

Integrated Science Assessment for Lead

Appendix 8: Reproductive and Developmental Effects

External Review Draft

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DOCUMENT GUIDE

1 This Document Guide is intended to orient readers to the organization of the Lead (Pb) Integrated Science
2 Assessment (ISA) in its entirety and to the sub-section of the ISA at hand (indicated in bold). The ISA consists of
3 the Front Matter (list of authors, contributors, reviewers, and acronyms), Executive Summary, Integrated Synthesis,
4 and 12 appendices, which can all be found at <https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=357282>.
5

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ACRONYMS AND ABBREVIATIONS

AAS	atomic absorption spectrometry	ft4	free thyroxine
AGD	anogenital distance	GA	gestational age
AGDap	anopenile distance	GDM	gestational diabetes mellitus
AGDas	anoscrotal distance	GEE	generalized estimating equation
ALAD	aminolevulinic acid dehydratase	GFAAS	graphite furnace atomic absorption spectrometry
ALSPAC	Avon Longitudinal Study of Parents and Children	GnRH	gonadotropin-releasing hormone
AMH	anti-Müllerian hormone	GSI	global severity index
As	arsenic	HAZ	height-for-age Z-score
AQCD	Air Quality Criteria Document	HC	head circumference
ART	Assisted reproductive technology	HCAZ	head circumference for age Z-scores
BKMR	Bayesian kernel machine regression	hCG	human chorionic gonadotropin
BLL	blood lead level	HFIAS	Household Food Insecurity Access Scale
BMI	body mass index	Hg	mercury
BMIZ	BMI-for-age Z-score	HOME	Home Observation for Measurement of the Environment
BW	birth weight	HTZ	height Z-score
BWGA	birth weight-for-gestational age	hr	hour(s)
BWZ	birth weight Z-score	ICP-AES	inductively coupled plasma atomic emission spectroscopy
C-ABCS	China-Anhui Birth Cohort Study	ICP-MS	inductively coupled plasma mass spectrometry
CANDLE	Conditions Affecting Neurocognitive Development and Learning in Early Childhood	ICP-QQQ	inductively coupled plasma triple quad
CCG	Charlotte-Concord-Gastonia	IgE	immunoglobulin E
Cd	cadmium	IGF	insulin-like growth factor 1
CD	cephalic diameter	IGT	impaired glucose tolerance
CHD	congenital heart disease	IL-33	interleukin-33
CHECK	Children's Health and Environmental Chemicals in Korea	INMA	Instituto de Nanociencia y Materiales de Aragón
CHL	crown-to-heel length	IQR	interquartile range
CI	confidence interval	ISA	Integrated Science Assessment
CMS	Charlotte Motor Speedway	IUGR	intrauterine growth restriction
d	day(s)	IVF	in vitro fertilization
DBP	diastolic blood pressure	JECS	Japan Environment and Children's Study
E2	estradiol	K6	Kessler Psychological Distress Scale
ELEMENT	Early Life Exposures in Mexico to Environmental Toxicants	K-XRF	K-shell X-ray fluorescence
ELISA	enzyme-linked immunoassay	LA-ICP-MS	laser ablation-inductively coupled plasma-mass spectrometry
EMASAR	Study on the Environment and Reproductive Health	LBW	low birth weight
ETS	environmental tobacco smoke	LGA	large for gestational age
fe2	free estradiol	LH	luteinizing hormone
FLEHS	Flemish Environment and Health Studies	LIFE	Longitudinal Investigation of Fertility and the Environment
FSH	follicle stimulating hormone	LMP	last menstrual period or last missed period
ft	free testosterone		
ft3	free triiodothyronine		

In	natural log-transformed	PROTECT	Puerto Rico Test site for Exploring Contamination Threats
LOD	limit of detection		
MAL-ED	Interactions of Malnutrition and Enteric Infections: Consequences for Child Health and Development	QUS	quantitative ultrasound
		ROS	reactive oxygen species
MII	metaphase II	RRR	relative risk ratio
min	minute(s)	rTL	relative telomere length
MIREC	Maternal-Infant Research on Environmental Chemicals	SBP	systolic blood pressure
		SD	standard deviation
miRNA	micro RNA	Se	selenium
MMP	matrix metalloproteinases	SE	standard error
Mn	manganese	SES	socioeconomic status
mo	month(s)	SGA	small for gestational age
MOCEH	Mothers' and Children's Environmental Health	SHBG	sex hormone binding globulin
		SNP	single nucleotide polymorphisms
MSA	Metropolitan Statistical Area	SPECT	Survey on the Prevalence in East China for Metabolic Diseases and Risk Factors
mtDNA	mitochondrial DNA		
NASCAR	National Association for Stock Car Auto Racing	T	testosterone
		TL	telomere length
NHANES	National Health and Nutrition Examination Survey	TPOAb	thyroid peroxidase antibodies
		TSH	thyroid-stimulating hormone
NICE	Nutritional impact on Immunological maturation during Childhood in relation to the Environment	TSLP	thymic stromal lymphopoietin
		tT	total testosterone
NTD	neural tube defects	tT3	total triiodothyronine
OFC	orofacial clefts	tT4	total thyroxine
OGTT	oral glucose tolerance test	TV	testicular volume
PECOS	Population, Exposure, Comparison, Outcome, and Study	UCB	umbilical cord blood
		WAZ	weight for age Z-score
PI	Ponderal Index	WC	waist circumference
PIR	poverty-to-income ratio	wk	week(s)
PND	postnatal day	WHEALS	Wayne County Health, Environment, Allergy and Asthma Longitudinal Study
PROGRESS	Programming Research in Obesity, Growth, Environment and Social Stressors		
		WHO	World Health Organization
PROM	premature rupture of membranes	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
Effects on Pregnancy and Birth Outcomes	Suggestive
Effects on Development	Causal
Effects on Female Reproductive Function	Suggestive
Effects on Male Reproductive Function	Causal

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

1

8.1 Introduction and Summary of the 2013 Integrated Science Assessment

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

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

8.1.1 Effects on Pregnancy and Birth Outcomes

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

8.1.2 Effects on Development

26 The 2013 Pb ISA ([U.S. EPA, 2013](#)) reported Pb associated effects on development in
27 epidemiologic and toxicological studies. Previous toxicological studies indicated that delayed pubertal
28 onset may be one of the more sensitive developmental effects of Pb exposure with effects observed after
29 gestational exposures leading to blood Pb levels (BLLs) in the female pup of 1.3–13 µg/dL ([Iavicoli et al.,
30 2006](#); [Iavicoli et al., 2004](#)). Toxicological studies have reported delayed male sexual maturity as measured
31 with sex organ weight, seeing significant decrements at BLLs of 20–34 µg/dL ([Ronis et al., 1998c](#); [Sokol et
32 al., 1985](#)). The 2013 Pb ISA also presented findings from a toxicological study that suggests Pb may act

1 through disruption of insulin-like growth factor 1 (IGF-1) to delay the onset of puberty, demonstrated by
2 the attenuation of Pb-induced delays in pubertal onset in female rats supplemented with IGF-1 ([Pine et al.,
3 2006](#)). Thus, data from the toxicological literature and from epidemiologic studies demonstrated that
4 puberty onset in both males and females is delayed with Pb exposure. Findings from epidemiologic
5 studies of the effect of Pb on postnatal growth were inconsistent and findings from the toxicological
6 literature of the effect of Pb exposure were mixed with recent growth findings showing adult-onset male
7 obesity after gestational and lactational Pb exposure. The 2013 Pb ISA concluded that, based on the
8 findings of delayed pubertal onset among males and females, there was sufficient evidence to conclude a
9 causal relationship between Pb exposure and developmental effects.

8.1.3 Effects on Female Reproductive Function

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

8.1.4 Effects on Male Reproductive Function

18 The 2013 Pb ISA ([U.S. EPA, 2013](#)) reported multiple studies in rodents and non-human primates
19 that observed Pb-induced sperm DNA damage, reduced sperm quality, reduced sperm production, and
20 histological and ultrastructural damage to male reproductive organs. Other toxicological studies reported
21 that Pb exposure was associated with decreases in reproductive organ weights, histological changes in the
22 testes and germ cell, and subfecundity. The 2013 Pb ISA also presented toxicological evidence suggesting
23 that Pb may damage sperm cells and sex organ tissue through induction of oxidative stress ([Salawu et al.,
24 2009](#); [Shan et al., 2009](#); [Madhavi et al., 2007](#); [Rubio et al., 2006](#); [Wang et al., 2006](#)). Specifically, one study
25 reported Pb-induced increases in oxidative stress markers and reductions of levels of antioxidant enzymes
26 in testicular plasma ([Salawu et al., 2009](#)). In addition, several studies reported attenuation of Pb-induced
27 reductions in sperm count, motility, and viability when animals were co-administered substances with
28 known antioxidant properties ([Salawu et al., 2009](#); [Shan et al., 2009](#); [Madhavi et al., 2007](#); [Rubio et al., 2006](#);
29 [Wang et al., 2006](#)). Epidemiologic studies were limited due to lack of consideration of potential
30 confounding factors or the use of men attending a fertility clinic, which could result in a biased sample.
31 However, a well-conducted epidemiologic study that enrolled men going to a clinic for either infertility
32 issues or to make a semen donation and controlled for other metals as well as smoking reported a

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

8.2 Scope

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

25 Epidemiologic Studies:

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

28 **Exposure:** Exposure to Pb² 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).

1 specific focus on Pb in blood, bone, and teeth; validated environmental indicators of Pb
2 exposure;¹ or intervention groups in randomized trials and quasi-experimental studies.

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

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

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

14 **Experimental Studies:**

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

18 **Exposure:** Oral, inhalation, or intravenous routes administered to a whole animal (in vivo) that
19 results in a blood Pb level (BLL) of 30 µg/dL or below.^{2,3}

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

22 **Outcomes:** Reproductive and developmental effects.

23 **Study design:** Controlled exposure studies of animals in vivo.

8.3 Effects on Pregnancy and Birth Outcomes

24 The 2013 Pb ISA reported inconsistent findings in the epidemiologic and toxicological literature
25 for birth outcomes. Among the epidemiologic studies, there were inconsistent associations between Pb
26 exposure and preterm birth. A single study of neural tube defects (NTDs) found no associations in the
27 2013 Pb ISA, but studies within the 2006 Air Quality Criteria Document for lead (Pb AQCD) ([U.S. EPA,
28 2006](#)) reported associations between Pb exposure and NTDs. There were some associations reported
29 between Pb and low birth weight when epidemiologic studies used measures of postpartum maternal bone
30 Pb or air exposures. There were less consistent associations for maternal blood Pb measured during
31 pregnancy or at delivery or umbilical cord and placenta Pb (maternal blood Pb or umbilical cord and

¹ Studies that estimate Pb exposure by measuring Pb concentrations in PM₁₀ 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-PM₁₀ and Pb-PM_{2.5} with blood Pb level (BLLs) are lacking.

² Pb mixture studies are included if they employ an experimental arm that involves exposure to Pb alone.

³ 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.

1 placenta Pb were the biomarkers most commonly used in studies of low birth weight). The effects of Pb
2 exposure during gestation in animal toxicological studies included mixed findings, but most studies
3 reported reductions in birth weight of pups or birth weight of litters when dams were treated with Pb.

4 The recent epidemiologic and toxicological studies are detailed in the following sections. Effects
5 on pregnancy and birth outcomes encompass a large range of outcomes. The following sections relating to
6 pregnancy and outcomes are categorized into seven main sections: (1) maternal health during pregnancy;
7 (2) prenatal growth; (3) preterm birth; (4) birth defects; (5) spontaneous abortion and pregnancy loss and
8 fetal and infant mortality; (6) placental function; and (7) other pregnancy and birth outcomes. The recent
9 epidemiologic and toxicological studies reported inconsistent findings across the seven main health
10 outcomes evaluated. While recent epidemiologic studies reported consistent null associations with
11 gestational diabetes mellitus (GDM), among all other pregnancy and birth outcomes (prenatal growth,
12 preterm birth, birth defects, spontaneous abortion and pregnancy loss, and placental function, and other
13 outcomes), there were inconsistent results. These inconsistent findings may be the result of the cross-
14 sectional designs, timing of the exposure, biomarkers examined for Pb, and in some instances, small
15 sample sizes. The recent evidence from the toxicological studies mostly reported no effects of Pb across
16 pregnancy and birth outcomes. This may be due to the exclusion of toxicological studies with BLLs
17 greater than 30 µg/dL, indicating the possibility that most pregnancy and birth outcomes are only affected
18 in laboratory animals at levels higher than most environmentally relevant Pb exposure levels.

8.3.1 Maternal Health During Pregnancy

19 Maternal health during pregnancy encompasses a wide range of health effects. The details of the
20 recent epidemiologic and toxicological studies evaluating the association between Pb exposure and
21 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

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

8.3.1.1.1 Epidemiologic Studies on Gestational Diabetes Mellitus

25 There were no studies on GDM in the 2013 Pb ISA. There were several recent epidemiologic
26 studies that evaluated the association between Pb exposure and GDM and/or impaired glucose tolerance
27 (IGT) ([Tatsuta et al., 2022a](#); [Zheng et al., 2021](#); [Zhou et al., 2021b](#); [Oguri et al., 2019](#); [Soomro et al., 2019](#); [Wang
28 et al., 2019](#); [Shapiro et al., 2015](#)). Generally, across the studies there were null associations between Pb

1 exposure and GDM and IGT, and/or GDM or IGT. In studies that evaluated Pb in maternal blood with
2 GDM outcomes, the timing of when Pb was measured differed between trimesters, but the difference in
3 what trimester Pb was measured did not impact the associations ([Oguri et al., 2019](#); [Soomro et al., 2019](#);
4 [Wang et al., 2019](#); [Shapiro et al., 2015](#)). Additionally, while maternal blood was the primary biomarker used
5 to measure Pb exposure, some studies have used other biomarkers such as maternal serum ([Zhou et al.,](#)
6 [2021b](#)) and maternal erythrocytes ([Zheng et al., 2021](#)); however, the type of biomarker measurement did not
7 influence the pattern of associations. Only one study reported a decrease of 0.5 (95% CI: -1.6, -0.6)
8 mg/dL difference in mid-gestational glucose concentration associated with an interquartile range (IQR)
9 (17.6 ng/g) change in blood erythrocyte Pb exposure ([Zheng et al., 2021](#)). Furthermore, multiple studies
10 also considered co-exposure to other metals in addition to Pb, but the associations remained null ([Zheng et](#)
11 [al., 2021](#); [Zhou et al., 2021b](#); [Oguri et al., 2019](#); [Wang et al., 2019](#)). Overall, the associations between Pb
12 exposure and GDM, IGT, and GDM or IGT were null, and the null associations persisted across the
13 different trimesters of when Pb levels were measured, the different biomarkers for Pb exposure, and
14 adjustment for co-exposure to other metals.

8.3.1.1.2 Epidemiologic Studies on Epigenetic Effects During Pregnancy

15 There were no studies on epigenetic effects during pregnancy evaluated in the 2013 Pb ISA. The
16 recent epidemiologic studies on epigenetic effects during pregnancy are limited but provide insight on
17 potential mechanistic pathways in which Pb exposure may impact pregnancy. A single study by [Sanders et](#)
18 [al. \(2015\)](#) assessed the association between maternal Pb levels in blood, patella, and tibial bone and altered
19 micro RNA (miRNA) expression in the cervix during the second trimester of pregnancy in a subset of 60
20 women enrolled in a prospective birth cohort, Programming Research in Obesity, Growth, Environment
21 and Social Stressors (PROGRESS), in Mexico City. Changes in cervical miRNA expression are a
22 potential mechanism that could alter gene expression leading to aberrant changes in cervix tissue function
23 and subsequently impact parturition ([Sanders et al., 2015](#)). Expression of certain miRNAs in the cervix
24 during pregnancy have been associated with subsequent gestational age (GA) at delivery ([Sanders et al.,](#)
25 [2015](#)). During mid-pregnancy (16–19 weeks gestation), samples from cervical exams were collected and
26 analyzed for the expression profiles of 800 miRNAs. Overall, there were distinct miRNAs measured in
27 cervical samples during pregnancy that are associated with the subsequent GA of offspring. [Sanders et al.](#)
28 [\(2015\)](#) also identified differentially expressed miRNAs with respect to preterm compared term birth in a
29 subset of women. There were two miRNAs expressed in the cervix that were identified in association
30 with maternal second trimester BLLs, seven miRNAs that were identified in association with maternal
31 patella bone Pb levels, and six miRNAs that were identified in association with maternal tibia Pb levels
32 (see Table 8-2). In another epigenetics study in the same PROGRESS cohort, [Sanchez-Guerra et al. \(2019\)](#)
33 assessed the association of blood Pb exposure during pregnancy with mitochondrial DNA (mtDNA)
34 content, which is a sensitive marker of mitochondrial function and oxidative stress, in cord blood.
35 Maternal blood Pb samples were obtained at three time points (second trimester n = 410, third trimester
36 n = 356, and at delivery n = 354), and cord blood (n = 346) Pb samples were obtained at delivery.

1 Maternal Pb levels during the second trimester (β : 0.017 [95% CI: 0.002, 0.031]) was associated with
2 higher mtDNA content; however, there were null associations between cord BLLs at delivery (β : 0.016
3 [95% CI: 0.001, 0.03]), maternal third trimester blood Pb (β : 0.015 [95% CI 0.00, 0.03]), and maternal
4 BLLs at delivery (β : 0.013 [95% CI: -0.001, 0.027]). These epigenetic studies provide support of
5 potential mechanistic pathways in which Pb exposure are associated with maternal health during
6 pregnancy.

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

7 There were several other outcomes related to maternal health during pregnancy. More specific
8 study details, including Pb levels, study population characteristics, potential confounders, and select
9 results from these studies are highlighted in Table 8-2. In other outcomes related to maternal health
10 during pregnancy, Pb exposure has been associated with decreased free thyroxine (fT4) during mid-
11 pregnancy ([Kahn et al., 2014](#)); increased thyroid peroxidase antibodies (TPOAb) during mid-pregnancy
12 ([Kahn et al., 2014](#)); small increases in umbilical cord blood Pb and elevations in systolic blood pressure
13 and diastolic blood pressure during labor and delivery ([Wells et al., 2011](#)); changes in global severity index
14 (GSI), depression and anxiety symptom scores ([Li et al., 2017b](#)); bone mineral density of the patella
15 ([Osorio-Yáñez et al., 2021](#)); increased matrix metalloproteinases (MMP), regulators of uterine remodeling
16 ([Kim et al., 2022](#)); and increased risk of preeclampsia ([Gajewska et al., 2021](#); [Wu et al., 2021](#)). However, there
17 was no associations between Pb exposure and reduced cortisol awakening response ([Braun et al., 2014](#));
18 maternal depression ([Ishitsuka et al., 2020](#)); anti-Müllerian hormone (AMH), a suggested marker of ovarian
19 function and biological marker of female fecundity ([Christensen et al., 2016](#)); hormone levels in pregnancy
20 ([Gustin et al., 2021](#)); and thyroid function ([Corrales Vargas et al., 2022](#)).

8.3.1.2 Toxicological Studies on Maternal Health During Pregnancy

21 Previous Pb ISAs and AQCDs did not report any toxicological studies that investigated the
22 effects of Pb on maternal health during pregnancy. Despite this lack of prior studies to compare to, recent
23 toxicological studies have reported on the effects of Pb on maternal weight gain during pregnancy (Table
24 8-3). Maternal weight gain is often used as an indicator of fetal growth and maternal overt toxicity.
25 Additionally, maternal weight gain shares associations with gestational conditions in humans ([Santos et al.,
26 2019](#)). Recent studies dosed Sprague-Dawley rats with Pb via gavage for the first 20 days of pregnancy
27 and reported that the 160 ppm Pb treatment group exhibited reduced weight gain during pregnancy
28 (maternal BLLs on GD 20 were reported to be 23.9–27.7 $\mu\text{g}/\text{dL}$) ([Saleh et al., 2019](#); [Saleh et al., 2018](#)). Of
29 note is that both studies by Saleh et al. ([Saleh et al., 2019](#); [Saleh et al., 2018](#)) reported reduced brain weight
30 of dams, indicating that overt toxicity may have contributed to the overall reduction in maternal weight.
31 Further, the reported maternal BLLs were higher than those observed in the following studies that

1 investigated the same outcomes. [Cory-Slechta et al. \(2013\)](#) and [Schneider et al. \(2016\)](#) both dosed C57BL/6
2 mice with 100 ppm Pb via drinking water starting two months prior to mating and reported no effects on
3 maternal bodyweight gain and observed much lower maternal BLLs with [Cory-Slechta et al. \(2013\)](#)
4 reporting 12.12 µg/dL at weaning and [Schneider et al. \(2016\)](#) reporting 12.61 µg/dL on lactation day 21.
5 Similarly, [Wang et al. \(2014\)](#) reported no effects in Wistar rats dosed with Pb via drinking water for various
6 durations during pregnancy. In [Wang et al. \(2014\)](#) dosing from GD 1–10, GD 11–20, and GD 1–20 resulted
7 in maternal BLLs of 26.4, 12.4, and 36.0 µg/dL, respectively, at termination of the study on GD 20.
8 Although some of these BLLs overlap with those seen in the studies by [Saleh et al. \(2018\)](#) and [Saleh et al.](#)
9 [\(2019\)](#) wherein suppression of maternal weight gain was observed, it is possible that the use of different
10 strains or different dosing routes could be attributed to the observed difference in effect on maternal
11 weight gain. Additionally, the reduction of brain weight observed in the dams used in the studies by [Saleh](#)
12 [et al. \(2018\)](#) and [Saleh et al. \(2019\)](#) suggest that maternal overt toxicity may be responsible for the observed
13 reduction in maternal weight gain.

8.3.1.3 Integrated Summary of Effects on Maternal Health During Pregnancy

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

8.3.2 Prenatal Growth

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

8.3.2.1 Epidemiologic Studies on Prenatal Growth

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

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

21 Several cross-sectional studies that used cord blood to assess Pb exposure reported null
22 associations with birth weight ([Lee et al., 2021](#); [Govarts et al., 2020](#); [Tatsuta et al., 2017](#); [Wang et al., 2017b](#);
23 [Govarts et al., 2016](#); [García-Esquinas et al., 2013](#); [Xie et al., 2013](#)), while a single cross-sectional study
24 reported a reduction in birth weight ([Xu et al., 2012](#)). Among these cross-sectional studies, there were also
25 inconsistent associations when examining cord blood Pb exposure and birth weight among infant sex.
26 [Tatsuta et al. \(2017\)](#) evaluated the associations between cord blood Pb and birth weight between male and
27 female infants, but the associations remained null. While there were null associations with birth weight,
28 birth length, HC, and PI when infant sexes were analyzed together, analyses stratifying by infant sex
29 reported associations in male infants, including increased birth weight (β : 206.50 [95% CI: 46.15,
30 366.86]) and decreased HC (β : -0.65 [95% CI: -1.24, -0.06]) per 1-unit increase \log_{10} -Pb cord blood
31 concentration. Among female infants, there was only a reduction in PI (β : -0.16 [95% CI: -0.30, -0.02])
32 per 1-unit increase in the \log_{10} -Pb cord blood concentration ([Wang et al., 2017b](#)).

1 In addition to birth weight, there were several other prenatal growth outcomes in these cross-
2 sectional studies that were evaluated in association with cord blood Pb; however, the associations were
3 inconsistent. [García-Esquinas et al. \(2013\)](#) also reported null associations between cord blood Pb and birth
4 length, and 1- and 5-minute Apgar scores from the 144 newborns who were a part of cross-sectional
5 biomonitoring study of the BioMadrid Project. [Xu et al. \(2012\)](#) also reported decreased mean GA of
6 0.57 weeks (95% CI: 0.51, 0.63), with increased risk of low birth weight rate (OR: 1.61 [95% CI: 1.37,
7 1.90]), and increased risk of intrauterine growth retardation rate (OR: 2.12 [95% CI: 1.68, 2.69]). [Xie et al.](#)
8 [\(2013\)](#) reported a negative association with birth length (β : -0.84 cm [95% CI: -1.52, -0.16]) per square
9 root 1- $\mu\text{g}/\text{dL}$ increase in cord blood Pb, but null associations with birth weight (β : -99.33 g [95% CI:
10 -217.33, 20.67]) and HC (β : -0.36 [95% CI: -0.81, 0.03]). A single cross-sectional study that was
11 conducted among 1,578 mother-infant pairs in Saudi Arabia reported no associations between cord BLLs
12 and PI below the 10th percentile (OR: 0.66 [95% CI: 0.42, 1.05]) ([Al-Saleh et al., 2014](#)).

13 Maternal blood was also used to measure Pb exposure in association with prenatal growth
14 outcomes in multiple cross-sectional studies, but the associations were inconsistent. [Xie et al. \(2013\)](#)
15 reported a negative association with birth weight (β : -148.99 g [95% CI: -286.33, -11.66]) per square
16 root 1- $\mu\text{g}/\text{dL}$ increase in maternal blood Pb, but null associations with birth length (β : -0.46 cm [95% CI:
17 -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
18 located on the south coast of Laizhou Bay, China between 2010 and 2011. However, [Kim et al. \(2020\)](#)
19 reported negative associations between maternal blood natural log-transformed (ln)-Pb and HC (β :
20 -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
21 associations with birth weight (β : 60 g [95% CI: -15, 135]), BMI (β : -0.14 kg/m^2 [95% CI: -0.39, 0.11]),
22 and SGA (OR: 0.69 [95% CI: 0.33, 1.46]) among participants of e-waste Recycling Exposure and
23 Community Health (e-REACH) Study. A study by [Xu et al. \(2022b\)](#) reported that a one ln-unit increase in
24 maternal BLLs was associated with increased GA (β : 0.18 weeks [95% CI: 0.05, 0.31]), decreased birth
25 length (β : -0.39 cm [95% CI: -0.66, -0.22]), and decreased HC (β : -0.22 cm [95% CI: -0.39, -0.06]),
26 but a null association with birth weight. There were also null associations across tertiles of maternal BLLs
27 and low birth weight.

28 In addition to cord blood and maternal blood, other biomarkers such as maternal serum, cord
29 blood serum, and placental tissue were used to assess Pb exposure with birth weight among other cross-
30 sectional studies and reported inconsistent associations ([Yang et al., 2020](#); [Freire et al., 2019](#); [Mikelson et al.,](#)
31 [2019](#); [Tang et al., 2016](#); [Hu et al., 2015](#)). A study that measured Pb in both maternal serum and cord blood
32 serum reported null associations with birth weight for both biomarkers ([Hu et al., 2015](#)), while another
33 study reported null associations birth weight-for-gestational-age Z-score, when modeled continuously or
34 categorized by quintiles ([Yang et al., 2020](#)). Although there were null associations with birth weight and
35 GA, there was a decrease in birth height and a decrease in HC per ln-Pb increase in umbilical cord serum
36 among 103 mother-newborn pairs from an island in the East China Sea ([Tang et al., 2016](#)). When placental
37 tissue was the biomarker of exposure for Pb, a single cross-sectional study reported null associations with
38 birth weight, low birth weight, birth, head, GA, and SGA ([Freire et al., 2019](#)), but another reported a

1 decrease in birth weight of 58.3 g (95% CI: -97.9, -18.8) per ln-Pb increase in placental tissue ([Mikelson](#)
2 [et al., 2019](#)).

3 The use of advanced statistical methods to evaluate the impact of co-exposure to other metals, or
4 mixtures, helps to address uncertainties of co-pollutant confounding. To assess the associations between
5 metal mixtures (arsenic [As], cadmium [Cd], manganese [Mn], and Pb) in umbilical cord blood and birth
6 weight, birth length, and HC, 1,088 participants of a birth cohort in Bangladesh were assessed in a cross-
7 sectional study ([Lee et al., 2021](#)). There were null associations with birth weight (β : -0.04 g [95% CI:
8 -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,
9 0.23]) in association with an IQR increase in ln-Pb cord blood concentrations, when adjusted for
10 confounders and other metals. In addition to the multivariable regression analysis, [Lee et al. \(2021\)](#) also
11 used Bayesian kernel machine regression (BKMR) to estimate the effects of co-exposure to metal
12 mixtures. BKMR is a method that estimates the multivariable exposure-response function in a flexible
13 and parsimonious way, conducts variable selection on the (potentially high-dimensional) vector of
14 exposures, and allows for a grouped variable selection approach that can accommodate highly correlated
15 exposures. In the BKMR analysis, there was an inverse association between the metal mixture overall and
16 birth length when all four metal concentrations were ≥ 60 th percentile and HC when all four metals were
17 ≥ 55 th percentile, compared to their median values, with stronger associations as the concentrations of the
18 four metals increased. However, when estimating the difference in birth size with an IQR increase in each
19 individual metal when the other metals were fixed at their 25th, 50th, or 75th percentiles, the associations
20 with Pb were null.

21 Overall, in the multiple longitudinal birth cohort studies, there were inconsistent findings between
22 various Pb exposure biomarkers and prenatal growth outcomes. The multiple longitudinal birth cohort
23 studies have reported inconsistent associations. These studies collected maternal samples during different
24 time periods during pregnancy and utilized different biomarkers to measure Pb exposure to evaluate
25 associations with a variety of prenatal growth outcomes. In the longitudinal studies that measured Pb
26 exposure from maternal blood, there were inconsistent patterns of association with prenatal growth
27 outcomes, regardless of the trimester Pb exposure was measured or prenatal growth outcome (see Table
28 8-4). Several studies reported null associations with birth weight ([Shih et al., 2021](#); [Woods et al., 2017](#);
29 [Taylor et al., 2016](#); [Bloom et al., 2015](#); [García-Esquinas et al., 2014](#); [Rabito et al., 2014](#)) and birth weight Z-score
30 (BWZ) ([Daniali et al., 2023](#)), while others reported reductions in birth weight ([Goto et al., 2021](#); [Hu et al.,](#)
31 [2021](#); [Rodosthenous et al., 2017](#); [Taylor et al., 2015](#)). Of note, [Rodosthenous et al. \(2017\)](#) measured Pb levels in
32 maternal blood during the second trimester among 944 mother-infant pairs in the PROGRESS cohort in
33 association with birth weight using both linear and quantile regression. While the linear regression
34 reported a null association with birth weight-for-gestational-age Z-score (β : -0.06 [95% CI: -0.13,
35 0.003]) per \log_2 -Pb blood level increase, the quantile regression analysis revealed larger magnitudes of
36 the association maternal blood Pb and birth weight-for-gestational-age Z-score. The magnitude of the
37 association was largest in the lowest (<30th) Z-score percentiles (difference in Z-score ranged from -0.13

1 to -0.08). The use of quantile regression provides insights to potential sensitivity to Pb exposure for
2 smaller infants, an association that was not detected by linear regression.

3 While some studies reported null associations with birth length ([Daniali et al., 2023](#); [Shih et al.,
4 2021](#); [Bloom et al., 2015](#)), a single study reported a 0.20 cm decrease (95% CI: -0.30, -0.10) in birth length
5 per 1 µg/dL increase in maternal BLL (collected during the during the second or third trimester) among
6 participants of the Japan Environment and Children's Study (JECS) ([Goto et al., 2021](#)). A single study
7 reported a reduction in HC of 0.03 cm (95% CI -0.06, -0.00) per 1 µg/dL increase of first trimester
8 maternal blood Pb ([Taylor et al., 2016](#)), but other studies reported null associations with HC and first
9 trimester maternal blood Pb ([Daniali et al., 2023](#); [Taylor et al., 2015](#)), pre-pregnancy maternal and parental
10 blood ([Bloom et al., 2015](#)), or second or third trimester maternal blood Pb ([Shih et al., 2021](#)). While there
11 was reported decreased GA (β : -1.9 days [95% CI: -3.1, -0.5]) per IQR increase in second trimester
12 maternal In-Pb blood level among those in Puerto Rico Testsite for Exploring Contamination Threats
13 (PROTECT) cohort ([Ashrap et al., 2020](#)), there were null associations with gestational and pre-pregnancy
14 maternal and parental blood ([Bloom et al., 2015](#)) and maternal BLLs during the second or third trimester
15 among the JECS ([Goto et al., 2021](#)); however, [Goto et al. \(2021\)](#) did report an increased risk of SGA (OR:
16 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
17 1 µg/dL increase in maternal BLL, but other studies did not report increased risk of SGA ([Thomas et al.,
18 2015](#)) and maternal blood (collected during the first and third trimesters of pregnancy) or second trimester
19 maternal blood ([Ashrap et al., 2020](#)). There were consistent null associations with PI and maternal blood
20 ([Shih et al., 2021](#); [Bloom et al., 2015](#)) and crown-to-heel length and first trimester maternal blood Pb ([Taylor
21 et al., 2016](#); [Taylor et al., 2015](#)).

22 In addition, some of the longitudinal studies considered different effect modifiers when assessing
23 the associations between maternal BLLs and prenatal growth outcomes. Among participants in the
24 Canadian Maternal-Infant Research on Environmental Chemicals (MIREC) study, there null associations
25 between maternal blood (collected during the first and third trimesters of pregnancy) and SGA across
26 tertiles of maternal blood Pb ([Thomas et al., 2015](#)). In addition, an exploratory analysis was conducted to
27 examine the potential effect modification of single nucleotide polymorphisms (SNP) in GSTP1 and
28 GSTO1 genes on the relationship of maternal blood Pb and SGA. There was a marginal interaction
29 between maternal Pb exposure and the GSTP1 A114V SNP ($p = 0.06$), but there was no indication of
30 effect modification by other GSTP1 and GSTO1 SNPs on the associations between maternal blood Pb
31 and SGA. In another study in the PROTECT cohort, the modifying effect of psychosocial stress on the
32 association between maternal blood Pb exposure and GA, BWZ, SGA, and LGA were examined in a
33 subset of 682 pregnant women ([Ashrap et al., 2021](#)). Maternal blood samples were collected at
34 18 ± 2 weeks gestation and 26 ± 2 weeks gestation. Among mothers who reported "good" psychosocial
35 status, there was decreased gestation age (β : -1.9 days [95% CI: -3.2, -0.6]); however, there were null
36 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:
37 0.89 [95% CI: 0.64, 1.23]). The associations for mothers who reported "poor" psychosocial status were
38 null across the birth outcomes.

1 In addition to the associations between prenatal growth outcomes and Pb levels, there were sex-
2 stratified differences. In a study by [García-Esquinas et al. \(2014\)](#), 97 mother-father-infants in the BioMadrid
3 Study were used to evaluate associations between prenatal Pb exposure and fetal development from three
4 biomarkers (maternal and paternal blood Pb at 34 weeks gestation and cord blood at delivery) with
5 different growth metrics at birth. While there were no associations between log-Pb blood levels (maternal,
6 paternal, or cord) and gestation age, birth weight, birth length, abdominal diameter, or cephalic diameter
7 (CD), associations were observed when analyses were stratified by infant sex. Among female infants,
8 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,
9 -0.07) per two-fold increase in paternal BLLs ($\mu\text{g/L}$), but there were no associations among male infants.
10 In the study by [Shih et al. \(2021\)](#), there were null associations between maternal blood \log_2 -Pb
11 concentrations (collected between 6 and 32 weeks of gestation) and prenatal growth outcomes (GA, birth
12 weight, birth length, HC, and PI). However, when stratified by infant sex, there were reductions in GA (β :
13 -0.98 weeks [95% CI: -1.67, -0.30]), birth weight (β : -381 g [95% CI: -583, -178]), birth length (β :
14 -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
15 association with PI (β : -1.07 kg/m³ [95% CI: -1.56, 0.39]) among female infants, while the associations
16 for these same outcomes were null among male infants.

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

28 In addition to maternal blood Pb, other biomarkers such as maternal erythrocytes, maternal
29 serum, and teeth were used to assess Pb exposure with prenatal birth outcomes, including birth weight,
30 birth length, or HC. Maternal erythrocytes from blood samples were collected during the third trimester
31 (mean: gestational week 29) from 584 mothers in the Nutritional impact on Immunological maturation
32 during Childhood in relation to the Environment (NICE) study in Northern Sweden ([Gustin et al., 2020](#)).
33 Maternal erythrocytes reflect exposure over the past 1–3 months. A doubling of maternal erythrocyte Pb
34 concentration was not associated with birth weight (β : -13 g [95% CI: -66, 41]), birth length (β :
35 -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
36 concentration less than the median of 14 $\mu\text{g/kg}$ and β : -0.24 cm [95% CI: -0.53, 0.056] for maternal
37 erythrocyte Pb concentration greater than median of 14 $\mu\text{g/kg}$). There was no interaction by infant sex.
38 When mutually adjusted for other maternal metal exposure to Cd and Hg, the null associations persisted.

1 In a subset of the Project Via prospective pre-birth cohort, individual and joint effects of metal mixture
2 components on birth weight, length, HC, and GA were estimated in association with maternal erythrocyte
3 Pb concentrations collected during early pregnancy (11.3 ± 2.8 weeks of gestation) from 1,423 mother-
4 infant pairs ([Rahman et al., 2021](#)). In single metal model, an IQR increase in maternal erythrocyte Pb
5 concentration was associated with a 33.9 g (95% CI: $-65.3, -2.5$) decrease in birth weight, but there were
6 no associations with birth length (β : -0.10 cm [95% CI: $-0.29, 0.09$]), HC (β : -0.07 cm [95% CI: $-0.17,$
7 0.04]), or GA (β : 0.03 weeks [95% CI: $-0.10, 0.16$]). When stratified by infant sex, the associations were
8 null for both male and female infants and birth weight, birth length, HC, and GA. There were no
9 associations between Pb and birth weight, birth length, HC, and GA in the metal mixture analysis overall
10 or in the infant sex-stratified analyses.

11 A total of 3,125 mother-infant pairs were recruited from the China-Anhui Birth Cohort Study (C-
12 ABCS) to investigate the associations between maternal serum Pb levels the first trimester (median of
13 11 weeks gestation) and in the second trimester (median of 16 weeks gestation) with growth metrics
14 ([Wang et al., 2017a](#)). Overall maternal serum Pb during pregnancy had a negative association with birth
15 weight (β : -2.74 g [95% CI: $-5.17, -0.31$]), but null associations with birth length, HC, and chest
16 circumference. When stratified by trimester, the negative association with birth weight persisted, with a
17 reduction of 4.40 g (95% CI: $-8.22, -0.58$) for first trimester maternal serum Pb and a 1.64 g (95% CI:
18 $-4.80, -0.58$) reduction for second trimester maternal serum Pb. There were no associations by trimester
19 maternal serum Pb for birth length, HC, or chest circumference. In addition, there was increased risk of
20 SGA of 1.45 (95% CI: 1.04, 2.02) for subjects with medium-Pb maternal serum (1.18 – 1.70 $\mu\text{g/dL}$) and
21 increased risk of SGA of 1.69 (95% CI: 1.22, 2.34) in subjects with high-Pb maternal serum
22 (≥ 1.71 $\mu\text{g/dL}$), compared to low-Pb maternal serum (< 1.18 $\mu\text{g/dL}$). When stratified by infant sex, there
23 was increased risk of SGA among female infants (OR: 1.51 [95% CI: 0.99, 2.31] for medium-Pb maternal
24 serum and OR: 1.68 [95% CI: 1.12, 2.54] for high-Pb maternal serum), but among male infants, the
25 associations were null. There was an increased risk of SGA with high first trimester maternal serum Pb
26 (OR: 2.13 [95% CI: 1.24, 3.38]), but there were null associations among second trimester maternal serum
27 Pb.

28 In a small cohort study, second and third trimester Pb levels were estimated from baby teeth from
29 145 participants in the Wayne County Health, Environment, Allergy and Asthma Longitudinal Study
30 (WHEALS) ([Cassidy-Bushrow et al., 2019](#)). There were no associations between tooth Pb in the second or
31 third trimester and BWZ (β : -0.15 [95% CI: $-0.35, 0.05$] for second trimester and β : -0.06 [95% CI:
32 $-0.24, 0.12$] for third trimester) or GA at delivery (β : 0.08 [95% CI: $-0.19, 0.35$] for second trimester and
33 β : 0.14 [95% CI: $-0.11, 0.39$] for third trimester) in the fully adjusted models. There was no indication
34 that there was a time effect (difference between the effect estimates in the second and third trimesters) for
35 birth weight for Z-score (β : -0.31 [95% CI: $-0.90, 0.28$]) or GA at delivery (β : -0.22 [95% CI: $-1.08,$
36 0.64]). Additionally, when stratified by child's sex, there were no associations between tooth Pb in the
37 second or third trimester and BWZ or GA at delivery.

1 In a study by [Bui et al. \(2022\)](#), effects of short-term maternal exposure to airborne Pb during
2 pregnancy on birth weight, low birth weight, and SGA was estimated using a quasi-experimental variation
3 in airborne Pb exposure based on the National Association for Stock Car Auto Racing (NASCAR)'s
4 deleading of racing fuel in a difference-in-difference model in the Charlotte-Concord-Gastonia
5 Metropolitan Statistical Area in North Carolina. There was an average increase in birth weight of
6 102.50 g (95% CI: 45.73, 159.2), decreased probability of low birth weight of 0.0445 (95% CI: -0.0697,
7 -0.0194), and reduction in the probability of SGA of 0.0396 (95% CI: -0.0638, -0.0155) among children
8 born to mothers residing less than 4000 meters of the Charlotte Motor Speedway, compared with those
9 residing greater than 10,000 meters.

8.3.2.2 Toxicological Studies on Prenatal Growth

10 The 2013 Pb ISA discussed a few studies that reported reduced birth weight of offspring from Pb-
11 treated dams ([Massó-González and Antonio-García, 2009](#); [Wang et al., 2009](#); [Teijón et al., 2006](#)). Recent
12 toxicological studies consistently report no effects of Pb on birth weight (Table 8-3). Most studies began
13 exposure of the dam prior to conception of the offspring ([Zhao et al., 2021](#); [Tartaglione et al., 2020](#); [Rao](#)
14 [Barkur and Bairy, 2016](#); [Schneider et al., 2016](#); [Barkur and Bairy, 2015](#); [Weston et al., 2014](#); [Cory-Slechta et al.,](#)
15 [2013](#)) and a few studies began exposure of the dam at the time of conception (GD 0) ([Rao Barkur and Bairy,](#)
16 [2016](#); [Barkur and Bairy, 2015](#); [Barkur et al., 2011](#)). Of note is that [Teijón et al. \(2006\)](#), a study discussed in the
17 2013 Pb ISA, elaborated that the observed reduction in litter weights born to Pb-treated dams was largely
18 driven by the reduced size of female pups, whereas males were unaffected. In agreement, some recent
19 studies that reported no effect of Pb on birth weight assessed weight in male pups only ([Barkur and Bairy,](#)
20 [2015](#); [Barkur et al., 2011](#)). However, all other recent studies included females in birth weight analyses and
21 reported no effects of Pb on birth weight of exposed offspring.

8.3.2.3 Integrated Summary of Effects on Prenatal Growth

22 The epidemiologic studies in the 2013 Pb ISA reported associations between maternal bone Pb
23 and low birth weight and with studies of Pb air exposures and birth weight. The associations were less
24 consistent when using maternal blood Pb or umbilical cord and placenta Pb as the exposure measurement
25 although some studies did demonstrate associations. The studies of Pb exposure and fetal growth were
26 limited by cross-sectional study design, small sample size, high Pb concentrations (air Pb as high as
27 30 µg/m³), and in some studies, the lack of control of confounders. Overall, the recent epidemiologic
28 studies reported inconsistent associations between Pb exposure and prenatal growth outcomes, while the
29 toxicological studies consistently reported no effects of Pb on offspring birth weight. The inconsistent
30 findings from the recent epidemiologic studies may be due to differences in study design, timing of when
31 the exposure was measured (e.g., during pregnancy, at delivery), biomarkers examined for Pb (e.g.,
32 maternal blood, cord blood, maternal red blood cells, maternal serum, placental tissue), difference in

1 growth metrics assessed (e.g., birth weight, birth length, GA), and small sample sizes in some studies.
2 While there were inconsistencies in the findings among the epidemiologic studies, the recent
3 epidemiologic studies were able to address a few of the uncertainties in the 2013 Pb ISA, with many of
4 the recent studies were conducted in well-designed longitudinal birth cohorts, considered the differences
5 in effects by infant sex, and controlled for wide range of confounders, including GA (when not an
6 outcome of interest), and maternal health factors (e.g., smoking, parity, BMI). Additionally, some
7 epidemiologic studies controlled for other metal exposure, and other studies evaluated the associations
8 with joint effects or as a mixture. A few toxicological studies were reviewed in the 2013 Pb ISA, all of
9 which reported reductions in birth weight of offspring born from Pb-exposed dams. However, recent
10 toxicological studies do not support previous studies and consistently report no effects of Pb on offspring
11 birth weight.

8.3.3 Preterm Birth

12 The recent epidemiologic and toxicological studies that examined the relationship between Pb
13 exposure and preterm birth are summarized in the text below. Study details of the recent epidemiologic
14 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

15 The epidemiologic studies reviewed in the 2013 Pb ISA reported inconsistent findings regarding
16 a relationship between indicators of Pb exposure and preterm birth. There were no apparent patterns
17 within the type of exposure measurement or Pb level. Many of these studies are limited by the small
18 number of preterm births and their cross-sectional design (i.e., studies of umbilical cord blood may not
19 adequately characterize BLLs earlier in pregnancy). Among the longitudinal cohort studies, the results
20 were mixed, with some studies reporting associations between maternal blood Pb during pregnancy and
21 preterm birth. Most studies controlled for potentially important confounders, such as maternal age and
22 smoking.

23 In the recent epidemiologic studies examining the risk of preterm birth and Pb exposure, the
24 findings were inconsistent (Table 8-5). In a cross-sectional study, cord blood samples were obtained from
25 432 infants born in an area with e-recycling (Guiyu) and 99 from an area without e-recycling (Xiamen) in
26 China, but there was no increased risk of preterm birth (OR: 1.09 [95% CI: 0.93, 1.28]) (Xu et al., 2012).
27 In a cross-sectional study of 696 mother-infant pairs in the Study on the Environment and Reproductive
28 Health (EMASAR) cohort in Argentina, the relationship between maternal Pb levels, which were
29 collected 36 ± 12 hours postpartum, and preterm birth was examined (Xu et al., 2022b). Among tertiles of
30 maternal Pb levels, there were null associations with preterm birth (OR: 1.24 [95% CI: 0.35, 4.4] in tertile
31 2 and OR: 1.26 [95% CI: 0.32, 5.00] in tertile 3). In another cross-sectional study, placental tissue Pb

1 levels were assessed in association with preterm birth among 327 mother-infant pairs who were part of
2 the Instituto de Nanociencia y Materiales de Aragón (INMA) Project in Spain and found no association
3 with risk of preterm birth (OR: 0.40 [95% CI: 0.04, 4.70]) ([Freire et al., 2019](#)).

4 In a case-control study, maternal serum Pb, collected during the first or second trimester, was not
5 associated with risk of spontaneous preterm birth (OR: 1.46 [95% CI: 0.97, 2.18]) among 147 cases and
6 381 controls ([Yu et al., 2019](#)). When stratified by the trimester of collection of maternal serum Pb, there
7 was null association for spontaneous preterm birth (OR: 1.63 [95% CI: 0.91, 2.91]) with first trimester
8 maternal serum Pb only or second trimester maternal serum Pb only (OR: 1.27 [95% CI: 0.71, 2.28]). In a
9 nested case-control study, the association between exposure to 41 metals/metalloids, including Pb, during
10 early pregnancy measured in maternal serum and risk of spontaneous preterm birth was investigated ([Xu
11 et al., 2022a](#)). There were 74 cases of spontaneous preterm birth and 74 controls. In the highest quartile of
12 maternal serum Pb levels, there was an increased risk of spontaneous preterm birth of 4.09 (95% CI: 1.31,
13 12.77) and there was evidence of potential exposure-response across the quartiles (p for trend: 0.017).

14 [Tsuji et al. \(2018\)](#) used data on 14,847 pregnant women who were participants of the JECS to
15 assess the association between second and third trimester maternal blood (collected at gestational weeks
16 14–39) and early preterm (22 to <34 weeks) and late preterm (34 to <37 weeks). Among the quartiles of
17 Pb exposure, there was no increased risk in early preterm birth or late preterm birth. There was also no
18 evidence of a linear exposure-response trend among the Pb exposure quartiles in either the early preterm
19 births (p for trend: 0.134) or late preterm (p for trend: 0.920). In another cohort study using data from the
20 JECS, per each 0.1 µg/dL increase in maternal BLL, there was no increased risk of preterm delivery (OR:
21 0.90 [95% CI: 0.70, 1.16]) ([Goto et al., 2021](#)).

22 In a small cohort (n = 98) from the Conditions Affecting Neurocognitive Development and
23 Learning in Early Childhood (CANDLE) study in Shelby County, TN, Pb was measured cord blood and
24 from maternal blood collected during the second and third trimester, at delivery ([Rabito et al., 2014](#)). Each
25 0.1-unit increase in maternal blood Pb in the second trimester (OR: 1.66 [95% CI: 1.23, 2.23]) and third
26 trimester (OR: 1.24 [95% CI: 1.01, 1.52]) was positively associated with preterm birth, but there was no
27 increased risk of early-term birth (≥37 to <39 weeks) associated with maternal blood Pb in the second
28 trimester (OR: 0.87 (95% CI: 0.63, 1.20)) and third trimester (OR: 0.88 [95% CI: 0.69, 1.13]).

29 In the Avon Longitudinal Study of Parents and Children, maternal blood samples were collected
30 as early as possible in pregnancy, with a median GA of 11 weeks at the time of sampling (range 1–
31 42 weeks, IQR 9–13 weeks) ([Taylor et al., 2015](#)). There was increased risk of preterm delivery (OR: 2.00
32 [95% CI: 1.35, 3.00]) for maternal BLLs ≥5 µg/dL. [Li et al. \(2017a\)](#) investigated the associations between
33 maternal serum Pb levels and risk of preterm birth in a population-based birth cohort (n = 3,125), part of
34 the China-Anhui Birth Cohort. Maternal serum Pb levels were categorized into tertiles: low-Pb
35 (<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
36 preterm birth in the medium-Pb tertile (OR: 2.33 [95% CI: 1.49, 3.65]) and high-Pb tertile (OR: 3.09
37 [95% CI: 2.01, 4.76]).

1 In a study by [Ashrap et al. \(2020\)](#), individual and mixture effects of metals and metalloids on
2 preterm birth among 731 pregnant women in the PROTECT cohort were examined. Maternal blood was
3 collected at 16–20 and 24–28 weeks gestation. There was an increased risk of preterm birth (OR: 1.63
4 [95% CI: 1.17, 2.28]) and spontaneous preterm birth (OR: 1.53 [95% CI: 1.00, 2.35]) per IQR increase in
5 maternal blood Pb in the individual pollutant model. The mixture pollutant models and elastic net
6 regularization identified Pb and zinc as the most important predictors of preterm birth, while BKMR
7 method identified Pb, zinc, and Mn as most predictive of preterm birth. In another study in the PROTECT
8 cohort, the modifying effect of psychosocial stress on the association between Pb and overall preterm
9 birth (<37 completed weeks of gestation) and spontaneous preterm birth (<37 completed weeks of
10 gestation defined as presentation of premature rupture of the membranes, spontaneous preterm labor, or
11 both) ([Ashrap et al., 2021](#)). There was an increased risk of overall preterm birth among mothers who
12 reported “good” psychosocial status (OR: 1.72 [95% CI: 1.14, 2.58]), but null association among mothers
13 who reported “poor” psychosocial status (OR: 1.43 [95% CI: 0.69, 2.97]). There were null associations
14 among mothers who reported “good” psychosocial status and “poor” psychosocial status and spontaneous
15 preterm birth (OR: 1.56 [95% CI: 0.93, 2.6] and OR: 1.22 [95% CI: 0.42, 3.56], respectively).

16 In a study by [Bui et al. \(2022\)](#), the effects of short-term maternal exposure to airborne Pb during
17 pregnancy on preterm birth was estimated using a quasi-experimental variation in airborne Pb exposure
18 based on NASCAR’s deleading of racing fuel in a difference-in-difference model in the Charlotte-
19 Concord-Gastonia Metropolitan Statistical Area in North Carolina. There was decreased probability of
20 preterm birth of 0.295 (95% CI: –0.0572, –0.000185) among children born to mothers residing less than
21 4000 meters of the Charlotte Motor Speedway, compared to those residing greater than 10,000 meters.

8.3.3.2 Toxicological Studies on Preterm Birth

22 Both the 2013 Pb ISA and the 2006 Pb AQCD did not describe any studies that reported on the
23 effects of Pb on preterm birth in animals. Only one recent study was found that reports on gestation
24 duration ([Betharia and Maher, 2012](#)). [Betharia and Maher \(2012\)](#) reported no effect of Pb on gestation term
25 when Sprague-Dawley rats were dosed from GD 0 to postnatal day (PND) 20. BLLs were measured in
26 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

27 In summary, there were inconsistencies in the recent epidemiologic studies examining the
28 relationship between Pb exposure and risk of preterm birth, similar to the 2013 Pb ISA. There was no
29 apparent pattern associated with any biomarker of Pb exposure. Several of the recent epidemiologic
30 studies were conducted in well-designed, longitudinal birth cohorts, and controlled for wide range of
31 confounders, including GA, other metals, and maternal health factors (e.g., smoking, parity, BMI). The

1 inconsistent findings may be due to differences in study design, timing of the exposure (e.g., during
2 pregnancy, at delivery), biomarkers examined for Pb (e.g., maternal blood, cord blood, maternal red blood
3 cells, maternal serum, placental tissue), and small sample sizes in some studies. There were no
4 toxicological studies that investigated the effects of Pb on preterm birth in the 2013 Pb ISA and the 2006
5 Pb AQCD, and recent toxicological data are sparse with only a single PECOS-relevant study available,
6 which reported no effects of Pb on gestation duration, making it difficult for toxicological data to support
7 epidemiological evidence.

8.3.4 Birth Defects

8 The recent epidemiologic and toxicological studies that examined the relationship between Pb
9 exposure and birth defects are summarized in the text below. Study details of the recent epidemiologic
10 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

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

15 A few recent epidemiologic studies examined the relationship between Pb levels and birth
16 defects. Several studies evaluated the association between NTDs in different biomarkers (placental tissue,
17 umbilical cord tissue, and maternal serum) ([Liu et al., 2021](#); [Tian et al., 2021](#); [Jin et al., 2013](#)). The cross-
18 sectional studies that measured Pb exposure from placental tissue or umbilical cord tissue reported no
19 increased risk for NTDs overall or by subtype ([Liu et al., 2021](#); [Jin et al., 2013](#)) (see Table 8-6 for details).
20 However, in a case-control study which evaluated the single and joint effects of 10 metals measured in
21 maternal serum during pregnancy, there was increased risk for NTDs ([Tian et al., 2021](#)). In the single
22 pollutant model, there was increased risk of NTD of 2.05 (95% CI: 1.05, 4.02) in the second tertile and
23 3.51 (95% CI: 1.76, 6.98) in the third tertile, relative to the lowest tertile of maternal serum Pb levels,
24 indicating an exposure-response relationship (p for trend: <0.001). There was also increased risk by NTD
25 subtype. There was increased risk of spina bifida of 2.16 (95% CI: 1.00, 4.88) in the second tertile and
26 5.16 (95% CI: 2.24, 11.87) in the third tertile, relative to the lowest tertile of maternal serum Pb levels,
27 with an indication of an exposure-response relationship (p for trend: 0.022). For anencephaly, there was
28 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
29 third tertile, relative to the lowest tertile of maternal serum Pb levels, with an indication of an exposure-
30 response (p for trend: 0.002). Among female infants, there was increased risk of NTD of 6.45 (95% CI:
31 2.20, 18.95) in the highest tertile, relative to the lowest tertile of maternal serum Pb levels, with exposure-

1 response relationship (p for trend: 0.001). Among male infants, there was increased risk of NTD of 2.16
2 (95% CI: 1.03, 4.59), and an indication of an exposure-response relationship (p for trend: 0.048).

3 [Pi et al. \(2018\)](#) investigated the associations between placental Pb concentrations and the risk of
4 orofacial cleft defects among 103 cases and 206 controls in northern China. With increasing tertiles of
5 placenta Pb concentrations (p for trend <0.001), there was increased odds of orofacial defects of 3.88
6 (95% CI: 1.78, 8.42) for those in the second (57.5–96.8 ng/g dry weight) tertile of placenta Pb exposure
7 and 5.17 (95% CI: 2.37, 11.29) for those in the highest (\geq 96.8 ng/g dry weight) tertile of placenta Pb
8 exposure, compared to the lowest (<57.5 ng/g dry weight). When restricting to those with higher than the
9 median placenta Pb concentration (\geq 77.2 ng/g), there was increased risk of 3.08 (95% CI: 1.74, 5.47) of
10 orofacial cleft defects among 71 cases and 84 controls. However, in a nested case-control study among a
11 subset of participants in the JECS, [Takeuchi et al. \(2022\)](#) did not find increased risk of cleft lip and palate
12 (n = 192 cases and n = 1,920 matched controls) and second trimester maternal blood Pb concentrations
13 (OR: 1.10 [95% CI: 0.55, 2.21]), which controlled for co-exposure to three other metals (Hg, Cd, and Mn)
14 in the multivariate model.

15 In another study of the JECS, maternal serum Pb samples were collected during mid- and late
16 gestation and were evaluated in association with congenital abdominal malformations ([Miyashita et al.,
17 2021](#)). There were 139 cases and 89,134 controls. There were null associations across the quartiles of
18 maternal serum Pb concentrations and any abdominal malformations, with no exposure-response
19 relationship across quartiles (p for trend: 0.233). The null associations persisted for the subtypes of
20 congenital abdominal malformations, but there was an inverse exposure-response relationship observed
21 across the quartiles of maternal serum Pb and omphalocele (p for trend: 0.033).

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

8.3.4.2 Toxicological Studies on Birth Defects

27 The 2013 Pb ISA did not report any toxicological studies that investigated the effects of Pb on
28 birth defects. The 2006 Pb AQCD described studies that reported Pb-induced birth defects; however,
29 these findings were confounded by maternal toxicity ([Dey et al., 2001](#); [Ronis et al., 1996](#); [Flora and Tandon,
30 1987](#)). Two recent studies published since the 2013 Pb ISA have investigated Pb-induced birth defects in
31 offspring in rodents (Table 8-3). Both studies dosed Wistar rats with 0.2% Pb in the drinking water for
32 varying duration, including dosing starting 30 days prior to gestation and ending the day prior to mating,
33 dosing from GD 0 to PND 21, and dosing from GD 0 to 21 ([Rao Barkur and Bairy, 2016](#); [Barkur and Bairy,
34 2015](#)). Offspring BLLs measured on PND 22 varied between 3.02–3.03 μ g/dL for animals from dams

1 dosed prior to gestation, 5.30–5.51 µg/dL for animals from dams dosed during gestation, and 31.6–
2 32.0 µg/dL for animals from dams dosed from the beginning of gestation to lactation day 21. No maternal
3 toxicity was apparent in any of the recent studies, suggesting that the contrast found between the lack of
4 malformations observed in these recent publications and the reported malformations described in the 2006
5 Pb AQCD may be attributed to a lack of maternal toxicity due to the use of lower doses in more recent
6 studies.

8.3.4.3 Integrated Summary of Effects on Birth Defects

7 The studies reviewed in the 2013 Pb ISA did not report associations between Pb exposure and
8 NTDs. Among the recent epidemiologic studies, there were inconsistent associations with Pb exposure
9 and NTDs, congenital heart defects, and orofacial clefts defects. While the associations were generally
10 null for NTDs and CHDs, there were positive associations with orofacial cleft defects. These findings are
11 limited by the different birth defects of interest, the small sample sizes, timing of Pb exposure (no
12 exposure measurements during pregnancy), differences in the biomarker tested, and the confounders
13 considered in the analyses. The recent epidemiologic studies controlled for a wide range of potential
14 confounders; however, which was a limitation from the 2013 Pb ISA. Further, some studies considered
15 co-exposure to other metals and differences by infant sex. Some previous toxicological studies reported
16 that Pb exposure resulted in birth defects in offspring, but it was noted that these studies often used doses
17 so high that maternal toxicity occurred as well. Recent toxicological studies report no effects of Pb on
18 birth defects in offspring and also do not report that maternal toxicity occurred, further supporting that
19 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

20 The 2013 Pb ISA concluded that the toxicological and epidemiologic data provided inconsistent
21 findings for the role of Pb in spontaneous abortions, while there were no available epidemiologic or
22 toxicological studies on the relationship between Pb levels and infant mortality. The recent epidemiologic
23 and toxicological studies examining the relationship between Pb exposure and spontaneous abortion,
24 pregnancy loss, and fetal and infant mortality are summarized in the text below. Study details of the
25 recent epidemiologic studies are included in Table 8-7 and the recent toxicological studies are in Table 8-
26 3.

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

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

13 There were only a few recent epidemiologic studies that evaluated Pb exposure and spontaneous
14 abortion and pregnancy loss. There were inconsistent findings among the studies and no apparent pattern
15 of association by biomarker of Pb exposure. In a cross-sectional study, cord blood samples were obtained
16 from 432 infants born in an area with e-recycling (Guiyu) and 99 from an area without e-recycling
17 (Xiamen) in China ([Xu et al., 2012](#)). There was an increased risk of 4.20 (95% CI: 3.40, 5.18) of stillbirth
18 rate with cord BLLs comparing infants from the area with e-recycling (Guiyu) compared to infants from
19 the area without e-recycling (Xiamen). In a recent cohort study, couples (n = 344) were prospectively
20 followed to explore the relationship between blood Pb concentrations at enrollment and with pregnancy
21 followed to estimate the risk of incident of pregnancy loss ([Louis et al., 2017](#)). Each participant's blood Pb
22 concentration and time to pregnancy loss was modeled individually and as a couple. In the individual
23 partner models, there was no increased risk of pregnancy loss for female partner blood Pb (HR: 1.01
24 [95% CI: 0.82, 1.25]) or male partner blood Pb (HR: 0.95 [95% CI: 0.77, 1.17]). In the couple-based
25 model, the associations were unchanged (female partner HR: 1.01 [95% CI: 0.80, 1.28] and male partner
26 HR: 0.96 [95% CI: 0.77, 1.22]). Among a cohort of 166 women in Iran, there was no increased risk (OR:
27 1.08 [95% CI: 0.98, 1.20]) of spontaneous abortion with maternal BLLs in early pregnancy ([Vigeh et al.,
28 2021](#)). In another prospective cohort among women seeking treatment at a fertility clinic in Turkey, blood
29 Pb concentrations were assessed in association with ongoing pregnancy ([Tolunay et al., 2016](#)). The study
30 participants were categorized into patients with ongoing pregnancy (n = 20) and patients who experienced
31 assisted reproductive technology (ART) failure, miscarriage, or biochemical pregnancy (n = 81). There
32 was a 2.2% lower risk (RR: 0.978 [95% CI: 0.957, 0.999]) for ongoing pregnancy for each 1 µg/dL higher
33 blood Pb concentration. Among a cohort of 1,184 women undergoing assisted reproductive therapy in
34 China, associations between maternal serum Pb concentrations and spontaneous abortion before
35 gestational week 12 were evaluated ([Li et al., 2022](#)). There was an increased risk of 1.39 (95% CI: 1.02,
36 1.91) of spontaneous abortion before gestational week 12 with increasing maternal Pb serum levels. When

1 categorized into tertiles, the associations between maternal Pb serum levels and spontaneous abortion
2 before gestational week 12 were null.

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

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

18 Postnatal offspring mortality was also investigated in some rodent studies, and some studies
19 reported on measures of offspring mortality that included postnatal death and survival until certain
20 timepoints after birth (e.g., weaning). These studies also did not report any effects of Pb exposure on
21 postnatal survival. Most studies utilized dosing paradigms that dosed before or during gestation ([Barkur
22 and Bairy, 2015](#); [Betharia and Maher, 2012](#)) and reported BLLs at different times postnatally (PND 2–60;
23 0.0318 µg/dL–5.30 µg/dL) with BLLs tending to be lower in time points with the longest amount of time
24 since cessation of exposure. Some studies utilized a dosing paradigm that exclusively exposed animals
25 postnatally ([Barkur and Bairy, 2015](#); [Graham et al., 2011](#)). In agreement, these studies also reported no
26 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

27 The 2013 Pb ISA reported inconsistent findings from the epidemiologic studies on Pb exposure
28 and spontaneous abortion and pregnancy loss. The findings from recent epidemiologic studies on Pb
29 exposure and spontaneous abortion and pregnancy loss were also inconsistent. A single cross-sectional
30 study reported increased risk of stillbirth with cord blood Pb. While recent cohort studies among healthy

1 participants did not find increased risk of pregnancy loss or spontaneous abortion, women seeking
2 treatment from a fertility clinic had increased risk of spontaneous abortion before gestational week 12 or
3 decreased risk of an on-going pregnancy. The women seeking fertility treatment that were recruited as
4 participants may be different from those in the general population, limiting the generalizability of the
5 results as the study populations may not be representative of the general population. Previous
6 toxicological studies reported increased rates of pregnancy loss and implantation loss in animals dosed
7 with Pb during gestation. This contrasts with more recent literature which did not report any effect of Pb
8 on pre- or postnatal offspring mortality. Although not always consistent, BLLs were generally lower in
9 recent toxicological literature when compared to previous literature, possibly explaining the observed
10 contrast in results.

8.3.6 Placental Function

11 In the 2013 Pb ISA, there were no epidemiological or toxicological studies available that
12 evaluated Pb concentrations and associations with placenta function. Recent epidemiologic and
13 toxicological studies evaluating the association between Pb exposure and placental function are limited.
14 The epidemiologic studies were cross-sectional studies. Study details for the recent epidemiological
15 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

16 In the 2013 Pb ISA, there were no epidemiological studies available that evaluated Pb
17 concentrations and associations with placenta function. In the recent cross-sectional epidemiological
18 studies, there were different markers of placental function evaluated. One marker of placental function
19 that was evaluated was placental thickness, which can restrict intrauterine fetal growth ([Al-Saleh et al.,
20 2014](#)). Maternal BLLs measured at delivery were found to be associated with the risk of placental
21 thickness below the 10th percentile (OR: 1.64 [95% CI: 1.12, 2.41]). In another study, using a cross-
22 section from the JECS, the relationship between maternal blood Pb collected during the second trimester
23 and placental previa and placenta accreta among 16,019 women was examined ([Tsuji et al., 2019](#)). Placenta
24 previa is a condition in which the placenta is attached to the lower uterine segment and completely or
25 partially covers the internal cervix, and when chorionic villi abnormally invade to myometrium, placenta
26 accreta occurs ([Tsuji et al., 2019](#)). There was increased odds of placenta previa in the second quartile
27 (4.80–5.95 ng/g) of maternal blood Pb (OR: 2.59 [95% CI: 1.40, 4.80]), but null associations the third
28 quartile (5.96–7.44 ng/g) maternal blood Pb (OR: 1.32 [95% CI: 0.66, 2.64]) and fourth quartile
29 (≥ 7.45 ng/g) maternal blood Pb (OR: 1.34 [95% CI: 0.67, 2.67]). There were null associations for
30 placenta accreta across the blood Pb quartiles (Table 8-8).

8.3.6.2 Toxicological Studies on Placental Function

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

8.3.6.3 Integrated Summary of Effects on Placental Function

18 There were no epidemiological studies available that evaluated Pb concentrations and
19 associations with placenta function in the 2013 Pb ISA. The recent epidemiological studies reviewed that
20 assessed the relationship of Pb exposure and placental are limited. These cross-sectional studies provide
21 insight into associations between concurrent Pb exposure and placental function. However, the studies are
22 limited by their cross-sectional design, making it difficult to establish the temporality of the effects or the
23 critical window of exposure to Pb results in changes in the placenta during pregnancy, and there were
24 only a small number of cases placental previa and placenta accrete. The differences in the different
25 markers of placental function make it difficult to judge coherence and consistency across these studies,
26 but these positive associations are an indication that exposure to Pb may result in effects on placental
27 function during pregnancy. Previous toxicological data on the effects of Pb on placental weight are
28 limited to a single study which reported decreased placental weight and histological alterations. Recent
29 studies also reported that dams dosed with Pb had reduced placental weight, but of note is that these
30 studies also reported reduced brain weight in dams, suggesting that overt toxicity may have occurred and
31 could be related to the observed reductions in placental weight.

8.3.7 Other Pregnancy and Birth Outcomes

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

8.3.7.1 Epidemiologic Studies on Other Pregnancy and Birth Outcomes

6 There were several recent studies with other outcomes related to pregnancy and birth. More
7 specific study details, including Pb levels, study population characteristics, potential confounders, and
8 select results from these studies are highlighted in Table 8-9. In studies of other pregnancy and birth
9 outcomes, maternal Pb blood concentrations were associated with high levels of leptin, a fetal marker of
10 metabolic function ([Ashley-Martin et al., 2015a](#)); and cord blood Pb concentrations were negatively
11 associated with cord blood relative telomere length (rTL) ([Herlin et al., 2019](#)). However, there was a null
12 association between maternal serum Pb levels and nuchal translucency, the subcutaneous space in the
13 fetal neck and is visible with ultrasound imaging in the first trimester and increased thickness in the first
14 trimester have been reported to be at risk for chromosomal abnormalities, genetic syndromes, congenital
15 heart defects, structural abnormalities, intrauterine infection, neurodevelopmental delay, and fetal demise
16 ([Liao et al., 2015](#)); maternal blood Pb concentrations and thymic stromal lymphopoietin (TSLP) and
17 interleukin-33 (IL-33), which are biomarkers of fetal immune system ([Ashley-Martin et al., 2015b](#));
18 maternal blood Pb concentrations and elevated cord blood concentrations of immunoglobulin E (IgE)
19 ([Ashley-Martin et al., 2015b](#)); maternal blood Pb and markers of fetal metabolic function (low leptin, low
20 adiponectin, and high adiponectin) ([Ashley-Martin et al., 2015b](#)). Additionally, there were inconsistent
21 associations between maternal BLLs during pregnancy and secondary sex ratio. Among participants in the
22 Avon Longitudinal Study of Parents and Children in the United Kingdom, [Taylor et al. \(2014\)](#) reported no
23 associations among quintiles of maternal Pb levels during the first trimester of pregnancy and secondary
24 sex ratio (odds of having a male child). Participants of the Longitudinal Investigation of Fertility and the
25 Environment (LIFE) cohort, there were associations with secondary sex ratio (ratio of live male to female
26 births, reflecting a male excess) and both maternal and parental blood samples were measured for Pb at
27 baseline (before pregnancy) ([Bloom et al., 2015](#)). However, [Tatsuta et al. \(2022b\)](#) reported increased odds
28 male births (secondary sex ratio) of 1.279 (95% CI: 1.224, 1.336) in the highest quintile of maternal blood
29 Pb among a subset of participants in the JECS.

8.3.7.2 Toxicological Studies on Other Pregnancy and Birth Outcomes

1 The 2013 Pb ISA summarized a single study reporting on other birth outcomes such as sex ratio.
2 [Dumitrescu et al. \(2008a\)](#) reported an increased female:male ratio in offspring born to Wistar rats that were
3 dosed with 100 or 150 ppb of Pb in the drinking water starting three months prior to mating and
4 continuing until birth. This study did not report on BLLs in dams or offspring, resulting in more
5 challenges when comparing this study to more recently published studies (Table 8-3). [Weston et al. \(2014\)](#)
6 was the only recent study to report an effect of Pb exposure on the sex ratio of pups born to exposed
7 dams. In agreement with [Dumitrescu et al. \(2008a\)](#), [Weston et al. \(2014\)](#) reported that Long-Evans rats dosed
8 starting 76 days prior to mating and continuing through birth gave birth to female skewed litters when
9 compared to control. However, it is worth noting that in [Weston et al. \(2014\)](#) control litters had unusually
10 high numbers of males that resulted in a 1.5 male:female ratio of pups born, whereas Pb-treated litters had
11 a more even distribution that resulted in a ratio closer to 1:1 (BLLs were 14.6 and 15.7 µg/dL in female
12 and male pups, respectively, on PNDs 5–6). Other recent studies contrast with these studies and report no
13 effects on sex ratio in Pb-treated females. One study using a dosing paradigm similar to the two studies
14 above (exposure beginning two months prior to dosing and continuing through birth) reported no effects
15 of Pb on sex ratio (BLLs 12.12 µg/dL in dams at weaning) in C57BL/6 mice ([Cory-Slechta et al., 2013](#)).
16 Similarly, [Tartaglione et al. \(2020\)](#) dosed Wistar rats from four weeks prior to mating through birth and
17 reported no changes in sex ratio (BLLs 25.5 µg/dL on PND 23 in pups). Additional studies in rats dosed
18 females from the beginning of pregnancy through birth and also reported no changes in sex ratio (BLLs
19 6.68–9.03 µg/dL in pups taken at ages PND 2 and PND 28 and ([Betharia and Maher, 2012](#)) and
20 ([Baranowska-Bosiacka et al., 2013](#)), respectively). With the only recent study reporting alterations in sex
21 ratio also reporting unusual sex ratios in the control group, the effects of Pb exposure on sex ratio is
22 equivocal.

8.3.7.3 Integrated Summary of Effects on Other Pregnancy and Birth Outcomes

23 There was a small body of recent epidemiologic studies across various other pregnancy and birth
24 outcomes; however, the small number of studies limits the ability to judge coherence and consistency
25 across these studies, although the associations reported demonstrate that Pb exposure could result in
26 physiological responses that contribute to adverse pregnancy and birth outcomes, such as markers of fetal
27 metabolic function, fetal immune system biomarkers, and rTL. Toxicological evidence regarding other
28 pregnancy and birth outcomes are equivocal. While the 2013 Pb ISA reported a study that found that Pb
29 exposure led to female-skewed litters, a few recent studies reported no effects of Pb on the ratio of male
30 to female pups born to Pb-exposed dams.

8.4 Effects on Development

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

8.4.1 Effects on Postnatal Growth

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

8.4.1.1 Epidemiologic Studies on Postnatal Growth

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

24 There were multiple recent epidemiologic studies that evaluated the relationship between Pb
25 exposure and postnatal growth. Overall, there were negative associations between Pb exposure and
26 specific postnatal growth outcomes among the cross-sectional studies. However, among cohort studies,
27 there were some inconsistencies in the associations of Pb exposure and different postnatal growth
28 outcomes. These inconsistencies in the cohort studies may be due to differences in the timing of when Pb
29 exposure was measured, the biomarker of Pb exposure, and the timing of the outcome.

1 Among the other cross-sectional studies of Pb exposure and postnatal growth, there were
2 consistent negative associations. In an NHANES (2013–2016) analysis of 6–11-year-old children
3 (n = 1,634), there were negative associations between an IQR difference in blood Pb concentrations
4 (median: 0.5 µg/dL) and standing height (β : -3.116 cm [95% CI: -5.03, -1.202]), waist circumference
5 (WC; β : -5.742 cm [95% CI: -8.769, -2.715]), upper arm length (β : -1.068 cm [95% CI: -0.625,
6 -0.512]), and BMI (β : -2.092 kg/m² [95% CI: -3.227, -0.957]) ([Signes-Pastor et al., 2021](#)). Among male
7 participants, the negative associations with postnatal growth outcomes persisted. Among female
8 participants, there were negative associations with BMI, WC, and upper arm length, but null associations
9 with standing height. Similarly, in a study of primary school children aged 7–11 years in China, there
10 were negative associations with concurrently measured BLLs (median: 2.61 µg/dL) and height (β :
11 -3.21 cm [95% CI: -4.24, -2.17]), weight (β : -1.96 kg [95% CI: -3.11, 0.82]), bust circumference (β :
12 -2.77 cm [95% CI: -3.79, -1.76]), and waistline (β : -3.65 cm [95% CI: -4.78, 2.52]); however, there
13 was a null associations with BMI (β : 0.20 kg/m² [95% CI: -0.65, 0.25]) ([Kuang et al., 2020](#)).

14 When standardizing postnatal growth metrics by z-score, the associations with Pb exposure were
15 mixed, even with all median BLLs across studies less than 5 µg/dL (range: 0.663–4.6 µg/dL). In a cross-
16 sectional study, among children \leq 6 years of age (n = 1,678) in China, there were negative associations
17 between children's log₁₀-BLLs and weight-for-age Z-score (WAZ) (β : -0.33 [95% CI: -0.56, -0.11]) and
18 height-for-age Z-score (HAZ) (β : -0.38 [95% CI: -0.63, -0.14]), but null associations with BMIZ ([Zhou
19 et al., 2020](#)). When the BLLs were grouped by tertiles, the children in the highest (>5 µg/dL) had lower
20 WAZ (β : -0.42 [95% CI: -0.62, -0.23]), lower HAZ (β : -0.36 [95% CI: -0.58, -0.15]), and lower BMIZ
21 (β : -0.29 [95% CI: -0.50, -0.07]) than those in the lowest tertile (<2.5 µg/dL). The patterns of
22 association held when stratified by child's sex (see Table 8-10). Among children ranging in age from 8 to
23 23 months in South Korea, BLLs was associated with post-birth weight gain (WAZ-BWZ, or the
24 difference of the weight for age Z-scores at the time of the study and birth weight Z-scores) (β : -0.238
25 [-0.391, -0.085], standard error [SE]: 0.078) and current HC for age Z-scores (HCAZs; β : -0.213
26 [-0.366, -0.06], SE:0.078) ([Choi et al., 2017](#)). However, among participants in the Canadian MIREC Child
27 Development Plus Study, there were no associations reported between blood Pb measured at two and
28 five years of age and HAZ, WAZ, or BMIZ overall or when stratified by child's sex ([Ashley-Martin et al.,
29 2019](#)).

30 Multiple cohort studies examined the relationship between Pb exposure at different time periods
31 (prenatally and/or at different time periods during childhood) with growth metrics, mainly height and
32 weight. Among the cohort studies that measured Pb in cord blood, there were inconsistent associations.
33 While a study among children in Krakow, Poland found no associations with change in mean height over
34 a nine-year follow-up period ([Jedrychowski et al., 2015](#)), a study in the Children's Health and
35 Environmental Chemicals in Korea (CHECK) study, reported positive associations with Z-scores for
36 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:
37 0.077, 1.313], respectively) ([Kim et al., 2017](#)). However, there were no associations between cord blood Pb
38 and the Z-scores of the child's weight, height, or BMI at any other time point (see Table 8-10 for details).

1 When stratified by children's sex, cord blood Pb was positively associated with an increase of birth height
2 (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
3 boys, but not in girls.

4 Among participants ($n = 1,150$) in the Mothers and Children's Environmental Health (MOCEH)
5 study in South Korea, maternal BLLs at delivery were negatively associated with Z-scores of weight for
6 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,
7 meaning that a 1- $\mu\text{g/dL}$ increase in late pregnancy Pb levels decreased weight and length at 24 months by
8 0.33 kg and 0.30 cm, respectively ([Hong et al., 2014](#)). However, there were no associations between
9 maternal BLLs in early pregnancy (before 20 weeks gestation) and cord blood Pb with weight and length.

10 Several cohort studies conducted in Mexico measured Pb exposure during pregnancy in maternal
11 blood, cord blood, and maternal bone and various postnatal growth outcomes. [Renzetti et al. \(2017\)](#)
12 investigated how Pb exposure during pregnancy is associated with children's growth outcomes, including
13 height, weight, BMI, and percentage body fat, measured between ages 4–6 years old in a Mexico City
14 pregnancy cohort (PROGRESS). Maternal blood Pb was measured during the second and third trimester
15 of pregnancy, as well as at delivery. Cord blood was measured at delivery. Bone Pb levels in the tibia and
16 patella were also assessed in mothers as a long-term biomarker one month postpartum. There were
17 negative associations between maternal third trimester BLLs and height-for-age (β : -0.10 [95% CI:
18 -0.19, -0.01]) and weight for age (β : -0.11 [95% CI: -0.22, -0.003]), but there were no associations
19 between any other marker of Pb exposure (maternal second trimester blood, cord blood Pb, maternal
20 blood at delivery) and height-for-age, weight for age, BMI, or percentage of body fat (see Table 8-10). In
21 the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) project, [Liu et al. \(2019a\)](#)
22 assessed Pb exposure in maternal bone (as a proxy for cumulative fetal exposure) at one month
23 postpartum and also in blood samples from children annually from 1 to 4 years in association with BMIZ,
24 WC, sum of skinfolds, and body fat percentage in 248 children aged 8–16 years. Maternal patella Pb
25 levels were associated with lower child BMIZ (β : -0.02 [95% CI: -0.03, -0.01]), WC (β : -0.12 cm [95%
26 CI: -0.22, -0.03]), sum of skinfolds (β : -0.29 mm [95% CI: -0.50, -0.08]), and body fat percentage (β :
27 -0.09% [95% CI: -0.17, -0.01]). However, there were no associations detected from the postnatal
28 exposure period (blood samples in children). In another study, children born between 1994 and 2005 in
29 Mexico City had Pb exposure measured in maternal patella Pb concentrations, a marker of prenatal period
30 exposure, and from infant and childhood measured in blood at birth to 24 months and 30–48 months
31 ([Afeiche et al., 2012](#)). Among infants with BLL exceeding the median (4.5 $\mu\text{g/dL}$), there was a decrease in
32 height of 0.84 cm (95% CI: -1.43, -0.26) compared to children with a level below the median. There
33 were no associations between prenatal Pb or childhood Pb and height and there were no associations with
34 BMI at any time point (prenatal, infancy, or childhood). In cohort of Mexican children aged 6–8 years
35 old, growth (height, HAZ, and knee height) were assessed in association with BLLs at baseline, after
36 6 months, and 12 months ([Kerr et al., 2019](#)). Additionally, as BLLs may differ by the aminolevulinic acid
37 dehydratase (ALAD) genotype, comparing children with the ALAD_{1-2/2-2} genotype to children with the
38 ALAD₁₋₁ genotype. There were negative associations with height (β : -0.11 cm [95% CI: -0.18, -0.04]),

1 knee height (β : -0.04 cm [95% CI: $-0.07, -0.02$]), and HAZ (β : -0.02 cm [95% CI: $-0.03, -0.01$]).
2 Children with ALAD₁₋₁ had decreased height, knee height, and HAZ, while children with the ALAD_{1-2/2-2}
3 had reduced knee height and HAZ, but not height. There were no associations between BLLs and growth
4 at 6- or 12-month follow-up was reported, irrespective of ALAD genotype. This epigenetic study
5 proposes a potential mechanistic pathway of BLLs differing by genotypes and the associations with
6 growth metrics during child developmental periods.

7 There were several studies that explored the associations between Pb exposure and postnatal
8 growth specifically by sex. In a study by [Burns et al. \(2017\)](#), associations of BLLs were assessed with
9 longitudinal age-adjusted height (HAZ) and BMI (BMIZ) among male participants in the Russian
10 Children's Study. Over 10 years of follow-up, after covariate adjustment, boys with higher (≥ 5 $\mu\text{g/dL}$)
11 BLLs compared with lower BLLs were shorter (adjusted mean difference in HAZ: -0.43 [95% CI $-0.60,$
12 -0.25]), translating to a 2.5 cm lower height at age 18 years. The decrement in height for boys with higher
13 BLLs was most pronounced at 12 to 15 years of age (interaction p: 0.03). However, boys with higher
14 BLLs were leaner (adjusted mean difference in BMIZ: -0.22 [95% CI: $-0.45, 0.01$]). [Deierlein et al. \(2019\)](#)
15 used data from the Breast Cancer and the Environment Research Program to investigate associations of
16 childhood blood Pb concentrations and anthropometric measurements among a multi-site, multiethnic
17 cohort of girls (n = 683). Blood Pb concentrations were collected before 10 years of age and height, BMI,
18 WC, percent body fat was measured between 7–14 years of age. There were decreases in height (range:
19 -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:
20 -2.9 to -1.7%) among girls ages 7 through 14 with BLLs of ≥ 1 $\mu\text{g/dL}$ compared to <1 $\mu\text{g/dL}$ (Table 8-
21 10).

22 There were a limited number of studies that examined stunting with exposure to Pb in children. A
23 single cross-sectional study in a subset of participants in the Interactions of Malnutrition & Enteric
24 Infections: Consequences for Child Health and Development (MAL-ED) study in Bangladesh reported
25 increased odds of stunting (OR: 1.78 [95% CI: 1.07, 2.99]) and being underweight (OR: 1.63 [95% CI:
26 1.02, 2.61]) with elevated (≥ 5 $\mu\text{g/dL}$) BLLs, but not wasting (OR: 1.18 [95% CI: 0.64, 2.19]) ([Raihan et al., 2018](#)).
27 In a cohort study among rural Bangladeshi children, Pb exposure was assessed from umbilical
28 cord blood at birth and blood Pb at 20–40 months of age with stunting ([Gleason et al., 2016](#)). The odds of
29 stunting at 20–40 months was 1.12 (95% CI: 1.02, 1.22) per each 1 $\mu\text{g/dL}$ increase in childhood BLL;
30 however, there was no association was found between cord BLL and risk of stunting (OR: 0.97 [95% CI:
31 0.94–1.00]).

8.4.1.2 Toxicological Studies on Postnatal Growth

32 The 2013 Pb ISA summarized several current studies and several from the 2006 Pb AQCD that
33 reported on the effects of Pb on offspring bodyweight and size. The reported effects were fairly
34 consistent, and nearly all studies reported reductions in bodyweight of offspring exposed to Pb during

1 developmental periods. Gestational exposure to Pb proved to be sufficient to reduce offspring bodyweight
2 and body length in rodent studies ([Massó-González and Antonio-García, 2009](#); [Wang et al., 2009](#); [Teijón et al.,
3 2006](#); [Ronis et al., 2001](#); [Ronis et al., 1998a](#); [Ronis et al., 1998c](#); [Ronis et al., 1996](#)). The only study in the 2013
4 Pb ISA that did not report a reduction in bodyweight was [Leasure et al. \(2008\)](#), which reported that
5 bodyweight increased at one year of age in male C57BL/6 offspring that were dosed starting prior to
6 conception and ending on PND 10.

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

23 Contrasting these recent studies and previous studies discussed in the 2013 Pb ISA are several
24 studies that reported no effects of Pb exposure on bodyweight in offspring. Studies in both mice and rats
25 utilizing dosing paradigms that begin exposure prior to conception ([Albores-Garcia et al., 2021](#); [Zhao et al.,
26 2021](#); [Sobolewski et al., 2020](#); [Rao Barkur and Bairy, 2016](#); [Barkur and Bairy, 2015](#)) reported no effects of Pb
27 exposure on bodyweight at any time point measured (BLLs ranged between 0.4–15.7 µg/dL across
28 various time points and studies). Similar null findings were reported in other rodent studies utilizing other
29 exposure windows including gestational ([Rao Barkur and Bairy, 2016](#); [Barkur and Bairy, 2015](#)), lactation ([Rao
30 Barkur and Bairy, 2016](#); [Barkur and Bairy, 2015](#); [Basgen and Sobin, 2014](#)), and a combination thereof ([Basha
31 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

32 There were inconsistencies in the associations between Pb exposure and postnatal growth among
33 the recent epidemiologic studies, much like the 2013 Pb ISA. The inconsistencies may be the result of the
34 differences in the timing of Pb exposure measurement (prenatally or postnatally) and the biomarker to

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

8.4.2 Effects on Puberty among Females

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

8.4.2.1 Epidemiologic Studies on Puberty among Females

20 The epidemiologic studies reviewed in the 2013 Pb ISA found consistent associations between
21 higher concurrent blood Pb and delayed pubertal development in females. The association persisted in
22 populations with mean and/or median concurrent BLLs of 1.2–9.5 µg/dL. While most of the studies had
23 large sample sizes and controlled for potential confounders, they were cross-sectional study designs, so
24 there are some uncertainties regarding temporality between Pb exposure and pubertal onset; additionally,
25 these studies were not able to separate out the influence of past Pb exposure, including prenatal
26 exposures, from more recent exposures.

27 The recent epidemiologic studies assessing the associations between blood Pb and onset of
28 puberty among females used different markers of puberty. A single cross-sectional study of NHANES
29 (2011–2012) data evaluated the associations between blood Pb concentration and circulating serum total
30 testosterone levels in 6–19-year-old children and adolescents ([Yao et al., 2019](#)). Testosterone is a principal
31 sex hormone needed for normal physiologic processes during all life stages and for females, testosterone

1 is of crucial importance for bone density and necessary for normal ovarian and sexual function, libido,
2 energy, and cardiovascular and cognitive functions ([Yao et al., 2019](#)). While there were no associations
3 between blood Pb and testosterone in female children (6–11 years), serum testosterone levels were
4 14.85% greater (95% CI: 0.83%, 30.81%) in female adolescents (12–19 years) in the lowest quartile of
5 BLLs (≤ 0.35 $\mu\text{g/dL}$) than those in the highest quartile (>0.63 $\mu\text{g/dL}$) in the fully adjusted model. For both
6 female children and adolescents, there were no significant trends with increasing quartiles of exposure (p
7 for trend 0.63 and 0.08, respectively).

8 In a cross-sectional study in Poland, two different groups of adolescent girls aged 7–16 years
9 (n = 436 in 1995 and n = 361 in 2007) were assessed for effects of Pb on the age attaining menarche
10 ([Sławińska et al., 2012](#)). While the associations between blood Pb and menarche from either group of girls
11 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
12 association between these two times periods suggest delayed menarche. Of note, not only did the
13 distribution in blood Pb decline over the time period, girls in the 2007 group were significantly taller,
14 weighed more, and had a higher BMI. In another cross-sectional study among school-age girls (n = 490)
15 in Poland, there was a pattern of decreased odds between blood Pb and age at menarche, whether
16 controlled for BMI (OR: 0.54 [95% CI: 0.26, 1.13]), percentage of body fat (OR: 0.52 [95% CI: 0.25,
17 1.08]), or sum of skinfolds (OR: 0.53 [95% CI: 0.26, 1.10]) ([Gomula et al., 2022](#)). While these cross-
18 sectional studies reported imprecise associations, the pattern of association is important to note. As BLLs
19 decline, the association between blood Pb and age of menarche may be attenuated by potential
20 confounders such as body weight and/adiposity.

21 Three successive, cross-sectional Flemish Environment and Health Studies (FLEHS I, FLEHS II
22 and FLEHS III) were conducted among adolescents (aged 14–5 years old) in Belgium between 2002–
23 2015 ([De Craemer et al., 2017](#)). Female puberty markers of age at menarche, breast development, and pubic
24 hair development were evaluated in relation to blood Pb exposure. There was a consistent pattern of
25 delayed age at menarche across the three study cohorts (FLEHS I OR: 0.039 [95% CI: –0.072, 0.15];
26 FLEHS II OR: 0.257 [95% CI: 0.091, 0.424]; FLEHS III OR: 0.126 [95% CI: –0.021, 0.273]). The
27 associations between blood Pb and breast development were inconsistent, but there was indication of
28 delayed development among FLEHS I participants (OR: 0.798 [95% CI: 0.653, 0.969]). There were no
29 associations between blood Pb and development of pubic hair among adolescent females across the three
30 study cohorts.

31 Multiple cohort studies examined the associations between Pb exposure and puberty in females.
32 These studies used different biomarkers of exposure and different markers of puberty ([Liu et al., 2019b](#);
33 [Jansen et al., 2018](#); [Nkomo et al., 2018](#)). Cord BLLs and BLLs at age 13 were evaluated in association with
34 puberty progression (development of pubic hair and development of breasts) among 684 females in the
35 Birth to Twenty Plus (BT20+) birth cohort in South Africa ([Nkomo et al., 2018](#)). In females with elevated
36 BLLs (≥ 5 $\mu\text{g/dL}$) at age 13, there was lower level of maturation (development of breasts) relative risk
37 ratio [RRR]: 0.45 [95% CI: 0.29, 0.68]) and slower progression of pubic hair (RRR: 0.46 [95% CI: 0.27,

1 0.77]), but there were no associations between cord blood Pb and pubic hair or breast development at age
2 13. In a cohort of Mexican children, cumulative blood Pb from 1–4 years old was associated with delayed
3 breast development (OR: 0.96 [95% CI: 0.92, 0.99]) and delayed pubic hair development (OR: 0.95 [95%
4 CI: 0.92, 0.99]), but maternal patella Pb and maternal tibia Pb were not associated with either breast or
5 pubic hair development in girls between 9–18 years old (n = 283) ([Liu et al., 2019b](#)). Additionally, the
6 highest tertile of maternal patella Pb and the second tertile of cumulative blood Pb from 1–4 years of age
7 was associated with delayed menarche. In a subset of the ELEMENT project cohort (n = 200), maternal
8 blood was measured during each trimester of pregnancy and daughters (mean age at follow-up assessment
9 13.8 ± 2.0 years) were asked about the occurrence of their first menstrual cycle ([Jansen et al., 2018](#)). Only
10 second trimester maternal BLLs were associated with later age at menarche (HR: 0.59 [95% CI: 0.28,
11 0.90]).

8.4.2.2 Toxicological Studies on Puberty among Females

12 There were no recent animal toxicological studies on the effects of Pb on puberty in females. The
13 2013 Pb ISA reported that one research group Iavicoli et al. ([Iavicoli et al., 2006](#); [Iavicoli et al., 2004](#))
14 observed that offspring exposed to Pb prior to birth and through puberty (BLLs 0.7–13 µg/dL) resulted in
15 a dose-dependent delay in multiple markers of sexual maturation (e.g., vaginal opening, age at first
16 estrus). The latter study by this group utilized a multigenerational dosing paradigm in which they
17 observed delays of pubertal onset in the F₂ generation similar to those seen in the F₁. The 2013 Pb ISA
18 also summarized a study in which Fisher 344 rats were dosed daily via gavage (12 mg/mL Pb) starting
19 30 days prior to breeding through weaning of the offspring (PND 23), resulting in delayed age at vaginal
20 opening in the offspring (BLLs of dams just prior to breeding averaged 39.8 µg/dL) ([Pine et al., 2006](#)). Of
21 particular interest is that the observed delay in vaginal opening was attenuated in offspring that received
22 IGF-1 injections starting on PND 28 until vaginal opening was observed, demonstrating that IGF-1 is a
23 critical element to Pb-induced pubertal onset delays. Reports of delayed puberty due to Pb exposure in the
24 2013 Pb ISA are consistent with studies in the 2006 Pb AQCD which observed delays in puberty in
25 female Fisher 344 and Sprague-Dawley rats exposed to Pb during gestation and/or lactation ([Dearth et al.,
26 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

27 There were several markers of puberty among females that were assessed for associations with Pb
28 exposures in the recent epidemiologic studies. Multiple cross-sectional studies and a single cohort study
29 reported an association between blood Pb and delayed menarche among females, with relevant BLLs
30 ([Gomula et al., 2022](#); [Jansen et al., 2018](#); [De Craemer et al., 2017](#); [Sławińska et al., 2012](#)). While these cross-
31 sectional studies reported imprecise associations, the pattern of association is important to note. As BLLs
32 decline, the association between blood Pb and age of menarche may be attenuated by potential

1 confounders such as body weight and/adiposity. There was also indication of slower breast development,
2 but the studies assessing breast development were limited ([Nkomo et al., 2018](#); [De Craemer et al., 2017](#)).
3 Additionally, there were a limited number of studies that evaluated the development of pubic hair, but
4 these results were inconsistent ([Liu et al., 2019b](#); [Nkomo et al., 2018](#); [De Craemer et al., 2017](#)). A single study
5 among NHANES participants reported increased serum total testosterone levels in female adolescents.
6 The recent epidemiologic studies assessing the associations between Pb exposure and puberty among
7 females were limited by the timing of the exposure to Pb and biomarker of exposure (blood, maternal
8 bone, cord blood). However, these studies consider a wide range of confounders, including height,
9 weight, and BMI, and the associations reported demonstrate that Pb exposure could result in
10 physiological responses that contribute to changes in puberty in females.

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

8.4.3 Effects on Puberty among Males

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

8.4.3.1 Epidemiologic Studies on Puberty among Males

21 The epidemiologic studies reviewed in the 2013 Pb ISA demonstrated an inverse relationship of
22 Pb on pubertal development among males at low blood Pb (mean and/or median BLLs of 3.0 to
23 9.5 µg/dL). The studies were mostly cross-sectional, but the findings from these studies were supported
24 by those from a prospective longitudinal study ([Williams et al., 2010](#)). Boys with higher (≥ 5 µg/dL) BLLs
25 at ages 8–9 years old had 24% to 31% reduction of pubertal onset based on testicular volume (TV),
26 genitalia staging, and pubic hair staging ([Williams et al., 2010](#)). While temporality of effects is difficult to
27 establish due to the nature of the cross-sectional study design, the larger studies controlled for potential
28 confounders, with a few studies considering the inclusion of dietary factors, but did not control of other
29 metal exposures that may impact the associations.

30 Multiple recent cross-sectional and cohort epidemiologic studies evaluated associations between
31 Pb exposure at different time points (maternal, at birth, and adolescents) and markers of puberty in males

1 ([Liu et al., 2019b](#); [Williams et al., 2019](#); [Yao et al., 2019](#); [Nkomo et al., 2018](#); [De Craemer et al., 2017](#); [Fleisch et](#)
2 [al., 2013](#)). Overall, there were inconsistent associations between Pb exposure and markers of puberty in
3 males.

4 In an NHANES (2011–2012) analysis, concurrent BLLs and serum total testosterone levels were
5 measured in 6–19-year-old children and adolescents ([Yao et al., 2019](#)). Testosterone is a principal sex
6 hormone needed for the normal physiologic processes during all life stages. In males, testosterone is
7 essential for the development and maintenance of secondary sexual traits, and can also influence bone
8 mass, muscle strength, mood, and intellectual capacity. When comparing the highest quartile of blood Pb
9 to the lowest, there was no association between serum testosterone levels in either male children (β :
10 -13.09% [95% CI: -34.45% , 15.22%]) or male adolescents (β : 6.32% [95% CI: -14.62% , 32.4%]).
11 Among three successive, cross-sectional Flemish Environment and Health Studies (FLEHS I, FLEHS II
12 and FLEHS III) of adolescents in Belgium between 2002–2015, blood Pb was negatively associated with
13 free estradiol (fE2; OR: 0.908 [95% CI: 0.839, 0.983]) and free testosterone (OR: 0.909 [95% CI: 0.828,
14 0.997]) in FLEHS II, but not in FLEHS I ([De Craemer et al., 2017](#)). The associations between blood Pb and
15 estradiol (E2), testosterone, sex hormone binding globulin (SHBG), luteinizing hormone (LH), and
16 follicle stimulating hormone (FSH) were generally null (see Table 8-12). In addition to sex hormones, [De](#)
17 [Craemer et al. \(2017\)](#) also evaluated the associations between blood Pb and genital development and pubic
18 hair development among male adolescents. Across the three cross-sectional studies, there was delayed
19 onset of genital development (FLEHS I OR: 0.843 [95% CI: 0.717, 0.99]; FLEHS II OR: 0.697 [95% CI:
20 0.462, 0.998]; FLEHS III OR: 0.621 [95% CI: 0.388, 0.967]) and pubic hair development (FLEHS I OR:
21 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%
22 CI: 0.327, 0.774]) in males with blood Pb exposure.

23 In the Birth to Twenty Plus (BT20+) birth cohort in South Africa, cord BLLs and blood levels at
24 age 13 were evaluated in association to puberty progression pubic hair development and genital
25 development in 732 males ([Nkomo et al., 2018](#)). In males, elevated cord BLLs (≥ 5 $\mu\text{g/dL}$) was associated
26 with slower pubic hair development (RRR: 0.28 [95% CI: 0.11, 0.74]). There were no associations
27 between cord blood Pb and genital development or BLLs at age 13 with pubic hair development or genital
28 development. Similarly, there were no associations between maternal patella Pb, maternal tibia Pb, and
29 cumulative blood Pb from 1–4 years old and pubertal development (genitalia, pubic hair, and TV) in boys
30 ([Liu et al., 2019b](#)).

31 However, in a longitudinal cohort of boys from the Russian Children’s Study, higher BLLs
32 (≥ 5 $\mu\text{g/dL}$) measured at age 8–9 years old (baseline) had pubertal onset 7.7–8.4 months later, on average,
33 than those with lower BLLs (< 5 $\mu\text{g/dL}$) ([Williams et al., 2019](#)). Boys with higher BLLs at baseline had later
34 adjusted mean age at sexual maturity, with 4.2–5.1 months later attainment compared to boys with lower
35 BLLs. There was a shift in mean age for age a pubertal onset for stage 2 genitalia (G2) of 8.40 months
36 (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
37 (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

1 genitalia (G5) of 4.20 months (95% CI: 0.56, 7.84) and 5.14 months (95% CI: 1.70, 8.58) for TV \geq 20 mL,
2 but a null association for stage 5 pubic hair (4.23 months [95% CI: -0.31, 8.77]). Furthermore, there was
3 no shift in the mean age for duration of pubertal progression for genitalia (G2 to G5), pubic hair (P2 to
4 P5), or TV (>3 mL to \geq 20 mL). In a mediation analysis, growth measurements at age 11 were included to
5 better understand what portion of the shift in mean age at sexual maturity was attributable to the effect of
6 BLL on growth. The association of peripubertal BLL with height Z-score (HTZ) at age 11 accounted for
7 34–53% of the total effect of BLLs on age at maturity, while BMI Z-score at age 11 only accounted for
8 6–23%. In another Russian Children’s Study, [Fleisch et al. \(2013\)](#) longitudinally measured serum insulin-
9 like growth factor (IGF-1) to assess the association with childhood BLLs. BLLs were measured at
10 baseline only and IGF-1 levels were only measured during the follow-up periods. Boys were enrolled
11 between the ages of 8–9 years and were prospectively followed, with IGF-1 measurements obtained at
12 two-year follow-up (ages 10–11 years) and at four-year follow-up (ages 12–13 years). The overall mean
13 IGF-1 concentration was 29.2 ng/mL lower (95% CI: -43.8, -14.5) for boys with high BLLs at age 8–
14 9 years (\geq 5 μ g/dL [max is 31 μ g/dL]) versus those with lower baseline BLLs (<5 μ g/dL) in adolescence
15 among boys.

8.4.3.2 Toxicological Studies on Puberty among Males

16 There were no recent toxicological studies on the effects of Pb on puberty in males, as was also
17 the case at the time of the 2013 Pb ISA. The 2006 Pb AQCD reported that one study found that prenatal
18 exposure to Pb delayed sexual maturation in a dose-dependent manner in male rats ([Ronis et al., 1998c](#)).
19 Specifically, [Ronis et al. \(1998c\)](#) reported that prostate weight (used in this study as a marker of sexual
20 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

21 The epidemiologic studies reviewed in the 2013 Pb ISA demonstrated an inverse relationship of
22 Pb on pubertal development among males at low blood Pb (mean and/or median BLLs of 3.0 to
23 9.5 μ g/dL). However, the recent epidemiologic studies assessing the associations between Pb exposure
24 and puberty among males reported more inconsistent findings at low BLLs. Differences in markers of
25 puberty in male (hormone levels, pubic hair development, genital development, TV) may explain the
26 inconsistency in findings across the studies. Additionally, there were differences in the timing of exposure
27 to Pb and different biomarkers of Pb exposure (maternal blood, maternal bone, cord blood, or concurrent
28 blood). The recent epidemiologic studies were able to consider a wide range of confounders, including
29 height, weight, and BMI, and some studies were conducted among established longitudinal cohorts. No
30 recent toxicological studies reported on the effects of Pb on male puberty. Similarly, the 2013 Pb ISA
31 reported no studies investigating Pb and male puberty. One study reported by the 2006 Pb AQCD
32 investigated the effects of Pb on puberty using prostate weight as a marker of sexual maturity in male rats

1 exposed to Pb starting on GD 5. Treatment with Pb resulted in reductions in prostate weight around the
2 time of puberty, possibly indicating that Pb delayed the onset of sexual maturation in Pb-treated animals
3 when compared to control.

8.4.4 Other Developmental Effects

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

8.4.4.1 Epidemiological Studies on Other Developmental Effects

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

8.4.4.2 Toxicological Studies on Other Developmental Effects

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

8.4.4.3 Integrated Summary of Other Developmental Effects

1 The recent epidemiologic studies have the potential to provide initial support of potential
2 mechanistic pathways for diurnal cortisol rhythms, lower salivary sialic acid levels, and DNA oxidative
3 stress damage from Pb exposure among children during developmental periods. However, the small
4 number of studies limits the ability to judge coherence and consistency across the outcomes evaluated in
5 these studies, although the associations with diurnal cortisol rhythms, lower salivary sialic acid levels, and
6 decrease in mitochondrial DNA copy number indicate that Pb exposure could result in physiological
7 responses that may contribute to adverse developmental effects. Recent toxicological studies on other
8 developmental effects of Pb largely pertain to the effects of Pb on developmental milestones of offspring.
9 Of the few toxicological studies available, no effects of Pb on developmental milestones were reported
10 with the only exception being a reduction at the age of eye opening, but this treatment group had BLLs
11 higher than 30 µg/dL.

8.5 Effects on Female Reproductive Function

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

8.5.1 Effects on Hormone Levels and Menstrual/Estrous Cycle

28 The recent epidemiologic and toxicological studies examining the relationship between Pb
29 exposure and hormone levels and menstrual/estrous cycle are summarized in the text below. Study details

1 of the recent epidemiologic studies are included in Table 8-14 and the recent toxicological studies are in
2 Table 8-15.

8.5.1.1 Epidemiologic Studies on Hormone Levels and Menstrual/Estrous Cycle

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

8.5.1.1.1 Epidemiologic Studies on Hormone Levels in Females

16 There were a few cross-sectional studies that evaluated the associations between Pb exposure and
17 different hormones in females ([Lee et al., 2019](#); [Chen et al., 2016](#); [Krieg and Feng, 2011](#)). These studies used
18 population-based surveys to evaluate associations between blood Pb and hormones and found consistent
19 positive associations with FSH in post-menopausal women. In an NHANES (1999–2002) analysis, [Krieg](#)
20 [and Feng \(2011\)](#) evaluated serum FSH and LH. Serum FSH slope increased per every log₁₀-blood Pb
21 increase in the post-menopausal women (β : 26.38 [95% CI: 13.39, 39.38]), women who had both ovaries
22 removed (β : 27.71 [95% CI: 1.64, 53.78]), and pre-menopausal women (β : 11.97 [95% CI: 3.27, 20.66]),
23 but serum FSH was not associated with BLLs in pregnant women, women who were menstruating, or
24 women who were taking birth control pills. Serum LH slope increased per every log₁₀-blood Pb increase
25 in the post-menopausal women (β : 11.63 [95% CI: 4.40, 18.86]) and women who had both ovaries
26 removed (β : 20.59 [95% CI: 2.14, 39.04]), but serum LH was not associated with BLLs in the pregnant
27 women, women who were menstruating, women who were taking birth control pills, and pre-menopausal
28 women. In another cross-sectional, population-based survey in China, [Chen et al. \(2016\)](#) examined the
29 associations between blood Pb and total testosterone (tT), E2, and SHBG, in addition to LH and FSH in
30 postmenopausal women (age >55 years). When comparing the highest quartile of blood Pb (>5.98 $\mu\text{g/dL}$)
31 to the lowest (<2.70 $\mu\text{g/dL}$), there were positive associations with BLLs and SHBG (β : 0.048, SE: 0.016,
32 $p < 0.01$), FSH (β : 0.046, SE: 0.016, $p < 0.01$), and LH (β : 0.037, SE: 0.016, $p < 0.05$). There were null

1 associations between BLLs and tT or E2. Across the quartiles of blood Pb, there were also positive trends
2 observed with SHBG (p for trend: 0.002), FSH (p for trend: 0.001), and LH (p for trend: 0.026),
3 suggesting a potential linear exposure response between blood Pb and these hormones. In a study of the
4 Korea National Health and Nutrition Examination Survey (KNHANES) (2012–2014), blood Pb and
5 serum FSH levels were assessed in postmenopausal women (aged 50 or older) ([Lee et al., 2019](#)). Serum
6 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

7 There were no available epidemiologic studies in the 2013 Pb ISA that evaluated Pb exposure
8 with menopause. There are a limited number of studies that examined the relationship between Pb
9 exposure and menopause, and these recent studies reported consistent positive associations. A recent
10 cross-sectional study, NHANES (1999–2010) data was used to examine the associations between blood
11 Pb and menopause among women aged 45–55 years (age range where menopause is likely to occur)
12 ([Mendola et al., 2013](#)). In the overall study sample (NHANES 1999–2010), with increasing quartiles of
13 blood Pb, there were increasing odds of menopause. Comparing the lowest BLLs (<1.0 $\mu\text{g}/\text{dL}$), the odds
14 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.
15 When adjusting for bone measurements (either bone alkaline phosphatase or femoral neck bone density),
16 the associations were similar. In a subset (n = 434) of the Nurse’s Health Study, the associations between
17 bone Pb levels and age at menopause were explored ([Eum et al., 2014](#)). Compared with women in the
18 lowest tertile of tibia Pb (<6.5 $\mu\text{g}/\text{g}$), those in the highest tertile (>13 $\mu\text{g}/\text{g}$) were 1.21 years younger at
19 menopause on average (95% CI: –2.08, –0.35; p for trend: 0.006). Women in the highest tertile of tibia Pb
20 had an increased odds of 5.30 (95% CI: 1.42, 19.78; p for trend: 0.006) for early menopause (menopause
21 before age 45) compared with women in the lowest tertile. The associations with early menopause were
22 null across tertiles for patella Pb and BLLs.

8.5.1.2 Toxicological Studies on Hormone Levels and Menstrual/Estrous Cycle

23 There are no recent animal toxicological studies on the effects of Pb on the menstrual/estrous
24 cycle. The 2013 Pb ISA did not report any studies that investigated the effects of Pb on the
25 menstrual/estrous cycle, however some studies were summarized in the 2006 Pb AQCD. Specifically,
26 studies conducted in non-human primates found that Pb exposure increased menstrual cycle variability,
27 reduced days of menstrual flow, increased cycle length, and reduced progesterone ([Franks et al., 1989](#);
28 [Laughlin et al., 1987](#)). Another study with a lower BLL than the previous studies (<40 $\mu\text{g}/\text{dL}$ versus 44–
29 89 $\mu\text{g}/\text{dL}$); however, did not report an effect on the menstrual cycle in a non-human primate species
30 ([Foster et al., 1992](#)). Impacts of Pb on estrous cyclicity were examined in two rat studies that both utilized
31 multiple dosing paradigms to assess the varying impacts Pb exposure may have during different
32 developmental periods. Specifically, one study used the following exposure windows: gestation only,

1 lactation only, gestation and lactation, postnatal (from birth and continued past weaning), and continuous
2 (from the beginning of gestation continued past weaning) ([Ronis et al., 1998a](#)). This study reported that
3 offspring in the postnatal and continuous exposure groups had fewer females who were regularly cycling.
4 The other study was conducted by the same research group and utilized the following dosing windows:
5 post-pubertal (PND 60 to PND 74), pre-pubertal (PND 24 to PND 74), and in utero (GD 5 to PND 85)
6 ([Ronis et al., 1996](#)). Rats in the pre-pubertal and in utero exposure paradigm groups experienced estrous
7 cyclicity disruption. While this study seems to indicate that pre-pubertal periods are more sensitive to
8 chemical insult, the previous study by [Ronis et al. \(1998a\)](#) suggests that normal cyclicity is recoverable
9 after cessation of exposure. However, it is worth noting that in both of these studies the BLLs were very
10 high, with a range of 63.2–264 µg/dL for treatment groups that displayed treatment-related effects.

11 There are no recent animal toxicological studies on the effects of Pb on reproductive hormones.
12 The 2013 Pb ISA reported on a few studies that investigated the effects of Pb on reproductive hormones,
13 but none on cyclicity. Rodent studies reported that gestational and lactational exposure decreased
14 circulating levels of progesterone and E2 ([Pillai et al., 2010](#); [Nampoothiri and Gupta, 2008](#)). [Dumitrescu et al.](#)
15 [\(2008b\)](#) reported similar findings in adult female Wistar rats that were exposed to Pb for 6 months via
16 drinking water. [Dumitrescu et al. \(2008b\)](#) reported reductions in E2, progesterone, and FSH and increases in
17 LH and testosterone. The 2006 Pb AQCD reports findings from some toxicological studies that show
18 effects of Pb on hormones and cyclicity. Reductions in progesterone were observed in a study wherein
19 monkeys had BLLs of 25 to 30 µg/dL, but no such reductions in progesterone were observed in monkeys
20 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

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

1 on circulating reproductive hormone levels, including sex steroid hormones (progesterone, testosterone,
2 and E2) and gonadotropin hormones (LH and FSH).

8.5.2 Effects on Female Fertility

3 Multiple epidemiologic and toxicological studies have examined the relationship between Pb and
4 female fertility. These studies are summarized in the text below. Study details of the recent epidemiologic
5 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

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

12 The recent epidemiologic studies also evaluated different outcomes to measure fertility. In an
13 NHANES (2013–2014 and 2015–2016) study, [Lee et al. \(2020\)](#) assessed whether BLLs were associated
14 with self-reported infertility by comparing BLLs of infertile women (n = 42) to pregnancy women
15 (n = 82). There was increased risk of 2.60 (95% CI: 1.05, 6.41) per two-fold increase in BLLs of
16 infertility. When BLLs were categorized into tertiles, risk of infertility was more pronounced (OR: 5.40
17 [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
18 (0.63–5.37 µg/dL), respectively). In the LIFE Study, a cohort of couples were followed prospectively to
19 assess persistent environmental chemicals and human fecundity ([Louis et al., 2012](#)). BLLs in both the
20 female and male partners were collected at baseline. Female BLLs were not associated with increased
21 time to pregnancy in the female exposure model (OR: 0.97 [95% CI: 0.85, 1.11]) or the couple exposure
22 model (OR: 1.06 [95% CI: 0.91, 1.24]). However, there was decreased odds, or longer time to pregnancy,
23 for male BLLs in both the male exposure model (OR: 0.85 [95% CI: 0.73, 0.98]) and the couple exposure
24 model (OR: 0.82 [95% CI: 0.68, 0.97]).

25 In studies conducted among couples undergoing in vitro fertilization (IVF), there were
26 inconsistent associations. In a cross-sectional study among infertile women in Taiwan, [Lai et al. \(2017\)](#)
27 examined the associations between BLLs and diagnosis of endometriosis, which can cause infertility.
28 Increasing tertiles of BLLs was associated with increasing odds of endometriosis (OR: 2.59 [95% CI:
29 1.11, 6.06] for T3 compared to T1). In a cohort study, among couples undergoing the first IVF cycle,
30 maternal Pb levels were assessed with pregnancy outcomes ([Li et al., 2022](#)). Pb levels in serum were
31 collected before oocyte retrieval. With increasing maternal serum Pb levels, there was a reduction in

1 successful implantation (OR: 0.85 [95% CI: 0.77, 0.94]) and clinical pregnancy (OR: 0.95 [95% CI: 0.91,
2 0.99]). Additionally, when maternal serum Pb was categorized into tertiles, there was a decreased rate of
3 successful implantation (OR: 0.58 [95% CI: 0.40, 0.85]) in the highest Pb tertile, compared to the lowest
4 Pb tertile. Among tertiles of Pb serum levels, the associations were null for clinical pregnancy.
5 Furthermore, there was a negative association with maternal serum Pb and high-quality embryo rate (β :
6 -0.14 [95% CI: $-0.32, -0.04$]), but there were null associations with all other embryo quality indicators
7 (Table 8-14). In a cohort of 195 couples undergoing IVF, Pb was measured in serum and follicular fluid
8 from the female partner and semen from the male partner in association with six IVF outcomes ([Zhou et](#)
9 [al., 2021a](#)). There were no associations between serum or follicular fluid Pb levels and any IVF outcomes
10 – normal fertilization, good embryo, blastocyst formation, high-quality blastocyst, pregnancy, or live
11 birth.

8.5.2.2 Toxicological Studies on Female Fertility

12 The 2013 Pb ISA reported some studies that investigated the effects of Pb on female fertility. A
13 handful of these studies reported that exposure to Pb reduced litter sizes in exposed female rats
14 ([Dumitrescu et al., 2008a](#); [Teijón et al., 2006](#)) and mice ([Iavicoli et al., 2006](#)). Contrasting this is a study that
15 found no changes in fertility rate or litter size in female rats treated prior to mating through pregnancy
16 ([Nampoothiri and Gupta, 2008](#)). Recent studies corroborate the findings of [Nampoothiri and Gupta \(2008\)](#) and
17 do not demonstrate any effects of Pb on female fertility in terms of litter size or number of litters
18 produced by dosed dams in mice ([Schneider et al., 2016](#); [Cory-Slechta et al., 2013](#)) or rats ([Rao Barkur and](#)
19 [Bairy, 2016](#); [Barkur and Bairy, 2015](#); [Weston et al., 2014](#); [Betharia and Maher, 2012](#)). Among these recent
20 studies, a variety of dosing paradigms were utilized, including exposure during preconception, lactation,
21 gestation, and combinations thereof (BLLs ranged between 3.02–26.86 $\mu\text{g/dL}$ in pups on PND 2–22). The
22 contrast in effects on litter size between studies that do and do not report effects of Pb on litter size is
23 perplexing, and the inconsistencies of BLL measurements (e.g., some measured Pb levels in offspring,
24 some measured in dams, some studies did not report BLLs at all) between studies further exacerbates the
25 difficulty of reconciling these contrasts. However, some plausible explanations for these differences exist
26 and primarily involve differences in study design. Studies that reported reductions in litter size due to Pb
27 exposure tended to either use higher doses ([Teijón et al., 2006](#)), longer dosing durations ([Iavicoli et al.,](#)
28 [2006](#)), or dosed sires in addition to dosing dams ([Dumitrescu et al., 2008a](#)) when compared to studies that
29 did not report reductions in litter sizes.

8.5.2.3 Integrated Summary of Effects on Female Fertility

30 Among the recent epidemiologic studies, there were inconsistent associations between Pb
31 exposure and female fertility. In studies among participants in the general population, there was an
32 increased risk of self-reported infertility and longer time to pregnancy. However, among studies with

1 women who were either seeking help at a fertility clinic or reported infertility, the associations were
2 inconsistent. Because the study participants included only a small sample of women who were either
3 seeking help at a fertility clinic or reported infertility, which may have resulted in selection bias and limits
4 the generalizability of the results. Additionally, the recent epidemiologic studies were limited by the
5 concurrently measured exposure and outcome, different biomarkers of exposure (blood, serum, and
6 follicular fluid), and a small number of participants. These studies did include adjustment for potential
7 confounders, however, including age, BMI, and partner exposure. Previous toxicological evidence
8 reported inconsistent effects of Pb on fertility in females. All recent toxicological studies reported that
9 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)

10 Recent epidemiologic and toxicological studies evaluating the association between Pb exposure
11 and morphology or histology of female sex organs (ovaries, uterus, fallopian tubes/oviducts, cervix,
12 vagina, and/or mammary glands) are limited. Study details for the single cross-sectional epidemiological
13 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)

14 In the 2013 Pb ISA, there were no epidemiological studies available that evaluated Pb
15 concentrations and associations with morphology or histology of female sex organs (ovaries, uterus,
16 fallopian tubes/oviducts, cervix, vagina, and/or mammary glands). A recent cross-sectional study
17 examined the association between BLLs and rate of uterine fibroids and uterine fibroid volume ([Ye et al.,
18 2017](#)). Among 288 (46 with fibroids and 242 without) pre-menopausal women included in the study, there
19 were null associations between blood Pb and the presence of uterine fibroids (OR: 1.39 [95% CI: 0.75.
20 2.56]) and volume of the largest fibroids (β : 0.12 [95% CI: -2.26, 2.51]). When blood Pb was categorized
21 into quartiles, the association with volume of uterine fibroids remained null. While the associations
22 between blood Pb and rate of uterine fibroids and uterine fibroid volume were generally null, the women
23 with uterine fibroids had higher geometric mean BLLs than women without fibroids (1.43 $\mu\text{g}/\text{dL}$ versus
24 1.35 $\mu\text{g}/\text{dL}$, 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)

1 There are no recent animal toxicological studies on the effects of Pb on morphology or histology
2 of female sex organs. The 2013 Pb ISA discussed a single study that reported Pb exposure increased
3 membrane fluidity in granulosa cells in Charles Foster rats that were dosed by intraperitoneal injection
4 doses for 15 days ([Nampoothiri and Gupta, 2006](#)). The 2006 Pb AQCD also reported that exposure to Pb
5 during early pregnancy caused structural changes in the uterine epithelium in mice ([Nilsson et al., 1991](#);
6 [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)

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

8.6 Effects on Male Reproductive Function

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

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

22 Multiple epidemiologic and toxicological studies have examined the relationship between Pb and
23 sperm and semen production, quality, and function. These studies are summarized in the text below.

1 Study details of the recent epidemiologic studies are included in Table 8-16 and the recent toxicological
2 studies are in Table 8-17. The majority of the recent epidemiologic studies are cross-sectional with
3 concurrent measurements of Pb levels in biological samples and sperm-related outcomes. Recent
4 toxicological studies use a variety of dosing paradigms, and those that dose for longer periods of time
5 (>30 days) or during a developmental window most often reported effects of Pb exposure on aspects of
6 sperm and semen quality.

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

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

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

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

1 reported the mean blood Pb for low-quality semen group of 5.198 µg/dL and 3.575 µg/dL for the normal-
2 quality semen group.

3 Other cross-sectional studies examined the relationship between Pb measured in seminal fluid and
4 metrics of sperm/semen production, quality, and function, but the associations were inconsistent ([Jia et al.,
5 2022](#); [Sukhn et al., 2018](#); [Pant et al., 2014](#)). [Pant et al. \(2014\)](#) measured Pb in semen and metrics of
6 sperm/semen production, quality, and function, and reported associations of higher sperm Pb with
7 decreased sperm motility (β : -2.43% [95% CI: -4.87%, -0.001%]), decreased sperm concentration (β :
8 1.97 10⁶/mL [95% CI: -3.16, -0.33]), increased tail length (β : 3.79 [95% CI: 0.56, 7.02]), increased
9 percent DNA in tail (β : 1.31 [95% CI: 0.17, 3.74]), and increased tail moment (β : 1.20 [95% CI: 0.23,
10 2.16]). However, [Sukhn et al. \(2018\)](#) assessed sperm characteristic relationships with Pb in seminal fluid
11 and reported increased odds of below-reference sperm viability and WHO morphology with higher
12 seminal fluid Pb, but null associations with volume, concentration, total count, and progressive motility.
13 [Jia et al. \(2022\)](#) reported no associations between seminal plasma Pb concentrations and semen parameters
14 (semen volume, sperm concentration, total sperm number, progressive motility, and normal
15 morphological rate).

16 A recent cohort study examined the associations between peripubertal blood Pb, collected at
17 enrollment, and parameters of sperm and semen production, quality, and function for 223 participants in
18 the Russian Children's Study, with the semen sample collected 10 years after enrollment ([Williams et al.,
19 2022](#)). There were null associations between peripubertal blood Pb and sperm parameters (sperm
20 concentration, total count, progressive motility, and total progressive motile sperm count, or probability
21 of having low semen quality based on sperm count/motility), whether blood Pb was modeled
22 continuously, categorized as tertiles, or categorized as low (<5 µg/dL) blood Pb versus high (≥5 µg/dL)
23 blood Pb (see Table 8-16).

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

24 The 2013 Pb ISA summarized several toxicological studies that investigated the effects of Pb
25 exposure on sperm-related outcomes. Utilizing a variety of dosing paradigms and animal models,
26 previously published studies have demonstrated that Pb exposure reduced sperm counts, reduced numbers
27 of viable sperm, reduced motility, and increased morphological abnormalities ([Pillai et al., 2012](#); [Anjum et
28 al., 2011](#); [Allouche et al., 2009](#); [Oliveira et al., 2009](#); [Salawu et al., 2009](#); [Shan et al., 2009](#); [Tapisso et al., 2009](#);
29 [Massanyi et al., 2007](#); [Piao et al., 2007](#); [Wang et al., 2006](#)). Results from recently published studies tend to
30 suggest that Pb exposure impacts sperm and semen parameters (Table 8-17). All available studies that
31 reported outcomes on sperm and semen parameters were conducted in mice. Only one study utilized a
32 developmental exposure paradigm and dosed lactating CD-1 mice from PND 0 to 21 which resulted in
33 reduced numbers of sperm at PND 70 in male offspring in the highest dose group (BLLs 19.1 µg/dL)
34 ([Wang et al., 2013a](#)). Other studies that directly exposed male mice after weaning also reported Pb-induced

1 sperm alterations including increased incidence of abnormal morphology, reduced density, and reduced
2 viability (BLLs 9.4–11.92 µg/dL) ([Zhang et al., 2021](#); [Xie et al., 2020](#); [Godínez-Solís et al., 2019](#)). However,
3 some studies also reported no Pb-induced effects on sperm motility, concentration, count, or viability
4 (BLLs 9.4–11.8 µg/dL) ([Pavlova et al., 2021](#); [Godínez-Solís et al., 2019](#)). It is worth noting that while [Pavlova](#)
5 [et al. \(2021\)](#) reported no Pb-induced effects on sperm count, Pb-treated animals had sperm counts 25%
6 lower than those of control mice, but this effect failed to reach statistical significance ($p = 0.146$). In
7 terms of patterns in the reported data, studies that utilized long-term exposure (>30 days) or dosed during
8 developmental periods tended to reported effects of Pb on sperm or semen parameters, and [Pavlova et al.](#)
9 [\(2021\)](#) the only study to use short-term exposure during adulthood, was the only study to report no effects
10 at all on any sperm or semen parameters.

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

11 Among the recent epidemiologic studies that evaluated associations between Pb exposure
12 (measured in blood, semen, seminal fluid, or seminal plasma) and effects on sperm/semen production,
13 quality, and function, there were inconsistent findings, which was similar to the conclusion in the 2013 Pb
14 ISA. More consistent associations were observed for blood Pb with decreased sperm/semen production,
15 quality, and function than for Pb measured in semen, seminal fluid, or plasma; however, there are
16 limitations in the recent epidemiologic studies. All the cross-sectional studies were conducted in males
17 attending fertility clinics, which may have resulted in selection bias and limits the generalizability of the
18 results. Further, the small sample size from these cross-sectional studies also reduces the statistical power
19 to determine the precision of the associations. With concurrent measurement of Pb exposure with
20 outcomes related to sperm/semen production, quality, and function, temporality cannot be established.
21 Lastly, the use of different biomarkers (e.g., blood, semen, seminal fluid, or seminal plasma) to measure
22 Pb exposure and the different metrics of sperm/semen production, quality, and function limits the ability
23 to judge coherence and consistency across studies. Despite these limitations, it is important to note that a
24 wide variety of potential confounders were controlled for, including hormone levels, which could
25 potentially impact sperm/semen production, quality, and function. Previous and recent toxicological
26 studies generally reported that Pb alters some aspect of sperm or semen quality, such as sperm density,
27 motility, morphology, and viability, especially those studies that employed dosing during developmental
28 periods or for periods 30 days or longer. All recent toxicological evidence was produced from mouse
29 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

30 The epidemiologic and toxicological studies reviewed in the 2013 Pb ISA reported inconsistent
31 results regarding changes in hormone levels in men and associations with Pb exposure. The results from

1 the 2013 Pb ISA were similar to the findings from the 2006 Pb AQCD. Recent epidemiologic and
2 toxicological studies are reported below. Epidemiologic studies were mostly cross-sectional with blood
3 Pb measured concurrently with hormone levels. Study details for the epidemiologic studies, including
4 BLLs, study population characteristics, potential confounder, and select results, are in Table 8-16.
5 Previous toxicological evidence regarding the effect of Pb on hormones in males is somewhat
6 inconsistent, but most studies reported impacts of Pb on hormone levels. Recent toxicological studies are
7 extremely limited, but support previous toxicological studies reported in the 2013 Pb ISA that observed
8 Pb-induced effects on hormones in males. Study details for the recent toxicological studies are in Table 8-
9 17.

8.6.2.1 Epidemiologic Studies on Hormone Levels in Males

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

21 The recent epidemiologic studies on hormone levels detailed in this section are specific to
22 hormones related to reproductive function and recent epidemiologic studies on other hormones are
23 described in [Section 9.4.2 in the Other Health Effects Appendix](#).

24 There are a few recent epidemiologic cross-sectional studies that evaluated the associations
25 between hormone levels in males and Pb exposure. There were consistent positive associations between
26 blood Pb and testosterone among these studies. One NHANES analysis combined three consecutive
27 cycles of NHANES (1999–2000, 2001–2002, and 2003–2004) to investigate the associations between
28 blood Pb and various sex hormones: testosterone, free testosterone, E2, fE2, androstenedione glucuronide,
29 and SHBG among men over 20 years old ([Kresovich et al., 2015](#)). Comparing the highest quartile of blood
30 Pb exposure ($>3.20 \mu\text{g/dL}$) to the lowest ($\leq 1.40 \mu\text{g/dL}$), testosterone was positively associated with blood
31 Pb (β : 0.79, SE: 0.22) and there was an indication of exposure-response (p for trend: 0.0026). There were
32 null associations between blood Pb and all other sex hormones. In another NHANES (2011–2012) study,
33 blood Pb and serum testosterone were measured in men of reproductive age (18–55 years old) ([Lewis and
34 Meeker, 2015](#)). Of the 484 men included in the analysis, there was a 6.65% (95% CI: 2.09%, 11.41%)

1 change in the serum testosterone concentration associated with a doubling (100% increase) in blood Pb
2 concentration. [Chen et al. \(2016\)](#) also reported positive associations between concurrent testosterone and
3 blood Pb concentrations. Utilizing data from a population-based survey, the Survey on the Prevalence in
4 East China for Metabolic Diseases and Risk Factors (SPECT)-China, 2,286 men were included in the
5 analysis to investigate the relationship between quartiles of BLLs and multiple reproductive hormones –
6 tT, SHBG, E2, LH, and FSH. When comparing the highest quartile of blood Pb (>6.249 µg/dL) to the
7 lowest (<2.90 µg/dL), there were positive associations with BLLs and tT (β : 0.033, SE: 0.010, $p < 0.01$),
8 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,
9 $p < 0.05$), but null associations with E2 (β : -0.003, SE: 0.017). Across the quartiles of blood Pb, there
10 were also positive trends observed with tT (p for trend: 0.012), SHBG (p for trend <0.001), FSH (p for
11 trend <0.001), and LH (p for trend <0.001), suggesting a potential linear concentration response.

12 While there were consistent positive associations between blood Pb and serum testosterone in the
13 cross-sectional studies, a single cohort study reported null associations. Among a subset of participants
14 (n = 453) in the Russian Children’s Study, there were no associations between peripubertal BLLs and
15 hormones levels (testosterone, LH, or FSH) measured between 8–19 years of age, whether blood Pb was
16 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

17 The 2013 Pb ISA discussed several studies that reported on the effects of Pb on hormone levels in
18 males. All studies were conducted in rats, and all directly dosed the tested animals save for one that
19 exposed gestating and lactating dams and measured hormones in offspring. Dosing durations varied from
20 21 days to 24 weeks, and most studies reported reductions in testosterone ([Pillai et al., 2012](#); [Anjum et al.,](#)
21 [2011](#); [Biswas and Ghosh, 2006](#); [Rubio et al., 2006](#)). One study observed increased testosterone ([Allouche et al.,](#)
22 [2009](#)) and another reported reductions in LH and FSH ([Biswas and Ghosh, 2006](#)). However, not all studies
23 observed effects on male hormones due to Pb exposure. One study observed no change in testosterone
24 ([Salawu et al., 2009](#)) and another reported no change in FSH and LH levels despite reporting increased
25 testosterone levels ([Allouche et al., 2009](#)). Only one recent PECOS-relevant toxicological study was
26 published that investigated the effects of Pb exposure on hormones in males (Table 8-17). This study
27 dosed nursing CD-1 mice from PND 0 to 21 and reported reduced serum testosterone at weaning and
28 PND 70 and reduced testicular testosterone at weaning in the highest dose group (19.1 µg/dL) ([Wang et](#)
29 [al., 2013a](#)).

8.6.2.3 Integrated Summary of Effects on Hormone Levels in Males

30 The recent cross-sectional epidemiological studies reported consistent associations between blood
31 Pb and testosterone; however, a single cohort study reported no associations. Of note, the recent cross-

1 sectional studies were in adult men, whereas the single cohort study were in male adolescents.
2 Additionally, the study by [Chen et al. \(2016\)](#) provides further support of a positive association with SHBG,
3 FSH, and LH and blood Pb. The positive trends among quartiles of blood Pb and testosterone, SHBG,
4 FSH, and LH provide insight on the possible concentration-response relationship. These studies have
5 robust sample sizes drawn from population-based surveys and controlled for a number of confounders,
6 including smoking, but the temporality of effects is difficult to establish due to the nature of cross-
7 sectional study design. Recent toxicological evidence regarding the effects of Pb on hormones in males is
8 extremely limited, but in agreement with most studies summarized in the 2013 Pb ISA which report
9 effects of Pb on hormones in males.

8.6.3 Effects on Male Fertility

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

8.6.3.1 Epidemiologic Studies on Male Fertility

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

27 There were a limited number of recent epidemiologic studies that examined associations between
28 Pb and male fertility. In the LIFE Study, a cohort of couples were followed prospectively to assess
29 persistent environmental chemicals and human fecundity ([Louis et al., 2012](#)). BLLs in both female and
30 male partners were collected at baseline. While female blood Pb was not associated with increased time to
31 pregnancy, there was decreased odds, or increased time to pregnancy, for male BLLs in both the male

1 exposure model (OR: 0.85 [95% CI: 0.73, 0.99]) and the couple exposure model (OR: 0.82 [95% CI:
2 0.68, 0.97]). In a cohort of 195 couples undergoing IVF, Pb was measured in blood serum and follicular
3 fluid from the female partner and semen from the male partner in association with six IVF outcomes
4 ([Zhou et al., 2021a](#)). There was a positive association between Pb in seminal plasma and the possibility of
5 obtaining a good embryo (RR: 1.86 [95% CI: 1.05, 3.11]), but the associations were null across all other
6 IVF outcomes (normal fertilization, blastocyst formation, high-quality blastocyst, pregnancy, or live
7 birth).

8.6.3.2 Toxicological Studies on Male Fertility

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

8.6.3.3 Integrated Summary of Male Fertility

14 Similar to the 2013 Pb ISA, there were only a few epidemiologic studies evaluating associations
15 between Pb exposure and male fertility and the findings were inconsistent. The results from these studies
16 are limited by the small sample size and the study population was recruited from a fertility clinic, which
17 may have resulted in selection bias and limits generalizability. Additionally, different biomarkers were
18 used to assess Pb exposure, as well as different metrics of male fertility across the studies. In terms of
19 toxicological evidence, previous and recent studies are few in number. However, all report a reduction of
20 male fertility in Pb-treated animals using outcomes such as litter size, implantations, and fertilized
21 oocytes.

8.6.4 Effects on Morphology and Histology of Male Sex Organs

22 The toxicological studies in the 2013 Pb ISA supported historical findings that showed an
23 association between Pb exposure and changes in the sex organs as well as germ cells. There were no
24 epidemiological studies available for review for the 2013 Pb ISA that examined the relationship between
25 Pb exposure and morphology or histology of male sex organs. The current epidemiologic and
26 toxicological studies examining the relationship between Pb exposure and effects on morphology and
27 histology of male sex organs are summarized in the text below with study details in Table 8-16 and Table
28 8-17, respectively.

8.6.4.1 Epidemiologic Studies of Morphology and Histology of Male Sex Organs

1 In the 2013 Pb ISA, there were no epidemiological studies available that evaluated Pb
2 concentrations and associations with morphology or histology of male sex organs. A recent cohort study
3 evaluated the associations between prenatal metal exposure and reproductive development in boys at 2–
4 3 years ([Huang et al., 2020](#)). Serum concentrations of multiple metals, including Pb, were obtained from
5 mothers in the Guangxi Birth Cohort Study throughout pregnancy, while reproductive development was
6 measured as TV and anogenital distance (AGD), categorized as anopenile distance (AGDap) and
7 anoscrotal distance (AGDas), in 2–3-year-old male children. When maternal serum Pb levels were
8 categorized by quartiles, infants in the highest quartile (serum Pb >1.23 µg/L) had, on average, a
9 0.064 mL (95% CI: –0.124, –0.004) smaller TV, 0.060 cm (95% CI: –0.110, –0.011) shorter AGDap, and
10 0.115 cm (95% CI: –0.190, –0.039) shorter AGDas than infants in the lowest quartile (serum Pb ≤
11 0.54 µg/L).

8.6.4.2 Toxicological Studies of Morphology and Histology of Male Sex Organs

12 This section is divided into the two main outcomes for the male sex organs: changes in weight of
13 male sex organs and changes in histology/morphology of male sex organs. The 2013 Pb ISA summarized
14 several studies that investigated the effects of Pb exposure on male sex organ weights. Several studies
15 reported decreases in weights of organs such as the testis, epididymides, vas deferens, seminal vesicles,
16 and prostate ([Anjum et al., 2011](#); [Pillai et al., 2010](#); [Dong et al., 2009](#); [Salawu et al., 2009](#); [Biswas and Ghosh,
17 2006](#); [Rubio et al., 2006](#)). The direction of effect was consistent, and any effects observed were only
18 decreases in organ weights. However, the 2013 Pb ISA noted that there were many other studies that did
19 not report effects on male reproductive organ weights even when using similar doses as those studies that
20 did observe effects, indicating that the impact of Pb on reproductive organ weights is somewhat
21 inconsistent. Recent studies have also investigated the effects of Pb exposure on male sex organ weight
22 (Table 8-17). [Wang et al. \(2013a\)](#) reported that dosing male CD-1 mouse pups via their dams' drinking
23 water from PND 0 to 21 led to reduced absolute weight of testes in both treatment groups at weaning and
24 reduced relative testis weight in the highest treatment group at weaning (BLLs 19.1–21.2 µg/dL on
25 PND 22 and 3.24–4.40 µg/dL on PND 70). However, they observed no effect on the weight of the
26 prostate, seminal vesicle, or epididymides at weaning and no effects on relative weights of any
27 reproductive organ on PND 70. Similarly, another study reported that dosing Sprague-Dawley rats from
28 GD –10 to PND 183 had reduced absolute and relative testis weights (BLLs 18.6 µg/dL) ([Wang et al.,
29 2013b](#)). However, some studies reported that Pb did not alter the weights of testes or epididymides in ICR
30 mice (BLLs 6.02–21.66 µg/dL) ([Pavlova et al., 2021](#); [Satapathy and Panda, 2017](#)).

31 The 2013 Pb ISA reported on studies that investigated the effects of Pb on the histopathology of
32 male sex organs in rodents exposed to Pb. One of the most common outcomes was alterations of
33 seminiferous tubule pathology, such as reduced length of some spermatogenic cycle stages within

1 seminiferous tubules, tubule damage, and tubule atrophy ([El Shafai et al., 2011](#); [Shan et al., 2009](#); [Massanyi et](#)
2 [al., 2007](#); [Rubio et al., 2006](#); [Wang et al., 2006](#)). A few recent Pb studies have also reported Pb-induced
3 histopathological changes in male sex organs (Table 8-17). All recent studies were conducted in mice,
4 and exposure paradigms used between recent studies varied from developmental to exposure only during
5 adulthood. One study in CD-1 mice that utilized developmental exposure (dosing dams from lactational
6 day 0 to 21) reported that Leydig cell numbers in the testes were reduced in the highest dose group at
7 weaning and layers of spermatogenic cells within the seminiferous tubules were decreased in both dose
8 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)
9 ([Wang et al., 2013a](#)). Some studies dosing mice for 90 days following weaning reported disruptions that
10 epithelial cells within the epididymis were “randomly arranged” (BLLs 6.02–11.8 µg/dL) ([Xie et al., 2020](#))
11 and that spermatogenic cells within seminiferous tubules were reduced in number (BLLs at 11.92 µg/dL)
12 ([Zhang et al., 2021](#)). Lastly, a study that dosed mice from PND 60 to 74 reported that the epithelium of the
13 seminiferous tubules was disorganized, the luminal region contained undifferentiated germ cells, and
14 some tubules had decreased diameter and germ cell number and displayed incomplete spermatogenesis
15 (BLLs 21.7 µg/dL) ([Pavlova et al., 2021](#)).

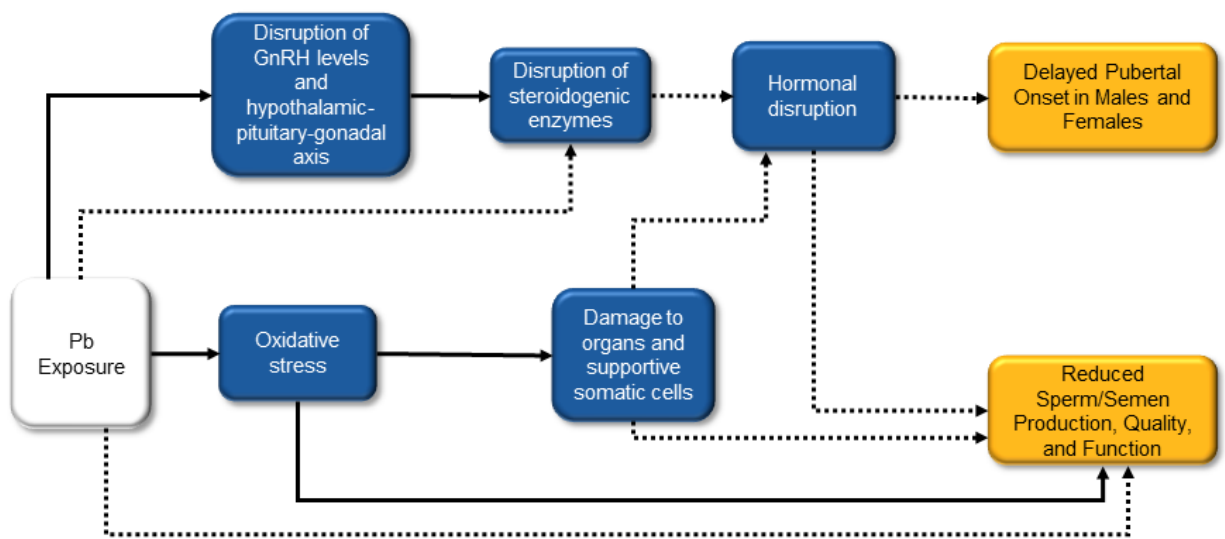
8.6.4.3 Integrated Summary of Morphology and Histology of Male Sex Organs

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

8.7 Biological Plausibility

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

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



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. Shading around multiple boxes is used to denote a grouping of these effects. Arrows may connect individual boxes, groupings of boxes, and individual boxes within groupings of boxes. Progression of effects is generally depicted from left to right and color-coded (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.

Pb = lead; GnRH = gonadotropin-releasing hormone

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

8.7.1 Pubertal Onset

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

1 exposure and delayed onset of puberty in males ([Williams et al., 2019](#); [Nkomo et al., 2018](#); [De Craemer et al.,](#)
2 [2017](#)) and females ([Gomula et al., 2022](#); [Jansen et al., 2018](#); [Nkomo et al., 2018](#); [De Craemer et al., 2017](#);
3 [Sławińska et al., 2012](#)). The proposed biologically plausible pathway through which Pb induces delays in
4 pubertal onset begins with the Pb-induced disruption of the gonadotropin-releasing hormone (GnRH)
5 levels which may occur through reduction of circulating IGF-1 levels. GnRH is a key hormone in the
6 hypothalamic-pituitary-gonadal axis and hormonal signaling pathways related to reproduction and
7 pubertal onset. A recent epidemiologic study found negative associations between BLLs at 8–9 years of
8 age and IGF-1 in boys two and four years later ([Fleisch et al., 2013](#)) and toxicological studies have reported
9 reduced IGF-1 levels and IGF-1R expression in the brains of animals exposed to Pb ([Li et al., 2016](#); [Li et](#)
10 [al., 2014](#); [Dearth et al., 2002](#); [Ronis et al., 1998b](#)). IGF-1 is known to act on GnRH neurons and affect GnRH
11 secretion ([Dees et al., 2021](#); [Daftary and Gore, 2005](#)), which is responsible for the release of LH and FSH
12 from the anterior pituitary, resulting in stimulation of the gonads to begin producing sex steroid hormones
13 and mature oocytes and spermatozoa. One toxicological study conducted in female Fisher 344 rats found
14 that Pb-induced delays of pubertal onset could be reversed by supplementation with IGF-1 ([Pine et al.,](#)
15 [2006](#)). This study reported that supplementation with IGF-1 also restored GnRH and LH levels in Pb-
16 exposed rats, demonstrating that IGF-1 disruption is a key component in delays in the onset of puberty
17 mediated by Pb at BLLs at/above 35 µg/dL.

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

8.7.2 Male Reproduction Function

29 The other health outcome proposed in Figure 8-1 is male reproductive function. Recent
30 epidemiologic studies have reported that Pb exposure is associated with reductions in a variety of semen
31 parameters, including sperm motility, sperm concentration, and normal sperm morphology ([Shi et al.,](#)
32 [2021](#); [Sukhn et al., 2018](#); [Li et al., 2015](#); [Pant et al., 2014](#)). These findings are generally consistent with the
33 epidemiologic evidence presented in the 2013 Pb ISA ([U.S. EPA, 2013](#)). Further, toxicological studies
34 provide supporting evidence that Pb negatively impacts male reproductive function (see Section 8.6.1)

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

3 The 2013 Pb ISA concluded that the evidence indicates a causal relationship between Pb
4 exposure and reduced quality of sperm, and that this relationship was likely mediated through the
5 generation of reactive oxygen species, leading to cellular damage ([U.S. EPA, 2013](#)). Specifically, the 2013
6 Pb ISA summarized one study that reported Pb-induced increases in oxidative stress markers and
7 reductions in antioxidant enzyme levels in testicular plasma of rats ([Salawu et al., 2009](#)). In addition,
8 several studies in the 2013 Pb ISA reported attenuation of Pb-induced reductions in sperm count, motility,
9 and viability when animals were co-administered substances with known antioxidant properties ([Salawu et](#)
10 [al., 2009](#); [Shan et al., 2009](#); [Madhavi et al., 2007](#); [Rubio et al., 2006](#); [Wang et al., 2006](#)). Further supporting the
11 proposed pathway through which oxidative stress mediates Pb-induced effects are additional studies that
12 report that Pb exposure dysregulates antioxidant enzymes, leading to oxidative stress and DNA damage in
13 the affected tissues ([Lopes et al., 2016](#); [Kägi and Vallee, 1960](#); [Ommati et al., In Press](#)). Additionally, recent
14 studies that report an attenuation of Pb-induced effects on aspects of male reproductive function (e.g.,
15 subfecundity, reduced sperm count) in animals supplemented with antioxidants ([Zhang et al., 2021](#);
16 [Abdelhamid et al., 2020](#); [Alotaibi et al., 2020](#); [Naderi et al., 2020](#); [Udefa et al., 2020](#); [Abdrabou et al., 2019](#); [Hassan](#)
17 [et al., 2019](#); [Ommati et al., 2019](#); [BaSalamah et al., 2018](#); [Hasanein et al., 2018](#); [Mabrouk, 2018](#); [El Shafai et al.,](#)
18 [2011](#); [Leiva et al., 2011](#); [Sainath et al., 2011](#); [Ommati et al., In Press](#)). Although many studies report negative
19 effects of Pb on supporting somatic cells that have key functions in the spermatogenic cycle (e.g., Leydig
20 cells, Sertoli cells), Pb may also have negative effects directly on sperm cells. Direct contact of Pb with
21 sperm cells has been documented by multiple studies ([Jia et al., 2022](#); [Sukhn et al., 2018](#); [Pant et al., 2014](#)).
22 One recent study reported that incubating sperm from healthy adult men for 4 hours with 30 µg/mL or
23 8 hours with either 15 or 30 µg/mL Pb increased DNA fragmentation, possibly due to oxidative stress and
24 Pb binding to DNA phosphate residues, disrupting the process of chromatin condensation ([Gomes et al.,](#)
25 [2015](#)). In another study, 4 hours of incubation of semen samples from healthy adult men with Pb reduced
26 intracellular levels of cyclic adenosine monophosphate (cAMP) (10, 50, and 100 µM) and Ca²⁺ (2.5, 10,
27 50, and 100 µM), both of which are important in regulating sperm cell function ([He et al., 2016](#)). In support
28 of this alternative mechanism of action is one study that reported an attenuation of Pb-induced effects on
29 reproduction in Pb-intoxicated male mice that were supplemented with CaCl₂ ([Golshan Iranpour and Kheiri,](#)
30 [2016](#)). Disruption of intracellular levels of key components such as cAMP and Ca²⁺ is another way in
31 which Pb can directly affect sperm health and function outside of oxidative stress.

32 In summary, pathways are suggested by which Pb exposure can delay pubertal onset and reduce
33 sperm/seminal production, quality, and function. Studies indicate that Pb exposure likely impacts the
34 hypothalamic-pituitary-gonadal axis in both males and females, leading to disruption of the onset of
35 puberty, a developmental period with increasing regard for its sensitivity to insult due to the vulnerability
36 of the various endocrinological events for which it is known. In addition, Pb exposure alters multiple
37 aspects of male reproductive function. The production of adequate quantities of viable sperm is essential
38 for proper male fertility and reproduction. Pb exposure hampers this by negatively impacting both the

1 sperm cell and the supportive somatic cells that play key roles in the spermatogenic cycle through
2 increased oxidative stress and disruption of other important intracellular functions.

8.8 Summary and Causality Determination

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

8.8.1 Summary of Effects on Pregnancy and Birth Outcomes

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

26 While there were no epidemiologic or toxicological studies examining Pb exposure and maternal
27 in the 2013 Pb ISA, recent epidemiologic and toxicological studies, reported inconsistent results
28 regarding maternal health outcomes and different maternal health outcomes were evaluated between the
29 epidemiologic and toxicological studies. Among the epidemiologic studies, there were consistent null
30 associations between maternal blood (blood, serum, and erythrocytes) and GDM, and with the reported
31 mean/median blood Pb below 10 µg/dL. Although some recent epidemiological studies investigated

1 various pregnancy-related endpoints, the small number limits the ability to judge coherence and
2 consistency across these studies. Among the few toxicological studies that investigated maternal health,
3 the only outcome reported was maternal weight gain during pregnancy. Most studies reported no effects
4 of Pb on maternal weight gain during pregnancy, and the few that reported reductions in maternal weight
5 gain also reported reductions in dam brain weight, a marker often indicative of overt toxicity. This
6 suggests that the observed reduction in maternal weight gain during pregnancy reported in these studies
7 may not be directly due to Pb exposure and may have been influenced by overt toxicity experienced by
8 the dams.

9 The recent epidemiologic and toxicological studies of birth outcomes reported inconsistent
10 findings overall. Among the recent epidemiologic studies of prenatal growth and Pb exposure, the
11 findings were inconsistent and no effects on birth weight were reported in the toxicological studies,
12 similar to the conclusion in the 2013 Pb ISA. The inconsistencies in the recent epidemiologic studies of
13 prenatal growth and Pb exposure may be due to differences in study design, the timing of the exposure,
14 differences in biomarkers of exposure, and the wide variation in prenatal growth outcomes assessed (birth
15 weight, birth length, HC, GA). A few studies were further limited by small sample size, which may cause
16 imprecision in the measures of association.

17 While a single recent toxicological study reported no effects of Pb exposure on gestation length,
18 there were inconsistent associations reported in the recent epidemiologic studies examining the
19 relationship between Pb exposure and risk of preterm birth, which was similar to the 2013 Pb ISA. While
20 the recent epidemiologic studies of preterm birth included populations for which mean/median maternal
21 blood Pb values were below 10 µg/dL and controlled for wide range of confounders, including GA, other
22 metals, and maternal health factors (e.g., smoking, parity, BMI), there were limitations among these
23 recent studies, including timing of the exposure (during pregnancy, at delivery), biomarkers examined for
24 Pb (maternal blood, cord blood, maternal red blood cells, maternal serum, placental tissue), small sample
25 sizes in some studies, and cross-sectional study design in some studies.

26 The recent epidemiologic studies of Pb exposure and birth defects, specifically NTDs, CHDs,
27 orofacial clefts defects and abdominal congenital malformations, reported inconsistent associations.
28 While the associations were generally null for Pb exposure (measured in placental tissue, umbilical tissue,
29 maternal blood serum, and umbilical cord serum) and NTDs, CHDs, and abdominal congenital
30 malformations, there were positive associations with orofacial cleft defects when Pb was measured in
31 placental tissue or maternal blood. The small number of studies limits the ability to judge consistency and
32 coherence across studies of different birth defects (e.g., NTDs, CHDs, orofacial clefts defects, and
33 abdominal congenital malformations), timing of Pb exposure (e.g., second trimester, third trimester, and
34 at delivery), differences in biomarkers (e.g., placental tissue, umbilical tissue, maternal blood serum, and
35 umbilical cord serum, maternal blood), and confounders considered in the analyses. Additionally, the
36 relatively small sample sizes in some studies reduce the statistical power to determine the precision of the
37 associations. Recent toxicological studies report no effects of Pb on birth defects in offspring. This

1 contrasts with some previously reviewed studies that reported defects in offspring of Pb-exposed dams.
2 However, dams in these previous studies also experienced overt toxicity due to the high Pb doses used,
3 which did not occur in recent toxicological studies, suggesting that maternal toxicity may have been
4 involved with the birth defects observed in previous studies.

5 There were only a few recent epidemiologic studies that evaluated Pb exposure and spontaneous
6 abortion and pregnancy loss. Studies that examine spontaneous abortion are difficult to conduct as many
7 spontaneous abortions or pregnancy losses occur during the first trimester. Women may miscarry before
8 being enrolled in a study and/or women may not have known they were pregnant when they miscarried,
9 thus limiting the ability of a study to detect subtle effects, e.g., if higher Pb exposures lead to increased
10 risk of early spontaneous abortions. In the recent epidemiologic studies, some of the studies assessing
11 spontaneous abortion and/or pregnancy loss were among women who were undergoing treatment at
12 fertility clinics, which may result in selection bias and limited generalizability of the results because the
13 study populations are not representative of the general population. In the recent toxicological studies,
14 there were no reported effects of Pb exposure on pre- or postnatal offspring mortality. Although not
15 always consistently so, BLLs were generally lower in recent toxicological literature when compared to
16 previous literature, possibly explaining the observed contrast in results.

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

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

1 Overall, there were inconsistent findings reported among the recent epidemiologic and
2 toxicological studies on Pb exposure and pregnancy and birth outcomes (Table 8-1). The recent
3 epidemiologic studies reported consistent null associations with GDM, but among all other pregnancy and
4 birth outcomes (prenatal growth, preterm birth, birth defects, spontaneous abortion and pregnancy loss,
5 placental function, and other outcomes) there were inconsistent results. Additionally, recent
6 epidemiological studies were often limited by cross-sectional design, timing of the exposure, biomarkers
7 examined for Pb, and in some instances, small sample sizes. Of note, the cohorts in the recent
8 epidemiologic literature would generally be expected to have had appreciable past exposures to Pb;
9 however, the extent to which adult BLLs in these cohorts reflect the higher exposure histories is unknown
10 as to the extent to which these past Pb exposures (magnitude, duration, frequency) may or may not elicit
11 effects on pregnancy and birth outcomes. The recent evidence from the toxicological studies mostly
12 reported no effects of Pb across pregnancy and birth outcomes. This may be due to the exclusion of
13 toxicological studies with BLLs greater than 30 µg/dL, indicating the possibility that most pregnancy and
14 birth outcomes are only affected in laboratory animals at levels higher than most environmentally relevant
15 Pb exposure levels. **In summary, the collective evidence is suggestive of, but not sufficient to infer, a**
16 **causal relationship between Pb exposure and effects on pregnancy and birth outcomes.**

8.8.2 Summary of Effects on Development

17 The 2013 ISA concluded that the collective body of evidence integrated across epidemiologic and
18 toxicological studies, based on the findings of delayed pubertal onset among males and females, was
19 sufficient to conclude that there is a causal relationship between Pb exposure and developmental effects.
20 Multiple epidemiologic studies of Pb and puberty in the 2013 Pb ISA showed associations between
21 concurrent BLLs and delayed pubertal onset for girls and boys. In cross-sectional epidemiologic studies
22 of girls (ages 6–18 years) with mean and/or median concurrent BLLs from 1.2 to 9.5 µg/dL, consistent
23 associations with delayed pubertal onset (measured by age at menarche, pubic hair development, and
24 breast development) were observed. In boys (ages 8–15 years), fewer epidemiologic studies were
25 conducted but associations between BLLs and delayed puberty were observed, including associations
26 among boys in a longitudinal study. These associations were consistently observed in populations with
27 mean or median BLLs of 3.0 to 9.5 µg/dL. Potential confounders considered in the epidemiologic studies
28 of both boys and girls that performed regression analyses varied. Most studies controlled for age and
29 BMI. Other variables, such as measures of diet, socioeconomic status (SES), and race/ethnicity, were
30 included in some of the studies. Adjustment for nutritional factors was done less often and this could be
31 an important confounder. A study using a cohort of girls from NHANES controlled for various dietary
32 factors as well as other potential confounders and reported an association between increased concurrent
33 BLLs and delayed pubertal onset ([Selevan et al., 2003](#)). A limitation across most of the epidemiologic
34 studies of BLLs and delayed puberty was the cross-sectional design, which does not allow for an
35 understanding of temporality. There was uncertainty with regard to the exposure frequency, timing,
36 duration, and level that contributed to the associations observed in these studies. Additionally, the

1 toxicological studies reviewed in the 2013 Pb ISA indicated that delayed pubertal onset may be one of the
2 more sensitive developmental effects of Pb exposure with effects observed after gestational exposures
3 leading to BLLs in the female pup of 1.3–13 µg/dL ([Iavicoli et al., 2006](#); [Iavicoli et al., 2004](#)). An additional
4 study reviewed in the 2013 Pb ISA reported increases in age at vaginal opening in Wistar rats that were
5 dosed prior to conception and in utero, but BLLs were not reported ([Dumitrescu et al., 2008a](#)). These results
6 are supported by studies reviewed in the 2006 Pb AQCD that reported delays in pubertal onset in female
7 rats and mice as measured by age at vaginal opening and age at first estrus ([Pine et al., 2006](#); [Dearth et al.,](#)
8 [2004](#); [Dearth et al., 2002](#); [Ronis et al., 1998a](#); [Ronis et al., 1998c](#); [Ronis et al., 1996](#)). BLL varied greatly
9 between studies with some reporting effects occurring in dose groups with levels below 30 µg/dL ([Dearth](#)
10 [et al., 2004](#); [Dearth et al., 2002](#)) while others only report effects in groups with BLLs higher than 30 µg/dL
11 ([Ronis et al., 1998a](#); [Ronis et al., 1998c](#); [Ronis et al., 1996](#)). A key study reviewed in the 2006 Pb AQCD, [Pine](#)
12 [et al. \(2006\)](#) reported increased age at vaginal opening in Fisher 344 rats that was attenuated by
13 supplementation of IGF-1. However, [Pine et al. \(2006\)](#) only reported BLLs of dams, making it difficult to
14 determine what BLLs in the offspring may have been achieved to elicit such effects on puberty.
15 Toxicological studies have also reported delayed male sexual maturity as measured by sex organ weight,
16 among other outcomes, seeing significant decrements at BLLs of 20–34 µg/dL ([Ronis et al., 1998c](#); [Sokol et](#)
17 [al., 1985](#)). Thus, the 2013 Pb ISA concluded that the data from the toxicological literature and from
18 epidemiologic studies demonstrated puberty onset in both males and females was delayed with Pb
19 exposure.

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

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

30 In the recent epidemiologic and toxicological literature, the relationship between Pb exposure and
31 puberty onset in both females and males, as well as postnatal growth, was reviewed. While there were no
32 recent PECOS-relevant toxicological studies in puberty in either females or males, the recent
33 epidemiologic studies reported consistent pattern of associations between blood Pb exposure and delayed
34 age of menarche ([Gomula et al., 2022](#); [Jansen et al., 2018](#); [De Craemer et al., 2017](#); [Sławińska et al., 2012](#)), and
35 some indication of slower breast development ([Nkomo et al., 2018](#); [De Craemer et al., 2017](#)) in females,
36 which is similar to the findings from the epidemiologic studies reviewed in the 2013 Pb ISA. However,
37 the associations between Pb exposure and male pubertal onset were inconsistent. The differences in

1 markers of puberty in males (hormone levels, pubic hair development, genital development, TV) may
2 explain the inconsistencies in findings across recent studies. While the studies assessing Pb exposure and
3 female and male puberty were limited by differences in the timing of exposure to Pb or Pb biomarker
4 (blood, maternal bone, cord blood), these studies consider a wide range of confounders, including height,
5 weight, and BMI.

6 The recent toxicological and epidemiologic studies that evaluated the relationship between Pb
7 exposure and postnatal growth were inconsistent. The majority of recent toxicological studies did not
8 report changes in postnatal growth due to Pb exposure ([Zhao et al., 2021](#); [Xie et al., 2020](#); [Rao Barkur and
9 Bairy, 2016](#); [Basha and Reddy, 2015](#); [Basgen and Sobin, 2014](#)). However, some recent toxicological studies
10 reported decreases ([Duan et al., 2017](#); [de Figueiredo et al., 2014](#); [Graham et al., 2011](#)) and increases ([Betharia
11 and Maher, 2012](#)) in body weight of offspring due to Pb exposure. The recent epidemiologic studies also
12 reported inconsistent findings overall. However, among epidemiologic studies that evaluated the
13 associations between blood Pb and postnatal growth in children (older than four years) there were more
14 consistent patterns of associations of decreased height and weight ([Signes-Pastor et al., 2021](#); [Kuang et al.,
15 2020](#); [Zhou et al., 2020](#); [Deierlein et al., 2019](#); [Kerr et al., 2019](#); [Choi et al., 2017](#)). The inconsistencies in the
16 associations in the epidemiologic literature seem to be due to different timings of exposure, different
17 biomarkers (maternal blood, maternal bone, cord blood, infant blood, childhood blood), and difference
18 timing of outcome measurement. The current inconsistent findings of exposure to Pb and postnatal
19 growth are similar to those reported in the 2013 Pb ISA.

20 There was a small body of epidemiologic studies across various other developmental effects;
21 however, the small number of studies limits the ability to judge coherence and consistency across these
22 studies, although the associations reported demonstrate that Pb exposure could result in physiological
23 responses that contribute to adverse developmental effects, including changes to diurnal cortisol rhythms,
24 lower salivary sialic acid levels, and DNA oxidative stress damage from Pb exposure among children
25 during developmental periods. However, the small number of studies limits the ability to judge coherence
26 and consistency across the outcomes evaluated in these studies. Recent studies that investigate other
27 developmental outcomes such as developmental milestones are scarce. Some toxicological studies
28 investigated developmental milestones in rodents (pinna detachment, eye slit formation, eye opening,
29 tooth eruption, and fur development). No effects of Pb exposure were reported on any of these milestones
30 in groups with PECOS-relevant BLLs.

31 In summary, there is consistent evidence across the recent epidemiological studies that reported
32 delayed age of menarche with blood Pb and this is supported by findings from previous toxicological and
33 epidemiologic evidence (Table 8-1). However, there were inconsistent findings in the toxicological and
34 epidemiologic studies that evaluated the relationship between Pb exposure and postnatal growth. There
35 was some indication of reduced body weight in the toxicological studies, however, and decreased height
36 and weight in children in the epidemiological studies of blood Pb. The cohorts in the recent epidemiologic
37 literature would generally be expected to have had appreciable past exposures to Pb; however, the extent

1 to which adult BLLs in these cohorts reflect the higher exposure histories is unknown as to the extent to
2 which these past Pb exposures (magnitude, duration, frequency) may or may not elicit developmental
3 effects, such as postnatal growth or puberty. Despite uncertainty due to inconsistent findings across the
4 recent epidemiologic studies, some toxicological evidence exists that supports biologically plausible
5 pathways of how Pb exposure exerts its effects on pubertal onset ([Li et al., 2016](#); [Li et al., 2014](#); [Pine et al.,
6 2006](#); [Dearth et al., 2002](#); [Ronis et al., 1998b](#)). In summary, toxicological studies suggest that Pb may impact
7 pubertal onset via dysregulation of IGF-1, resulting in a cascade of effects that alters levels of hormones
8 important during the pubertal period. Further, epidemiologic and toxicological studies both suggest that
9 Pb may impact sperm and semen quality primarily through oxidative stress. In summary, toxicological
10 studies suggest that Pb may impact pubertal onset via dysregulation of IGF-1, resulting in a cascade of
11 effects that alters the levels of hormones important during the pubertal period. Further, epidemiologic and
12 toxicological studies both suggest that Pb may impact sperm and semen quality primarily through
13 oxidative stress. **Overall, the collective evidence is sufficient to conclude a causal relationship
14 between Pb exposure and effects on development.**

8.8.3 Summary of Effects on Female Reproductive Function

15 The 2013 ISA concluded that the relationship observed with female reproductive function, such
16 as fertility and hormone levels in some epidemiologic and toxicological studies is sufficient to conclude
17 that evidence is suggestive of a causal relationship between Pb exposure and female reproductive
18 function. Epidemiologic and toxicological studies of reproductive function among females investigated
19 whether Pb biomarker levels were associated with hormone levels, fertility, estrous cycle changes, and
20 morphology or histology of female reproductive organs. Some of the epidemiologic studies reviewed in
21 the 2013 Pb ISA reported associations with concurrent BLLs and altered hormone levels in adults, but
22 results varied among studies, possibly due to the different hormones examined and the different timing in
23 menstrual and life cycles. There was some evidence of a potential relationship between Pb exposure and
24 female fertility, but findings were mixed. The majority of the epidemiologic studies were cross-sectional
25 and adjustment for potential confounders varied from study to study, with some potentially important
26 confounders, such as BMI, not included in all studies. Further, most of the epidemiologic studies on
27 female reproductive function reviewed in the 2013 Pb ISA had small sample sizes and were generally
28 conducted in women attending infertility clinics. Toxicological study design often employed prenatal or
29 early postnatal Pb exposures at relevant Pb levels, with Pb contributing to decreased ovarian antioxidant
30 capacity, altered ovarian steroidogenesis, and aberrant gestational hormone levels ([U.S. EPA, 2013](#)).
31 Although epidemiologic and toxicological studies provide information on different exposure periods, both
32 types of studies, including some high-quality epidemiologic and toxicological studies, support the
33 conclusion that Pb may affect some aspects of female reproductive function.

34 There were no recent PECOS-relevant toxicological studies of the effects of Pb exposure on
35 hormone levels in females or menstrual/estrous cyclicity; however, there were several recent

1 epidemiologic studies. The recent epidemiological studies examining the relationship between Pb
2 exposure and hormone levels reported consistent positive associations between blood Pb and FSH and LH
3 in women who were post-menopausal. While these studies were limited by their cross-sectional study
4 design, the studies were conducted in well-established population-based surveys. These studies
5 considered a range of confounders, including controlling for BMI, smoking, and co-exposure with Cd, but
6 not all studies adjusted for some potential important confounders such as age at menarche, pregnancy
7 history, oral contraceptive use, and female hormone use, such as IVF or hormone therapy. Additionally,
8 the recent studies examining the relationship between menopause and Pb exposure found consistent
9 positive associations of early risk of menopause. The results from a study of concurrent exposure of blood
10 Pb with menopause were supported by the results from a longitudinal cohort that reported that bone Pb, a
11 cumulative biomarker of Pb exposure, was associated with difference in age at menopause and risk of
12 early menopause.

13 Among the recent epidemiologic studies, there were inconsistent associations between Pb
14 exposure and female fertility. In studies among participants in the general population, there was an
15 increased risk of self-reported infertility and longer time to pregnancy ([Lee et al., 2020](#); [Louis et al., 2012](#)).
16 However, among studies with women who were either seeking help at a fertility clinic or reported
17 infertility, the associations were inconsistent. Because the study participants included only a small sample
18 of women who were either seeking help at a fertility clinic or self-reported infertility, selection bias may
19 exist and limits the generalizability of the results. Additionally, these studies were limited by the
20 concurrently measured exposure and outcome, different biomarkers of exposure (blood, serum, and
21 follicular fluid), and a small number of participants. These studies did include adjustment for potential
22 confounders, including age, BMI, and partner exposure. The recent toxicological studies in female
23 fertility did not observe alterations in the number of litters or the litter size in Pb-exposed dams that began
24 dosing prior to conception.

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

31 In summary, there was inconsistent evidence from recent epidemiologic and toxicological studies
32 of Pb exposure and female reproductive function overall (Table 8-1). The recent epidemiologic studies
33 reported consistent positive associations between blood Pb and FSH and LH in women who were post-
34 menopausal and positive associations of early risk of menopause with blood Pb. While these studies were
35 limited by their cross-sectional study design, the studies considered a range of confounders, including
36 controlling for BMI, smoking, and co-exposure with Cd, but not all studies adjusted for some potential
37 important confounders such as age at menarche, pregnancy history, oral contraceptive use, and female

1 hormone use, such as IVF or hormone therapy. The evidence from the recent toxicological studies did not
2 observe alterations to female fertility, while the recent epidemiologic studies reported inconsistent
3 findings with Pb exposure and female fertility. The inconsistencies in the epidemiologic studies may be
4 the result of concurrently measured exposure and outcome, different biomarkers of exposure (blood,
5 serum, and follicular fluid), exposure circumstances (magnitude, duration, timing, and frequency), and a
6 small number of participants who were either seeking help at a fertility clinic or self-reported infertility,
7 which may have resulted in selection bias and limits the generalizability of the results. **Overall, the
8 collective evidence is *suggestive of, but not sufficient to infer, a causal relationship between Pb
9 exposure and female reproductive function.***

8.8.4 Summary of Effects on Male Reproductive Function

10 The 2013 ISA concluded that based on the consistency and coherence of findings for the
11 detrimental effects of Pb exposure on aspects of sperm and semen quality in the toxicological literature,
12 with support from epidemiologic studies, and biologically plausible pathways, there was sufficient of a
13 causal relationship between Pb exposures and male reproductive function. Toxicological studies with
14 relevant Pb exposure routes reported effects on rodent sperm quality and sperm production rate (BLL
15 range: 34–37 µg/dL) ([Sokol and Berman, 1991](#); [Sokol et al., 1985](#)), sperm DNA damage with BLL of 19 and
16 22 µg/dL ([Nava-Hernández et al., 2009](#)), and histological or ultrastructural damage to the male reproductive
17 organs in studies from rodents at BLL of 5.1 µg/dL ([El Shafai et al., 2011](#)) and non-human primates (BLL
18 of 43 µg/dL) ([Cullen et al., 1993](#)). These effects were found in animals exposed to Pb during peripuberty or
19 adulthood for 1 week to 3 months. The toxicological studies reported that Pb exposure decreased
20 reproductive organ weight and caused histological changes in the testes and germ cells. Subfecundity
21 (decreased number of pups born/litter) was reported in unexposed females mated to Pb-exposed males.
22 Also, sperm from Pb-exposed rats (BLLs: 33 to 46 µg/dL) used for in vitro fertilization of eggs harvested
23 from unexposed females yielded lower rates of fertilization ([Sokol et al., 1994](#)). Supporting evidence was
24 provided by decrements in sperm quality from rabbits administered Pb subcutaneously (BLLs of
25 25 µg/dL) ([Moorman et al., 1998](#)).

26 The 2013 Pb ISA reported detrimental effects of Pb on sperm observed in epidemiologic studies
27 with concurrent BLLs of 25 µg/dL and greater among men occupationally exposed ([Hsu et al., 2009](#);
28 [Kasperczyk et al., 2008](#); [Naha and Manna, 2007](#); [Naha and Chowdhury, 2006](#)). Findings of these epidemiologic
29 studies are limited due to these high exposure levels among the occupational cohorts and the lack of
30 consideration for potential confounding factors, including occupational exposures other than Pb. Studies
31 among men with lower Pb levels were limited to infertility clinic studies, which may produce a biased
32 sample and findings that lack generalizability. However, a well-conducted epidemiologic study that
33 enrolled men going to a clinic for either infertility issues or to make a semen donation and controlled for
34 other metals, as well as smoking, reported a positive association of blood Pb with various detrimental
35 effects in sperm ([Telišman et al., 2007](#)). The median concurrent BLL in this study was 4.92 µg/dL (range:

1 1.13–14.91). A similar study also reported possible associations between concurrent blood Pb and various
2 semen parameters, but the results were extremely imprecise (large confidence intervals [CIs]), making it
3 difficult to draw conclusions ([Meeker et al., 2008](#)).

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

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

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

36 There were a limited number of recent epidemiologic and toxicological studies that examined the
37 relationship between Pb and hormones in males. While recent epidemiologic and toxicological studies

1 reported changes in hormone levels among males, the direction of the observed relationships differed
2 across disciplines. Specifically, the epidemiologic studies reported Pb-associated increases in
3 testosterone, whereas the toxicological studies reported a reduction in testosterone following exposure to
4 Pb. Additionally, recent cross-sectional epidemiologic studies reported inconsistent associations between
5 blood Pb and other sex hormones. One study reported positive associations between blood Pb and SHBG,
6 FSH, and LH, as well as positive trends among quartiles of blood Pb, suggestive of a potential exposure-
7 response relationship. In contrast, an NHANES study reported null associations between blood Pb and
8 E2, fE2, androstenedione glucuronide, and SHBG. Recent toxicological evidence regarding the effects of
9 Pb on male sex hormones is limited to a single study that reported that exposure through the dam's milk
10 from birth to weaning (PND 21) in CD-1 mice was sufficient to reduce testosterone in the serum at
11 weaning and on PND 70.

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

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

34 In summary, there is coherent evidence across the epidemiologic and toxicological studies of
35 detrimental effects of Pb exposure on male reproductive function (Table 8-1). While recent epidemiologic
36 and toxicological studies suggest that Pb exposure may result in alterations in testosterone levels, fertility,
37 and changes in morphology or histology of male sex organs, the strongest evidence of effects of Pb on

1 male reproductive function is seen in consistency of the reported effects of Pb on sperm and semen
2 parameters. Epidemiologic studies consistently report associations with Pb measured in blood and
3 decreased sperm/semen production and quality, and toxicological studies consistently report Pb-induced
4 reductions of a variety of semen parameters such as sperm density, motility, viability, and normal sperm
5 morphology. There are biological plausible pathways through which Pb exposure may alter sperm/semen
6 production and quality. Specifically, Pb exposure has been shown to cause oxidative stress, which can
7 damage the supportive somatic cells in the testis (Leydig cells and Sertoli cells) as well as damage the
8 sperm cells directly. Supportive somatic cells are responsible for regulating producing sex steroid
9 hormones and regulating spermatogenesis, and disruption of either of these functions can impact the
10 quality and quantity of the sperm produced. **Overall, the collective evidence is sufficient to conclude a**
11 ***causal* relationship between Pb exposure and male reproductive function.**

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 – Suggestive			
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, preterm birth, 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 birth weight, but recent studies report few impacts of Pb on birth weight, 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			
<i>Delay Puberty Onset</i>			
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 and controlled for potential confounding by covariates such as age and BMI.	See Section 8.4.2.1 and Section 8.4.3.1	Female Puberty BLLs: 0.65–6.57 µg/dL Male Puberty BLLs: 0.66–6.5

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	Pb Biomarker Levels Associated with Effects ^c
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
<i>Postnatal Growth</i>			
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
Effects on Female Reproductive Function – Suggestive			

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	Pb Biomarker Levels Associated with Effects ^c
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
Lack of large, well-conducted epidemiologic studies examining associations between Pb levels and fertility, but overall inconsistent evidence	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. 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			
<i>Sperm/Semen Production, Quality, and Function</i>			
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	See Section 8.6.1.1	BLLs: 2.18–3.26 µg/dL

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	Pb Biomarker Levels Associated with Effects ^c
	exposure (blood, semen, seminal plasma, seminal fluid).		
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
<i>Hormone Levels</i>			
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
<i>Fertility</i>			
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

Rationale for Causality Determination ^a	Key Evidence ^b	Key References ^b	Pb Biomarker Levels Associated with Effects ^c
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BLL = blood lead level; BMI = body mass index; BW = birth weight; IGF-1 = insulin-like growth factor 1; IVF = in vitro fertilization; Pb = lead.

^aBased 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](#)).

^bDescribes 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.

^cDescribes 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)	MIREC n: 1274	Blood	Maternal health during pregnancy: GDM	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
Canada	Women at least 18 years of age during the first trimester of pregnancy (6 to <14 weeks gestation) with singleton, live births	Maternal blood was measured by ICP-MS	IGT and GDM were assessed by chart review based on the results of a 50-g glucose challenge test and 75 or 100-g oral glucose tolerance test (OGTT)		
2008–2011		Age at Measurement: Maternal age during first trimester of pregnancy	Age at outcome: Maternal age at IGT or GDM diagnosis during pregnancy		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
Cohort		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			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 Cross-sectional	Etude des Déterminants pré et post natus du développement de la santé de l'Enfant study n: 623 Pregnant women between 24 and 28 weeks of gestation	Blood Maternal blood measured by EAAS with Zeeman background correction Age at Measurement: Maternal age at 24–28 weeks 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 weeks, 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 weeks 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 Cross-sectional	Japan Environment and Children's Study 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 weeks 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 years or older with GA of 20 weeks 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 weeks were excluded	Blood Maternal blood was measured by ICP-MS Age at Measurement: Mean maternal age for GDM: 31.00 years Mean maternal age for non-GDM: 30.97 years 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 h blood glucose >10.0 mmol/L, or (3) 2 h 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 (0.78, 1.30) p for trend: 0.963 Multi-pollutant Model: Low: Reference Middle: 1.06 (0.80, 1.41) High: 1.10 (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 weeks) and	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: Tertile 1: Reference Tertile 2: 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	singleton 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 years Median ^{2c} : 2.53 µg/dL 75th ^c : 4.00 µg/dL Tertiles (µg/dL): Tertile 1: ≤1.96 Tertile 2: 1.961–3.41 Tertile 3: ≥3.411	the International Association for Diabetes in Pregnancy Study Group’s criteria. Age at outcome: maternal mean age: 30.14 years	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	Tertile 3: 0.89 (0.76, 1.03) Model 2: Tertile 1: Reference Tertile 2: 1.05 (0.90, 1.22) Tertile 3: 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 weeks at recruitment.	Blood Maternal blood (erythrocyte) measured in the first trimester measured by ICP-MS Age at measurement: maternal age during first trimester mean (standard deviation, SD): 32.3 (4.6) years Median: 17.6 ng/g 75th: 23.6 ng/g	Maternal health during pregnancy: gestational glucose Glucose tolerance test 26–28 weeks gestation, as measured by non-fasting 50 g oral glucose challenge test. Age at outcome: maternal age at 26–28 weeks gestation mean (SD): 32.3 (4.6) years	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	JECS n: 78,964 Women who delivered a live infant with singleton pregnancy. Women	Blood Maternal blood measured by ICP-MS Age at measurement:	Maternal health during pregnancy: GDM GDM diagnosed by OGTT in second or third trimester	Logistic regression adjusted for pre-pregnancy BMI, age at blood collection, smoking/drinking habits during pregnancy, history of GDM, history of	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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Cross-sectional	were excluded if there was a missed blood sample, missed diagnosis of GDM, missing HbA1c data, HbA1c $\geq 6.5\%$ at <24 gestational weeks, or a history of type 1 or type 2 diabetes.	Maternal age at second or third trimester; non-GDM mean age 31.0 years; GDM mean age 33.3 years Median: 5.9 ng/g 95th: 10.6 ng/g	overt GDM diagnosed prior to OGTT was excluded. Age at outcome: maternal age at second or third trimester; non-GDM mean age 31.0 years; GDM mean age 33.3 years	delivering a macrosomia, regional center, fish intake and co-exposure to Cd, Mn, and Se	Q5: 0.974 (0.824, 1.151)
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 years participating in the PROGRESS birth cohort in Mexico City, and who consented to a cervical swab during mid-pregnancy (16–19 weeks 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-shell X-ray fluorescence (K-XRF) instrument within 1 month of delivery Age at Measurement: Maternal age at exposure sampling (mean 27.9 years with a range of 18–40) Mean: Blood: 2.85 $\mu\text{g}/\text{dL}$ Patella ^d : 4.16 Tibia ^d : 1.45 Max: Blood: 9.38 $\mu\text{g}/\text{dL}$ Patella ³ : 20.90 Tibia ³ : 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 years 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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					hsa-miR-361-3p: 2.8 (0.0, 5.7) Tibia: 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)	PROGRESS Study n: 410 mother-infant pairs Mexico City, Mexico December 2007–July 2011 Cohort Participants who were <20 weeks gestation; maternal age of ≥18 years 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 years) 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:	Maternal health during pregnancy: altered cord blood mitochondrial DNA (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 years)	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, premature rupture of membranes (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
		4.73 µg/dL; at delivery: 5.28 µg/dL; cord blood: 4.45 µg/dL			
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 weeks 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 years; Mitrovica Mean: 26.7 years 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 years; Mitrovica Mean: 26.7 years	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 Cross-sectional	Baltimore Tracking Health Related to Environmental Exposures Study n: 285 Singleton births with cord blood available, with complete covariates data	Blood Umbilical cord blood (UCB) was measured by ICP-MS Age at Measurement: Maternal age at delivery (range: 14–43, mean: 26) Geometric mean:	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	Multivariable linear regression models were adjusted for maternal age, maternal race, neighborhood median household income, 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

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		0.66 µg/dL 75th: 0.96 µg/dL Max: 6.47 µg/dL	of blood pressure measurements from each mother were recorded: systolic blood pressure (SBP) and diastolic blood pressure (DBP) at admission, the maximum SBP and corresponding DBP, and the minimum SBP and corresponding DBP. Age at outcome: maternal age at delivery (range: 14–43, mean: 26)		Admission DBP: Q1: Referent 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)	N: 1,485	Blood	Maternal health during pregnancy: maternal stress	Generalized additive models were adjusted for maternal age, ethnicity, maternal education, family monthly income, years living in Shanghai	β (95% CI) ^b
Shanghai China 2010 Cross-sectional	Pregnant women during late pregnancy (28–36 gestational weeks)	Maternal blood was measured by background corrected GFAAS collected gestational week 28–36 Age at measurement: 13–42 years old Geometric mean: 3.99 µg/dL	Maternal life event stress and emotional stress were assessed using the Life-Event-Scale-for-Pregnant-Women (LESPW) and Symptom-Checklist-90-Revised (SCL-90-R), respectively.		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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		Max: 14.84 µg/dL	Age at outcome: 13–42 years old		Anxiety: 0.01 (–0.06, 0.08) Log-blood Pb >0.41 µg/dL 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)	PROGRESS n: 668	Blood and bone Maternal blood was measured by ICP-QQQ; bone Pb measured by K-shell X-ray fluorescence and obtained two estimated for patella and tibia (one for each leg), which were measured 26–55 days postpartum	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 quantitative ultrasound (QUS). Age at outcome: Median (SD): 27 (5.5) years	Linear models adjusted for maternal age, socioeconomic status, 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) ¹ 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)
Mexico 2007–2011 Cohort	Women enrolled during second trimester of pregnancy, were ≥18 years of age, lived in Mexico City for the following 3 years	Age at measurement: Median (SD): 27 (5.5) years 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			

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		3rd Trimester: 28.25 µg/dL Tibia: 30.1 µg/g Patella: 43.2 µg/g			
Kim et al. (2022) Puerto Rico and United States 2010 Cohort	PROTECT n: 617 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.	Blood Maternal blood, collected at up to two study visits (median 18- and 26-weeks gestation), was measured by ICP-MS Age at measurement: Mean (SD) age at enrollment: 26.9 (5.5) years 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	Maternal health during pregnancy: matrix metalloproteinases 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) years	Linear mixed effects models adjusted for maternal age, education, exposure to second-hand tobacco smoke, and pre-pregnancy BMI	B (95% CI) ¹ as percent change in MMP per IQR increase in blood Pb 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	Blood Maternal blood was measured by ICP-MS Age at measurement: Mean: 29.16 years Median: 28 years Range: 18–47 years	Maternal health during pregnancy: preeclampsia Diagnosis of preeclampsia was based on the definition from the American College of Obstetrics and Gynecologists. Age at outcome:	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) ¹ : 2.65 (1.2, 5.86)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	hospital or routine testing.	All Participants: Mean (SD): 2.63 (1.34) µg/dL Median: 2.6 µg/dL Preeclampsia Participants: Mean (SD) 3.36 (1.23) Median: 3.49 µg/dL Max: All Participants: 6.1 µg/dL Preeclampsia Participants: 6.1 µg/dL	Mean: 29.16 years Median: 28 years Range: 18–47 years		
Wu et al. (2021)	n: 2174 China, Foshan, Guangdong Province August 2019–November 2019 (participants followed from 8–12 week of pregnancy to birth) Cohort	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) weeks of pregnancy and before date of diagnosed preeclampsia, was measured by AAS Age at measurement: Mean age at delivery (SD): 29.04 (4.25) years 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 weeks of gestation. Hypertension was defined as systolic ≥140 mmHg or diastolic ≥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 weeks 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:

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					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) 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 week gestation, ≥18 years old, free of heart or kidney disease, have access to a	Blood and bone Maternal blood was measured by GFAAS during the second trimester. Maternal bone was measured by K-shell X-ray fluorescence instrument ~1 month postpartum Age at measurement: ≥18 years old Mean: blood: 3.7 µg/dL tibia: 2.7 µg/g	Maternal health during pregnancy: hypothalamic-pituitary-adrenal axis function measured from salivary cortisol concentrations Between 14 and 35 weeks of gestation (mean [SD]: 19.7 [2.4] week), 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,	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-hours 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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	telephone, plan to reside in Mexico City for the next 3 years, not use steroids (including glucocorticoids) or anti-epilepsy drugs, and not consume alcohol on a daily basis.	<p>patella: 4.6 µg/g</p> <p>Blood Pb Quintiles</p> <p>Q1: 0–<1.8 µg/dL</p> <p>Q2: 1.8–<2.4 µg/dL</p> <p>Q3: 2.4–<3.4 µg/dL</p> <p>Q4: 3.4–<5.1 µg/dL</p> <p>Q5: ≥5.1 µg/dL</p> <p>Tibia Pb Quintiles</p> <p>Q1: <2 µg/g</p> <p>Q2: 2–<4.3 µg/g</p> <p>Q3: 4.3–<6.7 µg/g</p> <p>Q4: 6.7–<11.1 µg/g</p> <p>Q5: ≥11.1 µg/g</p> <p>Patella Pb Quintiles</p> <p>Q1: <2 µg/g</p> <p>Q2: 2–<4.5 µg/g</p> <p>Q3: 4.5–<7.8 µg/g</p> <p>Q4: 7.8–<12.7 µg/g</p> <p>Q5: >12.7–43.2 µg/g</p>	<p>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.</p> <p>Age at outcome: maternal age at the time of outcome measurement</p>		<p>Patella Pb Quintiles:</p> <p>Q1: Reference</p> <p>Q2: 1 (–8, 12)</p> <p>Q3: –6 (–14, 4)</p> <p>Q4: 12 (1, 24)</p> <p>Q5: 4 (–6, 16)</p>
<p>Ishitsuka et al. (2020)</p> <p>Japan</p> <p>January 2011 – March 204</p> <p>Cross-sectional</p>	<p>JECS</p> <p>n: 17,267</p> <p>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</p>	<p>Blood</p> <p>Maternal blood was measured by ICP-MS</p> <p>Age at measurement: maternal age at 27 weeks of gestation (mean age: 31 ± 5 years)</p>	<p>Maternal health during pregnancy: maternal depression</p> <p>Psychological symptoms during middle or late pregnancy were assessed using the Kessler Psychological Distress Scale (K6).</p> <p>Age at outcome:</p>	<p>Multivariable logistic regression models adjusted for age, parity, marital status, education, employment status, household income, and smoking and alcohol status</p>	<p>OR (95% CI)</p> <p>Pb per one-unit increase</p> <p>K6 ≥13: 1.00 (0.76, 1.32)</p> <p>K6 ≥5: 0.98 (0.88, 1.09)</p> <p>K6 ≥13:</p> <p>Q1: Reference</p> <p>Q2: 0.94 (0.69, 1.27)</p> <p>Q3: 0.97 (0.71, 1.31)</p> <p>Q4: 0.92 (0.68, 1.25)</p>

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	not use steroids during pregnancy	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 age at 27 weeks of gestation (mean age: 31 ± 5 years)		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)
Christensen et al. (2016)	Climate Change, Environmental Contaminants, and Reproductive Health Ukraine and Greenland 2002–2004 Women at least 18 years 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: anti-müllerian hormone (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 In-Pb increase: -0.0423 (-0.4989, 0.4144)
Gustin et al. (2021)	NICE n: 544 Sweden, Norrbotten county Enrollment: 2015–2018, follow-up through 29 gestational weeks Pregnant women visiting their local maternity clinics who were residents of southern or eastern Norrbotten county and planned to give birth at Sunderby	Blood Maternal blood (erythrocyte) was measured by ICP-MS Age at measurement: Median: 30 years	Maternal health during pregnancy: hormone Levels (fT4, tT4, fT3, tT3, TSH, fT4:tT4, fT3:tT3, fT3:fT4) Plasma samples from gestation 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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Cohort	Hospital. Only first pregnancies and singleton births included. Those with thyroid dysfunction were excluded.	Median: 11 µg/kg 95th: 27 µg/kg			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 Matina County, Limon Coast Rica 2010–2011 Cohort	Blood Maternal blood measured by ICP-MS Age at measurement: Maternal age at collection (recruited <33 weeks gestation with 2nd blood sample 10 weeks later) Median: 0.666 µg/dL 75th: 0.908 µg/dL 90th: 1.211 µg/dL Max: 3.43 µg/dL	Maternal health during pregnancy: thyroid function TSH, ft4, and ft3 measured in serum using electrochemiluminescence	Linear regression models adjusted for age, GA, cotinine detection, pre-pregnancy BMI, and severe vomiting during pregnancy	β (95% CI) for % change in 1st measurement of outcomes per 10% increase in blood Pb (µg/L) at enrollment: 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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
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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; 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; ICP-MS = inductively coupled plasma mass spectrometry; ICP-QQQ = inductively coupled plasma triple quad; IGT = impaired glucose tolerance; IQR = interquartile range; Japan Environment and Children's Study = JECS; K6 = Kessler Psychological Distress Scale; K-XRF = K-shell X-ray fluorescence; matrix metalloproteinases = MMP; MIREC = Maternal-Infant Research on Environmental Chemicals; miRNA = micro RNA; 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 Testsite for Exploring Contamination Threats; Q = quartile; QUS = quantitative ultrasound; SBP = systolic blood pressure; 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.

^aEffect 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.

^bEffect estimates unable to be standardized.

^cPb measurements were converted from µg/L to µg/dL.

^dNo 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 months prior to mating. Offspring were continued on the same exposure as their dams until the end of the experiment at 12 months 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	Birth Weight, 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 months prior to mating through lactation (weaning assumed to be PND 21). Dams were also treated to a	Dams at weaning (assumed PND 21): 0.22 µg/dL for control 12.61 µg/dL for 100 ppm Pb	Birth Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL As Reported (µg/dL)	Endpoints Examined
			non-stress or prenatal stress condition. Only data from dams in the non-stress condition were used.	Pups (PND 5–6): 0.37 µg/dL for control 10.2 µg/dL for 100 ppm Pb	
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 months 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	Birth Weight, 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 month)	Pups (PND 22): 0.19 µg/dL for control	Stillborn Pups, Birth Weight

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	PND 21; GD 0 to PND 21	prior to conception), Gestation Only (21 days), Lactation Only (21 days), and Gestation and Lactation (42 days).	3.03 µg/dL for 0.2% Pb in Pregestation Only group	
	0.2% Pb Pregestation Only, n = 6 dams			5.51 µg/dL for 0.2% Pb in Gestation Only group	
	0.2% Pb Gestation Only, n = 6 dams			26.86 µg/dL for 0.2% Pb in Lactation Only group	
	0.2% Pb Lactation Only, n = 6 dams			31.59 µg/dL for 0.2% Pb in Gestation and Lactation group	
	0.2% Pb Gestation and Lactation, F, n = 6 dams				
Barkur and Bairy (2015)	Rat (Wistar) Control (untreated), 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 month prior to conception), Gestation Only (21 days), Lactation Only (21 days), and Gestation and Lactation (42 days).	Pups (PND 22): 0.18 µg/dL for control 3.02 µg/dL for 0.2% Pb in Pregestation Only group	Stillborn Pups, Birth Weight
	0.2% Pb Pregestation Only, F, n = 6 dams			5.30 µg/dL for 0.2% Pb Gestation Only group	
	0.2% Pb Gestation Only, F, n = 6 dams			26.7 µg/dL for 0.2% Pb in Lactation Only group	
	0.2% Pb Lactation Only, F, n = 6 dams			32.0 µg/dL for 0.2% Pb in Gestation and Lactation group	
	0.2% Pb Gestation and Lactation, F, n = 6 dams				
Tartaglione et al. (2020)	Rat (Wistar) Control, M/F, n = NR	GD -28 to PND 23	Dams were dosed via drinking water starting 4 weeks 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	Birth Weight, Sex Ratio
	50 mg/L Pb, M/F, n = NR				

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 weeks 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	Birth Weight
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	Birth Weight
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; F = female; GD = gestational day; M = male; Pb = lead; PND =postnatal day.

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 Cross-sectional	n: 252 Pregnant women aged 18 years or older, planning to deliver at the Binhai hospital, and more than 3 years of residence in the Laizhou Bay; exclusion criteria included diagnoses of gestational or preexisting diabetes, hypertension, HIV, or AIDS; GA <28 weeks; 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 days 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: Birth weight (BW), birth length, head circumference (HC) BW, birth length, and HC were measured by several trained midwives within 1 hour 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 Cross-sectional	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-minute 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 years, 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 Cross-sectional	Flemish human environmental health survey (FLEHS II) n: 248 Women with uncomplicated live-born singleton pregnancies, living in Flanders for at least 10 years, 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
Cross-sectional	born at term (36–42 weeks 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 Cross-sectional	n: 1,009 mother-infant pairs Singleton pregnant women who had lived in Shanghai for at least 2 years, were aged 18 years 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, birth length, HC, and the ponderal index Neonatal anthropometry, including BW, birth length, 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 birth length 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	β (95% CI) ^b All Infants BW (g): 50.68 (-69.53, 170.88) birth length (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) birth length (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) birth length (cm): 0.35 (-0.35, 1.05)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
				household income per capita, mode of delivery	HC (cm): -0.65 (-1.24, -0.06) PI (g/cm ³): 0.09 (-0.04, 0.21)
Govarts et al. (2020)	Flemish Environment and Health Studies (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 five years in the selected study areas (FLEHS I), at least 10 years in Flanders (FLEHS II), at least 5 years 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 In-Pb: 16.98 g (-13.14, 47.11) per 2.94 interquartile fold change in In-Pb
Lee et al. (2021)	Dhaka Community Hospital Trust n: 1088	Cord blood UCB measured by acid digestion and ICP-MS Age at measurement: birth	Prenatal growth: BW, birth length, HC Trained staff measured anthropometer at birth; GA estimated using ≤16-weeks ultrasound.	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 In-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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Cross-sectional		Geometric mean (Geometric SD): 3.18 (2.35) µg/dL Median: 3.07 µg/dL 75th: 6.04 µg/dL Max: 83.5 µg/dL	Age at outcome: birth		Untransformed birth size measurements 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 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	Prenatal growth: BW, low BW (LBW) rate, intrauterine growth restriction (IUGR) rate, gestational age 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 (weeks): 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 Cross-sectional	n: 1,578 Women aged 16–50 years 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:	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
		UCB: 2.689 µg/dL Max: UCB: 56.511 µg/dL			
Kim et al. (2020) Guiyu and Haojiang China Cross-sectional	e-waste Recycling Exposure and Community Health (e-REACH) Study n: 314 Women 18 years 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 months 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 last menstrual period or last missed period (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, environmental tobacco smoke (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/m ³): -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	EMASAR n: 696 Women who either were about to deliver or had given birth within the last 48 hours at one	Blood Maternal blood measured by ICP-MS Age at measurement:	Prenatal growth: GA, BW, birth length, HC, LBW Medical records were used to obtain measures at 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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
2011–2012 Cross-sectional	of the two hospitals. Women had to be above 18 years of age.	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	Age at outcome: birth		GA (weeks): 0.18 (0.05, 0.309) OR (95%CI) LBW: Tertile 1: Reference Tertile 2: 0.59 (0.10, 3.55) Tertile 3: 0.53 (0.09, 3.16)
Hu et al. (2015) Beigin, Lanzhou, Taiyuan, Xiamen China June-August 2011 Cross-sectional	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 years (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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Yang et al. (2020) Wuhan China 2014–2015 Cross-sectional	Births at Women and Children Medical and Healthcare Center of Wuhan n: 734 The participants were enrolled at their first antenatal examination (<gestational 16 weeks). 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.	Cord blood UCB (serum) was measured by ICP-MS Age at Measurement: birth Geometric mean: 1.65 µg/L Median: 2.71 µg/L 75th: 4.29 µg/L Quartiles ⁵ Q1: <25th percentile Q2: 25th – 50th percentile Q3: 50th – 75th percentile Q4: >75th percentile	Prenatal growth: BW (birth weight-for-gestational-age Z-score [BWGA]) Midwives immediately measured BW after delivery and was standardized for gestational weeks to construct BWZ. Age at outcome: birth	Generalized linear regression models adjusted for maternal age, annual household income levels, pre-pregnancy BMI, parity, passive smoking during pregnancy, maternal weight gain during pregnancy, fetal sex	β (95% CI) ^b , per unit increase in ln-Pb UCB serum Continuous: 0.01 (–0.002, 0.05) Quartiles: 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 Cross-sectional	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	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	Prenatal growth: BW, length (height), and HC and gestational age All of these infant anthropometric measurements were collected at birth by professional healthcare workers. GA was obtained using the reported date of the last menstrual period and delivery date.	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 (weeks): –0.21 (–0.44, 0.03) BW, in g: T1: Reference

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	births and had no congenital diseases.	Tertiles (µg/dL): T1: <5.633 T2: 5.633–9.197 T3: >9.197	Age at outcome: birth		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) HC, in cm: T1: Reference T2: -0.31 (-0.59, -0.02) T3: -0.13 (-0.40, 0.14) GA, in weeks: T1: Reference T2: -0.23 (-0.50, 0.05) T3: -0.20 (-0.49, 0.08)
Freire et al. (2019) Spain 2000–2008 Cross-sectional	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 years old, (iii) to have a	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 (limit of detection [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 last menstrual period to the end of pregnancy; LBW was defined by a BW of less than 2500 g at term, newborns were defined as SGA when	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	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 (weeks): -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
	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 communication problems		below the 10th percentile of the expected weight according to the Spanish BW curve adjusted for GA and sex Age at outcome: birth	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 education and maternal working during pregnancy	
Mikelson et al. (2019)	n: 374 Chattanooga, TN United States Cross-sectional	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)	LIFE n: 235 Michigan (4 counties) and Texas (12 counties) United States 2005–2009 Cohort	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) years and paternal mean age: 31.52 (SD:4.57) years	Prenatal growth: GA, BW, birth length, 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	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,	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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	organic pollutants. Inclusion criteria comprised a committed heterosexual relationship, women aged 18–40 years (men >18), English or Spanish speaker, no use of an injectable contraceptive within 12 months, and a menstrual cycle length of 21–42 days.	<p>Mean (SD): Maternal: 0.71 (0.30) µg/dL Paternal: 1.13 (0.63) µg/dL</p> <p>Median: Maternal: 0.66 µg/dL Paternal: 0.98 µg/dL</p> <p>Max: Maternal: 2.23 µg/dL Paternal: 6.43 µg/dL</p> <p>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)</p> <p>Paternal Blood Pb T1: <0.84 (<33rd percentile) T2: 0.84–1.16 (33rd to 67th percentile) T3: >1.16 (>67th percentile)</p>	<p>the ratio of live male to female births, reflecting a male excess.</p> <p>Age at outcome: birth</p>	<p>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)</p>	<p>T3: 0.61 (–0.31, 1.53) p for trend: 0.416</p> <p>BW, in kg Maternal Exposure: T1: Reference T2: 81.80 (–79.94, 2238.55) T3: –34.885 (–197.76, 128.06) p for trend: 0.202</p> <p>Paternal Exposure: T1: Reference T2: 20.46 (–134.17, 175.09) T3: 62.91 (–94.73, 220.55) p for trend: 0.882</p> <p>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</p> <p>Paternal Exposure: T1: Reference T2: 0.19 (–0.70, 1.08) T3: 0.61 (–0.31, 1.53) p for trend: 0.416</p> <p>HC, in cm Maternal Exposure: T1: Reference</p>

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					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 Pl, 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	Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study n: 98 Healthy pregnant woman between the ages of 16 and 40 years, carrying a single fetus with the intent to deliver the fetus, residence within	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 years); birth Median: Second trimester: 0.43 µg/dL Third trimester: 0.43 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
	Shelby County, Tennessee, and having the intent to deliver at one of three area-based hospitals	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			
Shih et al. (2021)	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 weeks 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	Prenatal growth: birth length, 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.	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 (weeks) 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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		Male infants: 2.86 µg/dL Female infants: 0.85 µg/dL	Age at outcome: birth		Overall: -0.343 (-2.92, 2.233) Males: 2.211 (-0.667, 5.089) 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 Observation for Measurement of the Environment (HOME) Study n: 272 Women were recruited between 13 and 19 weeks of pregnancy from prenatal clinics and were >18 years old, <19 weeks 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 weeks 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 gestational age	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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Taylor et al. (2016) Bristol, UK April 1991–December 1992 Cohort	Avon Longitudinal Study of Parents and Children (ALSPAC) n: 4,190 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	Blood Maternal blood was measured by ICP-MS Age at measurement: maternal age at measurement (median GA of sampling: 11 weeks) Median: 3.40 µg/dL 75th: 4.33 µg/dL Max: 19.41 µg/dL	Prenatal growth: BW, HC, crown-heel length HC and crown-heel length (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	Multivariable fractional polynomials and modeled adjusted for maternal educational attainment, smoking, GA (centered at 40 weeks), maternal height and pre-pregnancy weight, and sex of the infant	β (95% CI) 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 years, to be expecting a single pregnancy, intend to deliver their babies at the public hospital assigned to them, lived in the study area	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	Prenatal growth: GA, BW, birth length, abdominal diameter (AD), or cephalic diameter (CD) GA, BW, birth length, 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 (weeks): 0.02 (-0.44, 0.47)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	(Madrid Autonomous Region) for more than a year, and did not have a blood transfusion in the previous year	was 33.9 (IQR 31.6–35.7) and at birth Geometric mean ^c : Maternal: 1.83 µg/dL Paternal: 3.17 µg/dL UCB: 0.45 µg/dL			<p>Paternal blood Pb</p> <p>BW (g): -110.8 (-235.6, 6.0)</p> <p>BL (cm): -0.44 (-1.12, 0.23)</p> <p>AD (cm): -0.81 (-1.64, -0.00)</p> <p>CD (cm): -0.32 (-0.65, 0.00)</p> <p>GA (weeks): -0.17 (-0.59, 0.26)</p> <p>UCB Pb</p> <p>BW (g): 80.0 (-36.8, 196.6)</p> <p>BL (cm): 0.30 (-0.33, 0.93)</p> <p>AD (cm): 0.56 (-0.12, 1.24)</p> <p>CD (cm): -0.16 (-0.47, 0.15)</p> <p>GA (weeks): -0.04 (-0.44, 0.35)</p> <p>Male Infants</p> <p>Maternal blood Pb</p> <p>BW (g): 62.6 (-145.2, 270.4)</p> <p>BL (cm): 0.29 (-0.83, 1.41)</p> <p>AD (cm): 1.10 (-0.25, 2.45)</p> <p>CD (cm): -0.16 (-0.47, 0.15)</p> <p>GA (weeks): 0.11 (-0.58, 0.81)</p> <p>Paternal blood Pb</p>

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					BW (g): -93.5 (-269.6, 82.5) BL (cm): 0.13 (-0.81, 1.06) AD (cm): -0.64 (-1.89, 0.61) CD (cm): -0.11 (-0.57, 0.35) GA (weeks): 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 weeks (-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 (weeks): -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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					AD (cm): -1.94 cm (-2.06, 0.18) CD (cm): -0.55 (-1.03, -0.07) GA (weeks): -0.41 (-1.02, 0.21) 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 (weeks): -0.13 (-0.79, 0.65)
Daniali et al. (2023)	Prospective Epidemiological Research Studies in Iran - Isfahan Center n: 263	Blood Maternal blood was measured by ICP-MS	Prenatal growth: BW, HC, birth length Standardized neonatal anthropometric measurements were obtained by trained midwives using calibrated instruments.	Infant sex, and maternal age, BMI at enrollment (12–14 weeks gestation), income, secondhand smoke exposure, parity, and education.	β (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)
Isfahan, Iran 2019–2020 Cress-sectional	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	Age at measurement: maternal age at first trimester (mean maternal age 29.94 years) Geometric mean ± SD: 2.534 ± 0.205 µg/dL Median: 2.786 µg/dL 25th: 1.741 µg/dL 75th: 4.01 µg/dL	Age at outcome: birth		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	risks of SGA and IUGR such as serious medical complications (hypertension or diabetes or kidney disease), cerclage until 24 weeks of pregnancy, 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 weeks) 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, crown-to-heel length (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	MIREC n: 1857 Women from the MIREC cohort who	Blood Maternal blood was measured by ICP-MS	Prenatal growth: BW Infant BW (g) abstracted from	Maternal age, race, education, pre-pregnancy BMI, smoking status, parity, infant sex, cubic-spline GA; multi-pollutant	β (95% CI), as two-fold increase in Pb blood Single pollutant model: -82.22 g (-145.46, -18.97)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
2008–2011 Cohort	delivered singleton live births, had complete sociodemographic information, and provided biological samples during the first trimester of the pregnancy.	Age at Measurement: Maternal age during first trimester Geometric mean ^c : 0.62 µg/dL Median ^c : 0.60 µg/dL 75th ^c : 0.85 µg/dL	medical records and examined continuously. Age at outcome: birth	model was also adjusted for As, Cd, Hg, and Mn	Multi-pollutant model: -75.89 g (-141.24, -10.54)
Goto et al. (2021) Japan January 2011–March 2014 Cohort	J ECS 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	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 years) 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.	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

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	(n = 263) or multiple births (n = 283)		Age at outcome: birth		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)
Rodosthenous et al. (2017)	PROGRESS n: 944	Blood	Prenatal growth: BWGA, SGA	Multivariable linear 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)
Mexico City Mexico	Inclusion criteria: singleton pregnancy, GA <20 weeks, maternal age of >18 years, expectation to live in Mexico City for the following 3 years, 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	Maternal blood measured by ICP-QQQ	Infants with a BWGA Z-score <10th percentile as SGA	BMI, SES, hemoglobin levels, and infant sex	β (95% CI) ^b , as the BWGA Z-score per log ₂ increase in maternal BLL
2007–2011		Age at measurement: maternal age at ~20 weeks gestation	Age at outcome: birth	Quantile regression models were adjusted for maternal age, BMI, SES, hemoglobin levels, and infant sex	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)
Cohort		Mean (SD): 3.7 (2.7) $\mu\text{g}/\text{dL}$ Quartile Mean (SD) ($\mu\text{g}/\text{dL}$): Q1: 1.4 (0.3) Q2: 2.4 (0.2) Q3: 3.6 (0.5) Q4: 7.3 (2.8) Median: 2.8 $\mu\text{g}/\text{dL}$ 75th: 4.5 $\mu\text{g}/\text{dL}$ Max: 22.9 $\mu\text{g}/\text{dL}$ Quartiles ($\mu\text{g}/\text{dL}$) Q1: <1.93 Q2: 1.93–2.79 Q3: 2.80–4.53 Q4: >4.53		Multivariable logistic regression models were adjusted for maternal age, BMI, SES, hemoglobin levels, and infant sex	

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					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) 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)	PROTECT n: 731	Blood	Prenatal growth: GA, SGA, LGA, BWZ	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):
Puerto Rico 2010–2017 Cohort	Participants were recruited at approximately 14 ± 2 weeks of gestation at seven prenatal clinics and	Maternal blood was measured by ICP-MS Age at measurement: 18–40 (collection between 18 and 26 weeks of	All the birth outcome data were extracted from medical records. GA was calculated; BWZ was defined as the number of SDs by		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	hospitals throughout Northern Puerto Rico and followed until birth; maternal age between 18 and 40 years; residence inside of the Northern Karst aquifer region; disuse of oral contraceptives within the 3 months prior to pregnancy; disuse of in vitro fertilization 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 weeks, 22 ± 2 weeks, and 26 ± 2 weeks of gestation).	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	which a birth weight 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 Age at outcome: birth		T1: Reference T2: -0.2 (-2.9, 2.4) T3: -2.9 (-5.5, -0.2) BW Z-score: T1: Reference T2: -0.12 (-0.32, 0.07) T3: 0.09 (-0.11, 0.29) OR (95% CI) ^b , per change per IQR increase in maternal blood In-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	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	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	Log binomial multivariate regression models estimated relative risk 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

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	French or English, >14 weeks gestation at the time of recruitment, <18 years of age, diagnosed with a fetal anomaly or a history of major chronic disease. Excluded from the analysis were: 18 women who withdrew 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	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	Age at outcome: birth		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 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)	PROTECT n = 682	Blood	Prenatal growth: GA, BWZ, small for	Linear and logistic regression models were adjusted for maternal age,	β (95% CI) ^b , per IQR increase in in maternal blood ln-Pb

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Puerto Rico 2011–2017 Cohort	Participants were recruited at approximately 14 ± 2 weeks of gestation at seven prenatal clinics and hospitals throughout Northern Puerto Rico and followed until birth; maternal age between 18 and 40 years; residence inside of the Northern Karst aquifer region; disuse of oral contraceptives within the 3 months prior to pregnancy; disuse of in vitro fertilization 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 weeks, 22 ± 2 weeks, and 26 ± 2 weeks of gestation)	Maternal blood was measured by ICP-MS Age at measurement: 18–40 (collection between 18 and 26 weeks 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	gestation, large for gestation Birth outcomes were extracted from medical records. Psychosocial status was evaluated using four questionnaires Age at outcome: birth	maternal education, pre-pregnancy BMI, second-hand smoke exposure	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 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 In-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	Blood Maternal blood (erythrocyte) was measured by ICP-MS Age at measurement: Maternal age at gestational week 24–36 (mean:	Prenatal growth: BW, birth length, and HC Information on the infants' weight (g), length (cm), and HC (cm) at birth was collected from the hospital records at	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-	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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	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 to be residents in Norrbotten county and be able to communicate in written and spoken Swedish.	31 years, range 19–45 years) Mean: 14 µg/kg Median: 11 µg/kg Max: 148 µg/kg	Sunderby hospital. Age at outcome: birth	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)	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) 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)	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	Blood Maternal blood (erythrocyte) was measured by ICP-MS. Age at measurement: maternal age at collection (mean 11.3 ± 2.8 weeks gestation); mean maternal age (SD): 32.3 (4.7) years	Prenatal growth: BW, birth length, HC, GA GA from reported last menstrual period, BW, birth length, 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):

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	answer questions in English, GA ≥22 weeks at recruitment and plans to move away from the study area before delivery.	Geometric mean: 17.99 ng/g Median: 17.7 ng/g 75th: 23.6 ng/g			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) Females: 0.00 (-0.15, 0.15) GA (weeks) Full Cohort: 0.03 (-0.10, 0.16) Males: 0.12 (-0.07, 0.30) Females: -0.04 (-0.22, 0.14)
Wang et al. (2017a)	C-ABCS n: 3,125	Blood	Prenatal growth: SGA, BW, birth length, HC, and chest circumference	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)
China 2009 Cohort	Pregnant women with singleton, live births	Maternal blood (serum) was detected by GFAAS Age at measurement: maternal age at collection (first trimester, median: 11 weeks) and second trimester (median: 16 weeks) (mean age: 27.5 years) Mean: Overall: 1.50 µg/dL First trimester: 1.52 µg/dL	SGA was defined as live-born infants with birth weight below 10th percentile for the babies of the same GA according to a global reference; BW, birth length, HC, and CC were measured at birth Age at outcome: birth		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		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 High: ≥1.71			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) 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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					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)	WHEALS n: 145	Teeth	Prenatal growth: BWZ and GA	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 : BW Z-score 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)
Wayne County, MI United States	Pregnant women were in their second trimester or later, were aged 21–49 years, and were living in a predefined geographic area in Wayne and Oakland counties that included the city of Detroit as well as the suburban areas immediately surrounding the city	Teeth, representing second and third trimester exposure, measured by laser ablation-inductively coupled plasma-mass spectrometry (LA-ICP-MS)	BWZ and GA obtained from prenatal and birth records		
September 2003 and December 2007 (December 2011 and January 2015)		Mean (SD) ^c : Second trimester: 0.04 (0.03) $\mu\text{g/g}$ Third trimester: 0.05 (0.04) $\mu\text{g/g}$	Age at outcome: birth		Boys Second trimester: -0.20 (-0.47, 0.07) Third trimester: -0.04 (-0.31, 0.23)
Cohort					Girls Second trimester: -0.12 (-0.39, 0.15) Third trimester: -0.06 (-0.33, 0.21)
					GA (weeks) 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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					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)	Charlotte-Concord-Gastonia (CCG) Metropolitan Statistical Area (MSA) n: 147,673 live births in the CCG MSA; Treatment group n: 1,138; Control group n: 13,398	Births where the mother's residential address was within 4,000 meters of CMS were classified as the treatment group, while births where mother's residential address was in the CCG MSA but at least 10,000 m from the CMS centroid.	Prenatal growth: birth weight, LBW, and SGA 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.	Difference-in-difference models were used to compare birth outcomes in 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 Toxic Releases Inventory (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 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)
North Carolina United States					
2004–2009					
Quasi-experimental	Exogenous variation in Pb exposure resulting from NASCAR's deleading of racing fuel in 2007 was used as a quasi-experiment. Charlotte Motor Speedway (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,		Age at outcome: birth		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	ensuring that all full and near full-term births in the sample were prenatally exposed via the mother to <i>at least</i> one NASCAR event.				<p>LBW</p> <p>All births</p> <p>Any exposure: -0.045 (-0.07, -0.019)</p> <p>Trimester 1: -0.062 (-0.178, 0.054)</p> <p>Trimester 2: -0.022 (-0.061, 0.017)</p> <p>Trimester 3: -0.158 (-0.314, -0.001)</p> <p>Full-term births</p> <p>Any exposure: 0.001 (-0.014, 0.016)</p> <p>Trimester 1: 0.05 (-0.038, 0.138)</p> <p>Trimester 2: -0.035 (-0.054, -0.016)</p> <p>Trimester 3: -0.006 (-0.07, 0.057)</p> <p>SGA</p> <p>All births</p> <p>Any exposure: -0.04 (-0.064, -0.016)</p> <p>Trimester 1: -0.042 (-0.242, 0.158)</p> <p>Trimester 2: -0.058 (-0.118, 0.002)</p> <p>Trimester 3: -0.038 (-0.122, 0.045)</p>

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					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)

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; CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CC = chest circumference; CCG = Charlotte-Concord-Gastonia; Cd = cadmium; CD = cephalic diameter; CHL = crown-to-heel length; CMS = Charlotte Motor Speedway; Cr = chromium; EMASAR = Study on the Environment and Reproductive Health; ETS = environmental tobacco smoke; GA = gestational age; GFAAS = graphite furnace atomic absorption spectrometry; HC = head circumference; Hg = mercury; 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; LBW = low birth weight; LA-ICP-MS = laser ablation-inductively coupled plasma-mass spectrometry; LGA = large for gestational age; LIFE = Longitudinal Investigation of Fertility and the Environment; LMP = last menstrual period or last missed period; ln = natural log-transformed; LOD = limit of detection; m = meters; MIREC = Maternal-Infant Research on Environmental Chemicals; min = minute(s); Mn = manganese; MSA = Metropolitan Statistical Area; NICE = Nutritional impact on Immunological maturation during Childhood in relation to the Environment; PI = Ponderal index; PROGRESS = Programming Research in Obesity, Growth Environment and Social Stress; PROTECT = Puerto Rico Test site for Exploring Contamination Threats; SD = standard deviation; SES = Socioeconomic status; SGA = small for gestational age; UCB = umbilical cord blood; WHEALS = Wayne County Health, Environment, Allergy and Asthma Longitudinal Study.

^aEffect 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.

^bEffect estimates unable to be standardized.

^cPb measurements were converted from µg/L to µg/dL.

^dNo 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 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	Preterm birth rate Preterm birth was defined as birth <37 weeks 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)	EMASAR n: 696	Blood	Preterm birth	Logistic models adjusted for maternal age, pre-pregnancy BMI, parity, smoking, education, and LBW	OR (95%CI) Tertile 1: Reference Tertile 2: 1.24 (0.35, 4.40) Tertile 3: 1.26 (0.32, 5.00)
Argentina 2011–2012 Cross-sectional	Women who either were about to deliver or had given birth within the last 48 hour at one of the two hospitals. Women had to be above 18 years of age.	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	Medical records were used to obtain measures at birth. Age at outcome: birth		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Freire et al. (2019)	INMA Project n: 327	Other: Placenta	Preterm delivery	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)
Spain	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 yeayrs 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 communication problems	Placenta (including maternal and fetal sides as well as central and peripheral parts) measured by GFAAS with Zeeman background correction	Preterm birth was defined as live birth before 37 weeks of pregnancy,		
2000–2008		Age at measurement: birth Median: <6.5 ng/g (LOD) 75th: <6.5 ng/g (LOD)	Age at outcome: birth		
Cross-sectional					

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Yu et al. (2019)	n: 528	Blood	Spontaneous preterm 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)
Shanxi Province China	Women with prenatal examination at ≤22 gestational weeks, ≥18 years old, and living in the local counties for ≥1 year	Maternal blood (serum) was measured by ICP-MS	Spontaneous preterm birth is defined as a live birth at <37 weeks GA without iatrogenic causes, including spontaneous preterm labor with intact membranes and PROM		
December 2009– December 2013		Age at measurement: maternal age at first trimester (≤12 weeks gestation) or second trimester (13–28 weeks)			
Case-control		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	Age at outcome: birth		
Xu et al. (2022a)	n: 148 (74 cases, 74 controls)	Blood	Spontaneous preterm 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
Pingding, Shouyang, and Taigu Counties Shanxi Province China	Pregnant women were recruited if over 18 years old, living locally for at least one year, 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.	Maternal blood (serum) measured by ICP-MS	Information about spontaneous preterm birth was collected from pregnancy health records at the hospitals		
December 2009– December 2013		Age at measurement: maternal age during 4–22 gestational week			
Case-Control		Median ^d : 0.049 µg/dL 75th ^d : 0.078 µg/dL	Age at outcome: birth		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Tsuji et al. (2018)	JECS n: 14,847	Blood	Preterm 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
Japan January 2011 and March 2014 Cohort	Women who delivered live birth infant with singleton pregnancies without missing exposure or covariate data	Maternal blood measured by ICP-MS Age at measurement: Maternal age at gestational weeks 14–39 (mean maternal age 31.4 years) 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 births were divided into early (<34 weeks) and late preterm births (34 to <37 weeks) Age at outcome: birth		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)	JECS n: 16423	Blood	Preterm birth (<37 gestational weeks) risk	Multivariable linear regression models were adjusted for maternal age at birth, body mass index before pregnancy, weight gain during pregnancy,	OR (95% CI), per 0.1 µg/dL increase in maternal blood Pb: 0.90 (0.70, 1.16)
Japan	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.	Maternal blood measured by ICP-MS	Preterm birth was defined as a GA of less than 37 completed weeks.	maternal educational background, a history of preterm birth, alcohol consumption during pregnancy, smoking habit during pregnancy, and parity	OR (95% CI), per doubling increment in maternal blood Pb: 0.978 (0.689, 1.39)
January 2011 to March 2014		Age at measurement: Maternal age at second or third trimester (mean age at delivery: 31 ± 5.0 years)	Age at outcome: birth		
Cohort		Mean: 0.69 µg/dL Median: 0.63 µg/dL 75th: 0.78 µg/dL Max: 7.4 µg/dL			

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Rabito et al. (2014)	CANDLE study n: 98	Blood and cord blood	Preterm 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
Shelby County, Tennessee United States	Healthy pregnant woman between the ages of 16 and 40 years, 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	Maternal blood, collected at second and third trimester and at delivery, and cord blood, collected at deliver, were measured by ICP-MS	Preterm birth (<37 weeks), early term birth (37–39 weeks), or full-term birth (≥39 weeks) based on GA, which was determined by expected due data and LMP		Preterm birth Second trimester: 1.66 (1.23, 2.23) Third trimester: 1.24 (1.01, 1.52)
2008–2011		Age at measurement: Maternal age at collection (median: 29.50 years)	Age at outcome: birth		Early term birth Second trimester: 0.87 (0.63, 1.20) Third trimester: 0.88 (0.69, 1.13)
Cohort		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			

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 weeks) 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 weeks 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 weeks of gestation at seven prenatal clinics and hospitals throughout Northern Puerto Rico and followed until birth; maternal age between 18 and 40 years; residence inside of the Northern Karst aquifer region; disuse of oral contraceptives within the 3 months prior to pregnancy; disuse of in vitro fertilization 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 weeks, 22 ± 2 weeks, and 26 ± 2 weeks of gestation)	Blood Maternal blood was measured by ICP-MS Age at measurement: 18–40 (collection between 18 and 26 weeks 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 In-Pb Preterm birth Overall: 1.63 (1.17, 2.28) Spontaneous: 1.53 (1.00, 2.35) Tertiles ^c : 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)	PROTECT n = 682	Blood	Preterm birth (overall and spontaneous preterm 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 In-Pb
Puerto Rico	Participants were recruited at approximately	Maternal blood was measured by ICP-MS	Birth outcomes were extracted from medical records. Psychosocial status was evaluated using four questionnaires		Preterm birth:
2011–2017	14 ± 2 weeks of gestation at seven prenatal clinics and hospitals throughout Northern Puerto Rico and followed until birth; maternal age between 18 and 40 years; residence inside of the Northern Karst aquifer region; disuse of oral contraceptives within the 3 months prior to pregnancy; disuse of in vitro fertilization 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 weeks, 22 ± 2 weeks, and 26 ± 2 weeks of gestation)	Age at measurement: 18–40 (collection between 18 and 26 weeks of gestation)			Good Psychosocial Status: 1.72 (1.14, 2.58) Poor Psychosocial Status: 1.43 (0.69, 2.97)
Cohort		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		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)	CCG MSA n: 147,673 live births in the CCG MSA; Treatment group n: 1,138; Control group n: 13,398	Births where the mother's residential address was within 4,000 meters of CMS were classified as the treatment group, while births where mother's residential address was in the CCG MSA but at least 10,000 m from the CMS centroid.	Preterm birth Preterm birth was defined as clinical GA <37 weeks. 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)
North Carolina United States 2004–2009 Quasi-experimental	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 <i>at least</i> one NASCAR event.				

ALSPAC = Avon Longitudinal Study of Parents and Children; As = arsenic; BMI = body mass index; CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CCG = Charlotte-Concord-Gastonia; Cd = cadmium; Cr = chromium; CMS = Charlotte Motor Speedway; EMASAR = Study on the Environment and Reproductive Health; GA = gestational age; GFAAS = graphite furnace atomic absorption spectrometry; Hg = mercury; ICP-MS = inductively coupled plasma mass spectrometry; INMA = Instituto de Nanociencia y Materiales de Aragón; LBW = low birth weight; LMP = last menstrual period or last missed period; LOD = limit of detection; MSA = Metropolitan Statistical Area; PROM = premature rupture of membranes; PROTECT = Puerto Rico Testsite for Exploring Contamination Threats; SD = standard deviation.

^aEffect 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.

^bEffects estimates unable to be standardized.

^cPb measurements were converted from µg/L to µg/dL.

^dPb measurements were converted from ng/mL to µg/dL.

^eNo 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 a neural tube defect 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: Neural tube defects 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
					<p>Medium: 2.97 (1.09, 8.12) Highest: 5.54 (1.89, 16.19) p for trend: 0.002</p> <p>Female Infants NTDs Lowest: Reference Medium: 2.63 (0.99, 7.24) Highest: 6.45 (2.20, 18.95) p for trend: 0.001</p> <p>Male Infants NTDs Lowest: Reference Medium: 2.11 (1.02, 4.34) Highest: 2.16 (1.03, 4.59) p for trend: 0.048</p>
<p>Pi et al. (2018)</p> <p>Shanxi Province (Pingding, Xiyang, Taigu, and Zezhou) China</p> <p>2005–2007</p> <p>Case-control</p>	<p>n: 103 cases and 206 controls</p> <p>Newborns or terminated fetuses with any major external structural defects, including orofacial clefts (OFCs), NTDs, congenital hydrocephalus, limb defects were recruited from five rural counties in Shanxi Province</p>	<p>Other: Placenta</p> <p>Placental tissue, collected immediately after delivery, was measured by ICP-MS</p> <p>Age at Measurement: birth</p> <p>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</p>	<p>Birth defects: OFCs</p> <p>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</p>	<p>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</p>	<p>OR (95% CI)</p> <p>Orofacial defects: T1: Reference T2: 3.88 (1.78, 8.42) T3: 5.17 (2.37, 11.29) p for trend: <0.001</p>

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 last menstrual period (±4 weeks), 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	OR (95% CI)

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 one month post birth Age at outcome: birth to month post birth	age, smoking habit, drinking habit, paternal smoking habit, birth year of child, sex of child	Abdominal congenital malformations 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

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					Q1: Reference Q2: 0.25 (0.03, 2.27) Q3: 0.50 (0.09, 2.75) 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)	n: 97 cases with CHDs and 201 controls without any abnormalities	Cord blood	Birth defects: CHDs	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)
China	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 weeks of the case fetus. Cases and controls with gestational ages from 14 to 40 weeks were selected for this study after the following exclusion criteria were applied: (1) multiple pregnancies; (2) CHD family history; (3) fetus	UCB (serum) was measured by ICP-MS	Cardiac defects diagnosed during prenatal examination were recruited as the case group.		Septal Defects Low: Reference Medium: 1.20 (0.57, 2.52) High: 1.61 (0.78, 3.32)
February 2010–October 2011		Age at Measurement: birth	Age at outcome: age at diagnosis		Conotruncal Defects Low: Reference Medium: 1.35 (0.60, 3.06) High: 1.47 (0.65, 3.34)
Case-control		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			

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	diagnosed with a chromosomal abnormality or hereditary syndrome; (4) fetus with 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: 0.696–0.826 High: ≥0.826			<p>Right-sided Outflow Tract Deformity</p> <p>Low: Reference Medium: 0.92 (0.37, 2.26) High: 1.21 (0.50, 2.94)</p> <p>Left-sided Outflow Tract Deformity</p> <p>Low: Reference Medium: 2.29 (0.62, 8.41) High: 1.32 (0.29, 5.91)</p> <p>Anomalous Pulmonary Venous Return</p> <p>Low: Reference Medium: 1.71 (0.37, 7.83) High: 1.49 (0.30, 7.44)</p> <p>Other Cardiac Structural Abnormalities</p> <p>Low: Reference Medium: 1.10 (0.36, 3.40) High: 1.41 (0.47, 4.22)</p>

BMI = body mass index; Cd = cadmium; CHD = congenital heart diseases/defects; GFAAS = graphite furnace atomic absorption spectrometry; Hg = mercury; ICP-MS = inductively coupled plasma mass spectrometry; Mn = manganese; NTD = neural tube defects; OFC = orofacial clefts; SD = standard deviation; UCB = umbilical cord blood.

^aEffect 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.

^bEffects estimates unable to be standardized.

^cPb measurements were converted from ng/mL to µg/dL.

^dNo cut points provided for the categorizations.

^ePb 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 weeks 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 years who were in a committed relationship; no physician diagnosis of infertility/sterility; off contraception <2 months; and an ability to communicate in English or Spanish. Female partners also had to have menstrual cycles ranging between 21 and 42 days 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 femal 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 human chorionic gonadotropin (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 years	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 weeks 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 weeks gestation and reported by study participant or research hospital. Age at outcome: before 20 weeks 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)	n: 101	Blood	Pregnancy loss	Log binominal regression analysis adjusted for age and BMI	RR (95% CI): 0.978 (0.957, 0.999)
Ankara Turkey	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)	Maternal blood was measured by AAS	Clinical pregnancy was defined as the presence of an embryo with a heartbeat at 6th gestational week.		
January 2012 and July 2012		Age at Measurement: 20–40	Ongoing pregnancy was defined when the pregnancy had completed 20 weeks of gestation.		
Cohort		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	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 weeks of gestation		
Li et al. (2022)	n: 1184	Blood	Spontaneous abortion	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)
Hefei China	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 years; 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	Maternal blood (serum) was measured by ICP-MS	Spontaneous abortion before gestational weeks 12 was followed upon the 65th day after embryo transfer.		Tertiles
October 2019-January 2020		Age at measurement: maternal age at collection (day before oocytes were retrieved for IVF); mean age was 30.22 years	Age at outcome: maternal age at outcome (before gestational week 12)		Low: Reference
Cohort		Geometric mean ^d : 0.0877 µg/dL Median ^d : 0.0924 µg/dL			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; GFAAS = graphite furnace atomic absorption spectrometry; hCG = human chorionic gonadotropin; ICP-MS = inductively coupled plasma mass spectrometry; IVF = in vitro fertilization; OR = odds ratio; UCB = umbilical cord blood.

^aEffect 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.

^bEffects estimates unable to be standardized.

^cPb measurements were converted from µg/L to µg/dL.

^dPb 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 years 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)	JECS n: 16,019	Blood	Placental function: Placenta previa and placenta accreta	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
Japan	Mothers who delivered a singleton pregnancy	Maternal blood, collected during the second trimester, was measured by ICP-MS	Data for those with and without placenta previa and placenta accreta were obtained from medical records.		
January 2011–March 2014		Age at Measurement: maternal age at second trimester	Age at outcome: maternal age at diagnosis		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
Cross-sectional		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: ≥7.45ng/g			

AAS = atomic absorption spectrometry; BMI = body mass index; CI = confidence interval; ICP-MS = inductively coupled plasma mass spectrometry; GA = gestational age; JECS = Japan Environment and Children's Study; OR = odds ratio; Q = quartile; SD = standard deviation; UCB = umbilical cord blood.

^aEffect 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.

^bEffect 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 weeks gestation at the time of recruitment, ≥18 years 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 enzyme-linked immunoassay (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	Blood, cord blood, and other: placenta	Other Pregnancy and Birth Outcomes: rTL	Multivariable-adjusted linear regression models; models with maternal blood	β (95% CI) ^c :

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
part) Argentina October 2012– December 2013 Cohort	All pregnant women living in 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	The rTL was measured in 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	Pb were adjusted for 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.	UCB: -0.038 (-0.074, -0.002) 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 weeks of gestation), was measured by ICP-MS Age at Measurement: Maternal age at first trimester (mean age 30.92 ± 3.09 years)	Other Pregnancy and Birth Outcomes: Fetal nuchal translucency thickness Fetal nuchal translucency thickness was measured at 10–14 weeks 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
		Geometric mean: 0.048 µg/L			
Ashley-Martin et al. (2015b)	MIREC Study n: 1256	Blood	Other Pregnancy and Birth Outcomes: Fetal immune system biomarkers	Logistic regression adjusted for maternal age	OR (95% CI)
Canada	Pregnant women in Canada who had singleton, term birth (>37 weeks)	Maternal blood was measured by ICP-MS	Immune system biomarkers were measured in the plasma of UCB samples; thymic stromal lymphopoietin (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		Maternal log ₁₀ -Pb blood concentrations with elevated (>80%) cord blood concentrations of IL-33 and TSLP: 0.79 (0.62, 1.01)
2008–2011		Age at measurement: maternal age at first and third trimester			
Cohort		Median: 0.62 µg/dL 75th: 1.03 µg/dL Max: 4.14 µg/dL			Maternal log ₁₀ -Pb blood concentrations with elevated (≥0.5 kU/L) cord blood concentrations of IgE: 0.99 (0.77, 1.26)
			Age at outcome: birth		
Taylor et al. (2014)	ALSPAC study n: 4,285	Blood	Other Pregnancy and Birth Outcomes: Secondary sex ratio	Logistic regression models adjusted for maternal and paternal age, and parity	OR (95% CI)
Bristol UK	Pregnant women enrolled in the ALSPAC study at a median GA of 11 weeks	Maternal blood was measured by ICP-MS	The sex of the infant was recorded at birth		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)
April 1991–December 1992		Age at Measurement: Maternal age at measurement (median GA of sampling: 11 weeks)			
Cohort		Median: Quintile 1: 2.11 µg/dL Quintile 2: 2.82 µg/dL Quintile 3: 3.43 µg/dL	Age at outcome: birth		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		Quintile 4: 4.13 µg/dL Quintile 5: 5.00 µg/dL Max: 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 years (men >18), English or Spanish speaker, no use of an injectable contraceptive within 12 months, and a menstrual cycle length of 21–42 days.	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) years and paternal mean age: 31.52 (SD:4.57) years 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	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
		<p>Tertiles ($\mu\text{g/dL}$):</p> <p>Maternal Blood Pb</p> <p>T1: <0.55 (<33rd percentile)</p> <p>T2: 0.55–0.73 (33rd to 67th percentile)</p> <p>T3: >0.73 (>67th percentile)</p> <p>Paternal Blood Pb</p> <p>T1: <0.84 (<33rd percentile)</p> <p>T2: 0.84–1.16 (33rd to 67th percentile)</p> <p>T3: >1.16 (>67th percentile)</p>			
<p>Tatsuta et al. (2022b)</p> <p>Japan</p> <p>January 2011–March 2014 (followed through birth)</p> <p>Cohort</p>	<p>JECS</p> <p>n: 85,171</p> <p>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 if 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</p>	<p>Blood</p> <p>Maternal blood was measured by ICP-MS.</p> <p>Age at measurement: maternal age at collection (middle or late pregnancy)</p> <p>Median: 5.85 ng/g</p> <p>Max: 110 ng/g</p> <p>Quartiles (ng/g)</p> <p>Q1: 1.20–4.46</p> <p>Q2: 4.47–5.39</p> <p>Q3: 5.40–6.35</p>	<p>Other Pregnancy and Birth Outcomes: Secondary sex ratio</p> <p>Sex of the infant obtained from the medical record transcripts by physicians, midwives, nurses, or trained research coordinators.</p>	<p>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)</p>	<p>OR (95% CI)</p> <p>Q1: Reference</p> <p>Q2: 1.082 (1.037, 1.129)</p> <p>Q3: 1.122 (1.074, 1.171)</p> <p>Q4: 1.214 (1.163, 1.268)</p> <p>Q5: 1.279 (1.224, 1.336)</p>

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		Q4: 6.36–7.76 Q5: 7.77–110			

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

^aEffect 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.

^bPb measurements were converted from µg/L to µg/dL.

^cEffect 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)	NHANES n: 1,634	Blood	Postnatal growth: weight, WC, upper arm length, standing height, and BMI	Linear regression models were adjusted for total calorie intake, race, poverty-to-income ratio, 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)
United States 2013–2016 Cross-sectional	Children aged 6–11 years old participating in the 2013–2014 and 2015–2016 NHANES cycles	Blood was measured by ICP-MS Age at measurement: 6–11 years old Median: Overall: 0.5 μ g/dL Girls: 0.5 μ g/dL Boys: 0.5 μ g/dL 75th: Overall: 0.8 μ g/dL Girls: 0.7 μ g/dL Boys: 0.8 μ g/dL Max: Overall: 5.8 μ g/dL Girls: 5.8 μ g/dL Boys: 5.0 μ g/dL	Physical examination was performed to obtain body measurements. Age at outcome: 6–11 years old		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)
Kuang et al. (2020)	n: 395 Students aged 7–11 years (grades 2 to 4)	Blood	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
Nanjing China 2012 Cross-sectional	were 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.	Blood was measured by ICP-MS Age at Measurement: 7–11 years 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 years		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 years or older	Blood Blood was measured by GFAAS Age at Measurement: ≥6 years 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 BMI-for-age Z-score (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 years		<p>BMIZ Tertiles</p> <p>T1: Reference T2: -0.18 (-0.39, 0.04) T3: -0.29 (-0.50, -0.07)</p> <p>Males:</p> <p>WAZ: -0.36 (-0.67, -0.06) HAZ: -0.38 (-0.72, -0.04) BMIZ: -0.15 (-0.49, 0.19)</p> <p>WAZ Tertiles:</p> <p>T1: Reference T2: -0.42 (-0.71, -0.13) T3: -0.52 (-0.81, -0.24)</p> <p>HAZ Tertiles:</p> <p>T1: Reference T2: -0.36 (-0.69, -0.004) T3: -0.43 (-0.75, -0.11)</p> <p>BMIZ Tertiles:</p> <p>T1: Reference T2: -0.28 (-0.60, 0.04) T3: -0.35 (-0.68, -0.03)</p> <p>Females</p> <p>WAZ: -0.29 (-0.61, 0.03) HAZ: -0.35 (-0.71, 0.01) BMIZ: -0.10 (-0.45, 0.26)</p> <p>WAZ Tertiles:</p> <p>T1: Reference T2: -0.17 (-0.42, 0.09)</p>

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)	n: 210 Seoul South Korea July 2014 to June 2016 Cross-sectional	Blood Blood was measured by ICP-MS Age at Measurement: 8–23 months 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 months	Linear regression models; BW, sociodemographic and feeding-related factors, and iron and anemia status	β (95% CI): WAZ-BWZ (difference of the weight for age Z-scores at the time of the study and birth weight Z-scores): -0.238 (-0.391, -0.085) HC for age Z-score: -0.213 (-0.366, -0.06)
Ashley-Martin et al. (2019)	MIREC Study n: 449 Vancouver, Edmonton, Winnipeg, Sudbury, Ottawa, Kingston,	Blood Blood was measured by ICP-MS Age at Measurement: 2–5 years	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 years	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) Female

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					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 Cohort Study n: 379	Blood and cord blood	Postnatal growth: Height gain	Generalized estimating equation (GEE) models were adjusted for	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)
Krakow Poland	The present analysis was restricted to 379 term-babies (born >36 weeks of gestation) who took part in the 9-year 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 for the study. Enrollment	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	At ages of 3–9 children were invited annually for pediatric examination during which height measurements were done. Age at outcome: 3–9 years old	maternal height, birth length, pre-pregnancy maternal weight, gestational weight gain, prenatal and postnatal ETS, breastfeeding, maternal education, and parity	

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	included only nonsmoking women with singleton pregnancies between the ages of 18 and 35 years who were free from such chronic diseases as diabetes and hypertension.	Geometric mean: UCB: 1.21 µg/dL Blood: 2.05 µg/dL UCB 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 months 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 months: –0.039 (–0.414, 0.335) 6 months: –0.391 (–0.814, 0.033) 9 months: 0.000 (–0.356, 0.357) 12 months: 0.125 (–0.302, 0.552) 15 months: 0.093 (–0.396, 0.582) 18 months: 0.897 (–0.171, 1.965) 24 months: 0.717 (0.195, 1.239) 27 months: 0.316 (–0.345, 0.977) Height At birth: 0.176 (–0.003, 0.354) 3 months: –0.023 (–0.384, 0.337)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					6 months: 0.033 (-0.458, 0.523)
					9 months: 0.049 (-0.346, 0.444)
					12 months: -0.058 (-0.531, 0.415)
					15 months: 0.226 (-0.220, 0.671)
					18 months: 0.909 (-0.222, 2.040)
					24 months: 0.138 (-0.530, 0.806)
					27 months: 0.354 (-0.497, 1.205)
					BMI
					At birth: -0.167 (-0.357, 0.023)
					3 months: -0.019 (-0.431, 0.392)
					6 months: -0.461 (-0.937, 0.014)
					9 months: -0.031 (-0.430, 0.369)
					12 months: -0.020 (-0.492, 0.452)
					15 months: -0.098 (-0.481, 0.285)
					18 months: 0.157 (-1.266, 1.580)
					24 months: 0.695 (0.077, 1.313)
					27 months: 0.409 (-0.398, 1.216)
					Males

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					Weight
					At birth: 0.088 (-0.140, 0.316)
					3 months: -0.008 (-0.597, 0.581)
					6 months: -0.023 (-0.543, 0.497)
					9 months: 0.167 (-0.398, 0.733)
					12 months: 0.202 (-0.631, 1.034)
					15 months: 0.365 (-0.467, 1.197)
					18 months: 1.324 (0.023, 2.626)
					24 months: 0.962 (0.181, 1.743)
					27 months: 0.417 (-0.631, 1.465)
					Height
					At birth: 0.270 (0.037, 0.502)
					3 months: 0.232 (-0.262, 0.726)
					6 months: -0.077 (-0.695, 0.540)
					9 months: 0.166 (-0.363, 0.695)
					12 months: -0.147 (-1.153, 0.859)
					15 months: 0.433 (-0.147, 1.013)
					18 months: 1.648 (0.270, 3.026)
					24 months: 1.062 (-0.132, 2.255)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					27 months: 1.618 (-0.450, 3.686)
					BMI
					At birth: -0.194 (-0.413, 0.025)
					3 months: -0.130 (-0.800, 0.540)
					6 months: 0.003 (-0.558, 0.563)
					9 months: -0.009 (-0.522, 0.504)
					12 months: 0.314 (-0.689, 1.318)
					15 months: -0.049 (-0.569, 0.470)
					18 months: 0.319 (-1.496, 2.135)
					24 months: 0.472 (-0.172, 1.116)
					27 months: 0.966 (-1.390, 3.322)
					Females
					Weight
					At birth: 0.006 (-0.236, 0.248)
					3 months: -0.072 (-0.640, 0.496)
					6 months: -0.828 (-1.502, -0.154)
					9 months: -0.098 (-0.602, 0.407)
					12 months: 0.101 (-0.443, 0.644)
					15 months: -0.039 (-0.722, 0.643)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					18 months: -0.826 (-15.627, 13.976)
					24 months: 0.821 (-0.087, 1.728)
					27 months: 0.236 (-1.089, 1.561)
					Height
					At birth: 0.102 (-0.177, 0.381)
					3 months: -0.249 (-0.875, 0.378)
					6 months: 0.106 (-0.732, 0.945)
					9 months: 0.104 (-0.526, 0.734)
					12 months: -0.057 (-0.608, 0.493)
					15 months: 0.121 (-0.664, 0.905)
					18 months: -0.788 ^d
					24 months: -0.176 (-1.225, 0.874)
					27 months: -0.153 (-1.405, 1.100)
					BMI
					At birth: -0.142 (-0.474, 0.189)
					3 months: 0.098 (-0.491, 0.687)
					6 months: -0.974 (-1.778, -0.170)
					9 months: -0.143 (-0.805, 0.519)
					12 months: -0.147 (-0.688, 0.393)
					15 months: -0.103 (-0.712, 0.505)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					18 months: -2.263 ^d 24 months: 1.108 (-0.147, 2.362) 27 months: 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 years. 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, and postnatal growth measurements were performed. Exclusion criteria: LBW (<2500 g); preterm birth (gestational week <37); and missing information on maternal age, BMI,	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 Late pregnancy: 1.27 µg/dL UCB: 0.93 µg/dL 75th: Early pregnancy: 1.65 µg/dL Late pregnancy: 1.64 µg/dL	Postnatal growth: weight Z-score, length z-cores Weights and lengths at 6 and 12 months 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 months 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. Age at outcome: 6, 12 and 24 months	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 months: -0.03 (-0.19, 0.13) 12 months: -0.10 (-0.26, 0.06) 24 months: -0.05 (-0.23, 0.12) Length Z-scores At birth: 0.01 (-0.15, 0.18) 6 months: -0.17 (-0.37, 0.02) 12 months: 0.04 (-0.15, 0.24) 24 months: -0.15 (-0.35, 0.04) Maternal Blood: Late Pregnancy Pb Weight Z-scores At birth: -0.01 (-0.15, 0.12) 6 months: -0.15 (-0.34, 0.03) 12 months: -0.15 (-0.34, 0.03) 24 months: -0.33 (-0.53, -0.13) Length Z-scores At birth: -0.07 (-0.25, 0.11) 6 months: -0.05 (-0.28, 0.16) 12 months: 0.10 (-0.12, 0.33) 24 months: -0.30 (-0.53, -0.08)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	education level, and gestational week; subjects with >2 SD for mean maternal BLLs and child BW or length	UCB: 1.19 µg/dL Max: Early pregnancy: 2.63 µg/dL Late pregnancy: 2.52 µg/dL UCB: 1.90 µg/dL			UCB Pb Weight Z-scores At birth: 0.08 (-0.04, 0.21) 6 months: 0.10 (-0.07, 0.28) 12 months: 0.06 (-0.10, 0.24) 24 months: -0.01 (-0.21, 0.18) Length Z-scores At birth: 0.14 (-0.03, 0.32) 6 months: 0.11 (-0.11, 0.33) 12 months: 0.22 (0.01, 0.44) 24 months: 0.004 (-0.22, 0.22)
Renzetti et al. (2017)	PROGRESS n: 513	Blood, cord blood, and bone	Postnatal growth: HAZ, WAZ, BMIZ, and percentage body fat	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 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)
Mexico City Mexico	Women were considered eligible for enrollment if they were 18 years or older, pregnant at <20 weeks 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 years	Maternal blood, collected in the second and third trimester of pregnancy and within 12 hours of delivery, and UCB, collected within 12 hours of delivery, were measured by ICP-QQQ. Maternal bone, measured at 1-month postpartum from tibia (cortical bone) and patella (trabecular bone), were measured using a K-shell X-ray fluorescence instrument Age at Measurement: Maternal age at second and third trimester and at birth; child's age at	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-score for age and sex based on WHO norms. Tetrapolar bioelectrical impedance was measured to estimate body fat mass and percent body fat Age at outcome: 4–6 years old		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		<p>follow-up (4–6 years)</p> <p>Mean (SD):</p> <p>Maternal blood – second trimester: 3.7 (2.6) µg/dL</p> <p>Maternal blood – third trimester: 3.9 (2.8) µg/dL</p> <p>Maternal blood – at delivery: 4.3 (3.1) µg/dL</p> <p>UCB: 3.5 (2.7) µg/dL</p> <p>Patella: 4.7 (8.8) µg/g</p> <p>Tibia: 2.9 (8.6) µg/g</p> <p>Geometric mean:</p> <p>Maternal blood – second trimester: 3.0 µg/dL</p> <p>Maternal blood – third trimester: 3.1 µg/dL</p> <p>Maternal blood – at delivery: 3.5 µg/dL</p> <p>UCB: 2.8 µg/dL</p> <p>Max:</p> <p>Maternal blood – second trimester: 17.8 µg/dL</p> <p>Maternal blood – third trimester: 28.3 µg/dL</p> <p>Maternal blood – at delivery: 21.9 µg/dL</p> <p>UCB: 18.5 µg/dL</p> <p>Patella: 43.2 µg/g</p> <p>Tibia: 30.1 µg/g</p>			<p>UCB: -0.03 (-0.15, 0.09)</p> <p>Maternal patella: 0.01 (-0.01, 0.02)</p> <p>Maternal tibia: -0.0003 (-0.01, 0.01)</p> <p>BMIZ-score</p> <p>Maternal blood, second trimester: 0.04 (-0.07, 0.15)</p> <p>Maternal blood, third trimester: -0.01 (-0.12, 0.10)</p> <p>Maternal blood, at delivery: -0.03 (-0.08, 0.14)</p> <p>UCB: 0.05 (-0.08, 0.17)</p> <p>Maternal patella: 0.01 (0.01, 0.02)</p> <p>Maternal tibia: 0.01 (-0.01, 0.02)</p> <p>Percentage of body fat</p> <p>Maternal blood, second trimester: -0.13 (-0.75, 0.49)</p> <p>Maternal blood, third trimester: -0.21 (-0.82, 0.41)</p> <p>Maternal blood, at delivery: -0.12 (-0.74, 0.50)</p> <p>UCB: 0.31 (-0.37, 0.99)</p> <p>Maternal patella: 0.01 (-0.06, 0.07)</p> <p>Maternal tibia: 0.01 (-0.06, 0.08)</p>
Liu et al. (2019a)	ELEMENT n: 248	Blood and bone	Postnatal growth: BMIZ, WC, sum of skinfolds, and body fat percentage	Multivariable linear regression models were adjusted for maternal	β (95% CI) ^c BMIZ

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Mexico City Mexico 1994–2003 Cohort	Pregnant women who were recruited from three maternity hospitals in Mexico City and followed for 12 months post-partum and children followed through age 4	Maternal tibia (cortical) and patella (trabecular) bone, measured at 1-month postpartum, were measured using a noninvasive spot-source Cd K-shell X-ray fluorescence instrument constructed at Harvard University. Blood, obtained from each child annually from 1 to 4 years, was measured by GFAAS Age at Measurement: maternal age at delivery and 1–4 years 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: Maternal patella: 19.7 µg/g Maternal tibia: 15.2 µg/g Blood (cumulative): 23.5 µg/dL Max:	At the follow-up visit, child weight, height, WC, and skinfold thickness (biceps, subscapular and suprailiac) were measured Age at outcome: 8–16 years old	age, parity, education and calcium treatment group, and children's age, sex, and pubertal stage	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: 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 weeks) and LBW (<2500 g) were excluded	Blood and bone Maternal bone, assessed at approximately 1 month postpartum, measured by in vivo K-X-ray fluorescence from the mid-tibial shaft (cortical bone) and the patella (trabecular bone); blood, obtained from children at 24 months or 30–48 months, was measured by GFAAS. Age at Measurement: Maternal age 1 month postpartum, with average age at delivery: 25.7 (SD: 5.3) years; birth–24 months; 30–48 months Median: Maternal tibia: 8.2 µg/g Maternal patella: 9.4 µg/g Infant blood (average from birth to 24 months): 4.5 µg/dL Childhood blood (average from 30–48 months): 5.6 µg/dL	Postnatal growth: Attained height and BMI Children’s weight and height were measured and recorded by trained staff members at birth and age 48 months using standard protocols Age at outcome: birth and 48 months	Linear regression models were adjusted for maternal height and calf circumference, number of previous pregnancies, marital status, education level, breastfeeding for 6 months, 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 birth length; 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
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 months after baseline (T2), and 12 months after baseline (T3), was measured by GFAAS Age at Measurement: 6–8 years 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 years 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 years and followed annually through 2012–2015 to age 18 years. For this analysis, 10 boys in the original cohort were excluded due to chronic	Blood Blood measured by GFAAS with Zeeman background corrected Age at Measurement: 8–9 at enrollment Median: 3.0 µg/dL Max: 31 µg/dL	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 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	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 baseline, and age for BMIZ models	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
	illnesses that could affect growth and/or pubertal development.		standards Age at outcome: 8–9 at enrollment and annually through age 18		
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 years 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 years 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 years	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) 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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					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 Household Food Insecurity Access Scale (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)
Gleason et al. (2016) Sirajdikhan and	n: 618 Children of mother's from Sirajdikhan and Pabna Upazilas of	Cord blood UCB were measured by ICP-MS and child's	Postnatal growth: Stunting Stunting status of children was determined using the WHO macros (Version	Logistic regression models were adjusted for maternal weight, maternal education, maternal protein intake,	OR (95% CI) UCB: 0.97 (0.93, 1.00) Blood at 20–40 months: 1.15 (1.00, 1.33)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Pabna Upazilas Bangladesh 2008–2011 (2010–2013) Cohort	Bangladesh between 2008 and 2011; Between 2010 and 2013, when children were aged 12 to 40 months, healthcare workers from Dhaka Community Hospital invited families to enroll their children in follow-up studies	blood, collected at 20 to 40 months, was measured by portable LeadCare II instruments Age at Measurement: at birth and 12–40 months Median: UCB: 3.1 µg/dL Blood: 4.2 µg/dL 75th: UCB: 6.3 µg/dL Blood: 7.6 µg/dL	3.2.2) Age at outcome: 12–40 months	and HOME Inventory score were all modeled as continuous variables; average water As and Mn levels were included as continuous variables	

ALAD = aminolevulinic acid dehydratase; BMI = body mass index; BMIZ = BMI-forage Z-score; BW = birth weight; BWZ = birth weight Z-score; CI = confidence interval; CHECK = Children's Health and Environmental Chemicals in Korea; 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; HFIAS = Household Food Insecurity Access Scale; HOME = Home Observation for Measurement of the Environment; hr = hour(s); ICP-MS = inductively coupled plasma mass spectrometry; ICP-QQQ = inductively coupled plasma triple quad; 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; MOCEH = Mothers' and Children's Environmental Health; NHANES = National Health and Nutrition Examination Survey; OR = odds 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.

^aEffect 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.

^bPb measurements were converted from µg/L to µg/dL.

^cEffect estimates unable to be standardized.

^dNo 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	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			19.6 µg/dL for low dose 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	GD -14 to PND 10	Dams were dosed via drinking water	Pups: PND 0	Offspring Body Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL As Reported (µg/dL)	Endpoints Examined
	109 ppm Pb, F, n = 6 dams		starting 2 weeks prior to mating and continued until PND 10.	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	
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 month prior to conception), Gestation Only (21 days), Lactation Only (21 days), and Gestation and Lactation (42 days).	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

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL As Reported (µg/dL)	Endpoints Examined
Barkur and Bairy (2015)	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, 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: Pregestation Only (1 month prior to conception), Gestation Only (21 days), Lactation Only (21 days), and Gestation and Lactation (42 days).	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	Offspring Body Weight
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 months 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 Month 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	Continuous exposure starting at GD -10	Dams were dosed via the diet starting 10 days prior to mating. After weaning (PND 21), offspring were put onto the same	Pups PND 14 <1.9 µg/dL for control males <1.9 µg/dL for control females	Offspring Body Weight

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL As Reported (µg/dL)	Endpoints Examined
	<p>Evaluated on PND 28</p> <p>Controls (untreated), F, n = 9 dams</p> <p>Controls (untreated), M/F, n = 16 (8/8) pups</p> <p>1500 ppm Pb, F, n = 8 dams</p> <p>1500 ppm Pb, M/F, n = 13 (7/6) pups</p>		diet as their dams.	<p>36.1 µg/dL for 1500 ppm Pb males</p> <p>37 µg/dL for 1500 ppm Pb females</p>	
	<p>Evaluated on PND 50</p> <p>Controls (untreated), F, n = 15 dams</p> <p>Controls (untreated), M/F, n = 15 (7/8) pups</p> <p>1500 ppm Pb, F, n = 14 dams</p> <p>1500 ppm, M/F, n = 15 (7/6) pups</p>			<p>PND 28</p> <p><1.9 µg/dL for control males</p> <p><1.9 µg/dL for control females</p> <p>21.1 µg/dL for 1500 ppm Pb males</p> <p>20.9 µg/dL for 1500 ppm Pb females</p>	
	<p>Evaluated on PND 120</p> <p>Controls (untreated), F, n = 13 dams</p> <p>Control (untreated), M/F, n = 13 (7/6) pups</p> <p>1500 ppm Pb, F, n = 9 dams</p> <p>1500 ppm Pb, M/F, n = 12 (6/6) pups</p>			<p>PND 50</p> <p><1.9 µg/dL for control males</p> <p><1.9 µg/dL for control females</p> <p>20.2 µg/dL for 1500 ppm Pb males</p> <p>22.1 µg/dL for 1500 ppm Pb females</p>	
				<p>PND 120</p> <p><1.9 µg/dL for control males</p> <p><1.9 µg/dL for control females</p> <p>19.6 µg/dL for 1500 ppm Pb males</p> <p>24.3 µg/dL for 1500 ppm Pb females</p>	

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL As Reported (µg/dL)	Endpoints Examined
Basgen and Sobin (2014)	Mouse (C57BL/6) Control (untreated), M/F, n = 12 (6/6) 30 ppm Pb, M/F, n = 12 (6/6) 330 ppm Pb, M/F, n = 12 (6/6)	PND 0 to PND 28	Dams were dosed via drinking water from birth of offspring until PND 28.	PND 28 0.03 µg/dL for control males 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	Offspring Body Weight
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)	GD 6 to 21	Dams were dosed via drinking water from GD 6 to PND 21. Only	Pups (males only): PND 21 0.21 µg/dL for control	Pinna Detachment, Tooth Eruption, Fur

Study	Species (Stock/Strain), n, Sex	Timing of Exposure	Exposure Details (Concentration, Duration)	BLL As Reported (µg/dL)	Endpoints Examined
	Control (untreated), F, n = 8 dams 0.2% Pb, F, n = 8 dams		male pups were retained for measurements of body weight and developmental milestones.	11.2 µg/dL for 0.2% Pb PND 28 0.33 µg/dL for control 12.3 µg/dL for 0.2% Pb Postnatal Month 4 0.19 µg/dL for control 5.9 µg/dL for 0.2% Pb	Development, Eye Slit Formation, Eye Opening, Offspring Body Weight, Offspring Body Size

BLL = blood lead level; GD = gestational day; F = female; M = male; 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
<i>Effects on Puberty in Females</i>					
Yao et al. (2019) United States 2011–2012 Cross-sectional	NHANES n: 426 female children, and 470 female adolescents Female children (age 6–11 years) and female adolescents (age 12–19 years) in NHANES 2011–2012	Blood Blood was measured by ICP-MS Age at Measurement: 6–19 years 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 years old	Weighted multivariable linear regression models; Model 1 controlled for age, race, and BMI. Model 2 controlled for poverty-to-income ratio (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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		Q3: 0.47–0.63 Q4: >0.63			p for trend: 0.08
Sławińska et al. (2012)	1995 n:436; 2007 n:346	Blood	Puberty among females: Short-term secular change in menarche	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)
Legnica-Głogów District Poland	Menarche status of school girls 7–16 years from villages in southwestern Poland was surveyed in 1995, 2001, 2004, and 2007.	Blood was measured by GFAAS with a Zeeman correction for background	Menarche through survey		
1995–2007		Age at Measurement: 7–16 years old	Age at outcome: 7–16 years		
Cross-sectional		Mean 1995: 6.57 µg/dL 2007: 4.24 µg/dL			
Gomula et al. (2022)	n: 490	Blood	Puberty among females: age at menarche	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)
Polkowice Poland	Girls aged 7–16 years who were attending several schools in Polkowice in 2008.	Blood was measured by AAS with Zeeman background correction	Menarche through survey		
2008		Age at measurement: 7–16 years old	Age at outcome: 7–16 years old		
Cross-sectional		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			

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	Flemish Environment and Health Studies (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 years	Blood Blood Pb was measured by ICP-MS Age at Measurement: 14–15 years 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 years 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	Birth to Twenty Plus (BT20+) birth cohort n: 683 Singleton births in which the infant resides in Johannesburg area for at least 6 months after birth; participants must have data for BLL at	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 years and cord BLLs adjusted for ethnicity and height at age 8	RRR (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
	age 13 and pubertal 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 75 th 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 years 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)	n: 547 (283 girls and 264 boys)	Blood and bone	Puberty among females: Pubertal stages	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 years: 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 years: 0.95 (0.92, 0.99)
Mexico City Mexico Cohort	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 years who had at least one measurement of maternal bone Pb or childhood blood Pb	Maternal bone, measured at the mid-tibial shaft (cortical bone) and patella (trabecular bone) was measured by X-ray fluorescence instrument; blood samples from children were measured by GFAAS Age at Measurement: Maternal age 1-month postpartum; blood measured between 1 and 4 years Median Patella: 8.20 µg/g Tibia: 7.63 µg/g Blood, cumulative 1–4 years: 13.83 µg/dL 75 th	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 years		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 year: 18.76 µg/dL IQR Patella: 13.57 µg/g Tibia: 13.30 µg/g Blood, cumulative 1–4 year: 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 years (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 years 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 years). 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 years; 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	<p>First trimester: 4.8 µg/dL Second trimester: 4.0 µg/dL Third trimester: 4.5 µg/dL</p> <p>75th: First trimester: 7.1 µg/dL Second trimester: 6.4 µg/dL Third trimester: 6.6 µg/dL</p>	<p>don't know/refused) and, if so, to recall the age (in years and months) it occurred.</p> <p>Age at outcome: age of menarche</p>	<p>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 years at the time of the interview and adjusted for maternal age, maternal parity, maternal education, and prenatal calcium treatment status</p>	<p>Second trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.59 (0.28, 0.90)</p> <p>Third trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.85 (0.42, 1.27)</p> <p>Cox models First trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.92 (0.65, 1.29)</p> <p>Second trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.91 (0.65, 1.27)</p> <p>Third trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.97 (0.69, 1.37)</p> <p>Cox models restricted to girls <14.5 years at interview First trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.80 (0.52, 1.25)</p> <p>Second trimester maternal blood <5 µg/dL: Reference ≥5 µg/dL: 0.64 (0.38, 1.09)</p>

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)
<i>Effects on Puberty Among Males</i>					
Yao et al. (2019)	NHANES n: 431 male children, 493 male adolescents	Blood Blood was measure by ICP-MS Age at Measurement: 6–19 years 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 75 th 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 years 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)	Flemish Environment and Health Studies (FLEHS I, FLEHS II and FLEHS III) FLEHS I n: 1659, FLEHS II n: 606, and FLEHS III n: 406 Adolescents aged 14–15 years	Blood Blood was analyzed by ICP-MS Age at Measurement: 14–15 years 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 (T), 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 years old	Logistic regression models for male pubic 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, hour of blood collection, BMI, smoking status; SHBG: age, fasting, BMI, smoking status, hour 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:

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					ratio T/E2: 1.002 (0.958, 1.049) 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)	Birth to Twenty Plus (BT20+) birth cohort n: 683 Singleton births in which the infant resides in Johannesburg area for at least 6 months 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 years 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	RRR (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

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					Trajectory Class 2: 0.94 (0.63, 1.39) 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)	n: 547 (283 girls and 264 boys)	Blood and bone	Puberty among males: Pubertal stages	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 years: 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 years: 1.004 (0.969, 1.04) TV Patella: 1.158 (0.804, 1.667) Tibia: 0.885 (0.503, 1.558)
Mexico City Mexico Cohort	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 years who had at least one measurement of maternal bone Pb or childhood blood Pb	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-month postpartum; blood measured between 1 and 4 years Median Patella: 7.44 µg/g Tibia: 7.10 µg/g Blood, cumulative 1–4 years: 14.33 µg/dL 75th	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 years		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		Patella: 14.56 µg/g Tibia: 15.93 µg/g Blood, cumulative 1–4 years: 18.90 µg/dL IQR Patella: 13.57 µg/g Tibia: 13.30 µg/g Blood, cumulative 1–4 years: 7.66 µg/dL			Blood, cumulative 1–4 years: 1.013 (0.954, 1.075)
Williams et al. (2019) Chapaevsk Russian 2003–2005 (2017) Cohort	Russian Children's Study n: 516 Healthy male children who were 8–9 years old between 2003 and 2005 in Chapaevsk, Russia.	Blood Blood was measured by Zeeman background corrected flameless GFAAS Age at Measurement: 8–9 years 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,	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 pubertal progression Genitalia (G2 to G5): –3.76 (–7.93, 0.42) Pubic hair (P2 to P5): –1.82 (–6.91, 3.28)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
			genitalia stage ≥ 2 (G2), 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-score (mediators) at age 11.	TV (>3 mL to ≥ 20 mL): -1.19 (-4.92, 2.54) Mediation Analysis, as % of total HTZ G5: 53.0% (β : 2.37 months) P5: 47.5% (β : 2.36 months) TV ≥ 20 mL: 34.2% (β : 1.78 months) BMIZ-score G5: 14.3% (β : 0.64 months) P5: 23.4% (β : 1.16 months) TV ≥ 20 mL: 6.1% (β : 0.32 months)
Fleisch et al. (2013) Chapaevsk Russia 2003–2005 Follow-up: 2-yr (at 10–11 years) and 4-yr (at 12–13 years) Cohort	Russian Children's Study n: 394 Boys ages 8–9 years old from Chapaevsk, Russia	Blood Blood was measured by Zeeman background corrected flameless GFAAS Age at Measurement: 8–9 years old Median: 3 $\mu\text{g/dL}$ 75th: 5 $\mu\text{g/dL}$ Max: 31 $\mu\text{g/dL}$	Puberty among males: insulin-like growth factor 1 (IGF-1) Serum IGF-1 concentrations were measured by a chemiluminescent immunometric assay using Siemens Immulite 2000. Age at outcome: 10–11 years (at 2-year follow-up); 12–13 (at 4-year 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 $\mu\text{g/dL}$: Reference BLL ≥ 5 $\mu\text{g/dL}$: -29.2 ng/mL (-43.8, -14.5) Pre-puberty BLL <5 $\mu\text{g/dL}$: Reference BLL ≥ 5 $\mu\text{g/dL}$: -14.1 ng/mL (-0.9, -27.2) Early puberty: BLL <5 $\mu\text{g/dL}$: Reference BLL ≥ 5 $\mu\text{g/dL}$: -18.0 (-3.5, -32.5) Mid-puberty BLL <5 $\mu\text{g/dL}$: Reference BLL ≥ 5 $\mu\text{g/dL}$: -41.9 ng/mL (-15.1, -68.7)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
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AAS = atomic absorption spectrometry; BMI = body mass index; BW = birth weight; E2 = estradiol; ELEMENT = Early Life Exposure in Mexico to Environmental Toxicants; fE2 = free estradiol; FLEHS = Flemish Environment and Health Studies; FSH = follicle stimulating hormone; fT = free testosterone; GEE = generalized estimating equation; GFAAS = graphite furnace atomic absorption spectrometry; HTZ = height Z-score; ICP-MS = inductively coupled plasma mass spectrometry; IGF-1 = insulin-like growth factor 1; LH = luteinizing hormone; NHANES = National Health and Nutrition Examination Survey; PIR = poverty-to-income ratio; RRR = relative risk ratio; SD = standard deviation; SHBG = sex hormone binding globulin; T = testosterone; tT = total testosterone; TV = testicular volume; UCB = umbilical cord blood.

^aEffect 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.

^bPb measurements were converted from µg/L to µg/dL.

^cEffect 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
Alegria-Torres et al. (2020) Salamanca Mexico Cross-sectional	n: 86 Healthy children 6–15 years of age were recruited from four primary schools	Blood Blood was measured by ICP-MS Age at Measurement: 6–15 years old Mean (SD): 3.78 (3.73) µg/dL Max: 22.61 µg/dL	Other developmental effects: Telomeric lengthening and mitochondrial DNA effects DNA was isolated from peripheral blood and relative telomere length and the mitochondrial DNA copy number were determined by real-time polymerase chain reaction Age at outcome: 6–15 years old	Linear regression analyses; TL models were adjusted for mtDNA copy number, 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) mtDNA copy number: –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 months n: 150 for 18–24 months 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-shell X-ray fluorescence instrument (K-XRF) during the first month postpartum visit Age at Measurement: Maternal age at second trimester, third trimester, and one month postpartum	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 months	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-month 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

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		<p>Mean</p> <p>2nd trimester blood for 12-month-old infants: 3.5 µg/dL</p> <p>2nd trimester blood for 18–24-month-old infants: 3.9 µg/dL</p> <p>3rd trimester blood for 12-month-old infants: 3.7 µg/dL</p> <p>3rd trimester blood for 18–24-month-old infants: 4.2 µg/dL</p> <p>Tibia for 12-month-old infants: 5.6 µg/g</p> <p>Tibia for 18–24-month-old infants: 4.9 µg/g</p> <p>Tertiles</p> <p>Lower Pb: <5 µg/dL</p> <p>Moderate Pb: 5 ≤ Pb <10 µg/dL</p> <p>High Pb: ≥10 µg/dL</p>			<p>Lower Pb: Reference</p> <p>Moderate Pb: 0.02 (–0.14, 0.19)</p> <p>Higher Pb: –0.03 (–0.21, 0.14)</p> <p>18–24-month infants</p> <p>Second trimester maternal blood</p> <p>Lower Pb: Reference</p> <p>Moderate Pb: 0.11 (–0.08, 0.30)</p> <p>Higher Pb: 0.23 (–0.19, 0.65)</p> <p>Third trimester maternal blood</p> <p>Lower Pb: Reference</p> <p>Moderate Pb: 0.01 (–0.17, 0.20)</p> <p>Higher Pb: –0.05 (–0.51, 0.41)</p> <p>Tibia</p> <p>Lower Pb: Reference</p> <p>Moderate Pb: 0.10 (–0.13, 0.32)</p> <p>Higher Pb: 0.14 (–0.08, 0.35)</p>
<p>Hou et al. (2020)</p> <p>Guiyu and Haojiang China</p> <p>November–December 2017</p>	<p>n: 574 (357 from Guiyu and 217 from Haojiang)</p> <p>Children 2.5–6 years of age that lived in Guiyu, an e-waste contaminated town or Haojiang, a city with</p>	<p>Blood</p> <p>Blood was measured by GFAAS</p> <p>Age at Measurement: 2.5–6 years old</p>	<p>Other developmental effects: Oral anti-inflammatory potential</p> <p>Participants were instructed to sit up straight and slightly forward in their chair. A sputum cup</p>	<p>Multivariable linear regression model adjusted for gender, age, BMI, outdoor activities, the sucking/biting of toys and pencils, diet (sweet consumption, bean products, marine</p>	<p>β (95% CI)^b: –3.65 (–8.07, 0.77)</p>

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Cross-sectional	similar culture but no e-waste recycling activity	Median 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	was used to collect the saliva. Decayed 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 years old	products), family member smoking, 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 years, 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 year), 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 months. Age at outcome: 1–6 months	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 months: 5.53 (6.98) 6 months: -7.77 (7.31) Richness - Fungal 1 months: 0.29 (1.65) 6 months: 1.7 (1.51) Evenness - Bacterial 1 months: 0 (0.01) 6 months: -0.02 (-0.01) Evenness - Fungal 1 months: 0.03 (0.05) 6 months: -0.02 (0.05) Faith's Diversity - Bacterial 1 months: 0.16 (0.39) 6 months: -0.19 (0.37) Faith's Diversity - Fungal 1 months: Not reported 6 months: Not reported

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

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

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
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BMI = body mass index; ELISA = enzyme-linked immunoassay; 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; SD = standard deviation; SE = standard error; TL = telomere length; WHEALS = Wayne County Health, Environment, Allergy and Asthma Longitudinal Study

^aEffect 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.

^bEffect 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
<i>Effects on Hormones Levels and Menstrual/Estrous Cycle</i>					
Krieg and Feng (2011)	NHANES n: 649	Blood	Female reproductive function: Serum FSH and LH	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)
United States 1999–2002 Cross-sectional	Women aged 35–60 years old	Blood was measured by AAS Age at Measurement: 35–60 years Geometric mean: 1.4 µg/dL Mean: 1.6 µg/dL Max: 17.0 µg/dL	Serum FSH and LH were measured using a microparticle enzyme immunoassay Age at outcome: 35–60 years		
					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 years) 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 years or over	Blood Blood was measured by GFAAS Age at Measurement: 50 years 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 years	Blood Blood was measured by AAS in 1999–2002 and ICP-MS in 2003–2010 Age at measurement: 45–55 years 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 months were categorized as “No” and those with natural menopause were “Yes” Age at outcome: 45–55 years	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 years 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-shell X-ray fluorescence (K-XRF) at each woman's mid-tibial shaft and patella. Blood was measured by GFAAS with Zeeman background correction Age at measurement: 46 years 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	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 years 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
		Tertiles Tibia (µg/g) 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			
<i>Effects on Female Fertility</i>					
Lee et al. (2020)	NHANES (2013–2014 and 2015–2016) n: 124	Blood	Female reproductive function: Female infertility	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
United States	Women aged 20–39 years without a history of hysterectomy and/or bilateral oophorectomy	Blood was measured by ICP-MS	Infertility is defined as the absence of pregnancy with unprotected intercourse for one year and was assessed through a self-reported questionnaire		OR (95% CI) T1: Reference T2: 5.40 (1.47, 19.78) T3: 5.62 (1.13, 27.90)
2013–2014 and 2015–2016		Age at Measurement: 20–39 years			
Cross-sectional		Geometric mean: 0.50 µg/dL (95% CI: 0.43, 0.57)	Age at outcome: 20–39 years		
		Tertiles (µg/dL) T1: 0.11–0.38 T2: 0.41–0.62 T3: 0.63–5.37			

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Louis et al. (2012) Michigan (4 counties) and Texas (12 counties) United States 2005–2009 Cohort	LIFE Study n: 501 Female ages 18–44 year and male ages ≥18 years; in a committed relationship; ability to communicate in English or Spanish; menstrual cycles between 21 and 42 days; 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: 19–40 years 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	Female reproductive function: 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 estrone-3-glucuronide (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	Cox models for discrete survival time, which is a proportional odds model, adjusted for age, body mass index, cotinine, parity, serum lipids, and site (Texas/Michigan)	OR (95% CI), as fecundability OR Female only exposure: 0.97 (0.85, 1.11) 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	Blood Blood was measured by ICP-MS Age at measurement: Mean age for women with endometriosis: 35.3 (SD: 4.1)	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)	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
	ovarian failure, repeated implantation failure or pregnancy were excluded	<p>Mean age for women without endometriosis: 35.3 (SD: 5.0)</p> <p>Geometric mean^c</p> <p>Women with endometriosis: 1.337 µg/dL</p> <p>Women without endometriosis: 0.853 µg/dL</p> <p>Median^c</p> <p>Women with endometriosis: 2.130 µg/dL</p> <p>Women without endometriosis: 0.464 µg/dL</p> <p>Tertiles^c (µg/dL)</p> <p>T1: <0.38</p> <p>T2: 0.38–3.05</p> <p>T3: >3.05</p>	Mean age for women without endometriosis: 35.3 (SD: 5.0)		
Li et al. (2022)	n: 1184	Blood	Female reproductive function – Effects on female fertility: Fertility - successful implantation, clinical pregnancy	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,	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
Hefei China	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 years; couples were diagnosed with infertility	Maternal blood (serum) was measured by ICP-MS	A serum hCG level ≥25 mIU/mL on the 14th day after embryo transfer was considered as successful implantation. Clinical pregnancy was defined as an ultrasound-confirmed		
October 2019- January 2020		Age at measurement: Maternal age at collection (day before oocytes were retrieved for IVF); female partner mean age was 30.22 years			
Cohort					

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	(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 partner or male factor or unexplained fertility.	Geometric mean ^e : 0.0877 µg/dL Median ^e : 0.0924 µg/dL 75th ^e : 0.14399 µg/dL Tertiles ^e (µg/dL) Low: 0.002–0.065 Medium: 0.065–0.125 High: 0.125–0.481	intrauterine pregnancy on the 30th day after embryo transfer. Age at outcome: Female partner mean age: 30.22 years	endometrial thickness on hCG day, and embryo quality. Linear regression models for metaphase II (MII) rate, fertility rate, 2PN rate, blastocyte rate, and high-quality embryo rate were adjusted for maternal age, BMI, education level, infertility type, FSH and sperm concentration	Continuous: 0.95 (0.91, 0.99) Tertiles Low: Reference Medium: 0.72 (0.37, 1.38) 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)	n: 195	Blood	Female reproductive function – Effects on female fertility: IVF outcome	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)
China 2018–2019 Cohort	Couples undergoing IVF. Women with endometriosis, hydrosalpinx, abnormal uterine cavity and men with azoospermia, severe oligozoospermia, asthenospermia and dysspermia were excluded from the study.	Maternal blood (serum), follicular fluid, and seminal plasma from male partner Age at Measurement: Female partner mean age: 30.27 years Male partner mean age: 31.57 years Mean ^c Maternal serum: 0.301 µg/dL	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 years Male partner mean age: 31.57 years		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
		Follicular fluid: 0.742 µg/dL Seminal plasma: 0.882 µg/dL			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)
		Median ^c Maternal serum: 0.245 µg/dL Follicular fluid: 0.178 µg/dL Seminal plasma: 0.486 µg/dL			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)
		75th ^c Maternal serum: 0.317 µg/dL Follicular fluid: 0.326 µg/dL Seminal plasma: 1.245 µg/dL			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
<i>Effects on Morphology or Histology of Female Sex Organs (Ovaries, Uterus, Fallopian Tubes/Oviducts, Cervix, Vagina, and/or Mammary Glands)</i>					
Ye et al. (2017)	n: 288 (46 with fibroids and 242 without)	Blood	Female reproductive function – Effects on morphology and histology of female sex organs: Uterine fibroids	Logistic regression models adjusted for age, BMI, gravidity, oral contraceptive pill administration history, regularity of menstrual cycle, hemoglobin level, and serum cotinine levels; linear regression models were adjusted for age, BMI, gravidity, oral contraceptive pill administration history, regularity of menstrual cycle, hemoglobin level, and serum cotinine levels	OR (95% CI) ^b Presence of uterine fibroids: 1.39 (0.75, 2.56)
Seoul South Korea	Premenopausal women between 30 and 49 years old, who were not pregnant or breastfeeding, whose heavy metal levels at the 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	Blood was measured by GFAAS	Diagnosis of uterine fibroids was based on pelvic ultrasonography and two questions		β (95% CI) ^b Volume of uterine fibroids: 0.12 (-2.26, 2.51)
September to November 2014		Age at Measurement: 30–49 years			
Cross-sectional		Geometric mean: 1.36 $\mu\text{g}/\text{dL}$	Age at outcome: 30–49 years		Q1: Reference Q2: -0.42 (-2.69, 1.85) Q3: 0.85 (-1.67, 3.37) Q4: -1.23 (-3.74, 1.29)
		Quartiles ($\mu\text{g}/\text{dL}$) Q1: <1.1 Q2: 1.1–1.3 Q3: 1.3–1.8 Q4: 1.8–3.2			

2PN = oocytes with two pronuclei; AAS = atomic absorption spectrometry; BMI = body mass index; E2 = estradiol; 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; NHANES = National Health and Nutrition Examination Survey; 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.

^aEffect estimates are standardized to a 1 $\mu\text{g}/\text{dL}$ increase in blood Pb or a 10 $\mu\text{g}/\text{g}$ 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.

^bEffects estimates unable to be standardized.

^cPb measurements were converted from $\mu\text{g}/\text{L}$ to $\mu\text{g}/\text{dL}$.

^dNo CIs provided.

^ePb measurements were converted from ng/L to $\mu\text{g}/\text{dL}$.

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 months prior to mating. Offspring were continued on the same exposure as their dams until the end of the experiment at 12 months 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 months 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 months 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; NR = not reported; Pb = lead; PND = postnatal day.

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
<i>Effects on Sperm/Semen Production, Quality, and Function</i>					
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 years 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 years	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 years of age, had a BMI of 18 to 30 kg/m ² , and had not been on any hormone therapy for the past 6 months, no diabetes, endocrine disease, fertility-related genetic disorders,	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 years 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	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
	obstructive azoospermia, 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	semen group B. Sperm 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 years		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)	n: 288	Blood	Male reproductive effects: Seminal parameters	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.	β (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
Hong Kong November 2015– November 2016 Cross-sectional	Male subjects who underwent semen analysis (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;	Blood was measured by ICP-MS Age at Measurement Mean age: 37.9 years Geometric mean ^b : 3.175 $\mu\text{g}/\text{dL}$ Median ^b : 2.719 $\mu\text{g}/\text{dL}$ 75th ^b : 3.437 $\mu\text{g}/\text{dL}$ Quartiles ^b ($\mu\text{g}/\text{dL}$) Q1: <2.159 Q2: >2.159–2.719 Q3: >2.719–3.437 Q4: >3.437	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 $\times 200$ or 400. Diff-Quik staining kit (Dade Behring AG, Düringen, 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 years		

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	failure to complete the lifestyle questionnaire; and refusal to donate blood or semen samples.				<p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p>

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
Pant et al. (2014)	n: 60 New Delhi India Cross-sectional	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)	n: 841 Henan Province China December 2017 to August 2018 Cross-sectional	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 years 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 In-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)	Russian Children's Study n: 223	Blood	Male reproductive effects: Semen parameters	Mixed effect linear regression models adjusted for boys' BW, total caloric intake, height Z-score at entry, breastfeeding duration, monthly household income, and abstinence time	β (95% CI) ^b , as adjusted mean
Russia	Boys enrolled at age 8–9 years in 2003–2005 and followed them annually for 10 years.	Blood was measured by Zeeman background corrected flameless GFAAS	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		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
2003–2005 (follow-up annually for 10 years)		Age at measurement: 8–9 years			
Cohort		Median: 3 µg/dL 75th: 5 µg/dL			Sperm concentration (mill/mL)
		Categories Lower: <5 µg/dL Higher: ≥5 µg/dL			
		Tertiles			

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

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					<p>High: 53.2 (50.9, 55.3) p for trend: 0.29</p> <p>Total progressive motile sperm count (mill)</p> <p>Continuous, per log-blood Pb: 0.01 (-0.27, 0.29)</p> <p>Categories</p> <p>Lower: 57.7 (48.9, 68.1) Higher: 55.7 (40.6, 76.4)</p> <p>Tertiles</p> <p>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</p> <p>Low semen quality (probability)</p> <p>Continuous, per log-blood Pb: 0.20 (-0.22, 0.65)</p> <p>Categories</p> <p>Lower: 0.51 (0.44, 0.58) Higher: 0.49 (0.39, 0.59)</p> <p>Tertiles</p> <p>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</p>
<i>Effects of Hormone Levels</i>					
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 years, no reported steroid or thyroid medication use, and no reported thyroid disease.	Blood was measured by AAS (1999–2002) or ICP-MS (2003–2004). Age at measurement: >20 years 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, androstenedione glucuronide, and SHBG were measured in blood serum, and E2 in plasma. All sex hormones were detected by immunoassay. Age at outcome: >20 years	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 Free testosterone (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 Androstenedione 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
					Free testosterone (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
					Androstenedione 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)	NHANES n: 484	Blood	Male reproductive effects: Testosterone	Multiple linear regression, adjusted for age, BMI, PIR, race, and serum cotinine	β (95% CI) ^c , as percent change in serum T associated with a doubling (100% increase) in blood Pb concentration: 6.65 (2.09, 11.41)
United States	Men that were 18–55 years old, that had complete data on the metals of interest, serum T, body mass index (BMI), PIR, race, serum cotinine, or urinary creatinine	Blood was measured by inductively coupled dynamic reaction-plasma mass spectrometry	Serum testosterone (total) were measured by isotope dilution–high performance liquid chromatography–tandem mass spectrometry		
2011–2012		Age at Measurement: 18–55 years	Age at outcome: 18–55 years		
Cross-sectional		Geometric mean: 1.06 $\mu\text{g/dL}$ 75th: 1.59 $\mu\text{g/dL}$			
Chen et al. (2016)	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
Shanghai, Jiangxi 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 years) 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
<i>Effects on Fertility</i>					
Louis et al. (2012) Michigan (4 counties) and Texas (12 counties) United States 2005–2009 Cohort	LIFE Study n: 501 Female ages 18–44 years and male ages ≥18 years; in a committed relationship; ability to communicate in English or Spanish; menstrual cycles between 21 and 42 days; 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 years Average age for male partner without pregnancy: 32.4 years 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 estrone-3-glucuronide (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 years Average age for males without pregnancy: 32.4 years	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,	Blood, other: follicular fluid, and other: semen Maternal blood (serum), follicular fluid, and seminal plasma from male partner	Male reproductive effects: IVF outcome The IVF outcomes included were normal fertilization, good embryo, blastocyst formation, high-	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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
	asthenospermia and dysspermia were excluded from the study.	Age at Measurement: Female partner mean age: 30.27 years Male partner mean age: 31.57 years 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	quality blastocyst, pregnancy, and live birth Age at outcome: Female partner mean age: 30.27 years Male partner mean age: 31.57 years		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) 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)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
					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)
<i>Effects on Morphology or Histology of Male Sex Organs</i>					
Huang et al. (2020)	Guangxi Birth Cohort Study n: 564 mother–child pairs	Blood	Male reproductive effects: TV and anogenital distance in infant boys	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)
Guangxi China	Women with singleton pregnancies that were included from 8 Maternity and Child Healthcare Hospitals in 6 cities of Guangxi, China	Maternal blood (serum) was measured by ICP-MS	TV, and AGD-TV measurements were undertaken by trained sonographers using ultrasonography.		
July 2015 to September 2018		Age at Measurement: Maternal age at time of measurement (mean age: 28.76 (SD: 4.66) years)	Transverse and longitudinal grey-scale images were used to calculate TV as $\pi/6 \times \text{length} \times \text{width} \times \text{height}$. 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		Anopenile distance Q1: Reference Q2: -0.039 (-0.085, 0.008) Q3: -0.037 (-0.085, 0.010) Q4: -0.060 (-0.110, -0.011)
Cohort		Median ^b : 0.077 $\mu\text{g/dL}$ 75th ^b : 0.123 $\mu\text{g/dL}$			
		Quartiles ^b ($\mu\text{g/dL}$) Q1: ≤ 0.054 Q2: 0.055–0.077 Q3: 0.078–0.123 Q4: > 0.123			Anoscrotal distance Q1: Reference Q2: -0.020 (-0.091, 0.052) Q3: -0.033 (-0.105, 0.039) Q4: -0.115 (-0.190, -0.039)

Reference and Study Design	Study Population	Exposure Assessment	Outcome	Confounders	Effect Estimates and 95% CIs ^a
			of the anus to the posterior base of the scrotum (AGDas). Age at outcome: birth		

AAS = atomic absorption spectrometry; AGD = anogenital distance; AGDap = anopenile distance; AGDas = anoscrotal distance; BMI = body mass index; BW = birth weight; CI = confidence interval; E2 = estradiol; fE2 = free estradiol; fT = free testosterone; FSH = follicle stimulating hormone; GA = gestational age; GFAAS = graphite furnace atomic absorption spectrometry; 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; NHANES = National Health and Nutrition Examination Survey; Q = quartile; OR = odds ratio; PIR = poverty-to-income ratio; 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.

^aEffect 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.

^bPb measurements were converted from µg/L to µg/dL.

^cEffects estimates unable to be standardized.

^dNo CIs provided.

Table 8-17 Animal toxicologic 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)	<p>Rat (Wistar) Control (untreated), M, n = 8</p> <p>Control (vehicle), M, n = 8</p> <p>25 mg/kg Pb, M, n = 8</p>	Adulthood (specific PND NR)	Adult male rats were dosed via oral gavage for 3 months. One control group was not gavaged (untreated control) and another control group was gavaged with vehicle (vehicle control).	<p>4.26 µg/dL for control (untreated)</p> <p>4.27 µg/dL for control (vehicle)</p> <p>5.27 µg/dL for 25 mg/kg Pb</p>	Sex Organ Histopathology
Wang et al. (2013b)	<p>Rat (Sprague-Dawley) Control (untreated), M, n = 15</p> <p>0.8/0.3 g/L Pb, M, n = 15</p> <p>1.5/0.9 g/L Pb, M, n = 15</p>	GD -10 to PND 183	Dams were dosed via drinking water (0, 0.8, or 1.5 g/L Pb) starting 10 days 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 months of age (approx. PND 183).	<p>2.65 µg/dL for control</p> <p>18.6 µg/dL for 0.8/0.3 g/L Pb</p> <p>55.0 µg/dL for 1.5/0.9 g/L Pb</p>	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 week old mice were acclimated for a week before being dosed via drinking water for 45 days.	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 day old mice were acclimated for a week before being dosed for 90 days 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 day old mice were dosed via oral gavage for 2 weeks. 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; F = female; GD = gestational day; IVF = in vitro fertilization; M = male; NR = not reported; Pb = lead; PND = postnatal day.

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