and Tehran city inhabitant were invited to participate in the study.	Blood Maternal blood was measured using ICP-MS Age at measurement: maternal age at first trimester Mean[c]: 4.96 µg/dL Max[c]: 70.982 µg/dL	Spontaneous abortion Spontaneous abortion defined as fetal demise before 20 wk gestation and reported by study participant or research hospital. Age at outcome: before 20 wk of gestation	Logistic regression models adjusted for maternal age, primipara, and previous abortion	OR (95% CI), per 0.1 µg/dL increase in maternal blood Pb: 1.08 (0.98, 1.20)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Tolunay et al. (2016) Ankara Turkey January 2012 and July 2012 Cohort	n: 101 The study group consisted of patients with ongoing pregnancy (n = 20) and the reference group consisted of patients experienced ART failure, miscarriage, or biochemical pregnancy (n = 81)	Blood Maternal blood was measured by AAS Age at Measurement: 20–40 Median Study group: 2.34 µg/dL Reference: group 5.11 µg/dL Max Study group: 7.97 µg/dL Reference group: 10.47 µg/dL for reference group	Pregnancy loss Clinical pregnancy was defined as the presence of an embryo with a heartbeat at 6th gestational week. Ongoing pregnancy was defined when the pregnancy had completed 20 wk of gestation. Implantation rate was calculated separately for each woman as the number of gestational sacs divided by the number of transferred embryos multiplied by 100. Age at outcome: completion of 20 wk of gestation	Log binominal regression analysis adjusted for age and BMI	RR (95% CI): 0.978 (0.957, 0.999)
Li et al. (2022) Hefei China October 2019 – January 2020 Cohort	n: 1184 Participants were selected from First Affiliated Hospital of Anhui Medical University while seeking IVF treatment and diagnosed with infertility with their partner. Inclusion criteria: women were aged between 20 and 45 yr; couples were diagnosed with infertility (failure to establish a clinical pregnancy with unprotected intercourse for at least 1 yr); and IVF indicators were tubal factor, ovulation failure, or other factors for female	Blood Maternal blood (serum) was measured by ICP-MS Age at measurement: maternal age at collection (day before oocytes were retrieved for IVF); mean age was 30.22 yr Geometric mean[d]: 0.0877 µg/dL Median[d]: 0.0924 µg/dL	Spontaneous abortion Spontaneous abortion before gestational week 12 was followed upon the 65th day after embryo transfer. Age at outcome: maternal age at outcome (before gestational week 12)	Logistic regression model for successful implantation adjusted for: maternal age, BMI, treatment protocol, numbers of retrieved oocytes, embryo quality	OR (95%CI)[b]: Spontaneous abortion: 1.39 (1.02, 1.91) Tertiles Low: Reference Medium: 1.49 (0.84, 2.63) High: 1.55 (0.87, 2.79)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	partner or male factor or unexplained fertility.	75th[d]: 0.14399 µg/dL Tertiles[d] (µg/dL): Low: 0.002–0.065 Medium: 0.065–0.125 High: 0.125–0.481			

AAS = atomic absorption spectrometry; BMI = body mass index; d = day(s); GFAAS = graphite furnace atomic absorption spectrometry; hCG = human chorionic gonadotropin; HR = hazard ratio; ICP-MS = inductively coupled plasma mass spectrometry; IVF = in vitro fertilization; mo = month(s); OR = odds ratio; UCB = umbilical cord blood; wk = week(s); yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. 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.

[b]Effects estimates unable to be standardized.

[c]Pb measurements were converted from µg/L to µg/dL.

[d]Pb measurements were converted from ng/L to µg/dL.

Table 8-8 Epidemiologic studies of Pb exposure and placental function

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Al-Saleh et al. (2014) Al-Kharj Saudi Arabia 2005–2006 Cross-sectional	n: 1,578 Women aged 16–50 yr who delivered in Al-Kharj hospital, Saudi Arabia	Blood, cord blood, and other: placenta Maternal blood, UCB, and placental tissue measured by AAS Age at Measurement: maternal age 16–50; birth Mean ± SD: Maternal blood: 2.897 ± 1.851 µg/dL UBC: 2.551 ± 2.592 µg/dL Placenta: 0.579 ± 2.176 µg/g Median: Maternal blood: 2.540 µg/dL UCB: 2.057 µg/dL Placenta: 0.450 µg/g 75th: Maternal blood: 3.314 µg/dL UCB: 2.689 µg/dL Placenta: 0.630 µg/g Max: Maternal blood: 25.955 µg/dL UCB: 56.511 µg/dL Placenta: 78 µg/g	Placental function: Placental thickness Placental weight and placental thickness were recorded by obstetrician in delivery room Age at outcome: birth	Logistic regression model was adjusted for maternal age, parity, mother's third trimester BMI, urinary cotinine, mother's highest education, total family income, and GA	OR (95% CI)[b], per unit increase in maternal blood Pb: 1.64 (1.12, 2.41)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Tsuji et al. (2019) Japan January 2011–March 2014 Cross-sectional	JECS n: 16,019 Mothers who delivered a singleton pregnancy	Blood Maternal blood, collected during the second trimester, was measured by ICP-MS Age at Measurement: maternal age at second trimester Median: 5.96 ng/g 75th: 7.45 ng/g Quartiles: Q1: ≤4.79 ng/g Q2: 4.80–5.95 ng/g Q3: 5.96–7.44 ng/g Q4: ≥7.45 ng/g	Placental function: Placenta previa and placenta accreta Data for those with and without placenta previa and placenta accreta were obtained from medical records. Age at outcome: maternal age at diagnosis	Multivariable logistic regression models were adjusted for age, smoking, smoking habits of the partner, drinking habits, gravidity, parity, number of cesarean deliveries, and geographic region; Placenta previa was added as a covariate when comparisons were performed with or without placenta accreta	OR (95% CI): Placenta previa Q1: Reference Q2: 2.59 (1.40, 4.80) Q3: 1.32 (0.66, 2.64) Q4: 1.34 (0.67, 2.67) p for trend: 0.007 Placenta accreta Q1: Reference Q2: 1.46 (0.57, 3.76) Q3: 1.68 (0.66, 4.24) Q4: 0.79 (0.27, 2.30) p for trend: 0.345

AAS = atomic absorption spectrometry; BMI = body mass index; CI = confidence interval; GA = gestational age; ICP-MS = inductively coupled plasma mass spectrometry; JECS = Japan Environment and Children's Study; OR = odds ratio; Q = quartile; SD = standard deviation; UCB = umbilical cord blood; yr = year(s).
[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. 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.
[b]Effect estimates unable to be standardized.

Table 8-9 Epidemiologic studies of Pb exposure and other pregnancy and other birth outcomes

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Ashley-Martin et al. (2015a) Vancouver, Edmonton, Winnipeg, Sudbury, Ottawa, Kingston, Toronto, Hamilton, Montreal, and Halifax Canada 2008–2011 Cohort	MIREC study n: 1,260 Women were recruited from 10 Canadian sites during their first trimester and consented to provide urine and blood samples. Women were eligible for inclusion if they were <14 wk gestation at the time of recruitment, ≥18 yr of age, able to communicate in French or English, and planning to deliver at a local hospital	Blood Maternal blood was measured by ICP-MS Age at Measurement: Maternal age during 1st and 3rd trimester Geometric mean (SD): 0.88 (1.61) µg/dL Quartiles (µg/dL): Q1: ≤0.63 Q2: 0.64 to ≤0.87 Q3: 0.88 to ≤1.20 Q4: >1.20	Other Pregnancy and Birth Outcomes: Fetal metabolic function Leptin and adiponectin were measured in plasma from 1363 stored UCB samples by ELISA using kits from Meso Scale Discovery. All samples were above the LOD. Age at outcome: birth	Logistic regression models were adjusted for maternal age at delivery, pre-pregnancy BMI, parity, and BWZ	OR (95% CI) Low leptin and maternal blood Pb: Q1: Reference Q2: 0.9 (0.5, 1.6) Q3: 0.6 (0.3, 1.1) Q4: 0.9 (0.5, 1.5) High leptin and maternal blood Pb: Q1: Reference Q2: 1.2 (0.7, 2.1) Q3: 1.0 (0.6, 1.8) Q4: 1.7 (1.0, 2.9) Low adiponectin and maternal blood Pb: Q1: Reference Q2: 1.3 (0.8, 2.2) Q3: 0.8 (0.5, 1.4) Q4: 1.1 (0.6, 1.9) High adiponectin and maternal blood Pb: Q1: Reference: Q2: 0.9 (0.5, 1.5) Q3: 1.1 (0.7, 1.9) Q4: 0.9 (0.5, 1.5)
Herlin et al. (2019) Salta Province (Andean	n: 194 enrolled of the 221 pregnant women All pregnant women living in	Blood, cord blood, and other: placenta	Other Pregnancy and Birth Outcomes: rTL The rTL was measured in	Multivariable-adjusted linear regression models; models with maternal blood Pb were adjusted for	β (95% CI)[c]: UCB: −0.038 (−0.074, −0.002)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
part) Argentina October 2012–December 2013 Cohort	the Andean part of the Salta province northern Argentina with estimated delivery date between October 2012 and December 2013, were invited to participate	Maternal blood, UCB, and placenta were measured using ICP-MS Age at Measurement: birth Median: Maternal blood[b]: 2.1 µg/dL UCB[b]: 1.4 µg/dL Placenta: 5.8 µg/kg Max: Maternal blood[b]: 9.9 µg/dL UCB[b]: 6.0 µg/dL Placenta: 38 µg/kg	maternal blood leukocytes (blood samples collected in late pregnancy, mainly third trimester), cord blood leukocytes, and placental tissue. We obtained high-quality DNA and measured rTL in 169 blood samples of the pregnant women, 99 of their placentas, and 98 cord blood samples of their babies. The rTL was measured as the ratio between the signal intensity of the telomere sequences and the signal intensity of a single-copy gene (hemoglobin β chain), using real-time polymerase chain reaction. Age at outcome: birth	maternal age, pre-pregnancy BMI, and education; models with placenta were also adjusted for GA at birth; models with UCB were adjusted for maternal age, pre-pregnancy BMI, GA at birth, and BW.	Maternal blood: 0.026 (−0.043, 0.095) Placenta: −0.029 (−0.074, 0.016)
Liao et al. (2015) Taiwan March–December 2010 Cross-sectional	n: 113 Pregnant women were recruited from a single institution in northern Taiwan	Blood Maternal blood (plasma), collected at the first trimester (between 10 and 14 wk of gestation), was measured by ICP-MS Age at Measurement: Maternal age at first trimester (mean age 30.92 ± 3.09 yr) Geometric mean: 0.048 µg/L	Other Pregnancy and Birth Outcomes: Fetal nuchal translucency thickness Fetal nuchal translucency thickness was measured at 10–14 wk of gestation by a gynecologist and three trained sonographers Age at outcome: Age at scan (between gestational week 10 and 14)	Multiple linear regression models were adjusted for maternal age, gestational weeks, pre-pregnancy BMI, supplement use, and medication	β (95% CI)[c]: 0.022 mm (−0.06, 0.10)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Ashley-Martin et al. (2015b) Canada 2008–2011 Cohort	MIREC Study n: 1256 Pregnant women in Canada who had singleton, term birth (>37 wk)	Blood Maternal blood was measured by ICP-MS Age at measurement: maternal age at first and third trimester Median: 0.62 µg/dL 75th:1.03 µg/dL Max: 4.14 µg/dL	Other Pregnancy and Birth Outcomes: Fetal immune system biomarkers Immune system biomarkers were measured in the plasma of UCB samples; TSLP concentrations were determined using a commercial antibody kit; IL-33 concentrations were analyzed using antibodies from an R & D systems duo set; IgE was determined from ELISA kits Age at outcome: birth	Logistic regression adjusted for maternal age	OR (95% CI) Maternal log_{10}-Pb blood concentrations with elevated (>80%) cord blood concentrations of IL-33 and TSLP: 0.79 (0.62, 1.01) Maternal log_{10}-Pb blood concentrations with elevated (≥0.5 kU/L) cord blood concentrations of IgE: 0.99 (0.77, 1.26)
Taylor et al. (2014) Bristol UK April 1991–December 1992 Cohort	ALSPAC study n: 4,285 Pregnant women enrolled in the ALSPAC study at a median GA of 11 wk	Blood Maternal blood was measured by ICP-MS Age at Measurement: Maternal age at measurement (median GA of sampling: 11 wk) Median: Quintile 1: 2.11 µg/dL Quintile 2: 2.82 µg/dL Quintile 3: 3.43 µg/dL Quintile 4: 4.13 µg/dL Quintile 5: 5.00 µg/dL Max:	Other Pregnancy and Birth Outcomes: Secondary sex ratio The sex of the infant was recorded at birth Age at outcome: birth	Logistic regression models adjusted for maternal and paternal age, and parity	OR (95% CI) Q1: Reference Q2: 1.04 (0.86, 1.42) Q3: 0.90 (0.70, 1.15) Q4: 1.01 (0.79, 1.30) Q5: 1.06 (0.82, 1.37)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Q1: 2.53 µg/dL Q2: 3.11 µg/dL Q3: 3.71 µg/dL Q4: 4.63 µg/dL Q5: 19.14 µg/dL			
Bloom et al. (2015) Michigan (4 counties) and Texas (12 counties) United States 2005–2009 Cohort	LIFE n: 235 Potential participants were identified, using fishing license registries or a commercially available direct marketing data base, from 12 counties in Texas and four in Michigan, respectively, with presumed exposure to persistent organic pollutants. Inclusion criteria comprised a committed heterosexual relationship, women aged 18–40 yr (men >18), English or Spanish speaker, no use of an injectable contraceptive within 12 mo, and a menstrual cycle length of 21–42 d.	Blood Maternal and paternal blood, collected before pregnancy (baseline), were measured by ICP-MS Age at Measurement: >18, maternal mean age: 29.75 (SD: 3.73) yr and paternal mean age: 31.52 (SD:4.57) yr Mean (SD): Maternal: 0.71 (0.30) µg/dL Paternal: 1.13 (0.63) µg/dL Median: Maternal: 0.66 µg/dL Paternal: 0.98 µg/dL Max: Maternal: 2.23 µg/dL Paternal: 6.43 µg/dL Tertiles (µg/dL): Maternal Blood Pb T1: <0.55 (<33rd percentile)	Other Pregnancy and Birth Outcomes: Secondary sex ratio Women were followed until delivery when they completed and returned birth announcements that captured date and sex of birth, weight and length, and HC. Secondary sex ratio is the ratio of live male to female births, reflecting a male excess. Age at outcome: birth	Log-binomial models for secondary sex ratio: effect of maternal exposure adjusted for paternal exposure, maternal age, difference in maternal and paternal age, and maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine (mg/dL); effect of paternal exposure adjusted for maternal exposure, paternal age, difference in maternal and paternal age, and maternal and paternal smoking, income, race, serum lipids (mg/dL), and creatinine for urine (mg/dL)	RR (95% CI) Maternal Exposure: T1: Reference T2: 0.97 (0.78, 1.22) T3: 1.00 (0.81, 1.24) p for trend: 0.884 Paternal Exposure: T1: Reference T2: 1.12 (0.89, 1.41) T3: 1.06 (0.84, 1.34) p for trend: 0.854

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		T2: 0.55–0.73 (33rd to 67th percentile) T3: >0.73 (>67th percentile) Paternal Blood Pb T1: <0.84 (<33rd percentile) T2: 0.84–1.16 (33rd to 67th percentile) T3: >1.16 (>67th percentile)			
Tatsuta et al. (2022b) Japan January 2011–March 2014 (followed through birth) Cohort	JECS n: 85,171 Pregnant women and their paternal partners were recruited from 15 regions of Japan. Participants delivered a live infant with singleton pregnancy and had child sex information. Participants were excluded is they had a stillbirth, abortion, multiple births, or withdrew before birth; missing blood sample information; missing confounders; or without partner's consent and with paternal age or occupational exposure to Pb deficits	Blood Maternal blood was measured by ICP-MS. Age at measurement: maternal age at collection (middle or late pregnancy) Median: 5.85 ng/g Max: 110 ng/g Quartiles (ng/g) Q1: 1.20–4.46 Q2: 4.47–5.39 Q3: 5.40–6.35 Q4: 6.36–7.76 Q5: 7.77–110	Other Pregnancy and Birth Outcomes: Secondary sex ratio Sex of the infant obtained from the medical record transcripts by physicians, midwives, nurses, or trained research coordinators.	Logistic regression models were adjusted for maternal age at parturition, season of birth, pre-pregnancy BMI, annual household income, gravidity, fertility treatments, score of the K6, maternal smoking status during pregnancy, passive smoking status during pregnancy, birth year and study area (regional center)	OR (95% CI) Q1: Reference Q2: 1.082 (1.037, 1.129) Q3: 1.122 (1.074, 1.171) Q4: 1.214 (1.163, 1.268) Q5: 1.279 (1.224, 1.336)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]

AAS = atomic absorption spectrometry; ALSPAC = Avon Longitudinal Study of Parents and Children; BMI = body mass index; BW = birth weight; BWZ = birth weight Z-score; d = day(s); ELISA = enzyme-linked immunosorbent assay; HC = head circumference; ICP-MS = inductively coupled plasma mass spectrometry; IgE = immunoglobulin E; IL-33 = interleukin-33; JECS = Japan Environment and Children's Study; K6 = Kessler Psychological Distress Scale; LIFE = Longitudinal Investigation of Fertility and the Environment; LOD = limit of detection; MIREC = Maternal-Infant Research on Environmental Chemicals; mo = month(s); OR = odds ratio; Q = quartile; RR = relative risk; rTL = relative telomere length; SD = standard deviation; T# = tertile #; TSLP = thymic stromal lymphopoietin; UCB = umbilical cord blood; wk = week(s); yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. If the Pb biomarker is log-transformed, effect estimates are standardized to the specified unit increase for the 10^{th}–90^{th} percentile interval of the biomarker level. Effect estimates are assumed to be linear within the evaluated interval. Categorical effect estimates are not standardized.

[b]Pb measurements were converted from µg/L to µg/dL.

[c]Effect estimates unable to be standardized.

Table 8-10 Epidemiologic studies of Pb exposure and postnatal growth

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Signes-Pastor et al. (2021) United States 2013–2016 Cross-sectional	NHANES n: 1,634 Children aged 6–11 yr old participating in the 2013–2014 and 2015–2016 NHANES cycles	Blood Blood was measured by ICP-MS Age at measurement: 6–11 yr old Median: Overall: 0.5 µg/dL Girls: 0.5 µg/dL Boys: 0.5 µg/dL 75th: Overall: 0.8 µg/dL Girls: 0.7 µg/dL Boys: 0.8 µg/dL Max: Overall: 5.8 µg/dL Girls: 5.8 µg/dL Boys: 5.0 µg/dL	Postnatal growth: weight, WC, upper arm length, standing height, and BMI Physical examination was performed to obtain body measurements. Age at outcome: 6–11 yr old	Linear regression models were adjusted for total calorie intake, race, PIR, children's age, smoker(s) in the household, outside-of-school and at-school activity scores, children's sex, and co-exposure to fluoride, Mn, Hg, and Se	β (95% CI) BMI (kg/m^2): −2.092 (−3.227, −0.957) Standing height (cm): −3.116 (−5.03, −1.202) WC (cm): −5.742 (−8.769, −2.715) Upper arm length (cm): −1.068 (−1.625, −0.512) Girls BMI (kg/m^2): −3.204 (−5.654, −0.754) Standing height (cm): −2.89 (−6.691, 0.911) WC (cm): −6.659 (−12.911, −0.408) Upper arm length (cm): −1.696 (−2.859, −0.534) Boys BMI (kg/m^2): −1.959 (−3.45, −0.467) Standing height (cm): −3.828 (−6.588, −1.068) WC (cm): −6.81 (−10.995, −2.626) Upper arm length (cm): −0.89 (−1.691, −0.089)
Kuang et al. (2020) Nanjing China	n: 395 Students aged 7–11 yr (grades 2 to 4) were	Blood Blood was measured by ICP-MS	Postnatal growth: height, weight, bust, waistline, and BMI	General linearized models were adjusted for age and gender	β (95% CI) Height (cm): −3.21 (−4.24, −2.17)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
2012 Cross-sectional	recruited from public primary schools in Nanjing, an industry city from East China. Students with congenital mental retardation (third-degree relatives included) and other serious diseases were excluded. Students and their parents were informed of the research content and purpose. Only completely matched groups of samples, including questionnaire information, blood samples, growth indexes and school performances, were included in the study.	Age at Measurement: 7–11 yr Mean (SD)[b]: 3.04 (1.72) µg/dL Median[b]: 2.61 µg/dL	Growth: Individual measurements were carried out by the medical staff according to the standard protocols of WHO. Height was measured using a mechanical height gauge to the nearest 0.1 cm. Weight was measured using digital scales to the nearest 100 g. Age at outcome: 7–11 yr		Weight (kg): −1.96 (−3.11, −0.82) Bust (cm): −2.77 (−3.79, −1.76) Waistline (cm): −3.65 (−4.78, −2.52) BMI (kg/m^2): −0.20 (−0.65, 0.25)
Zhou et al. (2020) Taizhou China April 2013–November 2013 Cross-sectional	n: 1,678 Children 6 yr or older	Blood Blood was measured by GFAAS Age at Measurement: ≥6 yr Mean[b]: 5.684 µg/dL Geometric mean[b]: 4.904 µg/dL Median[b]: 4.644 µg/dL 75th[b]: 6.4 µg/dL Max[b]: 46.8 µg/dL Tertiles[b] (µg/dL)	Postnatal growth: HAZ, WAZ and BMIZ Children's body weight and supine length or standing height were measured. BMI was calculated by the formula BMI = weight (kg)/height (m)^2; Z-scores of anthropometric parameters, such as HAZ, WAZ and BMIZ, were calculated with the WHO Child Growth Standards.	Multivariable linear models were adjusted for age, sex, BW, maternal education	β (95% CI)[c]: WAZ: −0.33 (−0.56, −0.11) HAZ: −0.38 (−0.63, −0.14) BMIZ: −0.13 (−0.37, 0.12) WAZ Tertiles T1: Reference T2: −0.28 (−0.47, −0.09) T3: −0.42 (−0.62, −0.23) HAZ Tertiles T1: Reference T2: −0.26 (−0.47, −0.04) T3: −0.36 (−0.58, −0.15)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
		T1: <2.5 T2: 2.5–5.0 T3: >5.0	Age at outcome: ≥6 yr		BMIZ Tertiles T1: Reference T2: −0.18 (−0.39, 0.04) T3: −0.29 (−0.50, −0.07) Males: WAZ: −0.36 (−0.67, −0.06) HAZ: −0.38 (−0.72, −0.04) BMIZ: −0.15 (−0.49, 0.19) WAZ Tertiles: T1: Reference T2: −0.42 (−0.71, −0.13) T3: −0.52 (−0.81, −0.24) HAZ Tertiles: T1: Reference T2: −0.36 (−0.69, −0.004) T3: −0.43 (−0.75, −0.11) BMIZ Tertiles: T1: Reference T2: −0.28 (−0.60, 0.04) T3: −0.35 (−0.68, −0.03) Females WAZ: −0.29 (−0.61, 0.03) HAZ: −0.35 (−0.71, 0.01) BMIZ: −0.10 (−0.45, 0.26) WAZ Tertiles: T1: Reference T2: −0.17 (−0.42, 0.09)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
					T3: −0.36 (−0.62, −0.09) HAZ Tertiles: T1: Reference T2: −0.17 (−0.45, 0.11) T3: −0.31 (−0.60, −0.02) BMIZ Tertiles: T1: Reference T2: −0.10 (−0.38, 0.18) T3: −0.25 (−0.54, 0.04)
Choi et al. (2017) Seoul South Korea July 2014 to June 2016 Cross-sectional	n: 210 Children ranging from 8 to 23 mo in age and healthy; no intake of herbal medicine, iron, or zinc supplements in the past 3 mo; no acute febrile disease or acute gastrointestinal disease in the past 2 wk; and no evidence of other acute or chronic diseases affecting growth on physical examination or in medical history	Blood Blood was measured by ICP-MS Age at Measurement: 8–23 mo Geometric mean: 0.96 µg/dL Median: 0.83 µg/dL 75th: 1.23 µg/dL Max: 3.5 µg/dL	Postnatal growth: Weight, height, HC Each infant's weight, height, and HC were measured by experienced nurse; iron deficiency and iron deficiency anemia, complete blood count, serum iron and ferritin concentrations, as well as total iron-binding capacity were measured from the venous blood samples of infants Age at outcome: 8–23 mo	Linear regression models; BW, sociodemographic and feeding-related factors, and iron and anemia status	β (95% CI): WAZ-BWZ (difference of the WAZ at the time of the study and BWZs): −0.238 (−0.391, −0.085) HCAZ: −0.213 (−0.366, −0.06)
Ashley-Martin et al. (2019) Vancouver, Edmonton, Winnipeg, Sudbury, Ottawa, Kingston,	MIREC Study n: 449 MIREC study is a national-level pregnancy cohort of 2001 women from 10 cities across	Blood Blood was measured by ICP-MS Age at Measurement: 2–5 yr	Postnatal growth: HAZ, WAZ, BMIZ Child anthropometry was performed during the home visit and served as a measure of growth at	Linear regression models adjusted for maternal education, maternal country of birth, age, postnatal BMI, maternal prenatal smoking, and paternal	β (95% CI)[b] HAZ Overall: T1: Reference T2: −0.015 (−0.23, 0.20)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
Toronto, Hamilton, Montreal, and Halifax Canada 2008–2011 Cross-sectional	Canada including Vancouver, Edmonton, Winnipeg, Sudbury, Ottawa, Kingston, Toronto, Hamilton, Montreal, and Halifax. Participants were recruited in the first trimester of pregnancy between 2008 and 2011 and followed through delivery.	Median: 0.663 µg/dL 75th: 0.962 µg/dL Max: 5.49 µg/dL Tertiles (µg/dL) T1: <0.54 T2: 0.54–0.82 T3: >0.82	that time. Weight and height were measured using a calibrated scale and calibrated stadiometer. All measurements were completed in duplicate or, if warranted due to predefined differences in duplicate measurements, in triplicate. Age at outcome: 2–5 yr	BMI; models were additionally adjusted for maternal metal concentrations	T3: 0.025 (−0.20, 0.25) Male T1: Reference T2: 0.003 (−0.28, 0.29) T3: −0.039 (−0.32, 0.24) Female T1: Reference T2: 0.022 (−0.31, 0.35) T3: 0.095 (−0.26, 0.45) WAZ Overall T1: Reference T2: 0.064 (−0.12, 0.25) T3: −0.004 (−0.20, 0.19) Male T1: Reference T2: 0.11 (−0.15, 0.36) T3: 0.074 (−0.18, 0.33) Female T1: Reference T2: 0.050 (−0.22, 0.32) T3: −0.11 (−0.40, 0.18) BMIZ Overall T1: Reference T2: 0.097 (−0.098, 0.29) T3: −0.041 (−0.24, 0.16) Male T1: Reference T2: 0.15 (−0.13, 0.42)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
					T3: 0.14 (−0.14, 0.41) Female T1: Reference T2: 0.039 (−0.24, 0.32) T3: −0.26 (−0.55, 0.033) Adjusted for maternal exposure: HAZ Overall: T1: Reference T2: −0.030 (−0.25, 0.19) T3: −0.008 (−0.25, 0.23) Male T1: Reference T2: −0.007 (−0.30, 0.28) T3: −0.067 (−0.38, 0.24) Female T1: Reference T2: 0.013 (−0.33, 0.36) T3: 0.081 (−0.30, 0.46) WAZ Overall T1: Reference T2: 0.041 (−0.15, 0.23) T3: −0.05 (−0.26, 0.16) Male T1: Reference T2: 0.09 (−0.16, 0.35) T3: 0.04 (−0.24, 0.32)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
					Female T1: Reference T2: 0.024 (−0.26, 0.30) T3: −0.15 (−0.46, 0.17) BMIZ Overall T1: Reference T2: 0.076 (−0.12, 0.28) T3: −0.086 (−0.30, 0.14) Male T1: Reference T2: 0.14 (−0.14, 0.41) T3: 0.11 (−0.19, 0.41) Female T1: Reference T2: 0.006 (−0.28, 0.29) T3: −0.32 (−0.64, 0.0036)
Jedrychowski et al. (2015) Krakow Poland January 2001–February 2004 Cohort	Krakow Cohort Study n: 379 The present analysis was restricted to 379 term-babies (born >36 wk of gestation) who took part in the 9-yr follow-up. Women who were residents of Krakow, one of the major cities in Poland, and attended ambulatory prenatal clinics in the first and second trimesters of pregnancy were eligible	Blood and cord blood Maternal and UCB, obtained at delivery, and blood (capillary), obtained at age 5, were measured by high-performance liquid chromatography atmospheric-pressure ionization tandem mass spectrometry Age at Measurement: Maternal age at delivery and 5 yr old	Postnatal growth: Height gain At ages of 3–9 children were invited annually for pediatric examination during which height measurements were done. Age at outcome: 3–9 yr old	GEE models were adjusted for maternal height, BL, pre-pregnancy maternal weight, gestational weight gain, prenatal and postnatal ETS, breastfeeding, maternal education, and parity	β (95% CI), as mean height growth (cm) by UCB tertiles T1: Reference T2: −0.671 (−1.610, 0.267) T3: −0.736 (−1.779, 0.307)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
	for the study. Enrollment included only nonsmoking women with singleton pregnancies between the ages of 18 and 35 yr who were free from such chronic diseases as diabetes and hypertension.	Geometric mean: UCB: 1.21 µg/dL Blood: 2.05 µg/dL UBC Tertiles (µg/dL) T1: ≤1.0 T2: 1.1–1.4 T3: >1.4			
Kim et al. (2017) Korea January 2011–December 2012 Cohort	CHECK n: 280 Healthy pregnant women with mature term singleton were recruited, who did not have preterm delivery, medical predisposition, or history of occupational exposure	Cord blood UCB was measured by GFAAS Age at measurement: birth Mean: Overall: 1.31 µg/dL Males: 1.39 µg/dL Females: 1.21 µg/dL	Postnatal growth: Weight, height, and BMI Weight and height were measured by the health professionals Age at outcome: 3, 6, 9, 12, 15, 18, 24, and 27 mo of age	Generalized linear model adjusted for maternal age, maternal BMI, gestational period, cesarean section, and smoking	β (95% CI)[b] Weight At birth: 0.037 (−0.128, 2.01) 3 mo: −0.039 (−0.414, 0.335) 6 mo: −0.391 (−0.814, 0.033) 9 mo: 0.000 (−0.356, 0.357) 12 mo: 0.125 (−0.302, 0.552) 15 mo: 0.093 (−0.396, 0.582) 18 mo: 0.897 (−0.171, 1.965) 24 mo: 0.717 (0.195, 1.239) 27 mo: 0.316 (−0.345, 0.977) Height At birth: 0.176 (−0.003, 0.354) 3 mo: −0.023 (−0.384, 0.337) 6 mo: 0.033 (−0.458, 0.523) 9 mo: 0.049 (−0.346, 0.444) 12 mo: −0.058 (−0.531, 0.415) 15 mo: 0.226 (−0.220, 0.671) 18 mo: 0.909 (−0.222, 2.040) 24 mo: 0.138 (−0.530, 0.806) 27 mo: 0.354 (−0.497, 1.205)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
					BMI At birth: −0.167 (−0.357, 0.023) 3 mo: −0.019 (−0.431, 0.392) 6 mo: −0.461 (−0.937, 0.014) 9 mo: −0.031 (−0.430, 0.369) 12 mo: −0.020 (−0.492, 0.452) 15 mo: −0.098 (−0.481, 0.285) 18 mo: 0.157 (−1.266, 1.580) 24 mo: 0.695 (0.077, 1.313) 27 mo: 0.409 (−0.398, 1.216) Males Weight At birth: 0.088 (−0.140, 0.316) 3 mo: −0.008 (−0.597, 0.581) 6 mo: −0.023 (−0.543, 0.497) 9 mo: 0.167 (−0.398, 0.733) 12 mo: 0.202 (−0.631, 1.034) 15 mo: 0.365 (−0.467, 1.197) 18 mo: 1.324 (0.023, 2.626) 24 mo: 0.962 (0.181, 1.743) 27 mo: 0.417 (−0.631, 1.465) Height At birth: 0.270 (0.037, 0.502) 3 mo: 0.232 (−0.262, 0.726) 6 mo: −0.077 (−0.695, 0.540) 9 mo: 0.166 (−0.363, 0.695) 12 mo: −0.147 (−1.153, 0.859) 15 mo: 0.433 (−0.147, 1.013) 18 mo: 1.648 (0.270, 3.026) 24 mo: 1.062 (−0.132, 2.255)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
					27 mo: 1.618 (−0.450, 3.686) BMI At birth: −0.194 (−0.413, 0.025) 3 mo: −0.130 (−0.800, 0.540) 6 mo: 0.003 (−0.558, 0.563) 9 mo: −0.009 (−0.522, 0.504) 12 mo: 0.314 (−0.689, 1.318) 15 mo: −0.049 (−0.569, 0.470) 18 mo: 0.319 (−1.496, 2.135) 24 mo: 0.472 (−0.172, 1.116) 27 mo: 0.966 (−1.390, 3.322) Females Weight At birth: 0.006 (−0.236, 0.248) 3 mo: −0.072 (−0.640, 0.496) 6 mo: −0.828 (−1.502, −0.154) 9 mo: −0.098 (−0.602, 0.407) 12 mo: 0.101 (−0.443, 0.644) 15 mo: −0.039 (−0.722, 0.643) 18 mo: −0.826 (−15.627, 13.976) 24 mo: 0.821 (−0.087, 1.728) 27 mo: 0.236 (−1.089, 1.561) Height At birth: 0.102 (−0.177, 0.381) 3 mo: −0.249 (−0.875, 0.378) 6 mo: 0.106 (−0.732, 0.945) 9 mo: 0.104 (−0.526, 0.734) 12 mo: −0.057 (−0.608, 0.493) 15 mo: 0.121 (−0.664, 0.905) 18 mo: −0.788[d]

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
					24 mo: −0.176 (−1.225, 0.874) 27 mo: −0.153 (−1.405, 1.100) BMI At birth: −0.142 (−0.474, 0.189) 3 mo: 0.098 (−0.491, 0.687) 6 mo: −0.974 (−1.778, −0.170) 9 mo: −0.143 (−0.805, 0.519) 12 mo: −0.147 (−0.688, 0.393) 15 mo: −0.103 (−0.712, 0.505) 18 mo: −2.263[d] 24 mo: 1.108 (−0.147, 2.362) 27 mo: 0.439 (−1.581, 2.460)
Hong et al. (2014) Seoul, Cheonan, and Ulsan South Korea May 2006 to December 2010 Cohort	MOCEH n: 1,751 This research was conducted as a part of MOCEH, which is a multicenter prospective hospital and community-based birth cohort study. Women who lived in these cities were enrolled in the first trimester. The participants fulfilled the inclusion criterion of age >18 yr. Written informed consent was obtained at the initial visit from all enrolled mothers on behalf of themselves and their children. The study subjects were restricted to those in which maternal and cord BLLs were assessed,	Blood and cord blood Maternal blood, obtained during early pregnancy (before gestational week 20) and at delivery, and UCB were measured by AAS Age at Measurement: maternal age at week 20 and at delivery; delivery Mean: Early pregnancy: 1.25 µg/dL Late pregnancy: 1.25 µg/dL UCB: 0.91 µg/dL Median: Early pregnancy: 1.29 µg/dL	Postnatal growth: weight Z-score, length z-cores Weights and lengths at 6 and 12 mo were taken by using an infantometer by laying infants on the center of a scale and were read to 1 decimal place for weight (0.1 kg) and length (0.1 cm). At 24 mo of age, weights and lengths were obtained by using an automatic measuring station for weight and length by standing on the center of the scale on both feet, and placing their heels, bottom, back, and posterior head on the measuring rod.	Multivariable regression models were adjusted for mother's age, education, pre-pregnancy BMI, GA, gender of the child, and clinic location, and calcium intake	β (95% CI)[b] Maternal Blood: Early pregnancy Pb Weight Z-scores At birth: −0.05 (−0.16, 0.07) 6 mo: −0.03 (−0.19, 0.13) 12 mo: −0.10 (−0.26, 0.06) 24 mo: −0.05 (−0.23, 0.12) Length Z-scores At birth: 0.01 (−0.15, 0.18) 6 mo: −0.17 (−0.37, 0.02) 12 mo: 0.04 (−0.15, 0.24) 24 mo: −0.15 (−0.35, 0.04) Maternal Blood: Late Pregnancy Pb Weight Z-scores At birth: −0.01 (−0.15, 0.12) 6 mo: −0.15 (−0.34, 0.03) 12 mo: −0.15 (−0.34, 0.03)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
	and postnatal growth measurements were performed. Exclusion criteria: LBW (<2500 g); preterm birth (gestational week <37); and missing information on maternal age, BMI, education level, and gestational week; subjects with >2 SD for mean maternal BLLs and child BW or length	Late pregnancy: 1.27 µg/dL UCB: 0.93 µg/dL 75th: Early pregnancy: 1.65 µg/dL Late pregnancy: 1.64 µg/dL UCB: 1.19 µg/dL Max: Early pregnancy: 2.63 µg/dL Late pregnancy: 2.52 µg/dL UCB: 1.90 µg/dL	Age at outcome: 6, 12 and 24 mo		24 mo: −0.33 (−0.53, −0.13) Length Z-scores At birth: −0.07 (−0.25, 0.11) 6 mo: −0.05 (−0.28, 0.16) 12 mo: 0.10 (−0.12, 0.33) 24 mo: −0.30 (−0.53, −0.08) UCB Pb Weight Z-scores At birth: 0.08 (−0.04, 0.21) 6 mo: 0.10 (−0.07, 0.28) 12 mo: 0.06 (−0.10, 0.24) 24 mo: −0.01 (−0.21, 0.18) Length Z-scores At birth: 0.14 (−0.03, 0.32) 6 mo: 0.11 (−0.11, 0.33) 12 mo: 0.22 (0.01, 0.44) 24 mo: 0.004 (−0.22, 0.22)
Renzetti et al. (2017) Mexico City Mexico July 2007–February 2011 Cohort	PROGRESS n: 513 Women were considered eligible for enrollment if they were 18 yr or older, pregnant at <20 wk of gestation, free of heart or kidney disease, did not use steroids or anti-epilepsy drugs, did not consume alcohol on a daily basis, had access to a telephone, and planned to reside in Mexico City for the following 3 yr	Blood, cord blood, and bone Maternal blood, collected in the second and third trimester of pregnancy and within 12 hr of delivery, and UCB, collected within 12 hr of delivery, were measured by ICP-QQQ. Maternal bone, measured at 1-mo postpartum from tibia (cortical bone) and patella (trabecular bone),	Postnatal growth: HAZ, WAZ, BMIZ, and percentage body fat Trained research assistants collected measures of anthropometry at the age 4–6-yr visit in which child weight and standing height were measured using a professional digital scale. BMI was calculated from height and weight and to determine BMIZ for age and sex based on WHO norms.	Multivariable linear regression adjusted for mother's age, BMI (height when the outcome is HAZ), education, GA (weeks), primiparity, smoke exposure, delivery mode, breastfeeding, sex of the child, food frequency questionnaire total dietary intake, LeadCare childhood blood Pb, and child's age (when the outcome is percent body fat)	β (95% CI)[c] HAZ Maternal blood, second trimester: −0.04 (−0.13, 0.04) Maternal blood, third trimester: −0.10 (−0.19, −0.01) Maternal blood, at delivery: −0.04 (−0.13, 0.05) UCB: −0.04 (−0.14, 0.06) Maternal patella: 0.01 (−0.003, 0.02) Maternal tibia: −0.003 (−0.01, 0.01) WAZ

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
		were measured using a K-XRF instrument Age at Measurement: Maternal age at second and third trimester and at birth; child's age at follow-up (4–6 yr) Mean (SD): Maternal blood – second trimester: 3.7 (2.6) µg/dL Maternal blood – third trimester: 3.9 (2.8) µg/dL Maternal blood – at delivery: 4.3 (3.1) µg/dL UCB: 3.5 (2.7) µg/dL Patella: 4.7 (8.8) µg/g Tibia: 2.9 (8.6) µg/g Geometric mean: Maternal blood – second trimester: 3.0 µg/dL Maternal blood – third trimester: 3.1 µg/dL Maternal blood – at delivery: 3.5 µg/dL UCB: 2.8 µg/dL Max: Maternal blood – second trimester: 17.8 µg/dL Maternal blood – third trimester: 28.3 µg/dL Maternal blood – at delivery: 21.9 µg/dL	Tetrapolar bioelectrical impedance was measured to estimate body fat mass and percent body fat Age at outcome: 4–6 yr old		Maternal blood, second trimester: −0.02 (−0.13, 0.09) Maternal blood, third trimester: −0.11 (−0.22, −0.003) Maternal blood, at delivery: −0.03 (−0.13, 0.08) UCB: −0.03 (−0.15, 0.09) Maternal patella: 0.01 (−0.01, 0.02) Maternal tibia: −0.0003 (−0.01, 0.01) BMIZ Maternal blood, second trimester: 0.04 (−0.07, 0.15) Maternal blood, third trimester: −0.01 (−0.12, 0.10) Maternal blood, at delivery: −0.03 (−0.08, 0.14) UCB: 0.05 (−0.08, 0.17) Maternal patella: 0.01 (0.01, 0.02) Maternal tibia: 0.01 (−0.01, 0.02) Percentage of body fat Maternal blood, second trimester: −0.13 (−0.75, 0.49) Maternal blood, third trimester: −0.21 (−0.82, 0.41) Maternal blood, at delivery: −0.12 (−0.74, 0.50) UCB: 0.31 (−0.37, 0.99) Maternal patella: 0.01 (−0.06, 0.07)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% Cis[a]
		UCB: 18.5 µg/dL Patella: 43.2 µg/g Tibia: 30.1 µg/g			Maternal tibia: 0.01 (−0.06, 0.08)
Liu et al. (2019a) Mexico City Mexico 1994–2003 Cohort	ELEMENT n: 248 Pregnant women who were recruited from three maternity hospitals in Mexico City and followed for 12 mo post-partum and children followed through age 4	Blood and bone Maternal tibia (cortical) and patella (trabecular) bone, measured at 1-mo postpartum, were measured using a noninvasive spot-source Cd K-XRF instrument constructed at Harvard University. Blood, obtained from each child annually from 1 to 4 yr, was measured by GFAAS Age at Measurement: maternal age at delivery and 1–4 yr old Mean: Maternal patella: 12.3 µg/g Maternal tibia: 8.9 µg/g Blood (cumulative): 19.6 µg/dL Median: Maternal patella: 10.6 µg/g Maternal tibia: 8.3 µg/g Blood (cumulative): 17.7 µg/dL 75th:	Postnatal growth: BMIZ, WC, sum of skinfolds, and body fat percentage At the follow-up visit, child weight, height, WC, and skinfold thickness (biceps, subscapular and suprailiac) were measured Age at outcome: 8–16 yr old	Multivariable linear regression models were adjusted for maternal age, parity, education and calcium treatment group, and children's age, sex, and pubertal stage	β (95% CI)[c] BMIZ Patella: −0.02 (−0.03, −0.01) Tibia: −0.00 (−0.02, 0.01) Blood: 0.02 (−0.40, 0.45) WC (cm) Patella: −0.12 (−0.22, −0.03) Tibia: −0.07 (−0.21, 0.07) Blood: −0.38 (−3.74, 2.97) Sum of skinfolds (mm) Patella: −0.29 (−0.50, −0.08) Tibia: −0.10 (−0.38, 0.19) Blood: −1.62 (−8.76, 5.52) Body of fat percentage (%) Patella: −0.09 (−0.17, −0.01) Tibia: −0.01 (−0.13, 0.10) Blood: 2.08 (−0.98, 5.13)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Maternal patella: 19.7 µg/g Maternal tibia: 15.2 µg/g Blood (cumulative): 23.5 µg/dL Max: Maternal patella: 50.1 µg/g Maternal tibia: 38.6 µg/g Blood (cumulative): 55.0 µg/dL			
Afeiche et al. (2012) Mexico City Mexico 1994–2005 Cohort	n: 773 Mothers were recruited from maternity hospitals serving low-to-moderate income populations in Mexico City; preterm (<37 wk) and LBW (<2500 g) were excluded	Blood and bone Maternal bone, assessed at approximately 1 mo postpartum, measured by in vivo K-XRF from the mid-tibial shaft (cortical bone) and the patella (trabecular bone); blood, obtained from children at 24 mo or 30–48 mo, was measured by GFAAS. Age at Measurement: Maternal age 1 mo postpartum, with average age at delivery: 25.7 (SD: 5.3) yr; birth–24 mo; 30–48 mo Median: Maternal tibia: 8.2 µg/g Maternal patella: 9.4 µg/g Infant blood (average	Postnatal growth: Attained height and BMI Children's weight and height were measured and recorded by trained staff members at birth and age 48 mo using standard protocols Age at outcome: birth and 48 mo	Linear regression models were adjusted for maternal height and calf circumference, number of previous pregnancies, marital status, education level, breastfeeding for 6 mo, cohort, calcium treatment group assignment during lactation and pregnancy, age at delivery, and child sex and GA at birth; all height models were additionally adjusted for BL; BMI models were additionally adjusted for BW	β (95% CI) Height differences (cm) Prenatal: −4.6 (−10.25, 1.05) Infant blood: −0.84 (−1.43, −0.26) Childhood blood: 0.41 (−0.17, 0.99) BMI difference (kg/m^2) Prenatal: −0.70 (−3.05, 1.65) Infant blood: −0.07 (−0.32, 0.18) Childhood blood: 0.09 (−0.15, 0.33)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		from birth to 24 mo): 4.5 µg/dL Childhood blood (average from 30–48 mo): 5.6 µg/dL			
Kerr et al. (2019) Torreon Mexico February 2001–June 2002 Cohort	n: 538 Children attending nine public elementary schools located within a 3.5 km radius from a foundry close to the city center participated in the study. Participants were randomized into one of four groups: iron (30 mg of ferrous fumarate), zinc (30 mg zinc oxide), a combination of iron and zinc or a placebo (sugar pill)	Blood Blood, collected at baseline (T1), 6 mo after baseline (T2), and 12 mo after baseline (T3), was measured by GFAAS Age at Measurement: 6–8 yr old Median: 10.1 µg/dL 75th: 23.7 µg/dL	Postnatal growth: height, knee height, and HAZ A single trained individual took anthropometric measures at each time point (T1, T2, T3), according to standard methods recommended by the WHO; Height and knee height were measured without shoes using a standardized measuring board or a knemometer, respectively, to the nearest 1 mm; Age at outcome: 6–8 yr old	Multivariable linear regression adjusted for age, sex, mother's education, crowding, and hemoglobin at baseline; HAZ models were not adjusted for age or sex; models were also stratified by ALAD genotype	β (95% CI) Height: −0.11 cm (−0.18, −0.04) Knee height: −0.04 cm (−0.07, −0.02) HAZ: −0.02 cm (−0.03, −0.01) $ALAD_{1–2/2–2}$ Height: −0.38 cm (−0.68, 0.09) Knee height: −0.14 cm (−0.25, −0.02) HAZ: −0.07 (−0.12, −0.02) $ALAD_{1–1}$ Height: −0.09 cm (−0.16, −0.02) Knee height: −0.04 cm (−0.06, −0.01) HAZ: −0.02 (−0.03, −0.004)
Burns et al. (2017) Chapaevsk Russia 2003–2005 (2012–2015) Cohort	Russian Children's Study n: 499 The Russian Children's Study is a prospective cohort of 499 boys residing in Chapaevsk, Russia, enrolled in 2003–2005 at ages 8–9 yr and followed	Blood Blood measured by GFAAS with Zeeman background corrected Age at Measurement: 8–9 at enrollment	Postnatal growth: HAZ and BMIZ At study entry and annual follow-up visits, a standardized anthropometric examination was performed according to a written protocol. Height was measured to the	Mixed effects linear regression models were adjusted for BW, preterm birth, percent calories from protein at baseline, and age for the HAZ models and BW, no biological father in home, percent calories from fat at	β (95% CI)[b], as estimated mean growth Z-scores comparing higher (≥5 µg/dL) to lower (<5 µg/dL) BLL HAZ: −0.43 (−0.60, −0.25) BMIZ: −0.22 (−0.45, 0.006)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	annually through 2012–2015 to age 18 yr. For this analysis, 10 boys in the original cohort were excluded due to chronic illnesses that could affect growth and/or pubertal development.	Median: 3.0 µg/dL Max: 31 µg/dL	nearest 0.1 cm using a stadiometer. Weight was measured to the nearest 100 g with a metric scale. HAZ and BMIZ were calculated using the WHO standards Age at outcome: 8–9 at enrollment and annually through age 18	baseline, and age for BMIZ models	
Deierlein et al. (2019) New York City, NY; Cincinnati, OH; and San Francisco, CA United States 2004–2007 Cohort	Breast Cancer and Environment Research Program n: 683 Girls ages 6–8 yr were enrolled in 2004–2007 at three sites: New York City, Cincinnati, and San Francisco; girls have no underlying endocrine medical conditions, be of Black or Hispanic race/ethnicity (New York City site only), and have been born in the Kaiser Permanente system (san Francisco)	Blood Blood was measured by ICP-MS Age at Measurement: 6–10 yr Median: 0.99 µg/dL Mean (SD): 1.16 (0.67) µg/dL Geometric mean: 1.03 µg/dL (95% CI: 0.99, 1.07) Max: 5.40 µg/dL	Postnatal growth: height, BMI, WC, and percent body fat Weight (kg), standing height (cm), and umbilical WC (cm) were collected at baseline and at biannual (Cincinnati) or annual (New York City and San Francisco Bay Area) follow-up visits by trained interviewers using a standard protocol; BMI was calculated as weight divided by squared height (kg/m^2). Percent body fat was estimated using bioelectrical impedance analysis Age at outcome: 7–14 yr	Linear mixed effects models with an unstructured correlation matrix were adjusted for age, age squared, race, an Interaction term between age and blood Pb concentrations, an interaction term between age squared and blood Pb concentrations, and an interaction term between race and age	β (95% CI) Height (cm) Age 7: −2.0 (−3.0, −1.0) Age 8: −1.9 (−2.8, −0.9) Age 9: −1.7 (−2.7, −0.8) Age 10: −1.6 (−2.6 −0.7) Age 11: −1.6 (−2.5, −0.6) Age 12: −1.5 (−2.5, −0.5) Age 13: −1.5 (−2.5, −0.5) Age 14: −1.5 (−2.5, −0.4) BMI (kg/m^2) Age 7: −0.7 (−1.2, −0.2) Age 8: −0.8 (−1.3, −0.3) Age 9: −0.9 (−1.4, −0.4) Age 10: −0.9 (−1.4, −0.4) Age 11: −0.9 (−1.5, −0.3) Age 12: −0.9 (−1.5, −0.3) Age 13: −0.8 (−1.5, −0.2) Age 14: −0.8 (−1.5, −0.02) WC (cm) Age 7: −2.2 (−3.8, −0.6) Age 8: −2.5 (−3.8, −1.1)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Age 9: −2.7 (−4.0, −1.4) Age 10: −2.9 (−4.9, 1.4) Age 11: −3.0 (−4.5, −1.4) Age 12: −3.0 (−4.7, −1.3) Age 13: −3.0 (−4.8, −1.1) Age 14: −2.9 (−4.8, −0.9) Percent body fat (%) Age 7: −1.8 (−3.2, −0.4) Age 8: −2.0 (−3.3, −0.7) Age 9: −2.1 (−3.4, −0.8) Age 10: −2.2 (−3.4, −0.9) Age 11: −2.1 (−3.4, −0.9) Age 12: −2.1 (−3.4, −0.8) Age 13: −1.9 (−3.2, −0.6) Age 14: −1.7 (−3.1, −0.4)
Raihan et al. (2018) Mirpur, Dhaka Bangladesh November 2009–December 2012 Cross-sectional	MAL-ED study n: 729 Children under the age of 2	Blood Blood was measured using GFAAS Age at measurement: under the age of 2 Mean: 8.25 µg/dL	Postnatal growth: Stunting, wasting, underweight Child's length and weight were measured using Seca 417 infantometer (precision: ± 1 mm) and Seca 354 Dual Purpose Baby Scale (precision: 10 gm). Age at outcome: under the age of 2	Logistic regression models were adjusted for child's gender, weight, maternal education, BMI, average household income and HFIAS categories in stunting models; child's gender, age, maternal education, BMI, average household income and HFIAS categories in the wasting models; and child's gender, length, maternal education, BMI, average household income and HFIAS categories in the underweight models	OR (95% CI) Stunting: 1.78 (1.07, 2.99) Wasting: 1.18 (0.64, 2.19) Underweight: 1.63 (1.02, 2.61)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Gleason et al. (2016) Sirajdikhan and Pabna Upazilas Bangladesh 2008–2011 (2010–2013) Cohort	n: 618 Children of mother's from Sirajdikhan and Pabna Upazilas of Bangladesh between 2008 and 2011; Between 2010 and 2013, when children were aged 12 to 40 mo, healthcare workers from Dhaka Community Hospital invited families to enroll their children in follow-up studies	Cord blood UCB were measured by ICP-MS and child's blood, collected at 20 to 40 mo, was measured by portable LeadCare II instruments Age at Measurement: at birth and 12–40 mo Median: UCB: 3.1 µg/dL Blood: 4.2 µg/dL 75th: UCB: 6.3 µg/dL Blood: 7.6 µg/dL	Postnatal growth: Stunting Stunting status of children was determined using the WHO macros (Version 3.2.2) Age at outcome: 12–40 mo	Logistic regression models were adjusted for maternal weight, maternal education, maternal protein intake, and HOME Inventory score were all modeled as continuous variables; average water As and Mn levels were included as continuous variables	OR (95% CI) UCB: 0.97 (0.93, 1.00) Blood at 20–40 mo: 1.15 (1.00, 1.33)

ALAD = δ-aminolevulinic acid dehydratase; BL = birth length; BMI = body mass index; BMIZ = BMI-for-age Z-score; BW = birth weight; BWZ = birth weight Z-score; CHECK = Children's Health and Environmental Chemicals in Korea; CI = confidence interval; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; ETS = environmental tobacco smoke; GEE = generalized estimating equation; GFAAS = graphite furnace atomic absorption spectrometry; HAZ = height-for-age Z-score; HCAZ = head circumference for age Z-score; HFIAS = Household Food Insecurity Access Scale; HOME = Health Outcomes and Measures of the Environment; hr = hour(s); ICP-MS = inductively coupled plasma mass spectrometry; ICP-QQQ = inductively coupled plasma triple quad; K-XRF = K-shell X-ray fluorescence; LBW = low birth weight; MAL-ED = Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development; MIREC = Maternal-Infant Research on Environmental Chemicals; mo = month(s); MOCEH = Mothers' and Children's Environmental Health; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PIR = poverty-income ratio; PROGRESS = Programming Research in Obesity, Growth, Environment and Social Stressors; SD = standard deviation; T# = tertile #; UCB = umbilical cord blood; WAZ = weight for age Z-score; WC = waist circumference; WHO = World Health Organization; wk = week(s); yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. 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.

[b]Pb measurements were converted from µg/L to µg/dL.

[c]Effect estimates unable to be standardized.

[d]No CI reported.

Table 8-11 Animal toxicological studies of Pb exposure and development

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Graham et al. (2011)	**Rat (Sprague-Dawley)** Control (vehicle), M/F, n = 14–16 (7–8/7–8) 1 mg/kg Pb, M/F, n = 14–16 (7–8/7–8) 10 mg/kg Pb, M/F, n = 14–16 (7–8/7–8)	PND 4 to 28	Offspring were dosed via gavage every other day from PND 4 until PND 28.	PND 29 0.267 µg/dL for control 3.27 µg/dL for 1 mg/kg 12.5 µg/dL for 10 mg/kg	Offspring Body Weight
de Figueiredo et al. (2014)	**Rat (Wistar)** 28 d old Control (untreated), M, n = 10 60 d old Control (untreated), M, n = 12 28 d old 30 mg/L Pb, M, n = 10 60 d old Control (assumed untreated), M, n = 12 60 d old 30 mg/L Pb, M, n = 17	PND 0 to PND 28 or PND 0 to PND 60	Male Wistar rats were dosed via drinking water from birth to PND 28 or 60.	PND 28 1.2 µg/dL for control 8.0 µg/dL 30 mg/L Pb PND 60 1.6 µg/dL for control 7.2 µg/dL for 30 mg/L Pb	Offspring Body Weight
Duan et al. (2017)	**Mouse (CD-1)** Dams Control (0 ppm Pb), F, n = 3 Low dose (27 ppm Pb), F, n = 3 High dose (109 ppm Pb), F, n = 3 Pups Control (0 ppm Pb), NR, n = 9 Low dose (27 ppm Pb), NR, n = 9	PND 1 to PND 21	Dams were dosed via drinking water starting on GD 1 and continued through weaning (PND 21).	Pups: PND 1 1.29 µg/dL for control 1.29 µg/dL for low dose 1.29 µg/dL for high dose PND 18 1.62 µg/dL for control 19.6 µg/dL for low dose	Offspring Body Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
	High dose (109 ppm Pb), NR, n = 9			29.16 µg/dL for high dose PND 35 1.51 µg/dL for control 28.7 µg/dL for low dose 38.0 µg/dL for high dose	
Betharia and Maher (2012)	**Rat (Sprague-Dawley)** Dams Control (untreated), F, n = 6 10 µg/mL Pb, F, n = 6 Pups Control (untreated), M/F, n = 36–48 (18–24/18–24) 10 µg/mL Pb, M/F, n = 36–48 (1824/18–24)	GD 0 to PND 20	Dams dosed via drinking water starting on GD 0 through weaning (PND 20).	Pups: PND 2 0.188 µg/dL for control 9.03 µg/dL for 10 µg/mL Pb PND 25 0.0880 µg/dL for 0 µg/mL 0.976 µg/dL for 10 µg/mL Pb PND 60 0.0244 µg/dL for control 0.0318 µg/dL for 10 µg/mL Pb	Offspring Body Weight
Zhao et al. (2021)	**Rat (Sprague-Dawley)** Control (untreated), F, n = 6 dams 109 ppm Pb, F, n = 6 dams	GD −14 to PND 10	Dams were dosed via drinking water starting 2 wk prior to mating and continued until PND 10.	Pups: PND 0 0.87 µg/dL for control 48.2 µg/dL for 109 ppm Pb	Offspring Body Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
				PND 10 0.87 µg/dL for control 11.5 µg/dL for 109 ppm Pb PND 21 0.87 µg/dL for control 2.81 µg/dL for 109 ppm Pb PND 30 0.87 µg/dL for control 1.20 µg/dL for 109 ppm Pb	
Rao Barkur and Bairy (2016)	**Rat (Wistar)** Control (untreated), F, n = 6 dams 0.2% Pb Pregestation Only, n = 6 dams 0.2% Pb Gestation Only, n = 6 dams 0.2% Pb Lactation Only, n = 6 dams 0.2% Pb Gestation and Lactation, F, n = 6 dams	GD −30 to GD −1; GD 0 to GD 21; PND 1 to PND 21; GD 0 to PND 21	Dams were dosed via drinking water for varying amounts of time: Pregestation Only (1 mo prior to conception), Gestation Only (21 d), Lactation Only (21 d), and Gestation and Lactation (42 d).	Pups (PND 22): 0.19 µg/dL for control 3.03 µg/dL for 0.2% Pb in Pregestation Only group 5.51 µg/dL for 0.2% Pb in Gestation Only group 26.86 µg/dL for 0.2% Pb in Lactation Only group 31.59 µg/dL for 0.2% Pb in Gestation and Lactation group	Offspring Body Weight, Pinna Detachment, Eye Opening, Tooth Eruption
Barkur and Bairy (2015)	**Rat (Wistar)** Control (untreated), F, n = 6 dams	GD −30 to GD −1, or GD 0 to 21, or PND 0 to 21, or GD 0 to PND 21	Dams were dosed via drinking water for varying amounts of time:	Pups (PND 22): 0.18 µg/dL for control	Offspring Body Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
	0.2% Pb Pregestation Only, n = 6 dams 0.2% Pb Gestation Only, n = 6 dams 0.2% Pb Lactation Only, n = 6 dams 0.2% Pb Gestation and Lactation, F, n = 6 dams		Pregestation Only (1 mo prior to conception), Gestation Only (21 d), Lactation Only (21 d), and Gestation and Lactation (42 d).	3.02 µg/dL for 0.2% Pb in Pregestation Only group 5.30 µg/dL for 0.2% Pb Gestation Only group 26.7 µg/dL for 0.2% Pb in Lactation Only group 32.0 µg/dL for 0.2% Pb in Gestation and Lactation group	
Sobolewski et al. (2020)	**Mouse (C57BL/6)** Control (untreated) F, n = 10, 100 ppm Pb, F, n = 10	GD −61 to PND 21 of F1 only	Dams were dosed via drinking water beginning 2 mo prior to breeding and ending on PND 21 of the F1 (weaning).	F1 PND 6–7 0.0 µg/dL for control, 12.5 µg/dL for 100 ppm Pb F3 Postnatal Mo 6–7 0.0 µg/dL for control, 0.4 µg/dL for 100 ppm Pb	Offspring Body Weight
Albores-Garcia et al. (2021)	**Rat (Long-Evans)** Evaluated on PND 14 Controls (untreated), F, n = 11 dams Controls (untreated), M/F, n = 14 (7/7) pups 1500 ppm Pb, F, n = 7 dams 1500 ppm Pb, M/F, n = 13 (6/7) pups Evaluated on PND 28 Controls (untreated), F, n = 9 dams	Continuous exposure starting at GD −10	Dams were dosed via the diet starting 10 d prior to mating. After weaning (PND 21), offspring were put onto the same diet as their dams.	Pups PND 14 <1.9 µg/dL for control males <1.9 µg/dL for control females 36.1 µg/dL for 1500 ppm Pb males 37 µg/dL for 1500 ppm Pb females	Offspring Body Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
	Controls (untreated), M/F, n = 16 (8/8) pups 1500 ppm Pb, F, n = 8 dams 1500 ppm Pb, M/F, n = 13 (7/6) pups Evaluated on PND 50 Controls (untreated), F, n = 15 dams Controls (untreated), M/F, n = 15 (7/8) pups 1500 ppm Pb, F, n = 14 dams 1500 ppm, M/F, n = 15 (7/6) pups Evaluated on PND 120 Controls (untreated), F, n = 13 dams Control (untreated), M/F, n = 13 (7/6) pups 1500 ppm Pb, F, n = 9 dams 1500 ppm Pb, M/F, n = 12 (6/6) pups			PND 28 <1.9 µg/dL for control males <1.9 µg/dL for control females 21.1 µg/dL for 1500 ppm Pb males 20.9 µg/dL for 1500 ppm Pb females PND 50 <1.9 µg/dL for control males <1.9 µg/dL for control females 20.2 µg/dL for 1500 ppm Pb males 22.1 µg/dL for 1500 ppm Pb females PND 120 <1.9 µg/dL for control males <1.9 µg/dL for control females 19.6 µg/dL for 1500 ppm Pb males 24.3 µg/dL for 1500 ppm Pb females	
Basgen and Sobin (2014)	**Mouse (C57BL/6)** Control (untreated), M/F, n = 12 (6/6)	PND 0 to PND 28	Dams were dosed via drinking water from birth of	PND 28 0.03 µg/dL for control males	Offspring Body Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
	30 ppm Pb, M/F, n = 12 (6/6) 330 ppm Pb, M/F, n = 12 (6/6)		offspring until PND 28.	0.03 µg/dL for control females 3.63 µg/dL for 30 ppm Pb males 2.74 µg/dL for 30 ppm Pb females 16.02 µg/dL for 330 ppm Pb males 13.35 µg/dL for 330 ppm Pb females	
Barkur et al. (2011)	**Rat (Wistar)** Control (untreated), F, n = 6 dams 0.2% Pb, F, n = 6 dams	GD 1 to PND 21	Dams were dosed via drinking water from GD 1 to PND 21. Only male pups were retained for measurements of body weight.	Pups (males only): PND 22 0.266 µg/dL for control 31.2 µg/dL for 0.2% Pb PND 120 0.234 µg/dL for control 0.468 µg/dL for 0.2% Pb	Offspring Body Weight
Basha and Reddy (2015)	**Rat (Wistar)** Control (untreated), F, n = 8 dams 0.2% Pb, F, n = 8 dams	GD 6 to 21	Dams were dosed via drinking water from GD 6 to PND 21. Only male pups were retained for measurements of body weight and	Pups (males only): PND 21 0.21 µg/dL for control 11.2 µg/dL for 0.2% Pb PND 28	Pinna Detachment, Tooth Eruption, Fur Development, Eye Slit Formation, Eye Opening,

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
			developmental milestones.	0.33 µg/dL for control 12.3 µg/dL for 0.2% Pb Postnatal Mo 4 0.19 µg/dL for control 5.9 µg/dL for 0.2% Pb	Offspring Body Weight, Offspring Body Size

BLL = blood lead level; d = day(s); GD = gestational day; F = female; M = male; mo = month(s); NR = not reported; Pb = lead; PND = postnatal day.

Table 8-12 Epidemiologic studies of exposure to Pb and puberty in females and puberty in males

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Effects on Puberty in Females					
Yao et al. (2019) United States 2011–2012 Cross-sectional	NHANES n: 426 female children, and 470 female adolescents Female children (age 6–11 yr) and female adolescents (age 12–19 yr) in NHANES 2011–2012	Blood Blood was measured by ICP-MS Age at Measurement: 6–19 yr old Geometric mean: Female children: 0.68 µg/dL Female adolescents: 0.47 µg/dL Median: Female children: 0.65 µg/dL Female adolescents: 0.47 µg/dL 75th: Female children: 0.93 µg/dL Female adolescents: 0.63 µg/dL Quartiles (µg/dL): Female children: Q1: ≤0.48 Q2: 0.48−0.65 Q3: 0.65−0.93 Q4: >0.93 Female adolescents: Q1: ≤0.35 Q2: 0.35−0.47	Puberty among females: Serum tT levels Serum tT levels were analyzed by isotope-dilution liquid chromatography-tandem mass spectrometry Age at outcome: 6–19 yr old	Weighted multivariable linear regression models; Model 1 controlled for age, race, and BMI. Model 2 controlled for PIR, seasons of collection, times of venipuncture, and serum cotinine, in addition to the covariates of model 1	β (95% CI), as percent difference in serum tT Model 1: Female children Q1: Reference Q2: 14.34 (−3.75, 35.81) Q3: −5.00 (−21.05, 14.32) Q4: −5.73 (−23.13, 15.61) p for trend: 0.36 Female adolescents Q1: Reference Q2: −8.55 (−18.52, 2.63) Q3: −1.95 (−13.04, 10.56) Q4: 13.12 (0.06, 27.88) p for trend: 0.14 Model 2: Female children Q1: Reference Q2: 14.9 (−3.54, 36.86) Q3: −0.96 (−17.80, 19.34) Q4: −2.40 (−21.00, 20.57) p for trend: 0.63 Female adolescents Q1: Reference Q2: −7.83 (−18.22, 3.88) Q3: −1.07 (−12.67, 12.06) Q4: 14.85 (0.83, 30.81) p for trend: 0.08

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Q3: 0.47−0.63 Q4: >0.63			
Sławińska et al. (2012) Legnica-Glogów District Poland 1995–2007 Cross-sectional	1995 n:436; 2007 n:346 Menarche status of schoolgirls 7–16 yr from villages in southwestern Poland was surveyed in 1995, 2001, 2004, and 2007.	Blood Blood was measured by GFAAS with a Zeeman correction for background Age at Measurement: 7–16 yr old Mean 1995: 6.57 µg/dL 2007: 4.24 µg/dL	Puberty among females: Short-term secular change in menarche Menarche through survey Age at outcome: 7–16 yr	Logistic regression models were adjusted for age, height (linear growth), BMI (weight-for-height), and Pb group (low Pb group: 2−5 µg/dL; high Pb group: 5.10–33.90 µg/dL)	OR (95% CI) 1995: 0.70 (0.27, 1.85) 2007: 0.31 (0.09, 1.06)
Gomula et al. (2022) Polkowice Poland 2008 Cross-sectional	n: 490 Girls aged 7–16 yr who were attending several schools in Polkowice in 2008.	Blood Blood was measured by AAS with Zeeman background correction Age at measurement: 7–16 yr old Mean Total: 3.6 µg/dL <3.7 µg/dL: 2.9 µg/dL ≥3.7 µg/dL: 4.4 µg/dL Median Total: 3.6 µg/dL <3.7 µg/dL: 2.8 µg/dL ≥3.7 µg/dL: 4.3 µg/dL	Puberty among females: age at menarche Menarche through survey Age at outcome: 7–16 yr old	Logistic regression models were adjusted for age and (1) BMI; (2) percent body fat; and (3) sum of skinfolds	OR (95% CI) Model with BMI: 0.54 (0.26, 1.13) Model with percent body fat: 0.52 (0.25, 1.08) Model with sum of skinfolds: 0.53 (0.26, 1.10)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
De Craemer et al. (2017) Belgium FLEHS I: 2002–2006, FLEHS II: 2007–2011, and FLEHS III: 2012–2015 Cross-sectional	FLEHS I, FLEHS II and FLEHS III n: FLEHS I: n = 1659, FLEHS II: n = 606, and FLEHS III: n = 406 Adolescents aged 14–15 yr	Blood Blood Pb was measured by ICP-MS Age at Measurement: 14–15 yr old Geometric mean[b] FLEHS I: 2.13 µg/dL FLEHS II: 1.38 µg/dL FLEHS III: 0.926 µg/dL Max[b] FLEHS I: 21.2 µg/dL FLEHS II: 7.69 µg/dL FLEHS III: 3.86 µg/dL	Puberty among females: Hormones and sexual maturation in adolescents Development of breasts in adolescent females and pubic hair was scored using the international scoring criteria of Marshall and Tanner, where stage 1 corresponds to the start of puberty and stage 5 to the adult stage. Information on menarche was obtained through self-assessed questionnaires. Age at outcome: 14–15 yr old	Logistic regression models for female pubic hair development and breast development were adjusted for age BMI, contraceptive pill usage; linear regression models for age at menarche were adjusted for age, BMI	OR (95% CI)[c] Breast development FLEHS I: 0.798 (0.653, 0.969) FLEHS II: 1.318 (0.936, 2.055) FLEHS III: 1.187 (0.886, 1.627) Pubic hair development FLEHS I: 1.113 (0.922, 1.349) FLEHS II: 1.322 (0.938, 2.083) FLEHS III: 0.919 (0.677, 1.229) β (95% CI)[c] Age of menarche FLEHS I: 0.039 (−0.072, 0.15) FLEHS II: 0.257 (0.091, 0.424) FLEHS III: 0.126 (−0.021, 0.273)
Nkomo et al. (2018) Johannesburg South Africa Cohort	BT20+ birth cohort n: 683 Singleton births in which the infant resides in Johannesburg area for at least 6 mo after birth; participants must have data for BLL at age 13 and pubertal	Blood and cord blood UCB collected at birth and blood at collected at age 13 were measured by AAS with a Zeeman background correction Age at Measurement: birth and age 13	Puberty among females: Pubertal trajectory classes Tanner stages of pubertal development refer to a standard clinical method used to describe physical measurements of secondary sexual characteristics using	Multinomial logistic regression was used to predict pubertal growth trajectory class based on BLLs at age 13 yr and cord BLLs adjusted for ethnicity and height at age 8	RR (95% CI) Development of pubic hair UCB Blood, ≥5 µg/dL vs. <5 µg/dL Trajectory Class 1: Reference Trajectory Class 2: 0.45 (0.29, 0.68)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	growth trajectory classes	Mean (SD) UCB: 5.8 (2.1) µg/dL Blood: 5.0 (1.9) µg/dL Median UCB: 6.0 µg/dL Blood: 4.8 µg/dL 75th UCB: 7.0 µg/dL Blood: 7.9 µg/dL	drawings to signal stage of pubertal development where stage 1 signifies lowest level of pubertal maturation and stage 5 denotes highest level of pubertal maturation in girls Age at outcome: 9–16 yr old		Trajectory Class 3: 0.55 (0.26, 1.17) Development of breasts Blood, ≥5 µg/dL vs. <5 µg/dL Trajectory Class 1: Reference Trajectory Class 2: 0.72 (0.47, 1.11) Trajectory Class 3: 0.63 (0.42, 0.94) Trajectory Class 4: 0.46 (0.27, 0.77)
Liu et al. (2019b) Mexico City Mexico Cohort	n: 547 (283 girls and 264 boys) Pregnant women were recruited at three public maternity hospitals (Manuel Gea Gonzalez Hospital, Mexican Social Security Institute and the National Institute of Perinatology) in Mexico City; and Children at age 9.8–18.0 yr who had at least one measurement of maternal bone Pb or childhood blood Pb	Blood and bone Maternal bone, measured at the mid-tibial shaft (cortical bone) and patella (trabecular bone) was measured by K-XRF instrument; blood samples from children were measured by GFAAS Age at Measurement: Maternal age 1-mo postpartum; blood measured between 1 and 4 yr Median Patella: 8.20 µg/g Tibia: 7.63 µg/g Blood, cumulative 1–4 yr: 13.83 µg/dL 75th	Puberty among females: Pubertal stages In girls, the stages of pubertal development were defined by a pediatrician using Tanner staging scales for the breast maturation and pubic hair growth. Menarche was measured via a self-reported questionnaire. Age at outcome: 9.8–18 yr	Ordinal regression models were adjusted for child age at visit, maternal education and marital status, and number of siblings at birth; Cox proportional hazard regression models were adjusted for number of siblings at birth, maternal education, and marital status	OR (95% CI), per IQR increase in Pb Breast development Patella: 0.79 (0.61, 1.01) Tibia: 1.01 (0.75, 1.36) Blood, cumulative 1–4 yr: 0.96 (0.92, 0.99) Pubic hair development Patella: 0.96 (0.76, 1.22) Tibia: 1.12 (0.84, 1.49) Blood, cumulative 1–4 yr: 0.95 (0.92, 0.99) HR (95% CI) Patella Continuous: 0.16 (0.02, 1.07) T1: Reference T2: 1.10 (0.76, 1.58)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Patella: 15.45 µg/g Tibia: 13.80 µg/g Blood, cumulative 1–4 yr: 18.76 µg/dL IQR Patella: 13.57 µg/g Tibia: 13.30 µg/g Blood, cumulative 1–4 yr: 7.66 µg/dL Tertiles Patella (µg/g) T1: <3.9 T2: 4.0–12.9 T3: 13.0–45.3 Tibia (µg/g) T1: <4.6 T2: 4.7–11.3 T3: 11.4–37.3 Blood, cumulative 1–4 yr (µg/dL) T1: <12.0 T2: 12.1–16.1 T3: 16.2–51.5			T3: 0.60 (0.41, 0.88) Tibia Continuous: 1.11 (0.12, 9.84) T1: Reference T2: 1.30 (0.86, 1.96) T3: 1.14 (0.75, 1.72) Blood, cumulative 1–4 yr Continuous: 0.91 (0.77, 1.08) T1: Reference T2: 0.65 (0.46, 0.91) T3: 0.76 (0.55, 1.06)
Jansen et al. (2018) Mexico City Mexico 1997–2004 (2015) Cohort	ELEMENT project n: 200 Mothers were recruited from prenatal clinics of the Mexican Social Security Institute in Mexico City who were not planning to leave the area	Blood Maternal blood was measured by GFAAS Age at Measurement: maternal age at sampling Median	Puberty among females: Menarche Girls were asked about menarche during the follow-up visit (between age 9.8 and 18.1 yr). They were asked whether or not menarche had occurred (Yes, no, or	Interval-censored Cox regression models, comparing the hazard of menarche among girls with prenatal maternal blood Pb ≥5 µg/dL to those with prenatal maternal BLL <5 µg/dL, were adjusted for maternal	HR (95% CI) Interval-censored Cox models First trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.85 (0.46, 1.24)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	within 5 yr; had a history of infertility, diabetes, or psychosis; consuming alcoholic beverages daily during pregnancy; addiction to illegal drugs; diagnosis of a high-risk pregnancy; or being pregnant with multiples	First trimester: 4.8 µg/dL Second trimester: 4.0 µg/dL Third trimester: 4.5 µg/dL 75th: First trimester: 7.1 µg/dL Second trimester: 6.4 µg/dL Third trimester: 6.6 µg/dL	don't know/refused) and, if so, to recall the age (in years and months) it occurred. Age at outcome: age of menarche	age, maternal parity, maternal education, and prenatal calcium treatment status; Cox regression models, using self-reported age at menarche as the time to event, were adjusted for maternal age, maternal parity, maternal education, and prenatal calcium treatment status; Cox regression models were also restricted to girls <14.5 yr at the time of the interview and adjusted for maternal age, maternal parity, maternal education, and prenatal calcium treatment status	Second trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.59 (0.28, 0.90) Third trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.85 (0.42, 1.27) Cox models First trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.92 (0.65, 1.29) Second trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.91 (0.65, 1.27) Third trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.97 (0.69, 1.37) Cox models restricted to girls <14.5 yr at interview First trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.80 (0.52, 1.25) Second trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.64 (0.38, 1.09)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Third trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.89 (0.56, 1.41)
Effects on Puberty Among Males					
Yao et al. (2019) United States 2011–2012 Cross-sectional	NHANES n: 431 male children, 493 male adolescents Male children (age 6–11 yr) and male adolescents (age 12–19 yr) in NHANES 2011–2012	Blood Blood was measure by ICP-MS Age at Measurement: 6–19 yr old Geometric mean Male children: 0.76 µg/dL Male adolescents: 0.68 µg/dL Median Male children: 0.72 µg/dL Male adolescent: 0.66 µg/dL 75th Male children: 1.02 µg/dL Male adolescents: 0.96 µg/dL Quartiles (µg/dL): Male children: Q1: ≤0.52 Q2: 0.52−0.72 Q3: 0.72–1.02 Q4: >1.02 Male adolescents: Q1: ≤0.47	Puberty among males: Serum tT levels in male children and adolescents Serum tT levels were analyzed by isotope-dilution liquid chromatography-tandem mass spectrometry Age at outcome: 6–19 yr old	Weighted multivariable linear regression models; Model 1 controlled for age, race, and BMI. Model 2 controlled for PIR, seasons of collection, times of venipuncture, and serum cotinine, in addition to the covariates of model 1	β (95% CI), as percent difference in serum tT Model 1: Male children Q1: Reference Q2: 4.1 (−18.47, 32.9) Q3: −6.13 (−27.64, 21.77) Q4: −12.83 (−33.68, 14.58) p for trend: 0.36 Male adolescents Q1: Reference Q2: −3.36 (−20.98, 18.2) Q3: 14.99 (−7.77, 43.37) Q4: 15.62 (−7.07, 43.86) p for trend: 0.18 Model 2: Male children Q1: Reference Q2: 11.75 (−13.06, 43.65) Q3: −4.63 (−26.97, 24.55) Q4: −13.09 (−34.45, 15.22) p for trend: 0.42 Male adolescents Q1: Reference Q2: −4.35 (−21.22, 16.14)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Q2: 0.47−0.66 Q3: 0.66−0.96 Q4: >0.96			Q3: 8.15 (−12.91, 34.3) Q4: 6.32 (−14.62, 32.4) p for trend: 0.58
De Craemer et al. (2017) Belgium FLEHS I: 2002–2006, FLEHS II: 2007–2011, and FLEHS III: 2012–2015 Cross-sectional	FLEHS I, FLEHS II and FLEHS III FLEHS I n: 1659, FLEHS II n: 606, and FLEHS III n: 406 Adolescents aged 14–15 yr	Blood Blood was analyzed by ICP-MS Age at Measurement: 14–15 yr old Geometric mean[b] FLEHS I: 2.13 µg/dL FLEHS II: 1.38 µg/dL FLEHS III: 0.926 µg/dL Max[b]: FLEHS I: 21.2 µg/dL FLEHS II: 7.69 µg/dL FLEHS III: 3.86 µg/dL	Puberty among males: Hormones and sexual maturation in adolescents Development of genitals in adolescent males and pubic hair was scored using the international scoring criteria of Marshall and Tanner, where stage 1 corresponds to the start of puberty and stage 5 to the adult stage. Sex hormones investigated in this study were E2, testosterone, fE2 and fT, SHBG, LH, and FSH. Hormone levels in adolescent males were measured in blood serum using commercial immunoassays. Age at outcome: 14–15 yr old	Logistic regression models for male public hair development and genital development were adjusted for age and BMI; linear regression models for hormones (ratio T/E2, E2, fE2, T, fT) were adjusted for age, hr of blood collection, BMI, smoking status; SHBG: age, fasting, BMI, smoking status, hr of blood collection; LH and FSH: age, BMI, smoking status	OR (95% CI)[c] Pubic hair development FLEHS I: 0.808 (0.686, 0.949) FLEHS II: 0.849 (0.563, 1.365) FLEHS III: 0.515 (0.327, 0.774) Genital development FLEHS I: 0.843 (0.717, 0.99) FLEHS II: 0.697 (0.462, 0.998) FLEHS III: 0.621 (0.388, 0.967) β (95% CI)[c] FLEHS I: Ratio T/E2: 1.022 (0.985, 1.059) E2: 1.011 (0.991, 1.031) fE2: 1.003 (0.975, 1.033) T: 1.039 (0.993, 1.087) fT: 1.026 (0.967, 1.09) SHBG: 1.024 (0.992, 1.056) LH: 0.995 (0.959, 1.033) FLEHS II: ratio T/E2: 1.002 (0.958, 1.049)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					E2: 0.968 (0.923, 1.016) fE2: 0.908 (0.839, 0.983) T: 0.959 (0.906, 1.015) fT: 0.909 (0.828, 0.997) SHBG: 1.005 (0.961, 1.052) LH: 0.974 (0.923, 1.028) FSH: 0.995 (0.942, 1.05)
Nkomo et al. (2018) Johannesburg South Africa Cohort	BT20+ birth cohort n: 683 Singleton births in which the infant resides in Johannesburg area for at least 6 mo after birth; participants must have data for BLL at age 13 and pubertal growth trajectory classes	Blood and cord blood UCB collected at birth and blood at collected at age 13 were measured by AAS with a Zeeman background correction Age at Measurement: birth and age 13 Mean (SD) UCB: 5.9 (2.0) µg/dL Blood: 6.6 (2.6) µg/dL Median UCB: 6.0 µg/dL Blood: 6.5 µg/dL 75th UCB: 7.0 µg/dL Blood: 6.0 µg/dL	Puberty among males: Pubertal trajectory classes Tanner stages of pubertal development refer to a standard clinical method used to describe physical measurements of secondary sexual characteristics using drawings to signal stage of pubertal development where stage 1 signifies lowest level of pubertal maturation and stage 5 denotes highest level of pubertal maturation in boys Age at outcome: 9–16 yr old	Multinomial logistic regression models were used to predict pubertal growth trajectory class based on (1) UCB Pb and adjusted for ethnicity; (2) blood Pb and adjusted for ethnicity and height at age 8	RR (95% CI) UCB Pubic hair development Trajectory Class 1: Reference Trajectory Class 2: 0.61 (0.25, 1.43) Trajectory Class 3: 0.28 (0.11, 0.74) Genital development Trajectory Class 1: Reference Trajectory Class 2: 0.27 (0.03, 2.26) Trajectory Class 3: 0.24 (0.03, 1.89) Trajectory Class 4: 0.13 (0.01, 1.24) Blood Pubic hair development Trajectory Class 1: Reference Trajectory Class 2: 0.94 (0.63, 1.39)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Trajectory Class 3: 1.35 (0.73, 2.47) Genital development Trajectory Class 1: Reference Trajectory Class 2: 0.77 (0.33, 1.77) Trajectory Class 3: 0.88 (0.38, 2.01) Trajectory Class 4: 1.02 (0.37, 2.83)
Liu et al. (2019b) Mexico City Mexico Cohort	n: 547 (283 girls and 264 boys) Pregnant women were recruited at three public maternity hospitals (Manuel Gea Gonzalez Hospital, Mexican Social Security Institute and the National Institute of Perinatology) in Mexico City; and Children at age 9.8–18.0 yr who had at least one measurement of maternal bone Pb or childhood blood Pb	Blood and bone Maternal bone was measured at the mid-tibial shaft (cortical bone) and patella (trabecular bone) and determined using the X-ray fluorescence instrument; blood samples from children were measured by GFAAS Age at Measurement: Maternal age 1-mo postpartum; blood measured between 1 and 4 yr Median Patella: 7.44 µg/g Tibia: 7.10 µg/g Blood, cumulative 1–4 yr: 14.33 µg/dL 75th Patella: 14.56 µg/g	Puberty among males: Pubertal stages In boys, the stage of sexual maturation was defined by the pediatrician using Tanner staging scales for the development of genitalia and pubic hair. Age at outcome: 9.8–18 yr	Ordinal regression models for genitalia and pubic hair and logistic regression models for TV were adjusted for adjusted for child age at visit, maternal education and marital status, and number of siblings at birth	OR (95%), per IQR increase in Pb Genital development Patella: 0.963 (0.734, 1.264) Tibia: 1.00 (0.711, 1.406) Blood, cumulative 1–4 yr: 0.995 (0.948, 1.044) Pubic hair development Patella: 1.094 (0.836, 1.432) Tibia: 1.00 (0.715, 1.398) Blood, cumulative 1–4 yr: 1.004 (0.969, 1.04) TV Patella: 1.158 (0.804, 1.667) Tibia: 0.885 (0.503, 1.558) Blood, cumulative 1–4 yr: 1.013 (0.954, 1.075)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Tibia: 15.93 µg/g Blood, cumulative 1–4 yr: 18.90 µg/dL IQR Patella: 13.57 µg/g Tibia: 13.30 µg/g Blood, cumulative 1–4 yr: 7.66 µg/dL			
Williams et al. (2019) Chapaevsk Russian 2003–2005 (2017) Cohort	Russian Children's Study n: 516 Healthy male children who were 8–9 yr old between 2003 and 2005 in Chapaevsk, Russia.	Blood Blood was measured by Zeeman background corrected flameless GFAAS Age at Measurement: 8–9 yr old Median: 3 µg/dL Max: 31 µg/dL	Puberty among males: Male sexual maturity Pubertal status was staged from 1 to 5 via examination by a single clinician according to internationally accepted criteria. Pubarche (pubic hair stage, P) was determined by the extent of terminal hair growth. Genital staging (G) was assessed by genital size and maturity. TV was measured using an orchidometer. Three different measures of sexual maturity were considered as separate indicators: TV ≥20 mL of either testis, genitalia stage 5 (G5), and pubic hair stage 5 (P5). Duration of pubertal progression was defined as time from pubertal onset (TV >3 mL, genitalia stage ≥2 (G2),	Interval-censored models were fit assuming a normal distribution for age at sexual maturity using accelerated failure time models to compare pubertal outcomes between boys with 'higher' (≥5 µg/dL) versus 'lower' (<5 µg/dL) peripubertal BLLs. Models were adjusted for boy's BW, prenatal exposure to maternal alcohol and tobacco, maternal age at son's birth, household characteristics including income level, parental education, and whether the biological father lived in the same household, the boy's physical activity, and his nutritional status determined by caloric	β (95% CI)[c], as shift in mean age in months Age at pubertal onset Genitalia (G2): 8.40 (3.70, 13.10) Pubic hair (P2): 8.12 (3.46, 12.78) TV (>3 mL): 7.68 (3.46, 11.90) Age at sexual maturity Genitalia (G5): 4.20 (0.56, 7.84) Pubic hair (P5): 4.23 −0.31, 8.77) TV (≥20 mL): 5.14 (1.70, 8.58) Duration of puberal progression Genitalia (G2 to G5): −3.76 (−7.93, 0.42) Pubic hair (P2 to P5): −1.82 (−6.91, 3.28) TV (>3 mL to ≥20 mL): −1.19 (−4.92, 2.54)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
			pubic hair stage ≥2 (P2), respectively) to sexual maturity, separately for each pubertal indicator. Age at outcome: age at follow-up in 2017	intake and percent of fat and protein intake. Mediation analysis was conducted to partition the effect of higher vs. lower BLLs on the age at sexual maturity into a direct effect of Pb exposure and indirect effect of Pb acting through HTZ and BMIZ (mediators) at age 11.	Mediation Analysis, as % of total HTZ G5: 53.0% (β: 2.37 mo) P5: 47.5% (β: 2.36 mo) TV ≥20 mL: 34.2% (β: 1.78 mo) BMIZ G5: 14.3% (β: 0.64 mo) P5: 23.4% (β: 1.16 mo) TV ≥20 mL: 6.1% (β: 0.32 mo)
Fleisch et al. (2013) Chapaevsk Russia 2003–2005 Follow-up: 2-yr (at 10–11 yr) and 4–yr (at 12–13 yr) Cohort	Russian Children's Study n: 394 Boys ages 8–9 yr old from Chapaevsk, Russia	Blood Blood was measured by Zeeman background corrected flameless GFAAS Age at Measurement: 8–9 yr old Median: 3 µg/dL 75th: 5 µg/dL Max: 31 µg/dL	Puberty among males: IGF-1 Serum IGF-1 concentrations were measured by a chemiluminescent immunometric assay using Siemens Immulite 2000. Age at outcome: 10–11 yr (at 2-yr follow-up); 12–13 (at 4-yr follow-up)	Linear regression models using a GEE approach to account for the repeated measures were fitted to predict the mean levels of serum concentrations of IGF-1 (ng/mL) in relation to BLLs, adjusted for baseline parental education, BW, nutritional intake, and baseline and follow-up age and BMI	β (95% CI)[c], as adjusted mean change BLL <5 µg/dL: Reference BLL ≥5 µg/dL: −29.2 ng/mL (−43.8, −14.5) Pre-puberty BLL <5 µg/dL: Reference BLL ≥5 µg/dL: −14.1 ng/mL (−0.9, −27.2) Early puberty: BLL <5 µg/dL: Reference BLL ≥5 µg/dL: −18.0 (−3.5, −32.5) Mid-puberty BLL <5 µg/dL: Reference BLL ≥5 µg/dL: −41.9 ng/mL (−15.1, −68.7)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]

AAS = atomic absorption spectrometry; BMI = body mass index; BMIZ = BMI-for-age Z-score; BT20+ = Birth to Twenty Plus; BW = birth weight; E2 = estradiol; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; fE2 = free estradiol; FLEHS = Flemish Environment and Health Study; FSH = follicle stimulating hormone; fT = free testosterone; GEE = generalized estimating equation; GFAAS = graphite furnace atomic absorption spectrometry; HR = hazard ratio; HTZ = height Z-score; ICP-MS = inductively coupled plasma mass spectrometry; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; mo = month(s); NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PIR = poverty-income ratio; RR = relative risk; SD = standard deviation; SHBG = sex hormone binding globulin; T = testosterone; tT = total testosterone; TV = testicular volume; UCB = umbilical cord blood; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. 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.

[b]Pb measurements were converted from µg/L to µg/dL.

[c]Effect estimates unable to be standardized.

Table 8-13 Epidemiologic studies of exposure to Pb and other developmental effects

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Alegría-Torres et al. (2020) Salamanca Mexico Cross-sectional	n: 86 Healthy children 6–15 yr of age were recruited from four primary schools	Blood Blood was measured by ICP-MS Age at Measurement: 6–15 yr old Mean (SD): 3.78 (3.73) µg/dL Max: 22.61 µg/dL	Other developmental effects: Telomeric lengthening and mtDNA effects DNA was isolated from peripheral blood and rTL and the mtDNAcn were determined by real-time polymerase chain reaction Age at outcome: 6–15 yr old	Linear regression analyses; TL models were adjusted for mtDNAcn, sex, age, and total white blood cell count; mtDNAcn models adjusted for TL, sex, age, and total white blood cell count	β (95% CI)[b] TL: 0.088 (−0.027, 0.097) mtDNAcn: −0.198 (−2.81, −0.17)
Tamayo y Ortiz et al. (2016) Mexico City Mexico 2007–2011 Cohort	PROGRESS birth cohort n: 255 for 12 mo n: 150 for 18–24 mo Women were invited to participate during their prenatal care visits at 4 clinics belonging to the Mexican Social Security System	Blood and bone Maternal blood, collected twice during pregnancy (second and third trimesters), was measured by ICP-MS. Maternal bone, from the mid-tibial shaft, was measured using a K-XRF instrument during the first month postpartum visit Age at Measurement: Maternal age at second trimester, third trimester, and 1 mo postpartum Mean 2nd trimester blood for 12-mo-old infants: 3.5 µg/dL	Other developmental effects: Cortisol levels Four saliva samples per day from their child at home; saliva samples were analyzed in duplicate using a chemiluminescence-assay Age at outcome: 12 or 18–24 mo	Longitudinal functional mixed effects regression models with penalized splines were adjusted for child's sex and maternal age at delivery, education, and pre-pregnancy BMI	β (95% CI)[b] 12-mo infants Second trimester maternal blood Lower Pb: Reference Moderate Pb: −0.07 (−0.24, 0.10) Higher Pb: −0.51 (−0.85, −0.18) Third trimester maternal blood Lower Pb: Reference Moderate Pb: −0.14 (−0.31, 0.03) Higher Pb: −0.02 (−0.31, 0.26) Tibia Lower Pb: Reference

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		2nd trimester blood for 18–24-mo-old infants: 3.9 µg/dL 3rd trimester blood for 12-mo-old infants: 3.7 µg/dL 3rd trimester blood for 18–24-mo-old infants: 4.2 µg/dL Tibia for 12-mo-old infants: 5.6 µg/g Tibia for 18–24-mo-old infants: 4.9 µg/g Tertiles Lower Pb: <5 µg/dL Moderate Pb: 5 ≤ Pb <10 µg/dL High Pb: ≥10 µg/dL			Moderate Pb: 0.02 (−0.14, 0.19) Higher Pb: −0.03 (−0.21, 0.14) 18–24-mo infants Second trimester maternal blood Lower Pb: Reference Moderate Pb: 0.11 (−0.08, 0.30) Higher Pb: 0.23 (−0.19, 0.65) Third trimester maternal blood Lower Pb: Reference Moderate Pb: 0.01 (−0.17, 0.20) Higher Pb: −0.05 (−0.51, 0.41) Tibia Lower Pb: Reference Moderate Pb: 0.10 (−0.13, 0.32) Higher Pb: 0.14 (−0.08, 0.35)
Hou et al. (2020) Guiyu and Haojiang China November–December 2017 Cross-sectional	n: 574 (357 from Guiyu and 217 from Haojiang) Children 2.5–6 yr of age that lived in Guiyu, an e-waste contaminated town or Haojiang, a city with	Blood Blood was measured by GFAAS Age at Measurement: 2.5–6 yr old Median	Other developmental effects: Oral anti-inflammatory potential Participants were instructed to sit up straight and slightly forward in their chair. A sputum cup was used to collect the saliva. Decayed	Multivariable linear regression model adjusted for gender, age, BMI, outdoor activities, the sucking/biting of toys and pencils, diet (sweet consumption, bean products, marine products), family member smoking,	β (95% CI)[b]: −3.65 (−8.07, 0.77)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	similar culture but no e-waste recycling activity	Reference group: 3.47 µg/dL Exposed group: 4.86 µg/dL 75th Reference group: 4.07 µg/dL Exposed group: 4.86 µg/dL	deciduous teeth were detected under natural and artificial light. The concentration of salivary sialic acids was determined using a quantitative competitive ELISA kit. Age at outcome: 2.5–6 yr old	paternal education levels, monthly household income	
Sitarik et al. (2020) Detroit, MI United States September 2003–December 2007 (December 2011–September 2019) Cohort	WHEALS birth cohort n: 146 All women were in their second trimester or later, were aged 21–49 yr, and were living in a predefined geographic area in Wayne and Oakland counties of Michigan. Teeth were selected for metal measurement if (1) the child had at least some outcome data available (birth outcomes and/or a 2-yr clinic visit) or early life microbiome data; and (2) the tooth sample met laboratory quality control/quality assurance guidelines	Teeth Teeth were measured by LA-ICP-MS. Teeth were sectioned, and the neonatal line (a histological feature formed in enamel and dentine at the time of birth) and incremental markings were used to assign temporal information to sampling points. Second trimester, third trimester, postnatal (birth through 1 yr), and childhood (age 1 to tooth shedding) Pb levels. Age at measurement: Estimated exposure from 2nd trimester, 3rd trimester, and postnatally (<1 yr of age)	Other developmental effects: Gut microbiota (in infants) Families were asked to retain the most recent soiled diaper prior to the home visit and stool samples from infants ages 1–6 mo. Age at outcome: 1–6 mo	Permutational multivariate analysis of variance models were adjusted for tooth type, tooth attrition, tooth batch, exact age at stool sample collection, and child race	β (SE)[b] Alpha diversity metrics Second trimester Richness - Bacterial 1 mo: 5.53 (6.98) 6 mo: −7.77 (7.31) Richness – Fungal 1 mo: 0.29 (1.65) 6 mo: 1.7 (1.51) Evenness – Bacterial 1 mo: 0 (0.01) 6 mo: −0.02 (−0.01) Evenness – Fungal 1 mo: 0.03 (0.05) 6 mo: −0.02 (0.05) Faith's Diversity – Bacterial 1 mo: 0.16 (0.39) 6 mo: −0.19 (0.37) Faith's Diversity – Fungal 1 mo: Not reported 6 mo: Not reported

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Shannon Diversity – Bacterial 1 mo: 0.01 (0.08) 6 mo: −0.11 (0.07) Shannon Diversity – Fungal 1 mo: 0.06 (0.15) 6 mo: 0 (0.14) Third trimester Richness - Bacterial 1 mo: 2.52 (6.37) 6 mo: −13.11 (8.36) Richness – Fungal 1 mo: 0.69 (1.82) 6 mo: 2.54 (1.56) Evenness – Bacterial 1 mo: −0.01 (0.01) 6 mo: −0.02 (−0.01) Evenness – Fungal 1 mo: 0.03 (0.05) 6 mo: 0.03 (0.05) Faith's Diversity – Bacterial 1 mo: 0.03 (0.35) 6 mo: −0.52 (0.42) Faith's Diversity – Fungal 1 mo: Not reported 6 mo: Not reported Shannon Diversity – Bacterial 1 mo: −0.05 (0.07) 6 mo: −0.12 (0.08) Shannon Diversity – Fungal 1 mo: 0.09 (0.16)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					6 mo: 0.15 (0.15) Postnatal Richness - Bacterial 1 mo: 2.18 (7.16) 6 mo: −2.55 (6.42) Richness – Fungal 1 mo: −1.85 (2.54) 6 mo: −0.35 (1.05) Evenness – Bacterial 1 mo: −0.02 (0.01) 6 mo: −0.01 (0.01) Evenness – Fungal 1 mo: 0.07 (0.1) 6 mo: 0.06 (0.06) Faith's Diversity – Bacterial 1 mo: −0.08 (0.39) 6 mo: 0.11 (0.32) Faith's Diversity – Fungal 1 mo: Not reported 6 mo: Not reported Shannon Diversity – Bacterial 1 mo: −0.1 (−0.08) 6 mo: −0.05 (−0.06) Shannon Diversity – Fungal 1 mo: −0.07 (0.23) 6 mo: −0.05 (0.1)

BMI = body mass index; ELISA = enzyme-linked immunosorbent assay; GFAAS = graphite furnace atomic absorption spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; K-XRF = K-shell X-ray fluorescence instrument; LA-ICP-MS = laser ablation-inductively coupled plasma-mass spectrometry; mo = month(s); mtDNA = mitochondrial DNA; mtDNAcn = mitochondrial DNA copy number; rTL = relative telomere length; SD = standard deviation; SE = standard error; TL = telomere length; WHEALS = Wayne County Health, Environment, Allergy and Asthma Longitudinal Study; yr = year(s).

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]

[a]Effect estimates are standardized to a 1 μg/dL increase in blood Pb or a 10 μg/g increase in bone Pb, unless otherwise noted. 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.
[b]Effect estimates unable to be standardized.

Table 8-14 Epidemiologic studies of exposure to Pb and female reproductive effects

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Effects on Hormones Levels and Menstrual/Estrous Cycle					
Krieg and Feng (2011) United States 1999–2002 Cross-sectional	NHANES n: 649 Women aged 35–60 yr old	Blood Blood was measured by AAS Age at Measurement: 35–60 yr Geometric mean: 1.4 µg/dL Mean: 1.6 µg/dL Max: 17.0 µg/dL	Female reproductive function: Serum FSH and LH Serum FSH and LH were measured using a microparticle enzyme immunoassay Age at outcome: 35–60 yr	Regression analyses: the slopes were adjusted for age, log10 serum bone alkaline phosphatase, log10 urine N-telopeptides, log10 serum cotinine, alcohol use, currently breastfeeding, hysterectomy, one ovary removed, Depo-Provera use, medical conditions or treatments, hormone pill use, and hormone patch use	β (95% CI)[b], as slope for serum FSH and LH per log10 blood Pb increase Serum FSH (IU/L) Post-menopausal: 26.38 (13.39, 39.38) Pregnant: −0.08 (−1.11, 0.95) Menstruating: 1.50 (−2.29, 5.30) Both ovaries removed: 27.71 (1.64, 53.78) Birth control pills: −0.33 (−6.52, 5.86) Pre-menopausal: 11.97 (3.27, 20.66) Serum LH (IU/L) Post-menopausal: 11.63 (4.40, 18.86) Pregnant: 2.12 (−14.62, 18.86) Menstruating: 0.87 (−2.20, 3.94) Both ovaries removed: 20.59 (2.14, 39.04) Birth control pills: 2.19 (−1.35, 5.72) Pre-menopausal: 7.44 (−0.26, 15.14)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Chen et al. (2016) Shanghai, Jiangxi Province and Zhejiang Province China 2014 Cross-sectional	SPECT-China n: 2286 men and 1571 postmenopausal women SPECT-China is a population-based cross-sectional survey on the prevalence of metabolic diseases and risk factors in East China. Men and postmenopausal women (age >55 yr) who were not taking hormone replacement therapy, without a history of hysterectomy and oophorectomy were recruited.	Blood Blood was measured by AAS Age at measurement: Median age 63 (IQR: 59–68) Median[c]: 4.1 µg/dL 75th[c]: 5.981 µg/dL Quartile[c] (µg/dL) Q1: <2.7 Q2: 2.7–4.099 Q3: 4.1–5.980 Q4: >5.980	Female reproductive function: Reproductive hormone levels Venous blood samples were drawn from all subjects after an overnight fast of at least 8 hr. HbA1c was assessed via high-performance liquid chromatography (MQ-2000PT, China). tT, E2, LH and FSH levels were measured using chemiluminescence assays (Siemens Immulite 2000, Germany). SHBG levels were detected using Cobas e601 electrochemiluminescence immunoassays (Roche, Switzerland). Age at outcome: Median age 63 (IQR: 59–68)	Linear regression models were adjusted for age, current smoking status, BMI, SBP, diabetes, and blood Cd level	β (SE)[d] SHBG Q1: Reference Q2: 0.010 (0.015) Q3: 0.018 (0.015) Q4: 0.048 (0.016) tT Q1: Reference Q2: −0.033 (0.019) Q3: −0.017 (0.019) Q4: −0.016 (0.020) E2 Q1: Reference Q2: −0.001 (0.019) Q3: −0.020 (0.019) Q4: −0.021 (0.020) FSH Q1: Reference Q2: 0.013 (0.015) Q3: 0.047 (0.015) Q4: 0.046 (0.016) LH Q1: Reference Q2: 0.022 (0.015) Q3: 0.027 (0.016) Q4: 0.037 (0.016)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Lee et al. (2019) Busan Korea 2012–2014 Cross-sectional	Second Korean National Environmental Health Survey n: 4,689 adults 2,763 men and 1,926 postmenopausal women aged 50 yr or over	Blood Blood was measured by GFAAS Age at Measurement: 50 yr or older Median: 2.05 µg/dL 75th: 2.67 µg/dL	Female reproductive function: Follicle-stimulating hormone levels Serum FSH levels were measured using a chemiluminescence immunoassay (chemiluminescent immunoassay; ADVIA Centaur XP; Siemens, Tarrytown, NY, United States)	Multiple linear regression adjusted for age, BMI, smoking status, and alcohol consumption	β (95% CI)[b]: 2.929 (0.480, 5.377)
Mendola et al. (2013) United States 1999–2010 Cross-sectional	NHANES n: 3,221 (2,158 menstruating and 1,063 menopause) Women aged 45–55 yr	Blood Blood was measured by AAS in 1999–2002 and ICP-MS in 2003–2010 Age at measurement: 45–55 yr Geometric mean: Menopausal women: 1.71 µg/dL Menstruating women 1.23 µg/dL Quartiles (µg/dL) Q1: LOD–1.0 Q2: 1.0–1.4 Q3: 1.4–2.1 Q4: 2.1–22.4	Female reproductive: Menopause Menopause was dichotomized: women with at least one menstrual cycle in the past 12 mo were categorized as ‘‘No’’ and those with natural menopause were ‘‘Yes’’ Age at outcome: 45–55 yr	Logistic regression models were adjusted for age, race/ethnicity, current hormone use, poverty, and smoking; NHANES 1999–2002 models also adjusted for bone alkaline phosphatase; and NHANES 2005–2008 models also adjusted for femoral neck bone density	OR (95% CI) NHANES 1999–2010 Q1: Reference Q2: 1.7 (1.0, 2.8) Q3: 2.1 (1.2, 3.6) Q4: 4.3 (2.6, 7.2) NHANES 1999–2002 Q1: Reference Q2: 1.0 (0.3, 3.5) Q3: 1.3 (0.4, 4.5) Q4: 5.1 (1.4, 18.0) Adjusted for bone alkaline phosphatase Q1: Reference Q2: 1.1 (0.3, 3.9) Q3: 1.2 (0.3, 4.7) Q4: 4.2 (1.2, 15.5) NHANES 2005–2008 Q1: Reference

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Q2: 3.0 (0.9, 9.8) Q3: 4.9 (1.5, 16.1) Q4: 10.5 (3.1, 35) Adjusted for femoral neck bone density Q1: Reference Q2: 3.4 (0.9, 12.2) Q3: 4.1 (1.1, 15.2) Q4: 9.7 (2.8, 33)
Eum et al. (2014) Boston, MA United States 1990–1994 (2001–2004) Cohort	Nurse's Health Study n: 434 Female registered nurses, 30 to 55 yr of age and living in 11 U.S. states, completed a questionnaire on their medical history and health-related behaviors; analysis restricted to women in the Boston area who did not have a history of a major, chronic disease; and were not obese from 1990–1994 and women no history of chronic diseases (no reported diagnosis of hypertension, cardiovascular disease, renal disease, diabetes, or malignancies) invited to participate from 2001 through 2004	Blood and bone Bone was measured by K-XRF at each woman's mid-tibial shaft and patella. Blood was measured by GFAAS with Zeeman background correction Age at measurement: 46 yr or older at the time of bone Pb measurement Median Tibia: 10 µg/g Patella: 12 µg/g Blood: 3 µg/dL 75th Tibia: 15 µg/g Patella: 18 µg/g Blood: 4 µg/dL Tertiles Tibia (µg/g)	Female reproductive function: Early menopause Menopausal status was determined on the first Nurse's Health Study questionnaire in 1976 and then again on each biennial questionnaire by asking whether the participants' menstrual periods had ceased permanently; early menopause as natural menopause occurring before 45 yr of age Age at outcome: Age at reporting of menopausal status	Ordinary least-squares linear regression to analyze age at menopause adjusted for sub-study group, age at bone Pb measure, age at bone Pb measure squared, year of birth, age at menarche, months of oral contraceptive use, parity, and pack-years of smoking; logistic regression for early menopause adjusted for sub-study group, age at bone Pb measure, age at bone Pb measure squared, year of birth, age at menarche, months of oral contraceptive use, parity, and pack-years of smoking	β (95% CI), as difference in age at natural menopause (year) Tibia T1: Reference T2: −0.80 (−1.67, 0.06) T3: −1.21 (−2.08, -.035) p for trend: 0.006 Patella T1: Reference T2: −0.32 (−1.18, 0.55) T3: −0.00 (−0.88, 0.87) p for trend: 0.99 Blood T1: Reference T2: 0.08 (−0.80, 0.96) T3: −0.28 (−1.13, 0.56) p for trend: 0.54

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		T1: <6.5 T2: 6.513 T3: >13 Patella (µg/g) T1: <8 T2: 8–15 T3: >15 Blood (µg/dL) T1: <3 T2: 3 T3: >3			
Effects on Female Fertility					
Lee et al. (2020) United States 2013–2014 and 2015–2016 Cross-sectional	NHANES (2013–2014 and 2015–2016) n: 124 Women aged 20–39 yr without a history of hysterectomy and/or bilateral oophorectomy	Blood Blood was measured by ICP-MS Age at Measurement: 20–39 yr Geometric mean: 0.50 µg/dL (95% CI: 0.43, 0.57) Tertiles (µg/dL) T1: 0.11−0.38 T2: 0.41−0.62 T3: 0.63–5.37	Female reproductive function: Female infertility Infertility is defined as the absence of pregnancy with unprotected intercourse for 1 yr and was assessed through a self-reported questionnaire Age at outcome: 20–39 yr	Logistic regression analyses were adjusted for age, ethnicity, annual family income, education, marital status, smoking history, alcohol consumption, physical activity, and BMI	OR (95% CI)[b]: 2.60 (1.05, 6.41) per 2-fold increase in BLLs OR (95% CI) T1: Reference T2: 5.40 (1.47, 19.78) T3: 5.62 (1.13, 27.90)
Louis et al. (2012) Michigan (4 counties) and Texas (12	LIFE Study n: 501 Female ages 18–44 yr	Blood Blood was measured by ICP-MS	Female reproductive function: Fecundity Women were instructed in	Cox models for discrete survival time, which is a proportional odds model, adjusted	OR (95% CI), as fecundability OR Female only exposure: 0.97 (0.85, 1.11)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
counties) United States 2005–2009 Cohort	and male ages ≥18 yr; in a committed relationship; ability to communicate in English or Spanish; menstrual cycles between 21 and 42 d; no hormonal contraception injections during past year; and no sterilization procedures or physician diagnosed infertility	Age at Measurement: 19–40 yr Geometric mean Pregnant female: 0.66 µg/dL Not pregnant female: 0.76 µg/dL Tertiles (µg/dL) T1: 0.23−0.57 T2: 0.58−0.78 T3: 0.79–5.84	the use of the Clearblue Easy fertility monitors consistent with the manufacturer's guidance commencing on day six for tracking daily levels of E3G and LH. Women also used the digital Clearblue Easy home pregnancy test upon enrollment to ensure the absence of pregnancy at study start and on the day menses was expected for each cycle under observation in the study. Age at outcome: Average age with pregnancy: 29.8 Average age without pregnancy: 30.6	for age, BMI, cotinine, parity, serum lipids, and site (Texas/Michigan)	Couple exposure: Female exposure: 1.06 (0.91, 1.24) Male exposure: 0.82 (0.68, 0.97)
Lai et al. (2017) Taipei Taiwan 2008–2010 Cross-sectional	n: 190 infertile women including 68 patients with endometriosis and 122 controls Women who visited the infertility clinic first time for a specific gynecologist at Taipei Medical University Hospital; women with diagnoses such as ovarian cyst, premature ovarian failure, repeated implantation failure or pregnancy were excluded	Blood Blood was measured by ICP-MS Age at measurement: Mean age for women with endometriosis: 35.3 (SD: 4.1) Mean age for women without endometriosis: 35.3 (SD: 5.0) Geometric mean[c]	Female reproductive function: Endometriosis among infertile women Endometriosis status was determined by laparoscopy Age at outcome: Mean age for women with endometriosis: 35.3 (SD: 4.1) Mean age for women without endometriosis: 35.3 (SD: 5.0)	Multivariate logistic regression adjusted for age, body fat proportion, educational level, age at menarche, and regularity of menstrual cycle	OR (95% CI) T1: Reference T2: 1.73 (0.77, 3.88) T3: 2.59 (1.11, 6.06)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Women with endometriosis: 1.337 µg/dL Women without endometriosis: 0.853 µg/dL Median[c] Women with endometriosis: 2.130 µg/dL Women without endometriosis: 0.464 µg/dL Tertiles[c] (µg/dL) T1: <0.38 T2: 0.38–3.05 T3: >3.05			
Li et al. (2022) Hefei China October 2019 – January 2020 Cohort	n: 1184 Participants selected from First Affiliated Hospital of Anhui Medical University while seeking IVF treatment and diagnosed infertility with their partner. Inclusion criteria: women were aged between 20 and 45 yr; couples were diagnosed with infertility (failure to establish a clinical pregnancy with unprotected intercourse for at least 1 yr); and IVF indicators were tubal	Blood Maternal blood (serum) was measured by ICP-MS Age at measurement: Maternal age at collection (day before oocytes were retrieved for IVF); female partner mean age was 30.22 yr Geometric mean[e]: 0.0877 µg/dL Median[e]: 0.0924 µg/dL 75th[e]: 0.14399 µg/dL	Female reproductive function – Effects on female fertility: Fertility – successful implantation, clinical pregnancy A serum hCG level ≥25 mIU/mL on the 14th d after embryo transfer was considered as successful implantation. Clinical pregnancy was defined as an ultrasound-confirmed intrauterine pregnancy on the 30th d after embryo transfer. Age at outcome:	Logistic regression model for successful implantation adjusted for maternal age, BMI, treatment protocol, FSH levels, sperm viability, cycle type, and embryo quality. Logistic regression model for clinical pregnancy adjusted for maternal age, BMI, treatment protocol, endometrial thickness on hCG day, and embryo quality. Linear regression models for MII rate, fertility rate,	OR (95%CI)[b]: Successful implantation Continuous: 0.85 (0.77, 0.94) Tertiles Low: Reference Medium: 1.11 (0.75, 1.63) High: 0.58 (0.40, 0.85) Clinical pregnancy Continuous: 0.95 (0.91, 0.99) Tertiles Low: Reference Medium: 0.72 (0.37, 1.38)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	factor, ovulation failure, or other factors for female partner or male factor or unexplained fertility.	Tertiles[e] (µg/dL) Low: 0.002−0.065 Medium: 0.065−0.125 High: 0.125−0.481	Female partner mean age: 30.22 yr	2PN rate, blastocyte rate, and high-quality embryo rate were adjusted for maternal age, BMI, education level, infertility type, FSH and sperm concentration	High: 0.56 (0.29, 1.06) β (95% CI)[b]: MII rate: 0.090 (−0.024, 0.204) Fertility rate: −0.033 (−0.151, 0.086) 2PN rate: −0.019 (−0.100, 0.062) Blastocyst rate: 0.046 (−0.052, 0.144) High quality embryo rate: −0.143 (−0.322, −0.037)
Zhou et al. (2021a) China 2018–2019 Cohort	n: 195 Couples undergoing IVF. Women with endometriosis, hydrosalpinx, abnormal uterine cavity and men with azoospermia, severe oligozoospermia, asthenospermia and dysspermia were excluded from the study.	Blood Maternal blood (serum), follicular fluid, and seminal plasma from male partner Age at Measurement: Female partner mean age: 30.27 yr Male partner mean age: 31.57 yr Mean[c] Maternal serum: 0.301 µg/dL Follicular fluid: 0.742 µg/dL Seminal plasma: 0.882 µg/dL Median[c]	Female reproductive function – Effects on female fertility: IVF outcome The IVF outcomes included were normal fertilization, good embryo, blastocyst formation, high-quality blastocyst, pregnancy, and live birth Age at outcome: Female partner mean age: 30.27 yr Male partner mean age: 31.57 yr	Poisson regression models were adjusted for age and BMI	RR (95% CI)[b] Normal fertilization Maternal serum: 0.94 (0.42, 1.93) Follicular fluid: 0.82 (0.18, 2.39) Seminal plasma: 1.55 (0.64, 3.3) Good embryo Maternal serum: 1.00 (0.36, 2.38) Follicular fluid: 0.78 (0.09, 3.03) Seminal plasma: 1.86 (1.05, 3.11) Blastocyst formation Maternal serum: 1.06 (0.2, 3.91) Follicular fluid: 0.41 (0, 3.63)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Maternal serum: 0.245 µg/dL Follicular fluid: 0.178 µg/dL Seminal plasma: 0.486 µg/dL 75th[c] Maternal serum: 0.317 µg/dL Follicular fluid: 0.326 µg/dL Seminal plasma: 1.245 µg/dL			Seminal plasma: 1.77 (0.78, 3.58) High-quality blastocyst Maternal serum: 1.68 (0.15, 9.43) Follicular fluid: 0.35 (0, 7.11) Seminal plasma: 2.66 (0.67, 8) Pregnancy Maternal serum: 0.18 (0.01, 1.91) Follicular fluid: 0.01 (0, 0.03) Seminal plasma: 0.04 (0, 1.45) Live birth Maternal serum: 0.25 (0.01, 2.8) Follicular fluid: 0 (0, 0.09) Seminal plasma: 0.01 (0, 1.08)
Effects on Morphology or Histology of Female Sex Organs (Ovaries, Uterus, Fallopian Tubes/Oviducts, Cervix, Vagina, and/or Mammary Glands)					
Ye et al. (2017) Seoul South Korea September to November 2014	n: 288 (46 with fibroids and 242 without) Premenopausal women between 30 and 49 yr old, who were not pregnant or breastfeeding, whose heavy metal levels at the	Blood Blood was measured by GFAAS Age at Measurement: 30–49 yr	Female reproductive function – Effects on morphology and histology of female sex organs: Uterine fibroids Diagnosis of uterine fibroids was based on pelvic ultrasonography and two	Logistic regression models adjusted for age, BMI, gravidity, oral contraceptive pill administration history, regularity of menstrual cycle, hemoglobin level, and serum cotinine levels; linear	OR (95% CI)[b] Presence of uterine fibroids: 1.39 (0.75, 2.56) β (95% CI)[b] Volume of uterine fibroids: 0.12 (−2.26, 2.51)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Cross-sectional	time might have been influenced by these circumstances and might have been less representative of heavy metal levels at the time of diagnosis, and who had received hysterectomies	Geometric mean: 1.36 µg/dL Quartiles (µg/dL) Q1: <1.1 Q2: 1.1–1.3 Q3: 1.3–1.8 Q4: 1.8–3.2	questions Age at outcome: 30–49 yr	regression models were adjusted for age, BMI, gravidity, oral contraceptive pill administration history, regularity of menstrual cycle, hemoglobin level, and serum cotinine levels	Q1: Reference Q2: −0.42 (−2.69, 1.85) Q3: 0.85 (−1.67, 3.37) Q4: −1.23 (−3.74, 1.29)

2PN = oocytes with two pronuclei; AAS = atomic absorption spectrometry; BMI = body mass index; d = day(s); E2 = estradiol; E3G = estrone-3-glucuronide; FSH = follicle stimulating hormone; GFAAS = graphite furnace atomic absorption spectrometry; hCG = human chorionic gonadotropin; ICP-MS = inductively coupled plasma mass spectrometry; IQR = interquartile range; IVF = in vitro fertilization; K-XRF = K-shell X-ray fluorescence instrument; LH = luteinizing hormone; LIFE = Longitudinal Investigation of Fertility and the Environment; LOD = limit of detection; MII = metaphase II; mo = month(s); NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; SBP = systolic blood pressure; SD = standard deviation; SHBG = sex hormone binding globulin; SPECT = Survey on the Prevalence in East China for Metabolic Diseases and Risk Factors; tT = total testosterone; yr = year(s).

[a]Effect estimates are standardized to a 1 µg/dL increase in blood Pb or a 10 µg/g increase in bone Pb, unless otherwise noted. 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.

[b]Effects estimates unable to be standardized.

[c]Pb measurements were converted from µg/L to µg/dL.

[d]No CIs provided.

[e]Pb measurements were converted from ng/L to µg/dL.

Table 8-15 Animal toxicological studies of Pb exposure and female reproductive effects

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Cory-Slechta et al. (2013)	**Mouse (C57BL/6)** Control (untreated), F, n = 16 100 ppm, F, n = 16	GD −61 to PND 365	Dams were dosed starting 2 mo prior to mating. Offspring were continued on the same exposure as their dams until the end of the experiment at 12 mo of age.	0.22 µg/dL for control dams at weaning 12.12 µg/dL for 100 ppm dams at weaning	Litter Size, Maternal Body Weight
Weston et al. (2014)	**Rat (Long-Evans)** Dams Control (untreated), F, n = 20 50 ppm Pb, F, n = 19 Pups Control (untreated), M/F, n = 12.4 (7/5.4 average number of male and female pups per litter in control) 50 ppm Pb, M/F, n = 7.4 (6.3/1.1 average number of male and female pups per litter in Pb NS group)	GD −76 to PND 21	Dams were dosed via drinking water starting 2–3 mo prior to breeding. Exposure ended at weaning (PND 21).	Dams (PND 21): 0.500 µg/dL for control 7.72 µg/dL for 50 ppm Pb Pups (PND 5–6): 0.603 µg/dL for control males 0.690 µg/dL for control females 15.7 µg/dL for 50 ppm Pb males 14.6 µg/dL for 50 ppm Pb females	Litter Size, Number of Litters

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Betharia and Maher (2012)	**Rat (Sprague-Dawley)** Control (untreated), F, n = 6 dams 10 µg/mL Pb, F, n = 6 dams	GD 0 to PND 20	Dams were dosed via drinking water throughout pregnancy until weaning (PND 20).	Pups: PND 2 0.188 µg/dL for control 9.03 µg/dL for 10 µg/mL Pb PND 25: 0.088 µg/dL for control 0.976 µg/dL for 10 µg/mL Pb PND 60: 0.0244 µg/dL for control 0.0318 µg/dL for 10 µg/mL Pb	Litter Size
Schneider et al. (2016)	**Mouse (C57BL/6)** Control (untreated), F, n = NR 100 ppm Pb, F, n = NR	GD - 61 to PND 21	Dams were dosed via drinking water starting 2 mo prior to mating through lactation (weaning assumed to be PND 21). Dams were also treated to a non-stress or prenatal stress condition. Only data from dams in the non-stress condition were used.	Dams at weaning (assumed PND 21): 0.22 µg/dL for control 12.61 µg/dL for 100 ppm Pb Pups (PND 5–6): 0.37 µg/dL for control 10.2 µg/dL for 100 ppm Pb	Maternal Body Weight, Litter Size
Saleh et al. (2018)	**Rat (Sprague-Dawley)** Control (vehicle), F, n = 8 160 ppm Pb, F, n = 8 320 ppm Pb, F, n = 8	GD 1 to 20	Dams were dosed via oral gavage. Authors report a significant decrease in brain weight occurred, indicating potential overt toxicity.	Dams (GD 20): 5.1 µg/dL for control 27.7 µg/dL for 160 ppm Pb 41.5 µg/dL for 320 ppm Pb	Maternal Body Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Baranowska-Bosiacka et al. (2013)	**Rat (Wistar)** Control (untreated), F, n = 3 dams 0.1% Pb, F, n = 3 dams Control, M/F, n = 36 (17/19) pups 0.1% Pb, M/F, n = 36 (18/18) pups	GD 1 to PND 21	Dams were exposed via drinking water throughout pregnancy until weaning (PND 21).	NR for Dams Pups (PND 28): 0.93 µg/dL for control 6.86 µg/dL for 0.1% Pb	Sex Ratio
Saleh et al. (2019)	**Rat (Sprague-Dawley)** Control (vehicle), F, n = 8 dams 160 ppm Pb, F, n = 8 dams 320 ppm Pb, F, n = 8 dams	GD 1 to 20	Dams were dosed via oral gavage. Authors report a significant decrease in brain weight occurred, indicating potential overt toxicity.	Dams (GD 20): 5.26 µg/dL for control 23.9 µg/dL for 160 ppm Pb 42.9 µg/dL for 320 ppm Pb	Maternal Body Weight

BLL = blood lead level; F = female; GD = gestational day; M = male; mo = month(s); NR = not reported; Pb = lead; PND = postnatal day; NS = non-stress.

Table 8-16 Epidemiologic studies on exposure to Pb and male reproductive effects

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Effects on Sperm/Semen Production, Quality, and Function					
Li et al. (2015) Taiwan May 2012 to February 2013 Cross-sectional	n: 154 Male participants were recruited from a reproductive medical center and did not have obstructive azoospermia, cryptorchidism, varicoceles, hydrocele, orchitis, or epididymitis; did not have testicular injury or underwent testicular surgery before the study period	Blood Blood was measured by ICP-MS Age at Measurement: Mean age: 34.8 yr Mean (SD)[b]: 2.78 (1.85) µg/dL	Male reproductive effects: Seminal parameters From semen samples the following parameters were assessed: sperm concentration, semen volume, number of sperm, percentage of total motility sperm, percentage of progressive motility sperm, and percentage of sperm with normal morphology Age at outcome: Mean age: 34.8 yr	Multiple logistic regression models were adjusted for FSH, LH, prolactin, and testosterone were input into the model and then adjusted for age and education	OR (95% CI) Low-quality semen: 1.040 (1.011, 1.069) Sperm concentration: 1.046 (1.015, 1.078) Numbers of sperm: 1.041 (1.012, 1.071) Total motility sperm: 1.057 (1.026, 1.089) Progressive motility sperm: 1.047 (1.014, 1.080) Sperm with normal morphology: 1.071 (1.025, 1.118)
Sukhn et al. (2018) Beirut Lebanon January 2003 and December 2009 Cross-sectional	Environment and Male Infertility study n: 116 Male partners of infertile heterosexual couples who attended the fertility clinic at the American University of Beirut Medical Center were recruited. Men were 18 to 55 yr of age, had a BMI of 18 to 30 kg/m^2, and had not been on any hormone therapy for the past 6 mo, no diabetes, endocrine disease, fertility-related genetic disorders, obstructive azoospermia,	Blood and other: seminal fluid Blood and seminal fluid were measured by ICP-MS equipped with a cell dynamic range Age at Measurement: 18–55 yr Mean[b] Blood Overall: 3.121 µg/dL Low-quality semen group: 5.198 µg/dL	Male reproductive effects: Semen quality Participants with a semen volume <1.5 mL, sperm concentration <15 million/mL, total count <39 million, progressive motility <32%, viability <58%, and/or normal WHO morphology <30% were assigned to the low quality semen group A. Participants whose semen analyses expressed better results in all the above parameters were assigned to the normal-quality semen group B. Sperm	Logistic regression; age, cigarette smoking, alcohol intake, and period of sexual abstinence	OR (95% CI) Blood Volume (<1.5 mL) Q1: Reference Q2: 0.53 (0.11, 2.44) Q3: 0.24 (0.02, 2.24) Q4: 1.32 (0.33, 2.56) p for trend: 0.26 Concentration (<15 M/mL) Q1: Reference Q2: 0.51 (0.16, 1.63) Q3: 1.17 (0.37, 3.73) Q4: 1.58 (0.53, 4.68)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	cryptorchidism, varicocele, hydrocele, orchitis. Epididymitis, and/or history of testicular injury or surgery	Normal quality semen group 3.575 µg/dL Seminal fluid Overall: 0.540 µg/dL Low-quality semen group: 1.626 µg/dL Normal quality semen group: 1.285 µg/dL Median[b] Blood Low-quality semen group: 3.257 µg/dL Normal quality semen group: 3.098 µg/dL Seminal fluid Low-quality semen group: 0.588 µg/dL Normal quality semen group: 0.470 µg/dL Quartiles[b] (µg/dL) Q1: LOD–2.199 Q2: 2.200–3.256 Q3: 3.257–5.357 Q4: >5.358	concentration (million/mL) and progressive motility (%) were determined manually using a Makler® counting chamber. Total sperm count (million) was calculated as sperm concentration × semen volume. Sperm morphology was determined by high-power magnification (× 1000) on air-dried smears stained with a Wright Giemsa stain based on the WHO guidelines. Age at outcome: 18–55 yr		p for trend: 0.26 Total count (<39 M) Q1: Reference Q2: 0.36 (0.11, 1.18) Q3: 0.83 (0.26, 2.65) Q4: 1.35 (0.46, 3.96) p for trend: 0.15 Progressive motility (<32%) Q1: Reference Q2: 0.70 (0.19, 2.62) Q3: 0.78 (0.19, 3.19) Q4: 1.47 (0.43, 5.02) p for trend: 0.66 Viability (<58%) Q1: Reference Q2: 0.44 (0.14, 1.39) Q3: 0.68 (0.21, 2.21) Q4: 1.35 (0.46, 3.96) p for trend: 0.23 WHO morphology (<30%) Q1: Reference Q2: 0.50 (0.15, 1.66) Q3: 0.93 (0.28, 3.10) Q4: 0.84 (0.26, 2.66) p for trend: 0.68 Seminal Fluid Blood Volume (<1.5 mL)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Q1: Reference Q2: 0.86 (0.16, 4.67) Q3: 1.34 (0.25, 7.17) Q4: 2.07 (0.37, 11.51) p for trend: 0.95 Concentration (<15 M/mL) Q1: Reference Q2: 1.57 (0.50, 4.92) Q3: 1.99 (0.62, 6.38) Q4: 1.94 (0.59, 6.35) p for trend: 0.64 Total count (<39 M) Q1: Reference Q2: 1.66 (0.51, 5.46) Q3: 3.33 (1.01, 10.99) Q4: 2.00 (0.58, 6.85) p for trend: 0.24 Progressive motility (<32%) Q1: Reference Q2: 4.36 (0.83, 22.81) Q3: 6.35 (1.21, 33.19) Q4: 2.40 (0.39, 14.49) p for trend: 0.09 Viability (<58%) Q1: Reference Q2: 8.00 (1.59, 40.30) Q3: 12.00 (2.34, 61.52) Q4: 10.15 (1.95, 52.92) p for trend: 0.006

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					WHO morphology (<30%) Q1: Reference Q2: 3.83 (0.924, 15.90) Q3: 6.57 (1.57, 27.43) Q4: 2.02 (0.426, 9.55) p for trend: 0.06
Shi et al. (2021) Hong Kong November 2015–November 2016 Cross-sectional	n: 288 Male subjects who underwent SA as part of the fertility assessment at the andrology laboratory of Prince of Wales Hospital. Participants were excluded with medical conditions azoospermia; andrological conditions (which are known to affect semen parameters including genetic conditions); history of mumps orchitis, severe varicocele, undescended testis; history of testicular torsion or scrotal injury, congenital bilateral absence of vas deferent, and urogenital infections; taking medication known to affect semen parameters, including steroid, finasteride, calcium channel blockers; history of malignant disease; known mental disorders; drug abuse; failure to complete the	Blood Blood was measured by ICP-MS Age at Measurement Mean age: 37.9 yr Geometric mean[b]: 3.175 µg/dL Median[b]: 2.719 µg/dL 75th[b]: 3.437 µg/dL Quartiles[b] (µg/dL) Q1: <2.159 Q2: >2.159–2.719 Q3: >2.719–3.437 Q4: >3.437	Male reproductive effects: Seminal parameters Semen volume was measured by a wide-bore graduated pipette with the graduation of 0.1-ml. Sperm concentration and motility were examined under a phase contrast microscope with the magnification of × 200 or 400. Diff-Quik staining kit (Dade Behring AG, Düdingen, Switzerland) and Tygerberg Strict Criteria were used to evaluate the sperm morphology. Sperm DNA fragmentation was measured by sperm chromatin structure assay. Age at outcome: Mean age: 37.9 yr	Multivariable linear regression adjusted for (1) male age and daily coffee intake for semen volume models; (2) abstinence time, average sleep duration for sperm concentration models; (3) male age, abstinence time, and daily coffee intake for total sperm count models; (4) male age and daily juice intake for the sperm motility models; (5) male age and abstinence time for total motility count models; (6) no adjustment for normal morphology or sperm vitality models; (7) male age, abstinence time, and irregular sleeping habit for DNA fragmentation index models; (8) daily juice intake for percentage of acrosome reacted sperm models.	B (95% CI) Semen volume Q1: Reference Q2: −0.05 (−0.70, 0.37) Q3: 0.04 (−0.39, 0.65) Q4: 0.08 (−0.32, 0.83) p for trend: 0.48 Sperm concentration Q1: Reference Q2: 0.02 (−0.45, 0.58) Q3: −0.02 (−0.57, 0.43) Q4: −0.10 (−0.85, 0.26) p for trend: 0.34 Total sperm count Q1: Reference Q2: −0.01 (−0.60, 0.53) Q3: −0.03 (−0.66, 0.43) Q4: −0.05 (−0.76, 0.44) p for trend: 0.55 Sperm motility Q1: Reference

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	lifestyle questionnaire; and refusal to donate blood or semen samples.				Q2: −0.09 (−10.21, 3.02) Q3: −0.15 (−12.47, 0.49) Q4: −0.08 (−10.26, 4.02) p for trend: 0.77 Total motility count Q1: Reference Q2: −0.07 (−0.97, 0.38) Q3: −0.08 (−0.97, 0.36) Q4: −0.12 (−1.20, 0.25) p for trend: 0.16 Normal morphology Q1: Reference Q2: −0.13 (−1.16, 0.13) Q3: −0.20 (−1.43, −0.16) Q4: −0.20 (−1.52, −0.10) p for trend: 0.20 Sperm vitality Q1: Reference Q2: 0.12 (−0.04, 0.17) Q3: 0.01 (−0.10, 0.12) Q4: −0.13 (−0.19, 0.04) p for trend: 0.13 Percentage of acrosome reacted sperm Q1: Reference Q2: −0.22 (−18.60, 0.97) Q3: −0.05 (−11.60, 7.71) Q4: −0.12 (−15.70, 5.79) p for trend: 0.75

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Pant et al. (2014) New Delhi India Cross-sectional	n: 60 Male partners of couples age 21–40 yr old attending the Andrology Laboratory of the Reproductive Biology Department, All India Institute of Medical Sciences, New Delhi, India for semen analysis to assess their inability to achieve a pregnancy were selected.	Other: Semen Semen measured by ICP-AES Age at Measurement: mean age: 31.81 (SD: 5.27) Mean (SD): 6.18 (2.16) µg/dL	Male reproductive effects: Semen quality Semen of volunteers was collected and analyzed the protocols of the WHO. Sperm morphology was determined according to Kruger's strict criteria. Comet assay: prepared sperm samples were observed under a fluorescence microscope with a total of 100 cells were scored. The percentage of tail DNA, tail length, and tail moment was evaluated by the CometScore software image analysis system. Age at outcome: mean age: 31.81 (SD: 5.27)	Multiple regressions, adjusted for toxicants (Cd, diethyl phthalate, dibutyl phthalate, di[2-ethylhexyl] phthalate), age, BMI, tobacco, smoking, alcohol, and diet	β (95% CI)[c] Sperm motility (%): 2.43 (−4.87, −0.001) Sperm concentration (10^6/ml): −1.97 (−3.16, −0.33) Tail length: 3.79 (0.56, 7.02) Percent DNA in tail: 1.31 (0.172, 3.74) Tail moment: 1.20 (0.23, 2.16)
Jia et al. (2022) Henan Province China December 2017 to August 2018 Cross-sectional	n: 841 Males ranging from 18 to 50 yr of age with no history of testicular injury, urologist diagnosed inflammation of the urogenital system; history of epididymitis; treatment history of varicocele; history of incomplete orchiocatabasis or any of the following that was detected by an urologist at physical examination:	Other: Semen Seminal plasma was measured by analyzed using the kinetic energy discrimination-based Thermo iCAP Q ICP-MS Age at Measurement Mean ± SD: 29.55 ± 5.45 yr Median: 1.70 ppb	Male reproductive effects: Seminal parameters Semen of volunteers was collected and analyzed the protocols of the WHO. Computer-assisted sperm analysis technology was used to analyze the collected semen samples. The quality indicators were complete liquefaction, semen volume, sperm concentration, total sperm count, progressive motility,	Multilinear regression models were adjusted for age, BMI, smoking, and alcohol consumption	β (95% CI)[c], per increase in ln-Pb seminal plasma Semen volume: −0.10 (−0.27, 0.07) Sperm concentration: 1.83 (−4.45, 8.12) Total sperm number: 0.80 (−17.61, 19.21) Progressive motility: 0.06 (−2.09, 2.21) Normal morphological rate: −0.04 (−0.41, 0.34)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	absence of prominentia laryngea, absence of pubes, abnormal breast, absence of testis, abnormal penis, epididymal knob, or varicocele.	75th: 2.36 ppb	non-progressive motility, sperm motility, and sperm motility parameters, such as curve line velocity (μm/s), straight line velocity (μm/s), velocity of average path (μm/s), lateral head movement (amplitude of lateral head displacement, μm), average motion degree (°), linearity (%), straightness (%), wobble, and beat cross frequency (beat cross frequency, Hz).		Curve line velocity: 0.35 (−1.17, 1.88) Straight line velocity: 0.54 (−0.50, 1.58) Velocity of average path: 0.37 (−0.96, 1.70) Linearity: 0.49 (−0.88, 1.86) Straightness: 0.46 (−1.07, 1.99) Wobble: 0.22 (−1.33, 1.77) Average motion degree: −0.33 (−1.22, 0.56) Beat cross frequency: 0.01 (-0.14, 0.15) Lateral head movement: −0.04 (−0.11, 0.03)
Williams et al. (2022) Russia 2003–2005 (follow-up annually for 10 yr) Cohort	Russian Children's Study n: 223 Boys enrolled at age 8–9 yr in 2003–2005 and followed them annually for 10 yr.	Blood Blood was measured by Zeeman background corrected flameless GFAAS Age at measurement: 8–9 yr Median: 3 μg/dL 75th: 5 μg/dL Categories Lower: <5 μg/dL Higher: ≥5 μg/dL Tertiles	Male reproductive effects: Semen parameters All semen samples were assessed by a single andrology technician and analyzed according to criteria of the Nordic Association for Andrology and European Society of Human Reproduction and Embryology-Special Interest Group in Andrology and serum hormonal levels were analyzed using the Architect i1000SR and chemiluminescent	Mixed effect linear regression models adjusted for boys' BW, total caloric intake, HTZ at entry, breastfeeding duration, monthly household income, and abstinence time	β (95% CI)[b], as adjusted mean Semen volume (mL) Continuous, per log-blood Pb: −0.40 (−0.82, 0.03) Categories Lower: 2.83 (2.61, 3.06) Higher: 2.60 (2.27, 2.93) Tertiles Low: 2.92 (2.50, 3.34) Medium: 2.79 (2.52, 3.06) High: 2.60 (2.27, 2.93) p for trend: 0.24 Sperm concentration (mill/mL)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
		Low: ≤2 µg/dL Medium: 3–4 µg/dL High: ≥5 µg/dL	microparticle immunoassay. Age at outcome: 18 yr or older		Continuous, per log-blood Pb: 0.09 (−0.13, 0.31) Categories Lower: 47.0 (41.3, 53.4) Higher: 49.0 (37.8, 63.4) Tertiles Low: 41.3 (33.2, 51.3) Medium:50.3 (42.8, 59.0) High: 49.1 (38.0, 63.6) p for trend: 0.33 Total sperm count (mill) Continuous, per log-blood Pb: −0.02 (−0.27, 0.23) Categories Lower: 111 (95.6, 129) Higher: 107 (80.0, 143) Tertiles Low: 99 (76.4, 128) Medium: 118 (95.5, 141) High: 107 (80.3, 143) p for trend: 0.68 Progressive sperm motility (%) Continuous, per log-blood Pb: 1.77 (−0.55, 4.08) Categories Lower: 53.2 (51.7, 54.7) Higher: 53.1 (50.9, 55.2) Tertiles Low: 51.2 (48.6, 53.9) Medium: 54.3 (52.5, 56.1)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					High: 53.2 (50.9, 55.3) p for trend: 0.29 Total progressive motile sperm count (mill) Continuous, per log-blood Pb: 0.01 (−0.27, 0.29) Categories Lower: 57.7 (48.9, 68.1) Higher: 55.7 (40.6, 76.4) Tertiles Low: 49.4 (36.8, 66.2) Medium: 62.6 (51.3, 76.5) High: 56.0 (40.8, 76.8) p for trend: 0.57 Low semen quality (probability) Continuous, per log-blood Pb: 0.20 (−0.22, 0.65) Categories Lower: 0.51 (0.44, 0.58) Higher: 0.49 (0.39, 0.59) Tertiles Low: 0.43 (0.31, 0.55) Medium: 0.55 (0.46, 0.63) High: 0.49 (0.39, 0.59) p for trend: 0.43
Effects of Hormone Levels					
Kresovich et al. (2015)	NHANES n: 869	Blood	Male reproductive effects: Hormones	Linear regression models were adjusted for age, BMI, race,	β (SE)[d] Testosterone (ng/mL) Q1: Reference

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
United States 1999–2004 Cross-sectional	Males who were aged >20 yr, no reported steroid or thyroid mediation use, and no reported thyroid disease.	Blood was measured by AAS (1999–2002) or ICP-MS (2003–2004). Age at measurement: >20 yr Median (weighted): 2.0 µg/dL 75th: 2.8 µg/dL Quartiles (µg/dL) Q1: ≤1.40 Q2: 1.40–2.10 Q3: 2.10–3.20 Q4: >3.20	Testosterone, androstanedione glucuronide, and SHBG were measured in blood serum, and E2 in plasma. All sex hormones were detected by immunoassay. Age at outcome: >20 yr	diabetes status (including prediabetes), smoking status, and alcohol intake; and Cd	Q2: 0.39 (0.21) Q3: 0.56 (0.22) Q4: 0.81 (0.20) p for trend: 0.0008 E2 (pg/mL) Q1: Reference Q2: −0.01 (0.03) Q3: −0.01 (0.04) Q4: −0.01 (0.04) p for trend: 0.7849 fT (ng/dL) Q1: Reference Q2: 0.83 (0.47) Q3: 0.55 (0.48) Q4: 0.81 (0.48) p for trend: 0.2374 fE2 (pg/ml) Q1: Reference Q2: −0.01 (0.03) Q3: −0.02 (0.04) Q4: −0.03 (0.04) p for trend: 0.4428 Androstanedione glucuronide (ng/mL) Q1: Reference Q2: 0.03 (0.03) Q3: −0.01 (0.03) Q4: 0.02 (0.04) p for trend: 0.8917

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					SHBG (nmol/L) Q1: Reference Q2: 0.01 (0.02) Q3: 0.05 (0.02) Q4: 0.05 (0.02) p for trend: 0.0187 Adjusted for Cd Testosterone (ng/mL) Q1: Reference Q2: 0.38 (0.23) Q3: 0.54 (0.21) Q4: 0.79 (0.22) p for trend: 0.0026 E2 (pg/mL) Q1: Reference Q2: 0.00 (0.03) Q3: 0.01 (0.04) Q4: 0.02 (0.04) p for trend: 0.6600 fT (ng/dL) Q1: Reference Q2: 0.95 (0.50) Q3: 0.70 (0.51) Q4: 1.06 (0.51) p for trend: 0.1388 fE2 (pg/ml) Q1: Reference Q2: 0.01 (0.03)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
					Q3: 0.00 (0.04) Q4: 0.01 (0.04) p for trend: 0.9456 Androstanedione glucuronide (ng/mL) Q1: Reference Q2: 0.03 (0.03) Q3: −0.02 (0.03) Q4: 0.01 (0.04) p for trend: 0.7620 SHBG (nmol/L) Q1: Reference Q2: −0.01 (0.02) Q3: 0.03 (0.02) Q4: 0.03 (0.03) p for trend: 0.1333
Lewis and Meeker (2015) United States 2011–2012 Cross-sectional	NHANES n: 484 Men that were 18–55 yr old, that had complete data on the metals of interest, serum testosterone, BMI, PIR, race, serum cotinine, or urinary creatinine	Blood Blood was measured by inductively coupled dynamic reaction-plasma mass spectrometry Age at Measurement: 18–55 yr Geometric mean: 1.06 µg/dL 75th: 1.59 µg/dL	Male reproductive effects: Testosterone Serum testosterone (total) were measured by isotope dilution–high performance liquid chromatography-tandem mass spectrometry Age at outcome: 18–55 yr	Multiple linear regression, adjusted for age, BMI, PIR, race, and serum cotinine	β (95% CI)[c], as percent change in serum testosterone associated with a doubling (100% increase) in blood Pb concentration: 6.65 (2.09, 11.41)
Chen et al. (2016) Shanghai, Jiangxi	SPECT-China n: 2286 men	Blood	Male reproductive effects: Reproductive hormone levels	Linear regression models were adjusted for age and current	β (SE)[d] SHBG

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Province and Zhejiang province China 2014 Cross-sectional	SPECT-China is a population-based cross-sectional survey on the prevalence of metabolic diseases and risk factors in East China. Men and postmenopausal women (age >55 yr) who were not taking hormone replacement therapy, without a history of hysterectomy and oophorectomy were recruited.	Blood was measured by AAS Age at Measurement: Median (IQR) age: 54 (44–63) Median[b]: 4.400 µg/dL 75th[b]: 6.230 µg/dL Quartiles[b] (µg/dL) Q1: <2.900 Q2: 2.900–4.399 Q3: 4.400–6.229 Q4: >6.229	Venous blood samples were drawn from all subjects after an overnight fast of at least 8 hr. HbA1c was assessed via high-performance liquid chromatography. tT, E2, LH and FSH levels were measured using chemiluminescence assays. SHBG levels were detected using electrochemiluminescence immunoassays. Age at outcome: Median (IQR) age: 54 (44–63)	smoking status, BMI, SBP, diabetes and, blood Cd level	Q1: Reference Q2: <0.001 (0.011) Q3: 0.021 (0.011) Q4: 0.038 (0.012) p for trend: <0.001 tT Q1: Reference Q2: 0.001 (0.010) Q3: 0.010 (0.010) Q4: 0.033 (0.010) p for trend: 0.001 E2 Q1: Reference Q2: −0.008 (0.016) Q3: 0.014 (0.017) Q4: −0.003 (0.017) p for trend: 0.794 FSH Q1: Reference Q2: 0.010 (0.014) Q3: 0.004 (0.014) Q4: 0.030 (0.015) p for trend: 0.067 LH Q1: Reference Q2: 0.018 (0.013) Q3: 0.015 (0.013) Q4: 0.028 (0.013) p for trend: 0.065

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Effects on Fertility					
Louis et al. (2012) Michigan (4 counties) and Texas (12 counties) United States 2005–2009 Cohort	LIFE Study n: 501 Female ages 18–44 yr and male ages ≥18 yr; in a committed relationship; ability to communicate in English or Spanish; menstrual cycles between 21 and 42 d; no hormonal contraception injections during past year; and no sterilization procedures or physician diagnosed infertility	Blood Blood was measured by ICP-MS Age at Measurement: Average age for male partner with pregnancy: 31.6 yr Average age for male partner without pregnancy: 32.4 yr Geometric mean Male partner with pregnancy result: 1.03 µg/dL Male partner without pregnant result: 1.18 µg/dL	Male reproductive effects: Fecundity Women were instructed in the use of the Clearblue Easy fertility monitors consistent with the manufacturer's guidance commencing on day six for tracking daily levels of E3G and LH. Women also used the digital Clearblue Easy home pregnancy test upon enrollment to ensure the absence of pregnancy at study start and on the day menses was expected for each cycle under observation in the study. Age at outcome: Average age for males with pregnancy: 31.6 yr Average age for males without pregnancy: 32.4 yr	Cox models for discrete survival time, which is a proportional odds model, adjusted for age, BMI, cotinine, parity, serum lipids, and site (Texas/Michigan)	OR (95% CI), as fecundability OR Male only exposure: 0.85 (0.73, 0.99) Couple exposure: Female exposure: 1.06 (0.91, 1.24) Male exposure: 0.82 (0.68, 0.97)
Zhou et al. (2021a) China 2018–2019 Cohort	n: 195 Couples undergoing IVF. Women with endometriosis, hydrosalpinx, abnormal uterine cavity and men with azoospermia, severe oligozoospermia, asthenospermia and	Blood, other: follicular fluid, and other: semen Maternal blood (serum), follicular fluid, and seminal plasma from male partner Age at Measurement:	Male reproductive effects: IVF outcome The IVF outcomes included were normal fertilization, good embryo, blastocyst formation, high-quality blastocyst, pregnancy, and live birth Age at outcome:	Poisson regression models were adjusted for age and BMI	RR (95% CI)[c] Normal fertilization Maternal serum: 0.94 (0.42, 1.93) Follicular fluid: 0.82 (0.18, 2.39) Seminal plasma: 1.55 (0.64, 3.3) Good embryo

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
	dysspermia were excluded from the study.	Female partner mean age: 30.27 yr Male partner mean age: 31.57 yr Mean[c] Maternal serum: 0.301 µg/dL Follicular fluid: 0.742 µg/dL Seminal plasma: 0.882 µg/dL Median[c] Maternal serum: 0.245 µg/dL Follicular fluid: 0.178 µg/dL Seminal plasma: 0.486 µg/dL 75th[c] Maternal serum: 0.317 µg/dL Follicular fluid: 0.326 µg/dL Seminal plasma: 1.245 µg/dL	Female partner mean age: 30.27 yr Male partner mean age: 31.57 yr		Maternal serum: 1.00 (0.36, 2.38) Follicular fluid: 0.78 (0.09, 3.03) Seminal plasma: 1.86 (1.05, 3.11) Blastocyst formation Maternal serum: 1.06 (0.2, 3.91) Follicular fluid: 0.41 (0, 3.63) Seminal plasma: 1.77 (0.78, 3.58) High-quality blastocyst Maternal serum: 1.68 (0.15, 9.43) Follicular fluid: 0.35 (0, 7.11) Seminal plasma: 2.66 (0.67, 8) Pregnancy Maternal serum: 0.18 (0.01, 1.91) Follicular fluid: 0.01 (0, 0.03) Seminal plasma: 0.04 (0, 1.45) Live birth Maternal serum: 0.25 (0.01, 2.8) Follicular fluid: 0 (0, 0.09) Seminal plasma: 0.01 (0, 1.08)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]
Effects on Morphology or Histology of Male Sex Organs					
Huang et al. (2020) Guangxi China July 2015 to September 2018 Cohort	Guangxi Birth Cohort Study n: 564 mother-child pairs Women with singleton pregnancies that were included from 8 Maternity and Child Healthcare Hospitals in 6 cities of Guangxi, China	Blood Maternal blood (serum) was measured by ICP-MS Age at Measurement: Maternal age at time of measurement (mean age: 28.76 (SD: 4.66) yr) Median[b]: 0.077 µg/dL 75th[b]: 0.123 µg/dL Quartiles[b] (µg/dL) Q1: ≤0.054 Q2: 0.055−0.077 Q3: 0.078−0.123 Q4: >0.123	Male reproductive effects: TV and AGD in infant boys TV, and AGD-TV measurements were undertaken by trained sonographers using ultrasonography. Transverse and longitudinal grey-scale images were used to calculate TV as π/6 × length × width × height. The volumes of both testes were measured and an average taken. Two different measurements of AGD were obtained using vernier calipers: the longer AGD was measured from the center of the anus to the cephalad insertion of the penis (AGDap), and the shorter AGD was measured from the center of the anus to the posterior base of the scrotum (AGDas). Age at outcome: birth	Multiple linear regression models were adjusted for BW, GA, blood sampling time (mother), alcohol use pre-pregnancy, BMI, and age at examination	β (95% CI)[c] TV Q1: Reference Q2: −0.017 (−0.077, 0.043) Q3: −0.024 (−0.085, 0.036) Q4: −0.064 (−0.124, −0.004) AGDap Q1: Reference Q2: −0.039 (−0.085, 0.008) Q3: −0.037 (−0.085, 0.010) Q4: −0.060 (−0.110, −0.011) AGDas Q1: Reference Q2: −0.020 (−0.091, 0.052) Q3: −0.033 (−0.105, 0.039) Q4: −0.115 (−0.190, −0.039)

AAS = atomic absorption spectrometry; AGD = anogenital distance; AGDap = anopenile distance; AGDas = anoscrotal distance; BMI = body mass index; BW = birth weight; CI = confidence interval; d = day(s); E2 = estradiol; E3G = estrone-3-glucuronide; fE2 = free estradiol; FSH = follicle stimulating hormone; fT = free testosterone; FSH = follicle stimulating hormone; GA = gestational age; GFAAS = graphite furnace atomic absorption spectrometry; HTZ = height Z-score; ICP-AES = inductively coupled plasma atomic emission spectrometry; ICP-MS = inductively coupled plasma mass spectrometry; IVF = in vitro fertilization; LH = luteinizing hormone; LIFE = Longitudinal Investigation of Fertility and the Environment; LOD = limit of detection; mo = month(s); NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; PIR = poverty-income ratio; Q = quartile; SA = semen analysis; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; SHBG = sex hormone binding globulin; SPECT = Survey on the Prevalence in East China for Metabolic Diseases and Risk Factors; T = testosterone; tT = total testosterone; TV = testicular volume; WHO = World Health Organization; yr = year(s).

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs[a]

[a]Effect estimates are standardized to a 1 μg/dL increase in blood Pb or a 10 μg/g increase in bone Pb, unless otherwise noted. 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.
[b]Pb measurements were converted from μg/L to μg/dL.
[c]Effects estimates unable to be standardized.
[d]No CIs provided.

Table 8-17 Animal toxicological studies of exposure to Pb and male reproductive effects

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
El Shafai et al. (2011)	**Rat (Wistar)** Control (untreated), M, n = 8 Control (vehicle), M, n = 8 25 mg/kg Pb, M, n = 8	Adulthood (specific PND NR)	Adult male rats were dosed via oral gavage for 3 mo. One control group was not gavaged (untreated control) and another control group was gavaged with vehicle (vehicle control).	4.26 µg/dL for control (untreated) 4.27 µg/dL for control (vehicle) 5.27 µg/dL for 25 mg/kg Pb	Sex Organ Histopathology
Wang et al. (2013b)	**Rat (Sprague-Dawley)** Control (untreated), M, n = 15 0.8/0.3 g/L Pb, M, n = 15 1.5/0.9 g/L Pb, M, n = 15	GD −10 to PND 183	Dams were dosed via drinking water (0, 0.8, or 1.5 g/L Pb) starting 10 d prior to mating through weaning. At weaning 15 males from each group were dosed via drinking water to lower levels of Pb than their dams (0, 0.3, or 0.9 g/L) until 6 mo of age (approx. PND 183).	2.65 µg/dL for control 18.6 µg/dL for 0.8/0.3 g/L Pb 55.0 µg/dL for 1.5/0.9 g/L Pb	Testicular Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Wang et al. (2013a)	**Mouse (CD-1)** Control (untreated), M, n = 12 200 ppm Pb, M, n = 12 2000 ppm Pb, M, n = 12	PND 0 to PND 21	Dams were dosed via drinking water from PND 0 to 21.	Pups: PND 22 17.4 µg/dL for control 21.2 µg/dL for 200 ppm Pb 19.1 µg/L for 2000 ppm Pb PND 70 4.40 µg/dL for control 3.24 µg/dL for 200 ppm Pb 5.09 µg/dL for 2000 ppm Pb	Testosterone Levels, Sex Organ Histopathology, Accessory Male Reproductive Organ Weight, Testicular Weight, Semen Parameters
Godínez-Solís et al. (2019)	**Mouse (ICR-CD-1)** Control (untreated), M, n = 4 0.01% Pb, M, n = 6	PND 91 to 136	12 wk old mice were acclimated for a week before being dosed via drinking water for 45 d.	BLL NR for controls 9.4 µg/dL for 0.01% Pb	Semen Parameters, Sperm Morphology, IVF

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL as Reported (µg/dL)	Endpoints Examined
Xie et al. (2020)	**Mouse (SPF ICR)** Control (untreated), M, n = 15 50 mg/L Pb, M, n = 15 200 mg/L Pb, M, n = 15	PND 28 to PND 118	21 d old mice were acclimated for a week before being dosed for 90 d via drinking water.	0.602 µg/dL for control 6.02 µg/dL for 50 mg/L Pb 11.8 µg/dL for 200 mg/L Pb	Semen Parameters, Sperm Morphology, Sex Organ Histopathology, Testicular Weight, Accessory Male Reproductive Organ Weight
Pavlova et al. (2021)	**Mouse (ICR)** Control (vehicle), M, n = 10 80 mg/kg Pb, M, n = 10	PND 60 to 74	60 d old mice were dosed via oral gavage for 2 wk. Two weeks following cessation of exposure, animals were sacrificed.	1.45 µg/dL for control 21.66 µg/dL for 80 mg/kg Pb	Testicular Weight, Semen Parameters, Sex Organ Histopathology

BLL = blood lead level; d = day(s); F = female; GD = gestational day; IVF = in vitro fertilization; M = male; mo = month(s); NR = not reported; Pb = lead; PND = postnatal day; T = testosterone; wk = week(s).

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