SUPPORTING DOCUMENT FOR EPIDEMIOLOGICAL STUDIES FOR LEAD

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Table 1. Epidemiology Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Burns et al. 2017 Prospective cohort of 481 Russian boys enrolled at age 8–9 years (2003–2005) and followed until age 18 years (2012–2015)	**PbB:** Median (range): • All: 3.0 (0.5–31.0) • Low (<5 µg/dL) (n=347): 3.0 (0.5–4.0) • High (≥5 µg/dL) (n=134): 6.0 (5.0–31.0) **Analysis:** Height was analyzed using linear regression and adjusted for birth weight, preterm birth, percent calories from protein at baseline, and age (years). BMI was adjusted using linear regression for birth weight, no biological father in home, percent calories from fat at baseline, and age (years).	Adjusted mean difference (95% CI) for HT-Z score and BMI-Z score for higher versus lower PbB (≥5 versus <5 µg/dL) in boys followed for up to 10 years: • HT-Z: -0.43 (-0.60, -0.25); p<0.001 • BMI-Z: -0.22 (-1.45, 0.006); p=0.06 Adjusted β (95% CI) for HT-Z and BMI-Z (z-score per unit lnPbB): • HT-Z: -0.26 (-0.40, -0.13); p<0.001 • BMI-Z: -0.14 (-0.31, 0.04); p=0.12
Cassidy-Bushrow et al. 2016 Birth cohort of 299 children (aged 2–3 years) from mothers who participated in a WHEALS study (2003–2007), Western Wayne Country, Michigan; 131 children had detectable PbB (≥1.0 µg/dL)	**PbB:** Mean (SD), n=131: 2.45 (2.53) **Analysis:** Obesity at age 2 years was defined as BMI ≥85th percentile. BMI was analyzed using linear regression and adjusted for race, sex, and birth weight Z-score.	PbB was negatively associated with body size. • Adjusted RR (95% CI) for BMI ≥85th percentile 0.57 (0.33, 0.98); p=0.041 • Adjusted β (95% CI) for BMI Z-score: -0.35 (-0.60, -0.10); p=0.012
Hauser et al. 2008 Cross-sectional study of 489 boys (aged 8–9 years); Chapaevsk, Russia (2003–2005)	**PbB:** • Mean: 3 • Range: 2–5 • PbB >10: 3% **Analysis:** PbB were log-transformed. Height, weight, and BMI were analyzed using multivariate logistic regression, adjusted for birth weight, gestational age, and age at exam. Birth weight was adjusted for height, BMI, penile length, and gestational age.	A negative association was observed between PbB and height and birth weight, but not BMI. Adjusted β (95% CI), per unit log-PbB: • Height: -1.439 (-2.25, -0.63); p<0.001 • Weight: -0.761 (-1.54, 0.02); p=0.067 • BMI: -0.107 (-0.44, 0.23); p=0.53

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Reference and study population	PbB (µg/dL) and analysis	Outcomes
Ronco et al. 2010 Cross-sectional study of 107 women of childbearing age (median age: 27 years) from Chile; data collection period not reported	**PbB:** Median (interquartile range) • All: 1.0 (1.0–4.8) • Low weight: 1.7 (1.0–3.8) • Normal weight: 2.3 (1.0–6.5) • Overweight: 1.0 (1.0–3.8) **Analysis:** Women were classified into three groups based on BMI: low weight (BMI <18.5 kg/m^2), normal weight (BMI >19–<24.9 kg/m^2), and overweight (BMI >25 kg/m^2). Data were analyzed using the nonparametric Kruskal-Wallis test.	No differences in PbB were observed between BMI categories.

Scinicariello et al. 2013
 	
Cross sectional study of children and adolescents (n=10,693; age 3–19 years) adults (n=15,899, age ≥20) using NHANES data (1999–2006)
	PbB:
	Gmean (SE)
	• Children/adolescents: 1.12 (0.02)
	• Adults: 1.59 (0.02)
	• Quartiles (all):
	  o Q1: ≤0.70
	  o Q2: 0.71–1.09
	  o Q3: 1.10–1.60
	  o Q4: ≥1.61
		A negative association was observed between PbB and BMI-z score in children and adolescents. Adjusted β (SE) (BMI-Z per quartile):
		• Q1: reference
		• Q2: -0.06 (0.04); p=0.20
		• Q3: −0.15 (0.06); p=0.01
		• Q4: -0.33 (0.07); p ≤ 0.01
		• p-trend: ≤0.01

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Reference and study population	PbB (µg/dL) and analysis	Outcomes
	Analysis: Linear regression of BMI Z-scores and PbB quartile. Multiple logit regression of overweight (BMI 25–29.9 kg/m^2, ≥85th–95th percentile) or obese (BMI ≥30 kg/m^2, ≥95th percentile) and PbB quartile; adjusted for age, sex, race/ethnicity, hematocrit, calorie intake, television and video game use, serum cotinine, and poverty income ratio. BMI data in adults were analyzed using multiple linear and logit regression, adjusted for race/ethnicity, sex, age, hematocrit, smoking status, serum cotinine, alcohol consumption, education, calorie intake, and moderate and vigorous activity.	A negative association was observed between PbB and overweight and obesity in children and adolescents. Adjusted OR (95% CI) for: Overweight • Q1: reference • Q2: 0.93 (0.77, 1.13) • Q3: 0.87 (0.67, 1.11) • Q4: 0.67 (0.52, 0.88) Obese • Q1: reference • Q2: 0.82 (0.67, 1.00) • Q3: 0.70 (0.54, 0.90) • Q4: 0.42 (0.30, 0.59) A negative association was observed between PbB and BMI in adults. Adjusted β (SE) (BMI per quartile): • Q1: reference • Q2: -0.90 (0.20); p ≤ 0.01 • Q3: -1.41 (0.22); p ≤0.01 • Q4: -2.58 (0.25); p ≤0.01 • p-trend: ≤0.01

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Reference and study population	PbB (µg/dL) and analysis	Outcomes
		PbB was negatively associated with overweight and obesity. Adjusted OR (95% CI): Overweight • Q1: reference • Q2: 1.04 (0.87, 1.25) • Q3: 1.02 (0.87, 1.19) • Q4: 0.79 (0.65, 0.95) Obese • Q1: reference • Q2: 0.76 (0.66, 0.87) • Q3: 0.66 (0.56, 0.77) • Q4: 0.42 (0.35, 0.40)

Table 1. Epidemiology Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Wang et al. 2015 Cross-sectional study of 5,558 adults (men: 2,235, ages 39–65 years; women: 3,323, ages 40–65 years) from 16 locations in China	**PbB:** Men • Median (interquartile range): 4.400 (2.900–6.216) • Quartiles: o Q1: ≤2.900 o Q2: 2.901–4.400 o Q3: 4.401–6.216 o Q4: ≥6.216 Women: • Median (interquartile range): 3.779 (2.513–5.435) • Quartiles: o Q1: ≤2.513 o Q2: 2.514–3.779 o Q3: 3.780–5.435 o Q4: ≥5.435 **Analysis:** Overweight adults were defined as a BMI of 25–29.9 kg/m^2; obesity was defined as BMI ≥30 kg/m^2. Data were analyzed by multiple linear regression and logistic regression adjusted for age, rural/urban residence, economic status, current smoking, diabetes, dyslipidemia, and hypertension.	BMI was positively associated with BMI in women (trend and Q4), but not men. β (SE) per PbB quartile: • Men o Q1: reference o Q2: -0.06 (0.19) o Q3: 0.05 (0.19) o Q4: 0.01 (0.20) o p-trend: 0.82 • Women o Q1: reference o Q2: -0.12 (0.17) o Q3: 0.27 (0.17) o Q4: 0.59 (0.17); p<0.05 o p-trend: <0.001 Adjusted ORs (95% CI) for obesity for women, but not men, were increased in Q4 compared to Q1. Men: • Overweight o Q1: reference o Q2: 1.02 (0.79,1.33) o Q3: 1.01 (0.77, 1.32) o Q4: 0.95 (0.72,1.26) o p-trend: 0.74 • Obesity o Q1: reference o Q2: 0.73 (0.40, 1.33) o Q3: 1.13 (0.64, 1.97) o Q4: 0.88 (0.48, 1.61) o p-trend: 0.99

Table 1. Epidemiology Studies Evaluating Effects on Body Weight at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		Women: • Overweight o Q1: reference o Q2: 0.82 (0.65, 1.04) o Q3: 1.07 (0.85, 1.35) o Q4: 1.16 (0.92, 1.46) o p-trend: 0.07 • Obesity o Q1: reference o Q2: 1.16 (0.70, 1.90) o Q3: 1.31 (0.80, 2.14) o Q4: 1.86 (1.16, 2.98) o p-trend: <0.01

BMI = body mass index; BMI-Z = BMI z-scores; CI = confidence interval; Gmean = geometric mean; HT-Z = height z-scores; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; RR = relative risk; SD = standard deviation; SE = standard error; WHEALS = Wayne County Health, Environment, Allergy and Asthma Longitudinal Study

Table 2. Epidemiology Studies Evaluating Effects on the Respiratory System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Changes in lung function		
Chung et al. 2015 Cross-sectional study of 870 adults (mean at 54.0 years) from the 5th Korea National Health and Nutrition Examination Survey, 2011	**PbB:** • Mean (SD): 2.50 (0.87) • Range: 0.66–5.14 • Tertiles: o T1: <2.03 o T2: 2.03–2.81 o T3: >2.81 **Analysis:** Pulmonary function tests (FVC, FVC%, FEV_1, FEV_1%, FEV_1/FVC ratio) were administered by spirometry. Data were analyzed by logistic multiple regression and adjusted for age, gender, BMI, smoking status, physical activity, types of residential area, types of occupation, education status, and SES.	A negative correlation was observed between PbB and FEV_1/FVC ratio, but not FVC% or FEV_1%. Results are indicative of pulmonary obstructive disease. Correlation coefficient: • FVC%: 0.070 • FEV_1%: 0.00 • FEV_1/FVC: -0.115; p<0.01 Adjusted OR for T3 was decreased compared to T1, with a significant trend over tertiles. Adjusted ORs (95% CI) for FEV_1/FVC ratio: • T1: 1 (reference) • T2: 0.409 (0.003, 4.454) • T3: 0.006 (0, 0.286) • p-trend=0.03
Leem et al. 2015 Pooled cross-sectional study of 5,972 adults (≥20 years of age) from the 4th and 5th Korea National Health and Nutrition Examination Surveys, 2007–2009 and 2010–2012	**PbB:** Mean: • Men: 2.92 • Women: 2.33 Quartiles (men and women) • Q1: ≤1.85 • Q2: 1.86–2.43 • Q3: 2.44–3.16 • Q4: ≥3.17 **Analysis:** Data were log-transformed and analyzed by analysis of co-variance or multivariate linear regression, adjusted for age, sex, BMI, and smoking status.	FEV_1/FVC (%) was decreased in Q4 relative to Q1. Mean (SE): • Q1 (reference): 79.0 (0.2) • Q2: 78.9 (0.2); p=0.753 • Q3: 79.1 (0.2); p=0.771 • Q4: 78.4 (0.2); mean difference (SE): -0.6 (0.3); p=0.025

Table 2. Epidemiology Studies Evaluating Effects on the Respiratory System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Little et al. 2017 Cross-sectional study of 184 boys and 189 girls, 10–15 years of age, in Poland; data collection period not specified	Mean (SE): • Boys: 5.27 (0.19) • Girls: 3.82 (0.10) **Analysis:** FVC was measured after physical activity (running and agility). Data were log-transformed and analyzed by linear regression, adjusted for height, weight, and run time.	FVC was decreased in girls, but not in boys, following physical exertion; β (SE), per log10 increase in PbB: • Boys: -5.11 (4.47); p=0.25 • Girls: -12.90 (5.25); p=0.02
Zeng et al. 2017 Cross-sectional study of 200 children (mean age: 5.53 years; age range; 5–7 years; 52% boys) living near an area of electronic waste and 100 controls (mean age: 5.54 years; 63% boys) in China; data collection period: November 2013–December 2013	**PbB:** Median (IQR) • Control: 3.57 (2.68–4.86) • Exposed: 5.53 (3.92–7.04); p<0.001 **Analysis:** Pulmonary function data were log-transformed and analyzed by linear regression models, adjusted for age, gender, height, RDW, family member daily smoking, family income level, parental education level, daily outdoor play time, and living area.	PbB was negatively associated with FEV_1: and FVC in children living near the exposed area. Regression coefficient β (95% CI): • FEV_1: -0.02 (-0.100, 0.043) • FVC: -0.015 (-0.093, 0.063)
Increased bronchial responsiveness		
Min et al. 2008a Cross-sectional study of 523 adults (mean age 39.8 years) in Seoul, South Korea; data collection period was not reported	**PbB:** Mean (SD): 2.96 (1.59) **Analysis:** Bronchial reactivity was assessed by methacholine provocation test. The bronchial reactivity index was calculated as: log [(% decline in FEV_1/log of final methacholine concentration) +10]. Multiple regression analysis was performed, with adjustments for age, sex, height, smoking status, baseline FEV_1, and presence of asthma.	A 1 µg/dL increase in PbB was associated with increased bronchial responsiveness. β (SE): 0.018 (0.007)

Table 2. Epidemiology Studies Evaluating Effects on the Respiratory System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Lung disease		
Joseph et al. 2005 Prospective study of 4,634 children (ages 3 months to 3 years) in southern Michigan; data collection period: 1995–1998	**PbB:** Mean (SD) • White: 3.2 (2.5) • Black: 5.5 (4.3) **Analysis:** Following PbB measurement, participants were evaluated for asthma and were followed for up to 12 months for a diagnosis of asthma. The association of PbB to incident asthma by race was evaluated by Cox proportional hazards multivariable analysis. Adjusted for annual income per person, birth weight, and sex.	Adjusted HRs (95% CI) for asthma diagnosis (based on a child having four or more asthma-medication-dispensing events in 12 months, and one or more emergency department visits for asthma, one or more hospitalizations for asthma, or four or more outpatient visits for asthma with at least two asthma-medication-dispensing events): Incident asthma by race • White (PbB <5): 1 (reference) • White (PbB ≥5): 2.7 (0.9, 8.1); 0.09 • White (PbB ≥10): 0 incidence (HR not reported) • Black (PbB <5): 1 (reference) • Black (PbB ≥5) 1.1 (0.8, 1.7), p=0.53 • Black (PbB≥10): 1.3 (0.6, 2.6), p=0.54 Incident asthma using one race-exposure reference group • White (PbB <5): 1 (reference) • White (PbB ≥5): 2.3 (0.8, 6.7); p=0.12 • White (PbB ≥10): not calculated • Black (PbB <5): 1.8 (1.3, 2.4); p<0.01 • Black (PbB ≥5): 1.5 (1.2, 1.8); p<0.01 • Black (PbB ≥10): 3.0 (1.2, 7.1); p-0.01

Table 2. Epidemiology Studies Evaluating Effects on the Respiratory System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Rokadia and Agarwal 2013 Cross-sectional study of pooled data from 9,575 participants from NHANES 2007–2010, including 8,411 participants without obstructive lung disease (OLD) (mean age: 42.3 years) and 1,164 participants with OLD (mean age: 4.4 years); prevalence of OLD was 12.4%	**PbB:** Geometric mean (SD) • Non-OLD: 1.18 (1.0 • OLD: 1.73 (1.02); p<0.001 compared to non-OLD **Analysis:** Mild OLD defined as FEV_1 ≥80% predicted; moderate-severe OLD defined as FEV_1 <80% predicted. Multivariate linear regression analysis was performed, with adjustments for age, sex, race, BMI, chronic kidney disease, diabetes, hyperlipidemia, hypertension, stroke, coronary artery disease, smoking, serum, C-reactive protein concentration, and serum cotinine concentration. Mild OLD defined as FEV_1 ≥80% predicted; moderate-severe OLD defined as FEV_1 <80% predicted.	The risk of all OLD and moderate-severe OLD was elevated with increasing concentration of PbB. OR (95% CI) • All OLD: 1.94 (1.10, 3.42) • Mild OLD: 1.21 (0.55, 2.65) • Moderate-severe OLD: 3.49 (1.70, 7.15)
Wang et al. 2017a Cross-sectional study of 930 children with a mean age of 5.74 years (boys: 469; girls: 461) in Taiwan; data collection period: 2011	**PbB:** Geometric mean (GSD) • All: 1.86 (1.21) • Boys: 1.89 (1.22) • Girls: 1.83 (1.20) **Analysis:** Data for asthma were dichotomized as <5 and ≥5 µg/dL and analyzed by univariate and multivariate logistic regression with adjustments for age, maternal age, maternal history of atopy, maternal nationality, parental education and occupation, family income, number of siblings, breast feeding, environmental tobacco smoke, incensing at home, dehumidifier at home, new paintings of houses, and residence using groundwater.	The risk of asthma was increased in the total population and in boys, but not in girls. ORs (95% CI), <5 versus ≥5 µg/dL: • All: 5.50 (1.69, 17.94); p=0.005 • Boys: 6.40 (1.49, 27.42);p=0.012 • Girls: 4.73 (0.44, 50.60); p=0.199

Table 2. Epidemiology Studies Evaluating Effects on the Respiratory System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Wells et al. 2014 Cross-sectional study of 1,788 children (ages 2–12 years) from NHANES 2005–2006; asthma analysis was limited to the subset of children aged 4–12 years (n=1,430)	**PbB:** Geometric mean (95% CI): 1.07 (0.99–1.17) **Analysis:** Data were analyzed by logistic regression and adjusted for 6-month season, age, sex, race/ethnicity, parental educational status, prenatal smoke exposure, BMI, presence of cockroaches in the home, and avoidance/removal of pets.	No association was observed between PbB and asthma. Adjusted ORs (95% CI), based on a 1 µg/dL increase of PbB: • Asthma with atopy: 0.97 (0.61, 1.55) • Asthma with no atopy: 1.07 (0.86, 1.33)
Zeng et al. 2016 Cross-sectional study of 470 children living near an electronic recycling area; Haojiang area (n=170: mean age 4.34 years; age range: 3–8 years; 57% boys, 43% girls; Guiyu area (n=300): mean age 4.66 years, 50% boys, 50% girls; data collection period: December 2012–January 2013	**PbB:** Median (IQR) • Haojiang area: 4.75 (3.98–5.76) • Guiyu area: 6.24 (4.55, 8.00) • p=0.000 **Analysis:** Comparison of PbB between groups was assessed by t-test on Ln-transformed data. Asthma data were analyzed by logistic regression analysis for PbB stratified by <5 or ≥5 µg/dL, adjusted for age, gender, passive smoking, living in Guiyu, whether use home as workshop, whether home close to e-waste recycling site, and whether child contact with electronic waste.	When stratified by PbB, PbB ≥5 µg/dL was associated with increased risk of asthma, compared to <5 µg/dL. OR (95% CI): 9.50 (1.16, 77.49); p<0.01

BMI = body mass index; CI = confidence interval; FEV_1: forced expiratory volume in 1 second (L/second); FEV_1% = percent of predicted FEV_1; FVC = forced vital capacity (L); FVC% = percent of predicted FVC; Gmean = geometric mean; GSD = geometric standard deviation; HR = hazard ratio; IQR = interquartile ratio; NHANES = National Health and Nutrition Examination Survey; OLD = obstructive lung disease; OR = odds ratio; RDW = red blood cell distribution width; SD = standard deviation; SE = standard error; SES = socio-economic status

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Mortality due to cardiovascular disease		
Aoki et al. 2016 Prospective study of 18,602 participants (≥40 years of age at baseline) from NHANES (1999–2001) with mortality follow-up through 2011	**PbB:** Mean (SE): 1.73 (0.02) **Analysis:** Participants were followed for mortality from baseline to 2011. PbB data were log_{10}-transformed. Data were analyzed by Cox proportional hazard regression, adjusted for race/ Hispanic origin, sex, and blood cadmium, serum iron, serum CRP, serum calcium, smoking, education, and alcohol intake.	A positive association was observed between PbB and RR of mortality due to cardiovascular disease. RR (95% CI), per 10-fold increase in hematocrit-corrected PbB: 1.44 (1.05, 1.98)
Khalil et al. 2009 Prospective cohort study of 533 women (age range: 65–87) years in Baltimore, Maryland and Monongahela Valley, Pennsylvania	**PbB:** Mean (SD): 5.3 (2.3) Range: 1–21 **Analysis:** Participants were followed for 12 years following baseline. Data were analyzed by Cox proportional hazards regression, adjusted for smoking, alcohol intake, estrogen use, hypertension, total hip bone mineral density, walking for exercise, and diabetes.	Mortality due to coronary heart disease was increased in women with PbB ≥8.0 µg/dL compared to women with PbB <8.0 µg/dL. HR (95% CI): 3.08 (1.23, 7.70); p=0.016.
Lanphear et al. 2018 Longitudinal study of 14,289 adults (age ≥20 years at baseline) from NHANES III (1988–1994), studied through 2011; follow-up to Menke et al. 2006	**PbB:** Geometric mean: 2.71 **Analysis:** Participants were followed for mortality a median period of 19.3 years. Data were analyzed by Cox proportional hazard regression analysis adjusted for age, race/ethnicity, sex, cigarette smoking, alcohol consumption, physical activity, household income, BMI, total cholesterol, diabetes mellitus, and hypertension.	An increase in PbB from 1.0 to 6.7 µg/dL was associated with increased mortality due to: • Cardiovascular disease (HR 1.70; 95% CI 1.30, 2.22 • Ischemic heart disease (HR 2.08; 95% CI 1.52, 2.85)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Menke et al. 2006 Longitudinal study of 13,946 adults (age ≥17 years) from NHANES III (1988–1994), studied through 2000	**PbB:** Baseline mean: 2.58 Tertiles: • T1: <1.94 • T2: 1.94–3.62 • T3: ≥3.63 **Analysis:** Participants were followed for mortality for 12 years after baseline PbB was obtained. Data were analyzed by Cox proportional hazard regression analysis adjusted for age, race/ethnicity, sex, urban residence, cigarette smoking, alcohol consumption, education, physical activity, household income, menopausal status, BMI, CRP, total cholesterol, diabetes mellitus, hypertension, and GFR.	PbB T3 was associated with increased risk of death due to cardiovascular disease, myocardial infarction, and stroke, with positive trends across tertiles. Adjusted HRs (95% CI): • Cardiovascular disease mortality; p-trend=0.003 o T1: 1 (reference) o T2: 1.03 (0.69, 1.55) o T3: 1.55 (1.08, 2.24) • Myocardial infarction mortality; p-trend=0.007 o T1: 1 (reference) o T2: 1.02 (0.55, 1.89) o T3: 1.89 (1.04, 3.43) • Stroke mortality; p-trend=0.017 o T1: 1 (reference) o T2: 2.19 (0.87, 5.53) o T3: 2.51 (1.20, 5.26)
Schober et al. 2006 Longitudinal study of 9,686 adults (age ≥40 years) from NHANES III (1988–1994), studied through 2000	**PbB:** Tertiles: • T1 (n=6,608): <5 • T2 (n=2,532): 5–9 • T3 (n=617): ≥10 **Analysis:** The median follow-up period following PbB measurement to death was 8.55 years. Data were analyzed by Cox proportional hazard regression analysis adjusted for sex, race/ethnicity, education, and smoking status.	Increased risk of death due to cardiovascular disease was observed in participants with PbB ≥10 µg/dL, compared to participants with PbB <5. µg/dL. No association was observed for participants with PbB 5–9 µg/dL. Adjusted RR (95% CI): • T1: 1 (reference) • T2: 1.20 (0.93, 1.55) • T3: 1.55 (1.16, 2.07) • p-trend: <0.01

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Weisskopf et al. 2009 Longitudinal study of 868 men (age >55 years) enrolled in the Normative Aging Study in Boston, Massachusetts; baseline PbB measurements obtained 1994 (±3 years)	**PbB:** Mean (SD): 5.6 (3.4) • Tertiles o T1: <4 o T2: 4–6 o T3: >6 **Analysis:** The median follow-up period following PbB and bone Pb measurement to death was 8.9 years (SD 3.9 years). Data were analyzed by Cox proportional hazard regression analysis adjusted for age, smoking status, and education.	No association was observed between PbB and increased risk of death due to cardiovascular disease. HRs (95% CI): • PbB (p-trend: 0.72) o T1: 1 (reference) o T2: 1.09 (0.69, 1.72) o T3: 1.10 (0.67, 1.80)
Blood pressure and hypertension in adults		
Almeida Lopes et al. 2017 Population-based study of 948 adults (421 men and 527 women), aged ≥40 years from an urban area in southern Brazil; data collection period: 2011	**PbB:** Gmean (range):1.97 (0.46–45.62) Quartiles: • Q1: ≤1.32 • Q2: 1.32–1.93 • Q3: 1.93–2.76 • Q4: >2.76 **Analysis:** PbB data were log transformed. Data SBP and DBP were analyzed by multiple linear regression, adjusted for sex, age, race, education, income, antihypertensive medication, total cholesterol, triglycerides, glycemia, smoking status, alcohol intake, and BMI.	PbB was positivity associated with DBP and risk of hypertension. Change (95% CI) of SBP and DBP by PbB quartile: • SBP o Q1: 0 (reference) o Q2: -0.00 (-0.00, -0.00) o Q3: -0.00 (-0.00, -0.00) o Q4: -0.00 (-0.00, -0.00) o p-trend=0.002 • DBP o Q1: 0 (reference) o Q2: 0.03 (0.01, 0.05) o Q3: 0.02 (0.00, 0.05) o Q4: 0.06 (0.04, 0.09) o p-trend<0.001

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		OR (95% CI) for hypertension by PbB quartile: o Q1: 1 (reference) o Q2: 0.11 (0.01, 1.59) o Q3: 0.40 (0.02, 6.87) o Q4: 2.54 (1.17, 5.53) o p-trend=0.003
Al-Saleh et al. 2005 Case-control study of 100 women with hypertension (ages 47–93 years) and 85 control subjects (ages 45–82 years) in Saudi Arabia; data collection: 2001–2002	**PbB:** Mean (SD); range • With hypertension: 4.75 (3.93); 1.45–28.3 • Controls: 4.56 (2.85); 1.19–17.6 **Analysis:** Data were analyzed using multiple logistic regression, adjusted for menopausal status, time since menopause, physical activity, history of breast feeding, family income, attended school, work status, family history of hypertension, heart diseases, rheumatologic diseases, other diseases, intake of supplements and minerals, age, and creatinine.	For PbB ≥3.86 µg/dL compared to PbB <3.86 µg/dL, the risk of hypertension was increased. OR (95% CI): 5.27 (0.93, 29.86); p=0.06
An et al. 2017 Cross-sectional study of 310 male smelter workers (ages 21–61 years); data collection period: January–December 2014	**PbB:** Gmean (95% CI): 5.839 (5.421, 6.068) **Analysis:** PbB data were $\log_2$ transformed. Data were analyzed by linear regression, adjusted for age, BMI, dyslipidemia, diabetes, alcohol consumption, smoking status, exercise, and family history of hypertension.	No association was observed between PbB and SBP or DBP. β (95% CI) per doubling of PbB: • SBP: -0.636 (-2.661, 1.389); p=0.537 • DBP: -1.182 (-2.763, 0.399); p=0.142

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Barry et al. 2019 Cross-sectional study of 211 male Pb workers (mean age: 61.9 years) residing in New York and New Jersey; data collection period: 2016–2017	**PbB:** Median (range): 2.5 (0–34.0) • Quartiles o Q1: <1.6 o Q2: 1.6–2.5 o Q3: 2.6–4.2 o Q4: ≥4.3 Bone Pb (tibia) median, µg/g (range): 13.8 (0–127.3) • Bone Pb quartiles: o Q1: <9.6 o Q2: 9.6–13.7 o Q3: 13.8–19.5 o Q4: ≥19.6 **Analysis:** Associations between PbB or bone Pb and SBP were analyzed by multivariable linear regression using both continuous and categorical (quartiles) models, adjusted for age, smoking pack years, and BMI.	A positive linear trend was observed between bone Pb and SBP, although no associations were observed for any bone Pb quartiles or for PbB (continuous or quartiles). SBP regression coefficient (SE): PbB • Q1: reference • Q2: 1.21 (4.35); p=0.78 • Q3: 0.49 (4.84); p=0.92 • Q4: 7.33 (4.40); p=0.10 • Continuous: 0.19 (0.30) 0.52 Bone Pb • Q1: reference • Q2: -0.44 (4.51); p=0.92 • Q3: 5.45 (4.69); p=0.25 • Q4: 5.32 (5.26); p=0.31 • Continuous: 0.36 (0.15); p=0.02

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Bost et al. 1999 Cross-sectional survey study of 2,563 men (mean age 47.5 years) and 2,763 women (mean age 47.7 years) in Great Britain in 1995	**PbB:** • Mean in men: 3.7 • Mean in women: 2.6 **Analysis:** Three sitting blood pressure measurements were taken on the day of assessment. Data were analyzed using multivariate linear regression (with log-transformed PbB), adjusted for covariates (age and BMI, alcohol consumption and tobacco smoking, SES, and region of residence; subjects who were on AH agents were excluded).	Increasing DBP was significantly associated with increasing PbB in males, but not in females. Standardized regression coefficients for males: • Subjects on AH drugs included: 0.061 ($p<0.001$) • Subjects on AH drugs excluded: 0.055 ($p<0.01$) Change in DBP (mmHg) in males per doubling of PbB (95% CI): • Subjects on AH drugs included: 0.78 (0.01, 1.55) • Subjects on AH drugs excluded: 0.88 (0.13, 1.63) No associations were observed for SBP for men or women (regression coefficients not reported).

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Bushnik et al. 2014 Population-based survey study of 2,214 men (mean age 49.5 years) and 2,336 women (mean age 50.5 years) using data collected from the Canadian Health Measures Survey (2007–2011)	**PbB:** Mean All participants: 1.64 Non-hypertensive: 1.59 Hypertensive: 1.74 **Analysis:** Six blood pressure measurements were taken on the day of assessment. Associations between PbB and blood pressure were analyzed by linear regression. Associations between PbB and hypertension were analyzed by logistic regression, with adjustments for age, sex, education, smoking, alcohol, physical activity, BMI, non-HDL cholesterol, diabetes, chronic kidney disease, family history of high blood pressure, and AH medication use.	An association was observed between PbB and increased DBP, but not SBP. No association was observed between PbB and increased prevalence of hypertension. SBP (mmHg) β mmHg per 1 µg/dL (95% CI) for: • Men and women: 1.85 (-0.20, 3.90); p=0.075 • Men: 2.17 (-0.08, 4.42); p=0.058 • Women: 0.76 (-2.72, 4.24); p=0.656 DBP (mmHg) β mmHg per 1 µg/dL (95% CI) for: • Men and women: 1.91 (0.75, 3.08); p=0.002 • Men: 2.36 (0.94, 3.79); p=0.002 • Women: 1.43 (-0.51, 3.38); p=0.142 Hypertension risk (SBP ≥140, DBP ≥90) logistic β (95% CI) for: • Men and women: -3.87 (-7.46, -0.29); p=0.035 • Men: -6.37 (-15.02, 2.29); p=0.142 • Women: -4.18 (-8.78, 0.42); p=0.073

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Cheng et al. 2001 Longitudinal study of 833 men (age range: 21-80; mean: 42 years) from the Normative Aging Study in Boston, Massachusetts; data collection: period 1991–1997	**PbB** (mean: • All (range): 6.09 (<1–35) • Normotensive (SD): 5.87 (4.01) • Borderline hypertension (SD): 6.00 (3.69) • Definite hypertension (SD): 6.37 (4.21) Tibia Pb (µg/g) • Normotensive (SD): 20.27 (11.55) • Borderline hypertension (SD): 23.46 (15.02) • Definite hypertension (SD): 22.69 (14.71) Patella Pb (µg/g) • Normotensive (SD): 28.95 (18.01) • Borderline hypertension (SD): 33.73 (21.76) • Definite hypertension (SD): 32.72 (19.55) **Analysis:** Data were analyzed by Cox's proportional hazards model for hypertension and by multivariate linear regression for SBP. Models were adjusted for age^2, BMI, family history of hypertension, race, educational level, pack-years of smoking, alcohol consumption, and dietary intakes of sodium and calcium.	An association between patella Pb (but not PbB or tibia Pb) and hypertension was observed. RR (95% CI), per 1 SD increase in: • PbB: 1.00 (0.76, 1.33) • Tibia Pb: 1.22 (0.95, 1.57) • Patella Pb: 1.29 (1.04, 1.61); p<0.05 An association between tibia Pb (but not PbB or patella Pb) and SBP was observed. RR (95% CI), per 1 SD increase in: • PbB: -0.13 (-1.35, 1.09) • Tibia Pb: 1.37 (0.02, 2.73); p<0.05 • Patella Pb: 0.57 (-0.71, 1.84)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Chu et al. 1999 Population-based survey study of 2,800 subjects (1,471 males and 1,329 females) (15–86 years of age) in Taiwan; data collection period: 1993–1994	**PbB:** Mean (SD); range • All participants: 6.5 (4.7); 0.1–69.1 • Men: 7.3 (5.2); 0.1–69.1) • Women: 5.7 (3.9); 0.1–40.1 **Analysis:** Two blood pressure measurements were taken on the day of assessment. Data were analyzed using multiple regression analyses with log_{10}-transformed PbB, adjusted for age, BMI, milk intake, alcohol consumption, and smoking.	An association was observed between PbB and increased SBP in men, but not in women. No association was observed between PbB and DBP in men or women. Regression coefficient β mmHg per 1 log_{10} µg/dL (SE) for: • SBP (mmHg) o Men: 0.185 (0.076); p=0.015 o Women: -0.057 (0.109); p=0.603 • DBP o Men: 0.075 (0.053); p=0.159 o Women: -0.083 (0.072); p=0.250
Den Hond et al. 2002 Cross-sectional study of 13,781 adults (age ≥20 years): white (4,685 males; 5,138 females) and black (1,761 males; 2,197 females) from NHANES III (1988–1994)	**PbB:** Median (IQR) • White males: 3.6 (2.3–5.3) • White females: 2.1 (1.3–3.4) • Black males: 4.2 (2.7–6.5) • Black females: 2.3 (1.4–3.9) **Analysis:** Data were analyzed by multivariate linear regression, adjusted for age, BMI, hematocrit, total serum calcium, and protein concentrations, smoking, alcohol and coffee consumption, dietary calcium, potassium, and sodium intakes, diabetes, and use of AH drugs.	SBP and DBP was positively associated with PbB in black males and females, but not in white males or females. Predicted covariate-adjusted increments in SBP and DBP per doubling of PbB (95% CI): • SBP: o White males: 0.3 (-0.2, 0.7); p=0.29 o White females: 0.1 (-0.4, 0.5); p=0.80 o Black males: 0.9 (0.04, 1.8); p=0.04 o Black females: 1.2 (0.4, 2.0); p=0.004 • DBP: o White males: -0.6 (-0.9, -0.3); p=0.0003 o White females: -0.2 (-0.5, -0.1); p=0.13 o Black males: 0.3 (-0.3, 1.0); p=0.28 o Black females: 0.5 (0.01, 1.1); p=0.047

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Elmarsafawy et al. 2006 Cross-sectional study of 471 men (mean age 67 years) from the Normative Aging Study in Boston, Massachusetts; data collection period: 1991–1994	**PbB:** Mean (SD) • All subjects: 6.6 (4.3) • Low calcium intake: 6.6 (4.0) • High calcium intake: 6.6 (4.6) **Analysis:** Data were analyzed by logistic regression adjusted for age, BMI, family history of hypertension, smoking, dietary sodium intake, and alcohol ingestion.	In subjects with low calcium intake, PbB was associated with an increased risk of hypertension. Adjusted ORs (95% CI) • Low calcium group (intake ≤800 mg/day): 1.07 (1.00, 1.15) • High calcium group (intake >800 mg/day): 1.03 (0.97, 1.11)
Faramawi et al. 2015 Cross-sectional study of 13,757 adults (mean age 42.74 years) from NHANES III (1988–1994)	**PbB:** Mean (SE): 3.44 (0.09) **Analysis:** Three blood pressure measurements were taken at the initial in-home visit and in the Mobile Examination Center in a follow-up within 1 month of the in-home visit. Data were analyzed by multivariable regression analyses, with adjustments for age, sex, race, smoking, and SES.	An association was observed between PbB and increased SBP variability (SD of multiple blood pressure measurements), but not DBP variability. Regression coefficient β for change in blood pressure SD per µg/dL (SE): • SBP (mmHg) o Mean variability: 3.33 mmHg o β (SE): 0.07 (0.02); p<0.01 • DBP (mmHg) o Mean variability: 1.74 mmHg o β (SE): 0.04 (0.03); p=0.08

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Gambelunghe et al. 2016 Cross-section study of 4,452 adults (mean age: 57 years; 66% women) residing in Sweden; data collection period 2007–2012	**PbB:** Mean (range): 2.8 (0.15–25.8) Quartiles, mean (range): • Q1: 0.15 (0.15–1.9) • Q2: 2.2 (1.9–2.5) • Q3: 2.8 (2.5–3.3) • Q4: 4.7 (3.3–28.5) • p (Q4 versus Q1–Q3): <0.001 **Analysis:** Blood pressure was measured after 10 minutes of supine rest. Hypertension was defined as SBP ≥140 mmHg or DBP ≥90 mmHg and/or current use of hypertension medication. Data for SBP and DBP were analyzed by multiple linear regression and data for hypertension were analyzed by multiple logistic regression. Both models were adjusted for sex, alcohol intake, smoking, waist circumference, education, and blood cadmium concentration.	PbB was positively associated with SBP, DBP, and risk of hypertension. Regression coefficient, β, for SBP and DBP, Q4 versus Q1–Q3: • SBP: 1.7; p=0.01 • DBP: 1.3; p<0.001 OR for hypertension (95% CI): 1.3 (1.1, 1.5); p=0.004

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Gerr et al. 2002 Cross-sectional study of 508 young adults (92 males and 118 females) ages 19–29 years (born 1965–1975); the study included two cohorts: (1) participants heavily exposed during childhood (near an active Pb smelter in Silver Valley, Idaho), and (2) referents who did not live near the smelter in childhood	**PbB:** Current PbB mean (SD) associated with the following bone (tibia) Pb concentrations: • <1 µg/g: 1.91 (1.58) • 1–5 µg/g: 2.31 (2.06) • 6–10 µg/g: 2.43 (2.36) • >10 µg/g: 3.15 (2.28) **Analysis:** Sitting blood pressure was measured on the day of assessment (number of measurements not reported). Multiple linear regression models were used to analyze data and were adjusted for age, sex, height, BMI, current smoking status, frequency of alcohol consumption, current use of birth control medication, hemoglobin level, serum albumin, and income.	For the >10 µg/g bone Pb group, SBP and DBP were increased compared to the <1 µg/g bone group. Blood pressure increases, mmHg (SE): • Systolic: 4.26 (1.48); p=0.004 • Diastolic: 2.80 (1.25); p=0.03
Glenn et al. 2003 Longitudinal study of 496 male workers (mean age 55.8 years) from the eastern United States studied during 1994–1996	**PbB:** Mean (SD): 4.6 (2.6) Range: 1–20 **Analysis:** Multiple seated blood pressure measurements were taken at each examination (three or four visits). General estimating equation models were used to evaluate associations between PbB and blood pressure. Covariates considered in the analyses included race; age and BMI; diagnosis of diabetes, arthritis, or thyroid disease; education; and blood pressure measurement interval.	SBP was significantly associated with baseline PbB. An increase in PbB of 1 SD was associated with the following increases in blood pressure (mmHg). β (SE; 95% CI): • SBP (mmHg): 0.64 (0.25; 0.14, 1.14) • DBP (mmHg): 0.09 (0.17; -0.24, 0.43)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Hense et al. 1993 Population survey study of 1,703 men and 1,661 women (ages 28–67 years) from Germany; data collection period: 1987–1988	**PbB:** Mean • Men: 8.3 • Women: 6.0 **Analysis:** Three sitting blood pressure measurements were obtained on the assessment day. Data were analyzed by multiple linear regression, adjusted for age, BMI, alcohol use, and hematocrit.	Regression coefficients per 1.0 µg/dL increase in PbB showed associations between PbB and increased SBP in men and increased DBP in women. β mmHg per 1 µg/dL (95% CI): • SBP: o Men: 0.29 (0.08, 0.49) o Women: 0.17 (-0.14, 0.48) • DBP o Men: 0.08 (-0.06, 0.23) o Women: 029 (0.09, 0.49)
Hu et al. 1996a Case-control study of 146 men (mean age 67 years) with hypertension and 444 age-matched controls, from the Normative Aging Study in Boston, Massachusetts; data collection: period 1991–1994	**PbB:** Mean (SD) • Cases: 6.9 (4.3) • Controls: 6.1 (4.0) **Bone Pb (µg/g)** mean (SD) • Tibia o Cases: 23.7 (14.0) o Controls: 20.9 (11.4) • Patella o Cases: 35.1 (19.5) o Controls: 31.1 (18.3) **Analysis:** Physical examinations, including seated blood pressure and medical history follow-ups, were conducted at approximately 3–5-year intervals. Risk of hypertension was assessed using a logistic regression model, adjusted for BMI and family history of hypertension.	Significant associations were observed between increasing tibia Pb and risk of hypertension. • Logistic β (SE) for 1 µg/g increase in tibia Pb: 0.19 (0.0078); p=0.01 • OR (95% CI) for 1 µg/g change in tibia Pb: 1.019 (1.004, 1.035) • OR (95% CI) for quintile range (8–37 µg/g): 1.5 (1.1, 1.8) No significant associations observed for PbB or patella Pb.

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Korrick et al. 1999 Case-control study of women (mean) age 61.1 years) with hypertension (n=89) and controls (n=195) from the National Nurses' Health Study; data collection period: 1993–1995	**PbB:** Combined cases and controls: • Mean (SD): 3 (2) • Range: <1–14 **Bone Pb (µg/g), mean (SD)** • Tibia: 13.3 (9.0) • Patella: 17.3 (11.1) **Analysis:** Risk of hypertension was assessed using a logistic regression model, adjusted for age, BMI, dietary sodium intake, alcohol consumption, smoking, and family history of hypertension.	Patella Pb was associated with an increased risk of hypertension. ORs (95% CI): 1.03 (1.00, 1.05); p=0.02. No association was observed for PbB or tibia Pb (ORs not reported).
Lee et al. 2016a Cross-sectional study of 5,920 men and 6,059 women, age ≥19 years, from the Korean National Health and Nutrition Examination Survey; data collection period: 2008–2013	**PbB:** Gmean (95% CI) • Men: 2.396 (2.362, 2.430) • Women: 1.919 (1.889, 1.949) Tertiles: • Men o T1: <2.096 o T2: 2.096–2.886 o T3: >2.886 • Women o T1: <1.516 o T2: 1.516–2.147 o T3: >2.147 **Analysis:** PbB levels were log_2-transformed. The mean difference in SBP and DBP per doubling of PbB was analyzed by regression analysis for continuous and tertial PbB. ORs for hypertension (DBP of at least 90 mmHg or SBP of at least 140 mmHg or self-reported current use of an anti-	Difference (95% CI) in SBP and DBP, T3 versus T1: DBP • Men o Continuous per doubling of PbB: 0.30 (-0.53, 1.14) o T1: 0 (reference) o T2: -0.34 (-1.38. 0.69) o T3: 0.25 (-0.90, 1.41) • Women o Continuous per doubling of PbB: 1.08 (0.26, 1.90) o T1: 0 (reference) o T2: 0.312 (-0.74, 1.368) o T3: 1.48 (0.29, 2.67) SBP • Men o Continuous per doubling of PbB: 0.59 (0.01, 1.17)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
	hypertensive medication) and prehypertension (DBP of at least 80 mmHg but below 90 mmHg or SBP of at least 120 mmHg but below 140 mmHg) were analyzed by logistic regression. All analyses were adjusted for sex, age group, BMI, residence area, smoking status, drinking status, education level, hypertensive status, physical activities, serum creatinine, hemoglobin, and year of examination.	o T1: 0 (reference) o T2: 0.35 (-0.43, 1.14) o T3: 0.73 (-0.12, 1.60) • Women o Continuous per doubling of PbB: 0.80 (0.28, 1.33) o T1: 0 (reference) o T2: 0.182 (-0.51, 0.879) o T3: 1.059 (0.308, 1.811) OR (95% CI) for hypertension • Men o T1: 1 (reference) o T2: 0.88 (0.71, 1.09) (n=582) o T3: 0.88 (0.72, 1.07) (n=787) • Women o T1: 1 (reference) o T2: 1.07 (0.85, 1.34) (n=426) o T3: 1.26 (0.999, 1.58) (n=647) OR (95% CI) for prehypertension • Men o T1: 1 (reference) o T2: 0.86 (0.73, 1.02) (n=1,183) o T3: 0.95 (0.79, 1.16) (n=1,437) • Women o T1: 1 (reference) o T2: 1.13 (0.94, 1.37) (n=838) o T3: 1.22 (1.01, 1.48) (n=1,082)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Lee et al. 2016b Cross-sectional study of 8,493 adults (3,945 men and 4,548 women), age ≥20 years, from the Korean National Health and Nutrition Examination Survey; data collection period: 2007–2013	**PbB:** (study population mean not reported) Quartiles: • Q1: 0.206–1.539 • Q2: 1.540–2.056 • Q3: 2.057–2.716 • Q4: 2.717–24.532 **Analysis:** ORs for prehypertension (DBP of at least 80 mmHg but below 90 mmHg or SBP of at least 120 mmHg but below 140 mmHg) were analyzed by logistic regression age, sex, sociodemographic factors (education, occupation, household income, and residence), health behavioral factors (smoking, alcohol drinking, and exercise level), hypertension-associated medical status (anemia and serum creatinine clearance), and chronic disease (central obesity, diabetes, elevated triglycerides, and decreased HDL).	PbB in all quartiles was positively associated with the risk of prehypertension. OR (95% CI): • Q1: 1 (reference) • Q2: 1.24 (1.04, 1.48) • Q3: 1.27 (1.06, 1.52) • Q4: 1.30 (1.07, 1.60) • p-trend: 0.0152
Martin et al. 2006 Cross-sectional study of 964 men and women (ages 50–70 years) in Baltimore, Maryland; data collection period 2001–2002	**PbB:** Mean (SD): 3.5 (2.3) **Bone Pb (µg/g), mean (SD)** • Tibia: 18.8 (12.4) **Analysis:** Three sitting blood pressure measurements were obtained on the day of assessment. Data were analyzed by multiple linear regression adjusted for age, sex, BMI, AH medication use, dietary sodium intake, dietary potassium intake, time of day, testing technician, serum total cholesterol, SES, and race/ethnicity.	PbB was associated with increased SBP and DBP. β (95% CI), mmHg per µg/dL PbB: • SBP: 0.99 (0.47,1.51); p<0.01 • DBP: 0.51 (0.24, 0.79); p<0.01 • No association was observed for tibia Pb

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Muntner et al. 2005 Cross-sectional study of 9,961 men and women (age ≥18 years) from NHANES (1999–2002)	**PbB:** • Mean (95% CI): 1.64 (1.59–1.68) • Quartiles: o Q1: <1.06 o Q2: 1.06–1.63* o Q3: 1.63–2.47* o Q4: ≥2.47 *Overlap of PbB of 1.63 µg/dL in Q2 and Q3 is as reported in Muntner et al. (2005). **Analysis:** Three sitting blood pressure measurements were obtained on the day of assessment. PbB were log-transformed. Race/ethnicity-stratified ORs of hypertension were analyzed by multivariable logistic regressions models adjusted for age, sex, BMI, diabetes mellitus, smoking status, health insurance status, alcohol consumption, and education.	Concurrent PbB was not associated with hypertension across race/ethnicity groups, although a positive trend was observed for Mexican Americans. Adjusted ORs (95% CI): • Non-Hispanic white: p-trend=0.61 o Q1: 1 o Q2: 1.12 (0.83, 1.50) o Q3: 1.03 (0.78, 1.37) o Q4: 1.10 (0.87, 1.41) • Non-Hispanic black: p-trend=0.06 o Q1: 1 o Q2: 1.03 (0.63, 1.67) o Q3: 1.12 (0.77, 1.64) o Q4: 1.44 (0.89, 2.32) • Mexican American: p-trend=0.04 o Q1: 1 o Q2: 1.42 (0.75, 2.71) o Q3: 1.48 (0.89, 2.48) o Q4: 1.54 (0.99, 2.39)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Nash et al. 2003 Cross-sectional study of 2,165 women (mean age 48.2 years; range 40–59 years) from NHANES III (1988–1994); the population included 1084 and 633 pre- and postmenopausal women, respectively	**PbB:** Mean: 2.9 Range: 0.50–31.1 Quartiles; mean (range) • Q1: 1.0 (0.5–1.6) • Q2: 2.1 (1.7–2.5) • Q3: 3.2 (2.6–3.9) • Q4: 6.4 (4.0–31.1) **Analysis:** Data were analyzed by multiple linear regression; adjusted for race, age, BMI, tobacco smoking, alcohol consumption, and kidney function (based on serum creatinine levels).	PbB was associated with increased SBP and the prevalence of hypertension in all participants. When stratified by menopausal status, DBP was associated with PbB in postmenopausal women. Distribution of blood pressure variables (all women): • SBP, mean (SE, mmHg; p-trend<0.001 o Q1: 117.2 (0.95) o Q2: 117.7 (0.83) o Q3: 119.3 (1.10) o Q4: 121.2 (0.92) • DBP, mean (SE, mmHg; p-trend=0.79 o Q1: 73.7 (0.51) o Q2: 74.2 (0.53) o Q3: 74.2 (0.62) o Q4: 74.3 (0.62) • Hypertension (%); p-trend<0.001 o Q1: 19.4 o Q2: 20.6 o Q3: 25.5 o Q4: 28.3

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		Regression coefficients (SE) for blood pressure (mmHg per 1 µg/dL): • All women (pre- and postmenopausal) o SBP: 0.32 (0.16); p=0.03 o DBP: 0.25 (0.09); p=0.009 • Premenopausal women o SBP: 0.14 (0.26); p=0.59 o DBP: 0.38 (0.25); p=0.12 • Postmenopausal women o SBP: 0.42 (0.21); p=0.29 o DBP: 0.14 (0.13); p=0.04 OR (95% CI) for general hypertension. • All women (pre- and postmenopausal) o Q1: 1.0 (reference) o Q2: 1.0 (0.63, 1.6) o Q3: 1.3 (0.87, 2.0) o Q4: 1.4 (0.92, 2.0) • Premenopausal women o Q1: 1.0 (reference) o Q2: 0.78 (0.38, 1.6) o Q3: 1.4 (0.82, 2.4) o Q4: 1.5 (0.78, 2.8) • Postmenopausal women o Q1: 1.0 (reference) o Q2: 0.73 (0.40, 1.3) o Q3: 1.3 (0.75, 2.2) o Q4: 1.3 (0.68, 2.3)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Park et al. 2009b Cross-sectional study of 12,500 participants (mean age 49.9 years) from NHANES III (1988–1994)	**PbB:** Mean (SE) • Overall: 3.52 (0.10) • White men o <50 years old (n=2,130): 4.02 (0.16) o ≥50 years old (n=2,152): 4.92 (0.18) • Black men o <50 years old (n=1,048): 4.55 (0.15) o ≥50 years old (n=540): 7.57 (0.22) • White women o <50 years old (n=2,429): 2.09 (0.07) o ≥50 years old (n=2,180): 3.53 (0.12) • Black women o <50 years old (n=1,409): 2.52 (0.09) o ≥50 years old (n=612): 4.49 (0.16) **Analysis:** Logistic regression models were adjusted for age, age^2, education, smoking status, pack-years of cigarettes, BMI, hematocrit, alcohol consumption, physical activity, AH medication use, and diabetes diagnosis.	The risk of hypertension associated with PbB was increased in all participants, men >50 years of age, all white women, all black women, and women <50 years of age. Adjusted ORs (95% CI) for hypertension per SD (0.75 µg/dL) in log blood Pb: • Overall: 1.12 (1.03, 1.23). • Men o White: 1.06 (0.92, 1.22) o Black: 1.17 (0.98, 1.38) o <50 years old: 0.98 (0.80, 1.22) o ≥50 years old: 1.20 (1.02, 1.41) • Women o White: 1.16 (1.04, 1.29) o Black: 1.19 (1.04, 1.38) o <50 years old: 1.23 (1.04, 1.46) o ≥50 years old: 1.09 (0.94, 1.26)
Obeng-Gyasi and Obeng-Gyasi 2018 Cross-sectional study of 22,747 adults (43.67% men; mean age: 44.64 years) participating in NHANES 2009–2016.	**PbB:** Mean (95% CI): 1.33 (1.27, 1.38) **Analysis:** PbB data were ln-transformed. Association between PbB and SBP and DBP were evaluated by linear regression, with adjustments for age, alcohol consumption, smoking, gender, ethnicity, and BMI.	Ln PbB was positively associated with SBP and DBP. β (95% CI), increase in blood pressure (mmHg) per unit increased in ln PbB: SBP: 0.238 (0.122, 0.355); p=0.0001 DBP: 0.132 (0.049, 0.215); p=0.002

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Perlstein et al. 2007 Cross-sectional study of 593 elderly men (age >60 years) enrolled in Normative Aging Study in Boston, Massachusetts (1991–1997)	**PbB:** Mean (SD); range: 6.12 (4.03); <1–35 Bone Pb (µg/g) mean: 19 Quintiles for tibia Pb, mean (range), and associated PbB mean (SD): • Q1: o Tibia Pb: 7.4 (-3–11) o Associated PbB: 4.9 (2.9) • Q2: o Tibia Pb: 14.1 (12–16) o Associated PbB: 5.3 (3.6) • Q3: o Tibia Pb: 18.9 (17–21) o Associated PbB: 5.6 (3.5) • Q4: o Tibia Pb: 24.9 (22–29) o Associated PbB: 6.7 (3.8) • Q5: o Tibia Pb: 40.9 (30–126) o Associated PbB: 8.1 (5.2) **Analysis:** Adjusted mean difference in pulse pressure was analyzed by multiple linear regression model, with adjustment for age, height, race, heart rate, waist circumference, diabetes, family history of hypertension, education level achieved, smoking, alcohol intake, fasting plasma glucose, and ratio of total cholesterol to HDL cholesterol.	For tibia Pb concentrations >19 µg/g, mean pulse pressure was 4.2 mmHg greater (95% CI 1.9, 6.5) than for men with tibia Pb concentrations <19 µg/g. No association between PbB or bone Pb quintiles and changes in pulse pressure were observed, although a positive trend was observed for bone Pb. Adjusted mean difference in pulse pressure (95% CI): PbB: p-trend=0.82 • Q1: 0 (reference) • Q2: -4.37 (-7.88, -0.86) • Q3: -2.56 (-5.78, 0.67) • Q4: -1.39 (-4.94, 2.15) • Q5: -1.49 (-4.93, 1.94) Bone Pb: p-trend=0.02 • Q1: 0 (reference) • Q2: -3.02 (-6.48, 0.44) • Q3: -0.73 (-4.27, 2.82) • Q4: 2.64 (-0.93, 6.21) • Q5: 2.58 (-1.15, 6.33)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Proctor et al. 1996 Cross-sectional study of 798 male participants (mean age: 66.1 years; age range 43–93 years) in the Normative Aging Study in Boston, Massachusetts; data collection period: 1992–1993	**PbB:** Mean (SD) • All participants: 6.5 (4.0); range 0.5–35 • ≤74 years (n=681): 6.5 (4.1) • >74 years (n=117): 6.3 (3.6) **Analysis:** Sitting blood pressure was measured in each arm, and the average was used in the analysis. Data were analyzed by multiple linear regression with ln-transformed PbB, adjusted for age, BMI, dietary calcium intake, alcohol use, sitting heart rate, exercise, hematocrit, and smoking status.	An association was observed between PbB and increased DBP, but not SBP (mmHg) for all participants and for participants ≤74 years of age. β mmHg per 1 ln µg/dL (95% CI): • All participants o SBP: 0.85 (-1.1, 2.7); p>0.05 o DBP: 1.2 (0.11, 2.2); p≤0.05 • Participants ≤74 years of age (n=681) o SBP: 1.2 (-0.86, 3.2); p>0.05 o DBP: 1.6 (0.42, 2.7); p≤0.01 After exclusion of persons on anti-hypertensive medication (whole cohort n=575; ≤74 years of age n=494), no association was found between PbB and SBP or DBP. No association was found for those >74 years old.
Schwartz 1995 Meta-analysis of 15 studies published during the period 1985–1993; number of participants was not reported	**PbB:** Reduction of PbB from 10 to 5 **Analysis:** Meta-analysis of 15 studies. Results of studies were weighted by the inverse of the variances.	A doubling of PbB from 5 to 10 µg/dL was associated with a 1.25 mmHg (95% CI, 0.87–1.63) increase in SBP (DBP not reported).

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Scinicariello et al. 2010 Cross-sectional study of 6,016 participants (age ≥17 years) from NHANES III (1988–1994)	**PbB:** Mean (SE) • All participants: 2.99 (0.09) • Non-Hispanic whites: 2.87 (0.09) • Non-Hispanic blacks 3.59 (0.20) • Mexican American 3.33 (0.11) Quartiles • Q1: 0.7–1.4 • Q2: 1.5–2.3 • Q3: 2.4–3.7 • Q4: 3.8–52.9 **Analysis:** Up to six blood pressure measurements were obtained at the assessment visit. Data were analyzed by multivariable linear regression of ln-transformed blood Pb level, with adjustments for age, sex, education, smoking status, alcohol use, BMI, serum creatinine, serum total calcium, glycosylated hemoglobin, and hematocrit.	PbB was associated with increased SBP in non-Hispanic whites and non-Hispanic blacks and increased DBP in non-Hispanic blacks. β (SE) (mmHg per ln µg/dL-PbB): • SBP o Non-Hispanic whites: 1.05 (0.37); p=0.01 o Non-Hispanic blacks: 2.55 (0.49); p=0.001 o Mexican Americans: 0.84 (0.46); p=0.08 • DBP o Non-Hispanic whites: -0.14 (0.49); p=0.77 o Non-Hispanic blacks: 1.99 (0.44); p=0.0002 o Mexican Americans: 0.74 (0.38); p=0.06

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		• Adjusted prevalence ORs (95% CI) for hypertension for PbB quartiles o Non-Hispanic whites ▪ Q4: 1.52 (0.80, 2.88) o Non-Hispanic blacks: ▪ Q1: reference ▪ Q2: 1.83 (1.08, 3.09) ▪ Q3: 2.38 (1.40, 4.06) ▪ Q4: 2.92 (1.58, 5.41) o Mexican Americans: ▪ Q4: 1.27 (0.59, 2.57) • Interactions with blood Pb and ALAD genotype for SBP were observed in non-Hispanic whites and non-Hispanic blacks.

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Scinicariello et al. 2011 Cross-sectional study of 16,222 participants (age ≥20 years) from NHANES (1999–2006)	**PbB:** • Mean (SE) All o 1999–2000: 1.75 (0.03) o 2005–2006: 1.41 (0.03) o % population PbB <10: 100% • White men (n=4,538): 2.20 (0.03) • White women (n=4,319): 1.55 (0.02) • Black men (n=1,767): 2.44 (0.05) • Black women (n=1,854): 1.81 (0.06) • Mexican-American men (n=1,925): 2.47 (0.06) • Mexican-American women (n=1,819): 1.56 (0.04) **Analysis:** Multivariable linear regression was used to examine the relationships among blood pressure measures (systolic, diastolic, and pulse pressure) and l mmHg per ln µg/dL PbB-transformed PbB. Logistic regression to calculate adjusted PORs for hypertension. Models were adjusted for age, BMI, self-reported diabetes, alcohol ingestion, smoking status, education, serum creatinine, serum total calcium, sodium, hematocrit, and blood cadmium.	Ln-transformed PbB was associated with: increased SBP in all participants and black men and women; increased DBP in all participants, white men and women, and black men; decreased DBP in Mexican-American men; and increased pulse pressure in Mexican-American men. Regression coefficient (SE) based on ln µg/dL for: • SBP (mmHg) o All: 1.07 (0.35); p<0.05 o White men: 0.87 (0.53); p>0.05 o White women: 0.89 (0.55); p>0.05 o Black men 2.30 (0.71); p<0.05 o Black women 2.40 (1.14); p<0.05 o Mexican-American men 0.10 (0.70); p>0.05 o Mexican-American women -0.03 (0.64); p>0.05 • DBP (mmHg) o All: 0.71 (0.27): p<0.05 o White men: 0.90 (0.45): p<0.05 o White women: 0.95 (0.38): p<0.05 o Black men: 2.75 (0.82); p<0.05 o Black women: 0.30 (0.81); p>0.05 o Mexican-American men: -1.34 (0.66); p<0.05 o Mexican-American women: -0.74 (0.44); p>0.05

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		• Pulse pressure (mmHg) o All: 0.37 (0.34); p>0.05 o White men: -0.02 (0.55); p>0.05 o White women: -0.03 (0.62); p>0.05 o Black men: -0.42 (0.93): p>0.05 o Black women: 2.21 (1.17); p>0.05 o Mexican-American men: 1.42 (0.70); p<0.05 o Mexican-American women: 0.70 (0.63); p>0.05 The risk of hypertension was associated with PbB in black men. PORs (95% CI) for hypertension: • All: 0.99 (0.89, 1.11); p>0.05 • White men: 0.97 (0.84, 1.13); p>0.05 • White women: 0.94 (0.77, 1.14); p>0.05 • Black men: 1.41 (1.05, 1.88); p<0.05 • Black women: 1.04 (0.76, 1.42); p>0.05 • Mexican-American men: 0.91 (0.67, 1.24); p>0.05 • Mexican-American women: 0.89 (0.69, 1.16); p>0.05

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Vupputuri et al. 2003 Cross-sectional study of 14,952 subjects (age ≥18 years); white (5,360 males; 5,188 females) or black (2,104 males; 2,300 females) from NHANES III	**PbB:** Mean (SE) • White males: 4.4 (0.1) • White females: 3.0 (0.1) • Black males: 5.4 (0.2) • Black females: 3.4 (0.1) **Analysis:** Data were analyzed by multivariate linear regression and logistic regression, adjusted for age, BMI, alcohol consumption, dietary calorie, potassium, and sodium intakes, and physical activity.	SBP and DBP was positively associated with PbB in black males and females, but not in white males or females. Predicted covariate-adjusted increments in SBP and DBP per 1 SD (3.3 µg/dL) increase of PbB (95% CI): • SBP: o White males: 0.29 (-0.24, 0.83); p>0.05 o White females: 0.34 (-0.49, 1.17, p>0.05 o Black males: 0.82 (0.19, 1.44); p<0.05 o Black females: 1.55 (0.47, 2.64); p<0.01 • DBP: o White males: 0.01 (-0.38, 0.40); p>0.05 o White females: -0.04 (-0.56, 0.47) p>0.05 o Black males: 0.64 (0.08, 1.20); p<0.05 o Black females: 1.07 (0.37, 1.77); p<0.01) • Adjusted OR for hypertension [SBP ≥140, DBP ≥90 (95% CI)]: o White males: 1.04 (0.93, 1.16); p=0.47 o White females: 1.32 (1.14, 1.52) p<0.001 o Black males: 1.08 (0.99, 1.99); p=0.08 o Black females: 1.39 (1.21, 1.61); p<0.001)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Zota et al. 2013 Cross-sectional study of 8,194 adults (ages 40–65 years) participating in NHANES 1999–2008	**PbB:** Mean (SE): 1.69 (0.02) Quintiles: • Q1: ≤1.05 • Q2: 1.06–1.44 • Q3: 1.45–1.90 • Q4: 1.91–2.69 • Q5: >2.70 **Analysis:** Data were analyzed using logistic regression models, adjusted for age, sex, race/ethnicity, education, marital status, smoking status, alcohol consumption, and AH medication use.	Risk elevated DBP was associated with PbB for Q3–Q5. No association was observed for SBP. Adjusted ORs (95% CI): • Elevated SBP (≥140 mmHg) o Q1: 1 (reference) o Q2: 0.87 (0.66, 1.15) o Q3: 1.00 (0.76, 1.31) o Q4: 1.03 (0.78, 1.37) o Q5: 1.23 (0.92, 1.65) o p-trend: 0.06 • Elevated DBP (≥90 mmHg) o Q1: 1 (reference) o Q2: 1.22 (0.82, 1.81) o Q3: 1.56 (1.11, 2.19) o Q4: 1.80 (1.24, 2.60) o Q5: 1.77 (1.25, 2.50) o p-trend: 0.0002

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Blood pressure in children		
Ahn et al. 2018 Cross-sectional study of 1,776 adolescents (age: 10–18 years; 917 males and 859 females) from the 2010–2016 Korean National Health and Nutrition Survey	**PbB:** Mean (95% CI): • All: 1.192 (1.165, 1.219) • Males: 1.308 (1.268, 1.348) • Females: 1.073 (1.037, 1.111) Quartiles • Males o Q1: <1.07 o Q2: 1.07–1.341 o Q3: 1.342–1.655 o Q4: >1.655 • Females o Q1: <0.839 o Q2: 0.839–1.076 o Q3: 1.077–1.371 o Q4: >1.371 **Analysis:** Adjusted mean differences in DBP and SBP for a doubling of PbB, BP were regressed against log_2-transformed PbB, with adjustments of covariates for both continuous variable and quartile analysis. ORs for prehypertension (90>DBP≥ 80 mmHg or 140>SBP≥120 mmHg) were calculated for log_2-transformed PbB by logistic regression analyses. Adjustments were sex, age, residence area, smoking status, drinking status, BMI, year of measurement, physical activities, hemoglobin, and serum creatinine.	No associations were observed between PbB and DBP, SBP, or risk of prehypertension. A significant negative association was observed for DBP in Q3, but not in Q4. Mean differences in DBP (95% CI): • Continuous variable for doubling of PbB: -0.680 (-1.581, 0.221) • Quartiles: o Q1: 0 (reference) o Q2: 0.065 (-2.238, 1.385) o Q3: -1.411 (-3.330, -0.017) o Q4: -0.511 (-1.363, 0.844) Mean differences in SBP, β (95% CI): • Continuous variable for doubling of PbB: -0.099 (-1.098, 0.898) • Quartiles: o Q1: 0 (reference) o Q2: -0.255 (-1.755, 1.223) o Q3: -0.788 (-1.773, 0.651) o Q4: -0.304 (-0.682, 1.218) OR (95% CI) for having prehypertension: • Continuous variable for doubling of PbB: 0.906 (0.629, 1.305) • Quartiles: o Q1: Reference o Q2: 0.943 (0.589, 1.509) o Q3: 0.797 (0.495, 1.282) o Q4: 1.002 (0.598, 1.678)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Gump et al. 2005 Prospective study of 122 children (62 males; 66 females) at 9 years of age (born 1991–1994) in Oswego, New York	**PbB:** • Cord PbB mean (SD): 2.97 (1.75) • Child PbB (measured at 2.6 years of age) mean (SD): 4.62 (2.51) • Quartiles (child PbB): o Q1: 1.5–2.8 o Q2: 2.9–4.1 o Q3: 4.2–5.4 o Q4: 5.5–13.1 **Analysis:** Cardiovascular endpoints (blood pressure, heart rate, stroke volume, cardiac output, total peripheral resistance) were assessed at rest and following acute pressor stress (arm immersion in ice water) at age 9.5 years. Associations between PbB and endpoints were examined by multivariate linear regression models with log-transformed cord PbB to untransformed child PbB, adjusted for HOME score, SES, birth weight, BMI, and sex.	Increasing cord PbB was associated with increasing covariate-adjusted resting SBP, but not DBP. β mmHg per log µg/dL (SE): • SBP (mmHg): 12.16 (4.96); p=0.016 • DBP (mmHg): 8.45 (4.54); p=0.066 Under acute pressor stress, child PbB was associated with increased total peripheral resistance and decreased stroke volume, but not blood pressure, heart rate, or cardiac output. The study authors stated that "a negative association between blood lead levels and stroke volume suggests that lead-induced increases in vascular resistance were sufficient to produce cardiac afterload, a situation arising when blood pressure in the aorta makes it difficult for the left ventricle to eject blood." β per µg/dL (95% CI): • Total peripheral vascular resistance • (dyne-s/cm^5): 0.088 (0.024, 0.152; p=0.007). • Stroke volume (mL): -0.069 (-0.124, • -0.015); p=0.013 • SBP (mmHg): -0.009 • (-0.074, 0.055); p=0.773 • DBP (mmHg): 0.069 (-0.001, 0.138); p=0.052

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		• Heart rate (beat/minute): 0.013 (-0.046, 0.072); p=0.659 • Cardiac output (L/minute): -0.056 (-0.113, 0.001); p=0.054 Positive trend (p-trend: 0.007) for increased vascular resistance under acute pressor stress over quartiles (data presented graphically). Estimated change in vascular resistance from baseline (%): • Q1: 3.25 • Q2: 13.76 • Q3: 10.1 • Q4: 14.6

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Gump et al. 2011 Cross-sectional study of 140 children ages 9–11 years in Oswego, New York	**PbB:** Mean:1.01 Quartiles: • Q1: 0.14–0.68 • Q2: 0.69–0.93 • Q3: 0.94–1.20 • Q4: 1.21–3.76 **Analysis:** Cardiovascular responses (blood pressure, total peripheral resistance, cardiac output, and heart rate) were measured in response to acute stress (mirror tracing task). Outcomes under stress were compared to baseline measurements. Regression analyses were adjusted for sex, SES, BMI, and age.	PbB was not associated with cardiovascular baseline values. Under acute stress, associations were observed between PbB and total peripheral resistance, cardiac output, and stroke volume, but not blood pressure or heart rate. Changes under acute stress: • SBP (mmHg): p-trend=0.31 o Q1: 5.30 o Q2: 7.33 o Q3: 7.07 o Q4: 7.23 • DBP (mmHg): p-trend=0.29 o Q1: 4.02 o Q2: 5.64 o Q3: 5.09 o Q4: 5.53 • Heart rate (beats/minute): p-trend=0.85 o Q1: 0.91 o Q2: 0.19 o Q3: 0.86 o Q4: 0.58 • Stroke volume (%): p-trend=0.04 o Q1: 2.23 o Q2: 0.91 o Q3: -3.47 o Q4: -0.89

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		• Cardiac output (%): p-trend=0.05 o Q1: 3.26 o Q2: 1.19 o Q3: -2.31 o Q4: -0.20 • Total peripheral resistance (%): p-trend=0.03 o Q1: 2.91 o Q2: 8.18 o Q3: 9.55 o Q4: 9.51

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Zhang et al. 2011 Prospective longitudinal study of 457 mother-child pairs in a birth cohort born 1994–2003 in Mexico City; evaluation of children was conducted at ages 7–15 years (during 2008–2010)	**PbB:** Mean (SD) • Umbilical cord: 5.51 (3.45) • Child (concurrent): 2.96 (1.72) Maternal postpartum bone Pb median (IQR), µg/g: • Tibia 9.3 (3.3, 16.1) • Patella: 11.6 (4.5, 19.9) **Analysis:** Data were analyzed using multiple regression models and generalized estimating equations (ln-transformed cord blood, untransformed concurrent blood, and maternal bone), adjusted for maternal education, smoking during pregnancy, pregnancy nutrition, birth weight, BMI, sex, and child concurrent age.	Maternal tibia Pb was associated with increased SBP and DBP in girls, but not boys. No associations were observed between patella Pb and umbilical cord PbB with blood pressure parameters in children. β mmHg per IQ increase (95% CI) in maternal tibia Pb (13 µg/g): • SBP o Boys: -0.34 (-1.98, 1.30) o Girls: 2.11 (0.69, 3.52); p=0.025 • DBP o Boys: -0.83 (-2.05, 0.38) o Girls: 1.60 (0.28, 2.91); p=0.007 β mmHg per IQ increase (95% CI) in umbilical PbB (4 µg/dL): • SBP o Boys: 0.88 (-1.03, 2.80) o Girls: 0.74 (-1.18, 2.67) • DBP o Boys: 0.65 (-1.97, 3.27) o Girls: 0.84 (-0.40, 2.09)
Blood pressure and hypertension during pregnancy		
Disha et al. 2019 Cross-sectional study of 44 healthy pregnant women (mean age: 24.54 years) and 23 pre-eclamptic women (mean age: 27.34); data collection period: February–October 2017	**PbB:** Mean (range) • Control: 2.38 (0.16–10.12) • Pre-eclampsia: 3.42 (1.28–8.6); p=0.013 **Analysis:** The relationship between PbB and SBP and DBP was analyzed by Pearson correlation. No adjustments were reported.	PbB was positively associated with SBP and DBP in women with pre-eclampsia. Pearson correlation: • SBP (mmHg): 0.71; p<0.0001 • DBP (mmHg): 0.57; p=0.004

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Rothenberg et al. 2002 Longitudinal study of 667 pregnant women (ages 15–44 years) in Los Angeles during the period 1995–2001	**PbB:** Mean (SD) • 3rd trimester: 1.9 • Postpartum: 2.3 Bone Pb (µg/g) mean • Tibia: 8.0 • Calcaneus: 10.7 **Analysis:** Measurements of sitting blood pressure and PbB were made during the 3rd trimester and at 10 weeks postpartum. Data were analyzed by multiple regression analysis with ln-transformed PbB and adjusted for age, BMI, parity, postpartum hypertension, tobacco smoking, and education.	An association was observed between calcaneus Pb, but not tibia Pb or PbB, and increased blood pressure and hypertension in the 3rd trimester. β (95% CI) for 3rd trimester measurements: • Ln-transformed PbB o SBP: -0.04 (-1.26, 1.18) o DBP: 0.20 (-0.78, 1.18) o Hypertension: 0.75 (0.21, 2.65) • Tibia Pb o SBP: 0.07 (-0.62, 0.77) o DBP: 0.18 (-0.38, 0.74) o Hypertension: 0.98 (0.92, 1.04) • Calcaneus Pb o SBP: 0.70 (0.04, 1.36) o DBP: 0.54 (0.01, 1.08) o Hypertension: 1.86 (1.04, 3.32) Associations were observed between ln PbB and blood pressure measures, β (95% CI), for the postpartum period, but not for tibia or calcaneus Pb: • PbB o SBP: -1.52 (-2.83, -0.20) o DBP: -1.67 (-2.85, -0.50)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Wells et al. 2011 Cross-sectional study of 285 pregnant women (mean age 26 years) during labor in Baltimore, Maryland	**PbB:** Umbilical cord • Mean: 0.66 • Quartiles: o Q1: <0.46 o Q2: 0.47–0.65 o Q3: 0.66–0.95 o Q4: 0.96–6.47 **Analysis:** Blood pressure was measured at admission, throughout labor, and at delivery. Data (blood pressure at admission and maximum blood pressure during labor/delivery) were analyzed by multivariable linear regression, adjusted for maternal age, maternal race, neighborhood median household income, primiparity, smoking during pregnancy, prepregnancy BMI, and anemia. BMD analysis was also conducted to estimate the PbB BMD and the associated lower confidence limit (BMDL) that was associated with 1 SD increase in blood pressure.	SBP and DBP recorded at admission and maximum values reached were elevated in Q1 compared to Q4. Change in blood pressure in mmHg (95% CI): • Admission SBP: o Q1: reference o Q2: 2.89 (-2.16, 7.94) o Q3: 1.05 (-4.04, 6.14) o Q4: 6.87 (1.51, 12.21); p<0.05 o p-trend: 0.033 • Admission DBP: o Q1: reference o Q2: 0.00 (-3.95, 3.96) o Q3: 0.81 (-3.17, 4.80) o Q4: 4.40 (0.21, 8.59); p<0.05 o p-trend: 0.036 • Maximum SBP: o Q1: reference o Q2: 2.47 (-3.08, 8.02) o Q3: -1.76 (-7.36, 3.85) o Q4: 7.72 (1.83, 13.60); p<0.05 o p-trend: 0.055

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		• Maximum DBP: o Q1: reference o Q2: 3.93 (-2.86, 10.72) o Q3: -0.42 (-7.27, 6.43) o Q4: 8.33 (1.14, 15.53); p<0.05 o p-trend: 0.086 BMDL (µg/dL) associated with 1 SD increase in blood pressure: • Admission SBP: 1.42 • Admission DBP: 1.43 • Maximum SBP: 1.41 • Maximum DBP: 1.43
Yazbeck et al. 2009 Cross-sectional study of 971 pregnant women (ages 18–45 years) in France; data collection: 2003–2005	**PbB:** Mean (SD) • Participants with PIH (n=106): 2.2 (1.4) • Participants without PIH (n=865): 1.9 (1.2); p=0.02 (compared to PIH group) **Analysis:** PbB was obtained at 24–28 weeks of gestation. Data were analyzed using multivariable logistic regression, with PIH as the dependent variable, using log_{10}-transformed PbB. Models were adjusted for maternal age, cadmium, manganese, and selenium blood levels, hematocrit, parity, BMI, gestational diabetes, education, SES, geographic residence, and smoking status during pregnancy.	PbB was associated with an increased risk of PIH. Adjusted OR (95% CI) for PIH for: • Increase of 1 log_{10} µg/dL in PbB; 3.29 (1.11, 9.74); p=0.03. • >2.30 µg/dL (<1.20 reference): 2.56 (1.05, 6.22), p=0.09

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Atherosclerosis		
Ari et al. 2011 Clinical study of 50 adult male and female non-diabetic hemodialysis patients and 48 age- and sex-matched controls (location and data collection period not reported); participants did not have known atherosclerotic disease	**PbB:** Mean (SD): • Hemodialysis patients: 0.41 (0.38) • Controls: 0.10 (0.05); p<0.001 (compared to hemodialysis patients) **Analysis:** Carotid artery intima-media thickness was assessed by carotid artery ultrasonography. Data were analyzed by multiple linear regression.	A positive association was observed between PbB concentration and greater carotid artery intima-media thickness. β mm per µg/dL (SE): 0.101 (0.040); p=0.013
Muntner et al. 2005 Cross-sectional study of 9,961 men and women (age ≥18 years) from NHANES (1999–2002)	**PbB:** • Mean (95% CI): 1.64 (1.59–1.68) • Quartiles: o Q1: <1.06 o Q2: 1.06–1.63 o Q3: 1.63–2.47 o Q4: ≥2.47 **Analysis:** Peripheral artery disease was assessed by ankle-brachial blood pressure. PbB were log-transformed and adjusted for age, sex, race/ethnicity, BMI, diabetes mellitus, smoking status, alcohol consumption, health insurance status, and education.	A positive trend over quartiles was observed for prevalence (%) of peripheral artery disease. Prevalence (SE): • Q1: 2.6 (0.6) • Q2: 3.0 (0.5) • Q3: 4.8 (0.6) • Q4: 7.7 (0.6) • p-trend: <0.001 Adjusted ORs showed a positive trend for increased risk of peripheral artery disease across quartiles and increased risk of peripheral artery disease in Q4 compared to Q1. Adjusted ORs (95% CI): • Q1: 1 (reference) • Q2: 1.00 (0.45–2.22) • Q3: 1.21 (0.66–2.23) • Q4: 1.92 (1.02–3.61) • p-trend: <0.001

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Navas-Acien et al. 2004 Cross-sectional study of 2,125 participants (≥40) from NHANES (1999–2000).	**PbB:** Mean (25th, 75th percentile): 2.07 (1.45, 2.90) Quartiles: • Q1: <1.45 • Q2: 1.45–2.07 • Q3: 2.07–2.90 • Q4: >2.90 **Analysis:** Peripheral artery disease was assessed by ankle-brachial blood pressure index. Regression models were adjusted for age, sex, race, education, BMI, alcohol intake, hypertension, diabetes, hypercholesterolemia, GFR, CRP, smoking status, and serum cotinine.	A positive trend (p=0.02) was observed across PbB quartiles for increased risk of peripheral artery disease. Adjusted ORs (95% CI); p-trend 0.02: • Q1: 1 (reference) • Q2: 1.63 (0.51, 5.15) • Q3: 1.92 (0.62, 9.47) • Q4: 2.88 (0.87, 9.47)
Heart disease and cardiac function		

Chen et al. 2017
 	
Cross-sectional study of 5,348 adults (men: 2,163; women: 3,185) aged ≥18 years (mean age 52 years) from East China; data collection period: February–June 2014
	PbB:
	Median (IQR)
	• Men
	  o With cardiovascular disease: 4.333 (2.900–6.867)
	  o No cardiovascular disease: 4.402 (2.900–6.216)
	  o p=0.63
	• Women
	  o With cardiovascular disease: 4.806 (3.407–7.1019)
	  o No cardiovascular disease: 3.700 (2.500–5.383)
	  o p<0.01
		PbB was association with an increased risk of cardiovascular disease in women, but not men, in Q3 and Q4. Over quartiles, a positive association for prevalence of cardiovascular disease and PbB were observed for women but not men.
		ORs (95% CI) for cardiovascular disease:
		• Men
		  o Q1: 1 (reference)
		  o Q2: 1.07 (0.61, 1.86)
		  o Q3: 0.55 (0.29, 1.04)
		  o Q4: 1.01 (0.58, 1.78)
		  o P-trend: 0.59
		• Women
		  o Q1: 1 (reference)
		  o Q2: 1.04 (0.62, 1.75)
		  o Q3: 1.65 (1.03, 2.66)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
	Quartiles: • Men o Q1: ≤2.900 o Q2: 2.901–4.400 o Q3: 4.401–6.248 o Q4: ≥6.249 • Women o Q1: ≤2.50 o Q2: 2.501–3.770 o Q3:3.771–5.460 o Q4: ≥5.461 **Analysis:** Cardiovascular diseases included CAD, stroke, and myocardial infarction. ORs were calculated using binary logistic regression analysis adjusted for age, current smoking, alcohol use, education level, diabetes, obesity, hypertension, hypertriglyceridemia, hypercholesterolemia, high LDL-C status, and low HDL-C status.	o Q4: 1.93 (1.22, 3.04) o p-trend: <0.01 Prevalence of cardiovascular disease (%): • Men o Q1: 5.3 o Q2: 3.8 o Q3: 3.7 o Q4: 6.5 o p-trend: 0.22 • Women o Q1: 3.9 o Q2: 4.4 o Q3: 6.9 o Q4: 10.3 o p-trend: <0.01

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Cheng et al. 1998 Longitudinal study of 775 men (age range 48–93 years; n=277 for men <65 years of age) with no history of heart disease, hypertension, or diabetes participating in the Normative Aging Study in Boston, Massachusetts; data collection period: 1991–1995	**PbB:** Mean (SD): 5.8 (3.4) Bone Pb, µg/g, mean (SD) • Tibia: 22.2 (13.4) • Patella: 30.8 (19.2) **Analysis:** Standard resting 12-lead EKG was used to assess heart conduction, IVCD, AVCD, and arrhythmia. Data were analyzed by multivariable linear and logistic models, with log-transformed bone and blood Pb, adjusted for age, alcohol intake, BMI, and DBP for the QT interval and for age, fasting glucose, and DBP for the QRS interval.	In men <65 years of age (but not ≥65 years of age), associations were observed between bone Pb, but not PbB, and a longer QT interval (mseconds). β (95% CI) mseconds per 10 µg/g increase in bone Pb or 10 µg/dL increase PbB: • Age <65 years o Tibia: 5.03 (0.83, 9.22); p=0.02 o Patella: 3.00 (0.16, 5.84); p=0.04 o PbB: -0.65 (-10.40, 9.10); p=0.90 • Age ≥65 years o Tibia: 1.41 (-0.67, 3.49); p=0.19 o Patella: 0.39 (-1.05, 1.83); p=0.60 o PbB: 5.63 (-3.79, 15.03); p=0.24

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		In men <65 years of age (but not ≥65 years of age), associations were observed between bone Pb, but not PbB, and a longer QRS interval (mseconds). β (95% CI) mseconds per 10 µg/g increase in bone Pb or 10 µg/dL PbB: • Age <65 years o Tibia: 4.83 (1.83, 7.83); p<0.01 o Patella: 2.23 (0.10, 4.36); p=0.04 o PbB: -3.49 (-10.72, 3.75); p=0.35 • Age ≥65 years o Tibia: -0.83 (-2.21, 0.56); p=0.24 o Patella: -0.11 (-1.07, 0.85); p=0.82 o PbB: 2.88 (-3.45, 9.19); p=0.37 Adjusted OR for IVCD (95% CI) for a 10 µg/g increase (age <65 years) for tibia Pb: 2.23 (1.28, 3.90); p<0.01 Adjusted OR for AVCD (95% CI) for a 10 µg/g increase (age ≥65 years) for tibia Pb: 1.22 (1.02, 1.47); p=0.03

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Eum et al. 2011 Prospective longitudinal study of 600 men (mean age at the first EKG: 66.7 years), with no previous EKG abnormalities, participating in the Normative Aging Study in Boston, Massachusetts	**PbB:** Baseline mean (SD): 5.8 (3.6) Tertiles: • T1: <4 • T2: 4–6 • T3: >6 Tibia Pb (µg/g) Baseline mean (SD): 21.6 (12.0) Tertiles: • T1: <16 • T2: 16–23 • T3: >23 Patella Pb (µg/g) Baseline mean (SD): 30.3 (17.7) Tertiles: • T1: <22 • T2: 22–23 • T3: >23 **Analysis:** EKG measured at baseline and 8 years later. Data were analyzed by repeated measures linear regression, adjusted for age, age^2, education, smoking, BMI, albumin-adjusted serum calcium, diabetes status at baseline, years between EKG tests, and QT-prolongation drugs at the time of EKG measurement.	Positive trends across tertiles were observed for QT prolongation based on tibia Pb and for atrioventricular conduction defect for tibia and patella Pb. No associations were observed for PbB. No associations were found for JT (JT=QTc-QRS duration) prolongation, intraventricular conduction defect, or arrhythmia for any lead biomarker. Adjusted ORs (95% CI) for: QT prolongation: • Tibia; p-trend=0.003 o T1: 1 (reference) o T2: 0.86 (0.39, 1.88) o T3: 2.53 (1.22, 5.25) • Patella; p-trend=0.14 o T1: 1 (reference) o T2: 2.67 (1.28, 5.56) o T3: 2.10 (0.96, 4.60) • PbB; p-trend=0.41 o T1: 1 (reference) o T2: 1.19 (0.60, 2.37) o T3: 1.31 (0.69, 2.48) Atrioventricular conduction defect • Tibia; p-trend=0.03 o T1: 1 (reference) o T2: 0.77 (0.29, 2.09) o T3: 0.23 (0.06, 0.87)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		• Patella; p-trend=0.01 o T1: 1 (reference) o T2: 0.49 (0.18, 1.31) o T3: 0.19 (0.05, 0.68) • PbB; p-trend=0.16 o T1: 1 (reference) o T2: 0.44 (0.13, 1.47) o T3: 0.52 (0.19, 1.45)
Jain et al. 2007 Longitudinal prospective study of 837 men (mean age 67 years) enrolled in Normative Aging Study in Boston, Massachusetts (1991–2001)	**PbB:** Baseline mean (SD) • Non-cases 6.2 (4.3) • Cases 7.0 (3.8) Range for cases: 1.0–20.0 Patella Pb (µg/g) baseline mean (SD) • Non-cases 30.6 (19.7) • Cases 36.8 (20.8) Range for cases: 5.0–101 Tibia Pb (µg/g) baseline mean (SD) • Non-cases 21.4 (13.6) • Cases 24.2 (15.9) Range for cases: -5–75 **Analysis:** At the follow-up visit, ischemic heart disease was defined as myocardial infarction or angina. Log-transformed data were analyzed by multivariate Cox-proportional hazard regression models, and adjusted for age, race, and serum HDL.	A 1 SD increase in PbB increased the risk of ischemic heart disease by 1.27 (95% CI: 1.01, 1.59). PbB and patella Pb were associated with increased risks of ischemic heart disease. Adjusted HRs (95% CI) per 1 log increase in Pb: • log PbB: 1.45 (1.01, 2.06); p=0.05 • Patella Pb: 2.64 (1.09, 6.37); p=0.05 • Tibia Pb: 1.84 (0.57, 5.90); p=0.31

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Jing et al. 2019 Cross-sectional study of 7,179 adults (2,592 men and 3,587 women) participating in NHANES III; data collection period 1988–1994	**PbB:** Gmean • Men: 4.10 • Women: 2.93 **Analysis:** QRS-T angle was evaluated by 12-lead EKGs. QRS-T angles were converted to degrees and stratified by tertiles. QRS-T angle tertiles for men: T1≤70.95; T2 >70.95–≤102.1; and T3: >102.1. QRS-T angle tertiles for women: T1: ≤54.95; T2: >54.95–≤82.94; and T3: >82.94. Data were analyzed using multivariate weighted logistic regression adjusted for age, race, smoking status, poverty index, blood glucose categories, and hypertension.	An increase in log PbB was associated increased odds of an abnormal QRS-T angle in men, but not in women. OR (95% CI) per increase in unit log Pb: • Men: 1.35 (1.05, 1.74) • Women: 1.05 (0.82, 1.36)
Park et al. 2009a Cross-sectional study of 613 men (mean age 67 years) enrolled in Normative Aging Study (1991–1995) in Boston, Massachusetts	**PbB:** Median (IQR): 5 (4–7) Bone Pb (µg/dL), median (IQR) • Patella: 26 (18–37) • Tibia: 19 (14–27) **Analysis:** Standard resting 12-lead EKGs were taken at the same time as subjects' bone lead and blood lead measurements. Linear regression models were adjusted for age, BMI, serum calcium, smoking status, and diabetes status.	Bone Pb, but not PbB was associated with an increased QTc interval corrected for heart rate. β (95% CI) for msecond increase per IQR: • PbB: 1.3 (-0.76, 3.36) • Patella: 2.64 (0.13, 5.15) • Tibia: 2.85 (0.29, 5.40)

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Yang et al. 2017 Prospective study of 179 adults (50.3% women) residing in Belgium; mean age at enrollment: 39.1 years; follow-up was 11.9 years after enrollment (2005–2010)	**PbB:** Gmean (at enrollment): 4.19 **Analysis:** Left ventricular systolic and diastolic function was assessed by Doppler imaging. Data were analyzed by multi-variable linear regression adjusted for sex, age, mean arterial pressure, heart rate, body mass index, fasting plasma glucose, total-to-HDL cholesterol ratio, serum creatinine, γ-glutamyl transferase, smoking, and antihypertensive treatment.	A negative association was observed between Pb and left ventricular systolic function. Left ventricular diastolic function was not associated with PbB (detailed results not reported). No association was observed between PbB and left ventricular mass. Systolic left ventricular function, β, per doubling of PbB: • Ejection fraction (%):0.150 (-1.019, 1.320); p=0.800 • Global longitudinal strain (%): -0.392 (-0.753, -0.030); p=0.034 • Regional longitudinal strain (%): -0.618 (-1.167, -0.068); p=0.028 • Regional longitudinal strain rate (per second): -0.056 (-0.097, -0.015); p=0.008 • Regional radial strain (%): -1.825 (-3.740, 0.090); p=0.062 • Regional radial strain rate (per second): -0.113 (-0.226, -0.0002); p=0.050 Left ventricular structure, β, per doubling of PbB: • Left ventricular mass (g/m^2): -1.399 (-4.504, 1.707); p=0.375 • End-diastolic diameter (cm): -0.064 (-0.134, 0.006); p=0.072 • Relative wall thickness: 0.0065 (-0.0031, 0.0162); p=0.185

Table 3. Selected Epidemiology Studies Evaluating Cardiovascular Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes

Yang et al. 2018
 	
Cross-sectional baseline assessment of 236 male lead-acid battery manufacturing and recycling workers (age 28.6 years ±9.4 SD) from a longitudinal cohort (Study for Promotion of Health in Recycling Lead United States); data collection period: 2015–2017
	PbB:
	Gmean (IQR): 4.50 (2.60–9.15)
	Quartiles:
	• Q1: <2.7
	• Q2: 2.7–4.6
	• Q3: 4.6–9.2
	• Q4: ≥9.2
	
	Analysis: Data for office and ambulatory SBP and DBP were analyzed by linear and logistic regression; adjusted for age, BMI, heart rate, smoking, mean arterial pressure, waist-to-hip ratio, total-HDL lipoprotein ratio, plasma glucose, serum γ-glutamyl transferase, and GFR_e.
		Regression (β) coefficients, expressed as change pressure (mmHg) per 2-fold increase in PbB (95% CI):
		• Office
		  o Systolic: 0.79 (-0.17, 1.76) p=0.11
		  o Diastolic: 0.87 (0.03, 1.72) p=0.043
		• 24-hour ambulatory
		  o Systolic: 0.29 (-0.82, 1.41) p=0.60
		  o Diastolic: -0.25 (-0.97, 0.48) p=0.50
		
		OR (95% CI) for hypertension:
		• Office: 0.89 (0.62–1.28); p=0.52
		• 24-hour ambulatory: 1.21 (0.94–1.57); p=0.14

Yu et al. 2019a Cross-sectional study of 328 newly hired male Pb workers (mean age: 28.3 years) from a longitudinal cohort (Study for Promotion of Health in Recycling Lead (United States); data collection period: May 2015–September 2017	**PbB:** Mean (IQR): 4.54 (2.60–8.90) **Analysis:** Heart rate variability was assessed by EKG in supine and standing positions. Data were analyzed by stepwise regression adjusted for age, heart rate (or heart rate change for orthostatic changes), mean arterial pressure, and serum insulin.	No association was observed between PbB and heart rate variability, expressed in total power (%). Regression (β) coefficients (95% CI) per 10-fold increase in PbB: • Supine position: 3.0 (-20.4, 33.0); p=0.82 • Standing position: -6.0 (-26.2, 19.7); p=0.61 • Orthostatic change: -8.8 (-31.8, 17.5); p=0.47

AH = antihypertensive; ALAD = aminolevulinic acid dehydratase; AVCD = atrioventricular conduction defect; BMD = benchmark dose; BMDL = benchmark dose limit; BMI = body mass index; CAD = coronary artery disease; CI = confidence interval; CL = confidence limit; CRP = serum C-reactive protein; DBP = diastolic blood pressure; EKG = electrocardiogram; GFR = glomerular filtration rate; Gmean: geometric mean; HDL = high-density lipoprotein cholesterol; HOME = Home Observation for Measurement of the Environment; HR = hazard ratio; IQ = intelligence quotient; IQR = interquartile range; IVCD = intraventricular conduction defect; LDL = low density lipoprotein cholesterol; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PIH = pregnancy-induced hypertension; POR = prevalence odds ratio; RR = relative risk or rate ratio; SBP = systolic blood pressure; SD = standard deviation; SE = standard error; SES = socio-economic status

Table 4. Selected Epidemiology Studies Evaluating Hematological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Ahamed et al. 2005 Cross-sectional study of 62 children (ages 4–12 years) from Lucknow, India	**PbB:** Mean (SD) • Group 1 (n=17): 3.93 (0.61) • Group 2 (n=27): 7.11 (1.25) **Analysis:** Student's t-test was used to compare group means.	No difference (p=0.4948) in blood δ-ALAD activity was observed between groups 1 and 2. Mean (SD), µmol δ-ALA/minute/L blood: • Group 1: 4.82 (1.25) • Group 2: 4.56 (1.20)
Ahamed et al. 2006 Cross-sectional study of 39 adolescent males (ages 15–18 years) from Lucknow, India	**PbB:** Mean (SD): 9.96 (3.63) Range: 4.62–18.64 **Analysis:** Data were analyzed by linear regression. No adjustments were reported.	A negative correlation was observed between PbB and blood δ-ALAD activity (r=-0.592; p<0.001).
Chen et al. 2019 Cross-sectional study of 158 adults (mean age: 44 years) living near an electronic waste area in China and 109 controls (mean age: 47 years); data collection period: January 2015–March 2015	**PbB:** Median (P_{25}, P_{75}) • Control: 5.1 (3.9, 8.4) • Exposed: 8.7 (6.2–12.2) • p=0.001 **Analysis:** To compare variables between groups, data were analyzed by Student's t-tests and Chi-square. No adjustments were reported.	Hemoglobin and RBC count were significantly increased compared to controls. Hemoglobin (g/dL), median (P_{25}, P_{75}): • Control: 123.0 (107.0, 143.0) • Exposed: 137.0 (119.5, 150.0), p=0.001 RBC count (x10^3), median (P_{25}, P_{75}): • Control: 4.2 (3.5, 4.6) • Exposed: 4.5 (4.1, 4.8), p=0.001

Table 4. Selected Epidemiology Studies Evaluating Hematological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Conterato et al. 2013 Cross-sectional of 50 painters and 36 controls from Brazil	**PbB:** Mean (SE); range • Control: 1.5 (0.1); 0.4–3.0 • Painters: 5.4 (0.4); 1.4–14.0 **Analysis:** Data were analyzed by one-way ANOVA.	Differences between controls and painters were observed for Hct, Hb, RBC count, and platelet count. Mean (SE): Hct (%) • Control: 45.3 (0.5) • Painters: 43.8 (0.4); p<0.05 Hb (g/dL) • Control: 15.4 (0.2) • Painters: 15.0 (0.1); p<0.05 RBC count ($1x10^6$/µL) • Control: 5.2 (0.7) • Painters: 5.0 (0.5); p<0.05 MCV (fL) • Control: 86.9 (0.6) • Painters: 87.9 (0.5) MCH (ρg) • Control: 29.6 (0.2) • Painters: 30.0 (0.2) MCHC (g/dL) • Control: 34.1 (0.1) • Painters: 34.2 (0.1) Platelet count ($1x10^3$/µL) • Control: 244.3 (8.3) • Painters: 203.7 (6.5); p<0.05

Table 4. Selected Epidemiology Studies Evaluating Hematological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Ergurhan-Ilhan et al. 2008 Cross-sectional study of 25 male automotive repair workers (mean age 16.8 years) and 24 male controls (mean age 16.3 years) from Isparta, Turkey	**PbB:** Mean (SD) • Controls: 2.6 (2.0) • Workers: 7.9 (5.2) **Analysis:** Data were analyzed using non-parametric Mann-Whitney U-test.	Differences between controls and workers were observed for ALAD index and ZPP:heme ratio (µmol ZPP/mol heme). ALAD index • Controls: 0.40 (0.34) • Workers: 0.73 (0.47); p=0.048 ZPP:heme ratio • Controls: 26.4 (7) • Workers: 37.2 (15.9); p=0.045
Liu et al. 2015a Cross-sectional study of 855 children (age range: 3–7 years; males: 469; females: 386) from China	**PbB:** • Median: 7.33 • Quartiles: o Q1: 2.20–5.16 o Q2: 5.16–7.33 o Q3: 7.33–10.62 o Q4: 10.62–37.78 Erythrocyte Pb (µg/dL) • Median: 19.30 o Q1: 5.98–13.52 o Q2: 13.52–19.35 o Q3: 19.35–28.42 o Q4: 28.42–101.01 **Analysis:** Data were analyzed by multivariate linear regression adjusted for age, sex, residence area, and SES.	Erythrocyte Pb, but not PbB, was negatively associated with blood Hb. Change in Hb in g/L (95% CI) from Q1: PbB • Q2: -0.63 (-2.35, 1.10) • Q3: 0.78 (-0.95, 2.51) • Q4: 1.45 (-0.28, 3.18) Erythrocyte Pb • Q2: -0.02 (-1.89, 1.52) • Q3: -3.01 (-4.71, 1.31); p<0.05[a] • Q4: -3.97 (-5.68, -2.27); p<0.05 A doubling of erythrocyte Pb was associated with a -2.44 g/L (-2.01, -2.86; p<0.05) decrease in Hb level.

Table 4. Selected Epidemiology Studies Evaluating Hematological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Olivero-Verbel et al. 2007 Cross-sectional study on 189 children (ages 5–9 years; 99 boys and 90 girls) from Cartagena, Columbia	**PbB:** Mean (SE): 5.49 (0.23) Range: <1.0–21.0 **Analysis:** Associations between PbB and hematological variables were evaluated by Spearman correlation analysis.	Negative associations were observed between PbB and MCV and MCH, but not Hb, MCHC, or erythrocyte count. Spearman correlation coefficients: • Hb: 0.069; p=0.348 • MCV: -0.159; p=0.029 • MCH: -0.171; p=0.019 • MCHC: -0.096; p=0.188 • Erythrocyte count: 0.208; p=0.004
Queirolo et al. 2010 Cross-sectional study of 222 children (age 5–45 months) from Uruguay	**PbB:** Mean (SD): 9.0 (6.0) Range: 1–35.6 **Analysis:** Data were analyzed by multiple linear regression. Data were adjusted for age and finger/ toy mouthing behavior.	Blood Hb <10.5 g/L was a significant predictor of PbB. β (95% CI): 2.40 (0.77, 4.03); p<0.01. It was also a significant predictor of likelihood to have elevated PbB (>10 µg/dL). OR (95% CI): 1.90 (1.08, 3.35); p<0.05.
Riddell et al. 2007 Cross-sectional study of 2,861 children (age 6 months–5 years)	**PbB:** Mean: 6.9 **Analysis:** PbB data were logarithmically transformed. Data on associations between PbB and Hb were analyzed by linear regression.	Blood Hb concentration was inversely associated with PbB. A 1 g/dL increase in PbB was associated with a 3% decrease in Hb (95% CI: 1, 5%; p=0.043).
Sakata et al. 2007 Cross-sectional studies of male tricycle taxi drivers (n=27) and age-matched non-drivers (n=9) from Kathmandu, Japan	**PbB:** Mean (SD); range • Non-drivers: 2.4 (1.1); 1.8–5.3 • Drivers: 6.4 (2.2); 1.9–11.9 (p<0.0001, compared to non-drivers) **Analysis:** Means between drivers and non-drivers were compared using Student's t-test.	Serum EPO in drivers was lower than in non-drivers, serum EPO, mean (SD), mU/mL: • Non-drivers:18.8 (4.6) • Drivers: 12.7 (3.5); p<0.01, compared to non-drivers There was no difference in other hematologic parameters (hematocrit or blood hemoglobin parameters) between drivers and non-drivers.

Table 4. Selected Epidemiology Studies Evaluating Hematological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Ukaejiofo et al. 2009 Cross-sectional study of male Pb workers (n=81) and controls (n=30) from Nigeria (ages 16–65 years) who were exposed between 6 months and 20 years	**PbB:** Mean (SD) • Controls: 3.00 (0.19) • Workers: 7.00 (0.07); p<0.05 compared to control **Analysis:** Statistical methods used to compare means between workers and controls were not reported.	Blood Hb and packed cell volume, but not MCHC, were lower in workers compared to controls. Mean (SD): Hemoglobin (g/dL): • Controls: 12.96 (0.089) • Workers: 12.05 (1.62); p<0.001 Packed cell volume (%): • Controls: 39.73 (0.24) • Workers: 37.97 (5.15); p<0.05 MCHC (g/L): • Controls: 32.94 (1.87) • Workers: 32.58 (1.32)

Wang et al. 2010
 	
Cross-sectional study of 307 children (ages 4–13 years) and 391 adults (ages 16–77 years) from China
	PbB:
	• All participants
	  o Mean (SD): 6.71 (0.17)
	  o Range: 1.09–51.4
	• Children mean (SD): 7.86 (0.16)
	• Adults mean (SD): 6.43 (0.17)
	
	Analysis: PbB data was logarithmically transformed. Data on associations between PbB and blood δ-ALAD and ZPP concentration in blood were evaluated by Pearson correlation analysis. Linear regression was also used to further investigate PbB with ALAD and ZPP (both natural-log transformed). Regression analyses were adjusted for age, sex, and alcohol consumption and smoking status (for adults only).
		Negative associations were observed between PbB and blood δ-ALAD activity in children and adults. Pearson correlation coefficients:
		• Children: -0.256; p<0.05
		• Adults: -0.213; p<0.05
		
		Positive associations were observed between PbB and ZPP (concentration in blood) for children and adults. Pearson's correlation coefficients:
		• Children: -0.256; p<0.05
		• Adults: -0.213; p<0.05

Table 4. Selected Epidemiology Studies Evaluating Hematological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Zentner et al 2006 Cross-sectional study of 55 newborns from Brazil	**PbB:** Umbilical PbB mean (SD): 3.9 (3.6) **Analysis:** Data were analyzed by Pearson's correlation. No information on adjustments was reported.	No association was observed between cord PbB and blood Hb. Pearson correlation coefficient: -0.04; p=0.721.

[a]The discrepancy between the 95% confidence limits and the p-value appears to be caused by an error in the reporting of the upper confidence limit. (i.e., -1.31, rather than 1.31).

δ-ALA: delta-aminolevulinic acid; δ-ALAD = delta-aminolevulinic acid dehydratase; ALAD index = log(active δ-ALAD/non-activated δ-ALAD); ANOVA = analysis of variance; CI = confidence interval; EPO = serum erythropoietin; Hb = hemoglobin; Hct = hematocrit; MCH = mean corpuscular hemoglobin; MCHC = mean cell hemoglobin concentration; MCV = mean corpuscular volume; Pb = lead; RBC = red blood cell; SD = standard deviation; SE = standard error; SES = socioeconomic status; ZPP = zinc-protoporphyrin

Table 5. Epidemiology Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Effects on bone		
Khalil et al. 2008 Prospective cohort study of 533 women (age range: 65–87 years) enrolled in the Study of Osteoporotic Fractures in Baltimore, Maryland and Monongahela Valley, Pennsylvania; data collection period: 1988–1994	**PbB:** Mean (SD): 5.3 (2.3) Range: 1–21 Tertiles: • T1 (n=122): ≤3 (reference) • T2 (n=332): 4–7 • T3 (n=79): ≥8 **Analysis:** Baseline calcaneus BMD was measured in 1988–1990, with follow-up measurements 1993–1994. PbB was measured 1990–1991. Multivariate analysis of annualized percentage of bone loss was adjusted for age, clinic, BMI, weight change between visit 2 and visit 4, smoking, chair stands, fracture history, estrogen use, and baseline BMD. HRs for non-spine fractures were adjusted for age, clinic, education, BMI, alcohol use, baseline total hip BMD, fractures after age 50, health status, fall in past year, smoking, estrogen use, calcium and vitamin D use, grip strength, reaction time lower limb, groove pegboard score, vibration and touch, visual acuity, walk speed, chair stands, and trail making B score.	A trend for increased percentage rate of bone loss with increased PbB was observed. Annualized percentage of calcaneus bone loss (95% CI): • T1: -1.01 (-1.27, -0.74) • T2: -1.41 (-1.57, -1.24) • T3: -1.49 (-1.86, -1.10) • p-trend: 0.03 The risk of non-spine factures was increased in T3 compared to T1. Adjusted HR (95% CI): • T1: 1 (reference) • T2: 1.13 (0.65, 1.95) • T3: 2.50 (1.25, 5.03) • p-trend: 0.016
Lee and Park 2018 Cross-sectional study of 443 adults (223 men and 221 women; ages 39–69 years) participating in the KARE cohort; data collection period: 2001–2002	**PbB:** Gmean (GSD): 4.44 (1.80) **Analysis:** BMD was measured at the distal radius and midshaft tibia. Data were analyzed by linear regression adjusted for age, sex, regional area, income, and activity.	BMD was negatively associated with PbB. Regression coefficient, β (SE), for BMD: -1.27 (0.48); p<0.01

Table 5. Epidemiology Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Machida et al. 2009 Cross-sectional study of 1,225 female Japanese farmers; data collection period: 2000–2001	**PbB:** Median (maximum) • Premenopausal (n=261): 1.6 (4.4) • Perimenopausal (n=319): 2.0 (7.9) • Younger postmenopausal (n=387): 1.8 (6.0) • Older postmenopausal (n=248): 1.7 (7.1) **Analysis:** Spearman correlations analysis to assess univariate associations for biochemical biomarkers of bone metabolism (BALP, OC, NTx, and BMD) were analyzed.	PbB was positively associated with markers of bone metabolism in all women and in peri-menopausal women. Spearman's correlation coefficients: • All women o BALP: 0.143 (p=0.000) o OC: 0.191 (p=0.000) o NTx: 0.181 (p=0.000) o BMD: -0.016 (p=0.570) • Perimenopausal women o BALP: 0.234 (p=0.000) o OC: 0.391 (p=0.000) o NTx: 0.261 (p=0.000) o BMD: -0.101 (p=0.071)

Table 5. Epidemiology Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Nelson et al. 2011 Cross-sectional study of 329 males (mean age: 65 years and 342 females (mean age: 62 years) from North Carolina; data collection period 2003–2008	**PbB:** Median (range) • Males: 2.2 (0.5–25.1) • Females: 1.9 (0.5–25.4) **Analysis:** Biochemical biomarkers of joint tissue metabolism (uNTX-I, uCTX-II, serum C2C, serum CPII, serum HA, and serum COMP) were natural log-transformed for analyses. Data were analyzed by multiple linear regression models, adjusted for age, race, current smoking status, and BMI.	In males, correlations were observed between PbB and COMP. In females, correlations were observed between PbB and uNTX-I and uCTX-II. Results are consistent with non-mineralized cartilage turnover in men and increased bone turnover and mineralized cartilage turnover in women. β (95% CI), change in biomarker level per 5 µg/dL increase in PbB: • Males o uNTX-I: 1.06 (0.95, 1.18) o uCTX-II: 1.07 (0.97, 1.18) o C2C (65 years): 1.00 (0.94, 1.04) o CPII: 0.99 (0.93, 1.05) o HA: 1.01 (0.88, 1.05) o COMP: 1.08 (1.00, 1.18) • Females o uNTX-I: 1.45 (1.21, 1.74) o uCTX-II: 1.28 (1.04, 1.58) o C2C (65 years): 1.00 (0.92, 1.08) o CPII: 1.09 (0.97, 1.22) o HA: 0.96 (0.71, 1.29) o COMP: 0.96 (0.87, 1.06)
Pollack et al. 2013 Cross-sectional study of 249 premenopausal women (ages 18–44 years) from Buffalo, New York; data collection period: 2005–2007	**PbB:** Mean (SD): 1.03 (0.64) **Analysis:** PbB was natural log-transformed in analyses. Data were analyzed by linear regression, adjusted for age, BMI, race, parity, average caloric intake, and age at menarche.	PbB was not associated with whole-body bone mineral density. β (95% CI), per log-unit increase in PbB: 0.004 (-0.029, 0.020). PbB was not associated with total hip, lumbar spine, or wrist bone mineral density either.

Table 5. Epidemiology Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Periodontal and dental effects		
Arora et al. 2009 Cross-sectional study of 333 men (age range: 50–94 years) enrolled in the Normative Aging Study in Boston, Massachusetts; data collection period: 1992–1994	**PbB:** Mean (95% CI) • 0 tooth loss: 5.3 (4.3–6.2) • 1–8 lost teeth: 6.2 (5.5–6.9) • ≥9 lost teeth: 6.3 (5.5–7.0) Tertiles • T1: ≤4.0 (reference) • T2: 4.2–6.4 • T3: 7.0–35.0 Bone Pb (µg/dL/g) Tertiles for tibia • T1: ≤15.0 (reference) • T2: 16.0–23.0 • T3: 24.0–96.0 Tertiles for patella • T1: ≤22.0 (reference) • T2: 23.0–36.0 • T3: 37.0–126.0 **Analysis:** Proportional odds models were used to estimate associations between PbB or bone Pb and tooth loss. Multivariate ORs were adjusted for age, smoking status, education, and diabetes.	Tooth loss was associated with bone Pb concentration, but not PbB. Adjusted ORs (95% CI) for tooth loss: PbB: • T1: 1 • T2: 0.86 (0.49, 1.50) • T3: 0.88 (0.52, 1.50) • p-trend: 0.57 Tibia Pb: • T1: 1 • T2: 1.81 (1.02, 3.18) • T3: 3.03 (1.60, 5.76) • p-trend: 0.001 Patella Pb: • T1: 1 • T2: 1.32 (0.75, 2.32) • T3: 2.41 (1.30, 4.49) • p-trend: 0.005

Table 5. Epidemiology Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Dye et al. 2002 Cross-sectional study in 10,033 participant (5,255 females and 4,778 males) in NHANES III (1988–1994); age range: 20–69 years	**PbB:** Mean (SE) • All participants: 2.5 (0.08) • Males: 3.3 (0.12) • Females: 1.9 (0.05) **Analysis:** Periodontal bone loss was analyzed by linear regression using log_{10} transformed PbB, adjusted for age, sex, race/ethnicity, education, SES, age of home, smoking, and dental furcation.	• Log PbB was associated with an increasing presence of dental furcation. β (SE): 0.13 (0.05); p=0.005
Gemmel et al. 2002 Cross-sectional study of 498 children (age range: 6–10 years) from rural (n=239) and urban (n=259) settings from Boston/ Cambridge, Massachusetts (urban) and Farmington, Maine (rural); data collection period not reported	**PbB:** Mean (SD) • Overall: 2.3 (1.7) • Rural: 1.7 (1.0) • Urban: 2.9 (2.0) **Analysis:** Natural log-transformed number for decayed and filled surfaces (lnDFS) was the primary outcome of interest. Data were analyzed by simultaneous multiple regression models using natural ln-transformed PbB, adjusted for sex, race/ethnicity, SES, maternal smoking, maternal education, and various dental hygiene variables.	PbB was positively associated with number of caries among urban children: regression coefficient (SE) ln of number per 1 ln µg/dL in blood Pb: • Rural: -0.15 (0.09); p=0.09 • Urban: 0.22 (0.08); p=0.005

Table 5. Epidemiology Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Kim and Lee 2013 Cross-sectional of 3,966 adults (≥20 years of age) participating in the Korea National Health and Nutrition Survey (2008–2009)	**PbB:** Mean (SE): • Men o No periodontitis: 2.625 (0.028) o Periodontitis: 3.118 (0.057); p<0.001 • Women o No periodontitis: 1.906 (0.025) o Periodontitis: 2.222 (0.052); p<0.001 **Analysis:** ORs for periodontitis were calculated for log-transformed PbB, adjusted for BMI, residence area, education level, household income, smoking and drinking status, hemoglobin, glucose, use of floss or interproximal toothbrush, decayed, missing, or filled permanent teeth, active caries, other blood metals, and menopausal status for women.	PbB was associated with an increased risk of having periodontitis in men but not women. OR (95% CI), per doubling of PbB: • Men: 1.699 (1.154, 2.503) • Women: 1.242 (0.833, 1.850) In the urban subgroup, children with PbB ≥4 µg/dL had, on average, two more carious surfaces than those with PbB ≤1µg/dL.
Kim et al. 2017a Cross-sectional study of 2,805 school-aged (age range: ≤9–≥12 years) children participating in the Children's Health and Environment Research group in South Korea; data collection period: 2005–2010	**PbB:** Gmean (GSD): 1.53 (1.57) Range: 0.11–4.89 **Analysis:** PRs for teeth with dental caries, filled surfaces, and combined dental caries and filled surfaces for deciduous and permanent teeth were determined using the Poisson zero-inflated negative binomial model, adjusted for gender, age, household income, and urinary cotinine level.	PbB was associated with increased prevalence of combined dental caries and filled deciduous teeth, but not permanent teeth. PR (95% CI): • Deciduous teeth o Dental caries: 1.16 (0.91, 1.49) o Filled teeth: 1.11 (0.98, 1.25) o Combined caries and filled: 1.14 (1.02, 1.27) • Permanent teeth o Dental caries: 0.69 (0.45, 1.07) o Filled teeth: 0.87 (0.73, 1.04) o Combined caries and filled: 0.83 (0.69, 0.99)

Table 5. Epidemiology Studies Evaluating Musculoskeletal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Moss et al 1999 Cross-sectional study of 24,901 participants (2–5 years: n=3,547; 6–11 years: n=2,894; ≥12 years: n=18,460) in NHANES III (1988–1994)	**PbB:** Mean (SE): • Age 2–5 years: 2.9 (0.12) • Age 6–11 years: 2.1 (0.08) • Age 12–17 years: 2.4 (0.06) **Analysis:** Prevalence of dental caries was analyzed by logistic regression using log-transformed PbB, adjusted for age, sex, race/ethnicity, poverty income ratio, exposure to cigarette smoke, geographic region, educational level of head of household, carbohydrate and calcium intakes, and dental visits.	There was a significant association between log-transformed PbB and caries status among all age groups. β (SE): • DFS o 2–5 years: 1.78 (0.59), p=0.004 o 6–11 years: 1.42 (0.51), p=0.007 • DFS o 6–11 years: 0.48 (0.22), p=0.003 o ≥12 years: 2.50 (0.69), p<0.001 • DMFS o ≥12 years: 5.48 (1.44), p<0.001 An increase in PbB of 5 µg/dL was associated with increased dental caries in children aged 5–17 years. Adjusted OR: 1.8 (95% CI 1.3, 2.5).

BALP = bone-specific alkaline phosphatase; BMD = bone mineral density; BMI = body mass index; C2C = cleavage neoepitope of type II collagen; CI = confidence interval; COMP = cartilage oligomeric matrix protein; CPII = type II procollagen synthesis C-propeptide; DFS = decayed filled surface; DMFS = decayed, missing, filled surface; Gmean: geometric mean; GSD: geometric standard deviation; HA = hyaluronic acid; HR = hazard ratio; KARE = Korean Association REsource; NHANES = National Health and Nutrition Examination Survey; NTx = N-telopeptide cross-linked collagen type I; OC = osteocalcin; OR = odds ratio; Pb = lead; PR = prevalence ratio; SD = standard deviation; SE = standard error; SES = socio-economic status; uCTX-II = C-telopeptide urine fragments of type II collagen; uNTX-I = urine cross-linked N telopeptide of type I collagen

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Åkesson et al. 2005 Population-based cross-sectional study of 820 adult women (ages 53–64 years) in Sweden; data collection period was June 1999 through January 2000	**PbB:** • Median: 2.2 (95% CI: 1.1, 4.6) • 10^{th}–90^{th} percentile: 1.3–3.8 **Analysis:** GFR was calculated using cystatin C data. Markers of renal function were analyzed by linear regression analysis, adjusted for age, BMI, diabetes, hypertension, regular use of nephrotoxic drug, smoking status, and urinary cadmium.	Spearman's rank correlation coefficients: • GFR (mL/minute): -0.11 (p≤0.05) • SCr (µmol/L): 0.13 (p≤0.001) • UPHC (µg/L) -0.01 • UNAG (U/g creatinine): 0.02 • CCr: -0.13 (p≤0.001) Linear regression β coefficients (µg Pb/L): • GFR: -0.20 (95% CI: -0.32, -0.09) • CCr: -0.18 (95% CI: -0.30, -0.06) • UPHC: reported as NS • UNAG: reported as NS
Barry et al. 2019 Cross-sectional study of 211 adult men (median age: 61.9 years) residing near New York City; data collection period not specified	**PbB:** Median (range): 2.5 (0–34.0) Quartiles: • Q1: <1.6 • Q2: 1.6–2.5 • Q3: 2.6–4.2 • Q4: ≥4.3 **Bone (tibia) Pb (µg Pb/g):** Median (range): 13.8 (0–127.3) Bone Pb quartiles: • Q1: <9.6 • Q2: 9.6–13.7 • Q3: 13.8–19.5 • Q4: ≥19.6 **Analysis:** GFR was calculated using urine creatinine, serum creatinine, and serum cystatin C. PbB data were analyzed by linear regression continuous models, adjusted for age, smoking pack years, race, and BMI.	No associations were observed between PbB or bone Pb and GFR. Linear regression coefficients (SE): PbB: • Q1: reference • Q2: 3.70 (4.02); p=0.36 • Q3: -1.93 (4.33); p=0.66 • Q4: -2.71 (4.16); p=0.52 • Continuous: -0.13 (0.28); p=0.65 Bone Pb: • Q1: reference • Q2: 2.60 (4.19); p=0.54 • Q3: 2.13 (4.30); p=0.62 • Q4: -5.66 (4.86); p=0.25 • Continuous: -0.15 (0.11); p=0.18

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
de Burbure et al. 2006 Cross-sectional study of >800 children (ages 8.5–12.3 years) from France, Poland, and the Czech Republic living near nonferrous smelters; exposed children lived near smelters for at least 8 years; control children did not live near smelters	**PbB (mean±SD):** • France o Control: (M) 3.42±0.19; (F) 2.81±0.19 o Exposed: (M) 4.21±0.20; (F) 3.64±0.17 • Poland o Control: (M) 3.81±0.15; (F) 3.42±0.14 o Exposed: (M) 6.51±0.17; (F) 5.72±0.15 • Czech Republic o Control: (M) 3.61±0.14; (F) 3.40±0.13 o Exposed: (M) 4.99±0.15; (F) 4.06±0.15 **Analysis:** Data for SCr and Sβ2M were analyzed by multiple regression analysis and ANOVA, adjusted for sex, cadmium, mercury, urinary creatinine, and interactions with cadmium and mercury.	PbBs in all exposed groups were higher than controls (p<0.05). PbB >5.59 µg/dL (mean 7.84 µg/dL): SCr (mg/100 mL) was decreased by approximately 7% (p<0.01; data presented graphically), compared to the lowest PbB quartile (<2.85 µg/dL). PbB >5.86 µg/dL (mean 7.84 µg/dL): Sβ2M (µg/L) was decreased by approximately 9% (p<0.001; data presented graphically), compared to the lowest quartile (<3.10 µg/dL).
Fadrowski et al. 2010 Cross-sectional study of 769 U.S. adolescents (ages 12–20 years) participating in the NHANES III study; data collection period was 1988–1994	**PbB:** • Median: 1.5 • Quartiles o Q1: <1.0 o Q2: 1.0–1.5 o Q3: 1.6–2.9 o Q4: >2.9 **Analysis:** Data for GFR (estimated by serum cystatin C or SCr) were analyzed by linear regression adjusted for age, sex, race/ethnicity, urban versus rural residence, tobacco smoke exposure, obesity, annual household income, and educational level of family reference person.	GFR (mL/minute/1.73 m^2) difference (cystatin C) β (95% CI) • Q1: 1 • Q2: -1.4 (-7.4, 4.5) • Q3: -2.6 (-7.3, 2.2) • Q4: -6.6 (-12.6, -0.7) • p-trend: 0.009 Mean difference in GFR associated with a 2-fold increase in blood lead level: -2.9 (-5.0, -0.7) GFR difference (creatinine): • Q1: 1 • Q2: -0.5 (-6.1, 5.1) • Q3: -1.7 (-6.9, 3.5) • Q4: -1.9 (-7.4, 3.5) • p-trend: 0.31

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Harari et al. 2018 Prospective cohort study of 2,567 adults (women: 60%) in Sweden; baseline data collected 1991–1994; 16-year follow-up data collected 2007–2012; mean age at baseline: 57 years; mean age at follow-up: 73 years	**PbB:** Median at baseline (range): 2.5 (0.15–25.8) Quartiles (range): • Q1: 1.5 (0.15–1.85) • Q2: 2.2 (1.85–2.47) • Q3: 2.9 (2.47–3.30) • Q4: 4.6 (3.30–25.8) Analysis: GFR was estimated by combined serum creatinine and cystatin C. Data were analyzed by multivariable-adjusted linear regression analysis, adjusted for age, sex, smoking, alcohol intake, hypertension, diabetes mellitus, waist circumference, corresponding GFR at baseline, and education level. Associations between PbB and CKD were analyzed by Cox proportional hazards regression, adjusted for age, sex, smoking, alcohol intake, hypertension, diabetes mellitus, waist circumference, education level, and baseline GFR.	At the 16-year follow-up assessment, mean GFR for Q1 was decreased from 89 to 62 mL/minute from baseline values. Additional decreases in GFR, mL/minute/1.73 m^2, (95% CI), per quartile: • Q1: reference • Q2: -1.2 (-2.6, 0.16); p<0.08 • Q3: -2.6 (-4.0, -1.2); p<0.001 • Q4: -2.3 (-3.8, -0.85); p=0.002 • p-trend: <0.001 HRs (95% CI) for CKD show an association between PbB and CKD for Q4 relative to combined Q1–Q3: <u>Versus Q1</u> • Q1: 1 (reference) • Q2: 0.83 (0.54, 1.28); p=0.4 • Q3: 0.83 (0.53, 1.29); p=0.4 • Q4: 1.30 (0.85, 2.00); p=0.2 <u>Versus Q1–Q3</u> • Q1–Q3: 1 (reference) • Q4: 1.49 (1.07, 2.08); p=0.02
Khan et al. 2010a Cross-sectional study of 123 children (ages 1–6 years) of Pb-workers and 123 age- and sex-matched controls from Pakistan; data collection period not specified	**PbB:** Median (range) • Control: 6.7 (1.4–13.3) • Exposed: 8.10 (1.0–20.9); p<0.01 **Analysis:** Comparison of serum creatinine levels between groups was conducted using Mann-Whiney test. Data also were analyzed by Spearman's correlation.	Serum creatinine (µmol/L): • Control: 52 • Exposed: 56; p≤0.01 Spearman's correlation coefficient: r=0.13; p≤0.05

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Kim et al. 1996a Retrospective cohort study of 459 men participating in the Normative aging study; data collection period was 1979–1992	**PbB:** • Mean±SD: 9.9±6.1 • Range: 0.2–54.1 **Analysis:** Multivariate model was adjusted for age at initial visit, time elapsed since initial visit, BMI, current smoking status, daily alcohol consumption, educational level, and hypertension. The multivariate model for change In SCr (from the current to the next visit) included time elapsed from the current to the next visit and current SCr.	PbB was associated with increased concurrent SCr concentration. SCr (µmol/L) for all participants: • Regression coefficient (SE): 0.033 per mg/dL (0.012); p=0.005 SCr (µmol/L) for participants with PbB ≤10 µg/dL: • Regression coefficient (SE): 0.060 per mg/dL (0.019); p=0.002
Lin et al. 2001 Prospective, longitudinal study of Taiwanese patients (ages 18–70 years) 110 [n=55 in "low" body Pb burden group (<80 µg); n=55 in "high-normal" body Pb group (≥80–<600 µg)] with chronic renal insufficiency	**PbB:** • Low Pb (Pb body burden <80 µg) o Mean±SD: 3.9±1.0 o Range: 1.0–7.9 • High Pb (Pb body burden ≥80–<600 µg) o Mean±SD: 6.6±3.5 (p<0.001, compared to Low Pb group) o Range 1.0–15 **Analysis:** Progression of renal insufficiency was evaluated at 3-month intervals for 24 months. Differences in group means evaluated with Student's t-test. Pb body burden was estimated by EDTA mobilization.	CCr in mL/second (mean±SD) • Baseline o Low Pb:0.67±0.22 o High Pb: 0.66±0.2 (p=0.78) • 3–18 months: no differences between groups • 18 months o Low Pb: 0.72±0.25 o High Pb: 0.59±0.22 (p=0.007) • 21 months o Low Pb: 0.70±0.24 o High Pb: 0.57±0.22 (p=0.006) • 24 months o Low Pb: 0.70±0.24 o High Pb: 0.55±0.22 (p=0.001)

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Lin et al. 2003 Prospective, longitudinal study of 202 Taiwanese patients (ages 25–80 years) with chronic renal insufficiency; patients had SCr 1.5–3.9 mg/dL and body lead burden <600 µg; patients had no known history of Pb exposure	**PbB:** • Baseline mean±SD: 5.3±2.9 • End of 24-month observation period (mean±SD) o Placebo: 5.9±3.0 (range: 1.3–14.8) o Chelation: 6.1±2.5 (range: 2.4–12.3) **Analysis:** Progression of renal insufficiency was evaluated at 3-month intervals for 24 months (SCr, CCr, GFR). At the end of the 24-month observation period, 64 patients with body Pb burdens ≥80 and <600 µg (estimated by EDTA mobilization) were randomly selected for repeated chelation or placebo treatment (n=32/group) for 27 months. Differences in group means evaluated with Student's t-test or Mann-Whitney test. Blood pressure was controlled with diuretics and ACE inhibitors.	End of 24-month observation period (mean±SD) • GFR (mL/minute/1.73 m^2) o Placebo: 31.5±9.0 o Chelation: 32.0±12.1 • CCr (mL/minute/1.73 m^2) o Placebo: 31.6±9.9 o Chelation: 32.3±12.9 Chelation therapy led to improvement in renal function and the slower progression of renal insufficiency. End of 27-month treatment period • GFR (mL/minute/1.73 m^2) o Placebo: 25.5±12.3 o Chelation: 34.4±14.7 (p=0.01) • Change in GFR following chelation o Placebo: -6.0±5.8 o Chelation: 2.1±5.7 (p>0.001) • CCr (mL/minute/1.73 m^2) o Placebo: 26.1±11.6 o Chelation: 34.8±14.7 (p=0.02) • Change in CCr following chelation o Placebo: -5.6±2.1 o Chelation: 2.1±4.9 (p>0.001)

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Lin et al. 2006a Prospective, longitudinal study of 124 Taiwanese patients (ages 18–80 years) with chronic renal insufficiency; patients had SCr 1.5–3.9 mg/dL and body lead burden <80 µg; patients had no known history of Pb exposure	**PbB:** • End of 24-month observation period (mean±SD) o Placebo: 3.0±1.1 (range: 1.2–4.6) o Chelation: 2.6±1.0 (range: 1.4–4.4) **Analysis:** Progression of renal insufficiency was evaluated at 3-month intervals for 24 months (SCr, CCr, GFR). At the end of the 24-month observation period, 32 patients with body Pb burdens ≥80 and <600 µg (estimated by EDTA mobilization) were randomly selected for repeated chelation or placebo treatment (n=16/group) for 27 months. Student's t-test or Mann-Whitney test was used for analysis of data.	End of 24-month observation period (mean±SD) • GFR (mL/minute/1.73 m^2) o Placebo: 42.6±9.7 o Chelation: 41.2±11.2 • CCr (mL/minute/1.73 m^2) o Placebo: 48.8±16.9 o Chelation: 45.0±9.0 End of 27-month treatment period • GFR (mL/minute/1.73 m^2) o Placebo:38.0±8.9 o Chelation: 47.9±17.0 (p=0.0493) • Change in GFR following chelation o Placebo: -4.6±4.3 o Chelation: 6.6±10.7 (p=0.0005) • CCr (mL/minute/1.73 m^2) o Placebo: 42.2±13.2 o Chelation: 46.6±12.8 (p=0.3537) • Change in CCr following chelation o Placebo: -5.1±4.1 o Chelation: 5.3±6.5 (p<0.001) No difference in 24-hour urine protein (g) was observed before or after treatment. 27-Month values (mean±SD): • Placebo: 1.11±1.63 • Chelation: 0.92±1.16 (p=0.6236)

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Lin et al. 2006b Prospective, longitudinal study of 238 Taiwanese patients with type II diabetes (ages 33–79 years) with progressive diabetic neuropathy; patients had SCr ≥1.5 and ≤3.9 mg/dL; patients had no known history of Pb exposure	**PbB:** • Baseline (mean±SD): 6.5±3.4 µg/dL (range: 1.6–19.1 µg/dL) • End of 12-month observation period (mean±SD) o Placebo: 5.9±2.2 (range: 2.4–10.4) o Chelation: 7.5±4.6 (range: 1.8–17.0; p=0.2477) **Analysis:** Progression of renal insufficiency was evaluated at 3-month intervals for 12 months (SCr, CCr, GFR). GFR was calculated based on serum creatinine. At the end of the 12-month observation period, 30 patients with body Pb burdens ≥20 and <80 µg (estimated by EDTA mobilization) were randomly selected for repeated chelation or placebo treatment (n=15/group) for 3 months, followed by a 24-month observation period. Differences in group means evaluated with Student's t-test or Mann-Whitney test. Blood pressure was controlled with diuretics and ACE inhibitors.	Each increase of 1 µg/dL in PbB levels resulted in a reduction in the GFR of 0.56 mL/minute/1.73 m^2 (p=0.028). End of 12-month observation period (mean±SD) • GFR (mL/minute/1.73 m^2) o Placebo: 37.0±9.2 o Chelation: 35.1±7.5 • CCr (mL/minute/1.73 m^2) o Placebo: 38.9±8.9 o Chelation: 36.4±9.1 Decrements in GFR at end of 27-month treatment/observation period • GFR (mL/minute/1.73 m^2) o Placebo: 13.1±4.5 o Chelation: 18.0±7.3 (p=0.0352) • Change in GFR following chelation o Placebo: 13.2±7.6 o Chelation: 4.4±6.9 (p=0.0045) • CCr (mL/minute/1.73 m^2) o Placebo: 15.3±8.4 o Chelation: 22.1±11.7 (p=0.0787) • Change in CCr following chelation o Placebo:13.3±7.7 o Chelation: 1.0±9.8 (p=0.0011)

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Lin-Tan et al. 2007 Placebo-controlled clinical study of 116 non-diabetic, Taiwanese patients with CKD; patients had SCr 1.5–3.9 mg/dL and body lead burden >60 and <600 µg; patients had no known history of Pb exposure	**PbB:** • Baseline (mean±SD) o Placebo: 5.1±2.6 (range: 1.3–14.8) o Chelation: 5.0±2.2 (range: 1.1–12.3; p=0.8305) • After 51-month chelation (mean±SD): o Placebo: 6.0±4.1 o Chelation: 3.5±1.5 (p=0.0306) **Analysis:** Patients with body lead burden ≥60 µg and <600 µg (estimated by EDTA mobilization) and serum creatinine ≤4.0 mg/dL randomly assigned to treatment with placebo or chelation therapy (n=58/group). Patients were administered treatment with placebo chelation therapy for 3 months, followed by 48 months of repeated chelation (or placebo) as needed. Differences in group means evaluated with Student's t-test or Mann-Whitney test. Blood pressure was controlled with diuretics or ACE inhibitors.	Baseline (mean±SD) • GFR (mL/minute/1.73 m^2) o Placebo: 36.0±11.2 o Chelation: 36.8±12.7 (p=0.6925) • CCr (mL/minute/1.73 m^2) o Placebo: 40.2±10.7 o Chelation: 21.9±14.6 • 24-Hour urine protein (g) o Placebo: 0.89±0.91 o Chelation: 0.82±0.92 (p=0.2996) End of 51-month treatment period • GFR (mL/minute/1.73 m^2) o Placebo: 23.7±10.8 o Chelation: 35.4±17.0 (p<0.0001) • Change in GFR following treatment o Placebo: -12.7±8.4 o Chelation: -1.8±8.8 (p<0.0001) • CCr (mL/minute/1.73 m^2) o Placebo: 27.7±10.3 o Chelation:40.3±16.7 (p<0.0001) • Change in CCr following chelation o Placebo: -12.6±8.1 o Chelation: -2.1±8.5 (p<0.0001) • 24-Hour urine protein (g) o Placebo: 0.96±1.04 o Chelation: 0.81±0.86 (p=0.3369)

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Mujaj et al. 2019 Cross-sectional study of 447 newly hired male workers (mean age: 28.7 years); data collection period: May 2015–September 2017	**PbB:** Gmean (IQR): 4.34 (2.59–7.90 **Analysis:** GFR was measured by combined serum creatinine and cystatin C. Data for GFR and ACR were analyzed by linear regression analysis, adjusted for age, mean arterial pressure, BMI, smoking, waist-to-hip ratio, total-to-HDL cholesterol ratio, plasma glucose, γ-glutamyl transferase, and antihypertensive drug treatment.	No associations were observed between PbB and GFR or ACR. β (95% CI), per doubling of PbB: • GFR: -0.281 (-3.07, 2.50); p=0.84 • ACR: -0.071 (-0.14, 0.59); p=0.06
Muntner et al. 2003 Cross-sectional study of 4,813 hypertensive (≥140 mmHg systolic pressure or ≥90 mmHg diastolic pressure) and 10,398 normotensive adults (≥20 years of age) participating in the NHANES III study; data collection period was 1988–1994	**PbB:** Normotensive • Mean±SD: 3.30±0.10 • Quartiles o Q1 (reference): 0.7–1.6 o Q2: 1.7–2.8 o Q3: 2.9–4.6 o Q4: 4.7–52.9 Hypertensive • Mean±SD): 4.21±0.14 (p<0.001, compared to normotensive) • Quartiles: o Q1 (reference): 0.7–2.4 o Q2: 2.5–3.8 o Q3: 3.9–5.9 o Q4: 6.0–56.0 **Analysis:** Data were analyzed by multivariate regression adjusted for age, race, sex, diabetes, systolic blood pressure, smoking, history of cardiovascular disease, BMI, alcohol consumption, household income, education level, marital status, and health insurance. The MDRD formula was used	Estimated GFR, mL/minute (mean±SD) • Normotensive: 115±0.7 • Hypertensive: 95±0.7 (p<0.001) Serum creatinine, mg/dL (mean±SD) • Normotensive: 1.05±0.004 • Hypertensive: 1.14±0.01 (p<0.001) Elevated serum creatinine, % • Normotensive: 1.8 • Hypertensive: 11.5 (p<0.001) CKD, % • Normotensive: 1.1 • Hypertensive: 10.0 (p<0.001) Normotensive: Adjusted ORs were not increased for SCr or CKD for Q2–Q4, compared to Q1. No trends were observed across quartiles. Hypertensive, adjusted ORs (95% CI) for • Elevated SCr o Q1: 1 o Q2: 1.47 (1.03, 2.10) o Q3: 1.80 (1.34, 2.42) o Q4: 2.41 (1.46, 3.97)

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
	to calculate the estimated GFR. CKD was defined as GFR <60 mL/minute/1.73 m^2.	o p-trend: <0.001 • CKD o Q1: 1 o Q2: 1.44 (1.00, 2.09) o Q3: 1.85 (1.32, 2.59) o Q4: 2.60 (1.52, 4.45) o p-trend<0.001
Navas-Acien et al. 2009 Cross-sectional study of 14,778 adults (≥20 years) participating in the NHANES (1999–2006) study	**PbB** • Mean: 1.58 • Quartiles (median): o Q1 (reference): ≤1.1 (0.8) o Q2: >1.1–1.6 (1.3) o Q3: >1.6–2.4 (1.9) o Q4: >2.4 (3.2) **Analysis:** Data for GFR and urine albumin were analyzed by logistic regression adjusted for survey year, age, sex, race/ethnicity, BMI, education, smoking, cotinine, alcohol intake, hypertension, diabetes, menopausal status, and blood cadmium. The MDRD formula was used to calculate the estimated GFR.	Adjusted ORs (95% CI) for albuminuria (≥30 mg/g creatinine) • Q1: 1 • Q2: 0.83 (0.66, 1.04) • Q3: 0.92 (0.76, 1.12) • Q4: 1.19 (0.96, 1.47) • p-trend: <0.001 Adjusted ORs (95% CI) for reduced GFR (<60 mL/minute/1.73 m^2) • Q1: 1 • Q2: 1.10 (0.80, 1.51) • Q3: 1.36 (0.99, 1.85) • Q4: 1.56 (1.17, 2.08) • p-trend: <0.001
Payton et al. 1994 Cross-sectional study of 744 men (ages 43–90 years) participating in the Normative Aging Study of the Department of Veterans Affairs; data were collected July 1988 through April 1991	**PbB** Mean±SD: 8.1±3.9 Range: <4.0–26.0 **Analysis:** Multivariate linear regression analysis (adjusted for age, BMI, blood pressure, alcohol intake, and use of diuretic and analgesic medication) was used to evaluate CCr data. Pearson's product-moment correlation was used to evaluate the relationship between PbB and CCr and estimated GFR.	Pearson's product-moment correlation for PbB • CCr (mL/minute): r = -0.082 (p=0.025) Multivariate regression coefficient, β (SE), µg/dL, for CCr (mL/minute): -0.0403 (0.0198); p=0.0426

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Pollack et al. 2015 Prospective cohort study of 257 premenopausal women (ages 18–44 years) from Buffalo, New York; data were collected 2005–2007; participants were divided into two groups: (1) those with reduced GFR (<90 mL/minute/1.73 m^2) (n=173), and (2) those without reduced GFR (≥90 mL/minute/1.73 m^2) (n=84)	**PbB** • Median: 0.88 • Tertiles o T1 (reference): <0.72 o T2: 0.72–1.10 o T3: >1.10 **Analysis:** Linear mixed models, adjusted for age, race, BMI, smoking, average calorie intake per menstrual cycle, menstrual cycle day, and average daily alcohol, were used to evaluate changes in kidney function (BUN, creatinine, glucose, GFR, protein) relative for PbB.	PbB was associated with increased SCr (mg/dL) and decreased GFR (mL/minute/1.73 m^2). No associations were observed for BUN, blood albumin, glucose, or protein. Regression β coefficients, expressed as percent change in outcome per 2-fold increase in PbB (95% CI): • SCr: 3.47 (0.85, 6.16) • GFR: -3.73 (-6.55, -0.83) • BUN: -0.13 (-4.97, 4.96) • Blood albumin: -0.38 (-1.28, 0.52) • Blood glucose: 0.93 (-0.28, 2.15) • Blood protein: -0.76 (-1.61, 0.09) Evaluation of outcomes by tertile showed that PbB was associated with increased SCr and decreased GFR. Regression β coefficients by tertile, expressed as percent change in outcome per 2-fold increase in PbB (95% CI): • SCr (mg/dL) o T1: reference o T2: 0.05 (0.02, 0.09); p<0.05 o T3: 0.05 (0.0006, 0.08); p<0.05 • GFR (mL/minute/1.73 m^2) o T1: reference o T2: -8.28 (-14.07, -2.50); p<0.05 o T3: -6.79 (-13.10, -0.49); p<0.05

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Spector et al. 2011 Cross-sectional study of 3,941 adults (≥20 years old; 1,332 <60 years old; 2,609 ≥60 years old) participating in the NHANES (1999–2002) study	**PbB** • Mean (IQR): 1.7 (1.1, 2.5) • <60 years (IQR): 1.6 (1.0, 2.3) • ≥60 years (IQR): 2.2 (1.6, 3.1) • Tertiles: o T1 (reference): ≤1.3 o T2: >1.3–2.2 o T3: >2.2 **Analysis:** GFR (mL/minute/1.73 m^2) was estimated by several methods (creatinine-based MDRD, creatinine-based CKD-EPI, cystatin C single variable, multivariable and combined creatinine/ cystatin C). Linear regression and logistic regression models were used to analyze data with log-transformed PbB or weighted tertiles. Models were adjusted for survey year, age, sex, race/ethnicity, BMI, education, smoking status (never, former, current), cotinine category, alcohol intake, hypertension, diabetes mellitus, and blood cadmium.	All participants: Negative trends (p-value range: 0.001–0.03) across the PbB range were observed for GFR for all except the CKD-EPI method. All methods showed associations between PbB and decreased GFR for T3. A 2-fold increase in PbB was associated with a decrease in GFR (mL/minute/1.73 m^2) based on the following methods: • Cystatin C single variable method: -1.9 (95% CI -3.2, -0.7) • Multivariable: -1.7 (-3.0, -0.5) • Combined creatinine/cystatin methods: -1.4 (-2.3, -0.5) • Creatinine-based MDRD method: -0.9 (-1.9, 0.02) • Creatinine-based CKD-EPI method: -0.9 (-1.8, 0.01) By tertiles for the cystatin C single variable method: • T1: reference • T2: -1.6 (-4.2, 1.0) • T3: -3.3 (-5.3, -1.4) • p-trend: 0.001 • ≥60 years: -4.5 (-5.6, -3.3)

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
		Participants ≥60 years old, adjusted ORs (95% CI) for reduced GFR by tertiles, based on cystatin C single variable method: • T1: reference • T2: 1.25 (0.86, 1.82) • T3: 1.57 (1.01, 2.46) • p-trend: 0.040 Participants <60 years old: No associations between PbB and decreased GFR or negative trends were observed for any GFR method (p-value for trends between 0.09 and 0.7). Participants ≥60 years old: Negative trends (p-values <0.001) across the PbB range were observed for all GFR methods. All methods showed associations between PbB and decreased GFR for T2 and T3. Based on the cystatin C single variable method, a 2-fold increase in PbB was associated with a -4.5 (95% CI -5.6, -3.3) mL/minute/1.73 m2 decrease in GFR. Adjusted ORs for all GFR methods showed increased risk of decreased GFR for T3 for all GFR methods. For the combined cystatin C multivariable method, ORs were increased for both T2 and T3 [adjusted ORs (95% CI)]: • T1: 1 • T2: 1.48 (1.04, 2.12) • T2: 2.02 (1.28, 3.17) • p-trend: 0.004

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
		A 2-fold increase in PbB was associated with a 1.53 decreased in GFR (mL/minute/1.73 m^2).
Staessen et al. 1992 Cross-sectional study of 1,981 adults (ages 20–88 years; 965 men; 1,016 women) in Belgium; data collection period was 1985–1989	**PbB** Mean (range) • Men: 11.4 (2.3–72.5) • Women: 7.5 (1.7–60.3) • p (difference between men and women): <0.001 **Analysis:** Data for CCr were analyzed by multivariate linear regression (with log-transformed PbB, adjusted for age, BMI, log γ-glutamyl transpeptidase, diabetes, and use of analgesics and diuretics.	An inverse relationship was observed between PbB and CCr (mL/L). A 10-fold increase in PbB was associated with decreases in calculated CCr (Cokcroft and Gault formula) of 13 and 30 mL/minute in men and women, respectively. Partial regression coefficients (SE) for CCr (mL/minute) per log µg /L: • Men: -13.1 (4.0); p≤0.001 • Women: -30.1 (3.4); p≤0.001

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Staessen et al. 2001 Cross-sectional study of 200 17-year-old adolescents (102 girls) from Belgium; 100 were in the exposed group and 100 were the control group; the exposed participants were from two locations (Exp1 group: Wilrijk, n=42; Exp2 group: Hoboken, n=58)	**PbB** Mean (95% CI) • C (control): 1.4 (1.3, 1.6) • Exp1 (Wilrijk): 1.8 (1.6, 2.1) • Exp2 (Hoboken): 2.7 (2.4, 3.1) • p-values comparing o C versus Exp1: 0.04 o C versus Exp2: <0.0001 o Exp1 versus Exp2: <0.0001 **Analysis:** Analysis of covariance with Bonferroni's correction, adjusted for sex, BMI, weeks of breastfeeding, parental social class, and dietary fat intake, was used to compare serum cystatin C means across groups.	Serum cystatin C, mg/L, mean (SE) • C: 0.65 (0.08) • Exp1: 0.63 (0.08) • Exp2: 0.71 (0.08) • p-values comparing o C versus Exp1: 0.13 o C versus Exp2: <0.0001 o Exp1 versus Exp2: <0.0001 A 2-fold increase in PbB was associated with a 3.6 (95% CI: 1.5, 5.7) percent increase in serum cystatin C. Urine β_2-microblobulin, µg/mmol creatinine, mean (95% CI) • C: 5.22 (4.59, 5.94) • Exp1: 5.30 (4.34, 6.48) • Exp2: 9.09 (7.67, 10.8) • p-values comparing o C versus Exp1: 0.90 o C versus Exp2: <0.001 o Exp1 versus Exp2: p<0.001 A 2-fold increase in PbB was associated with a 16.0 (95% CI: 2.7, 31) percent increase in urine β_2-microblobulin.

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
Tsaih et al. 2004 Prospective study of 448 subjects from the Normative Aging Study who had serum creatinine, blood lead, and bone lead measurements taken during the period 1991–1995 (baseline), with follow-up serum creatinine measurements made 4–8 years later; mean age of the study group was 66 years at the time of baseline evaluation and 72 years at follow-up	**PbB** Mean (SD) • At baseline: 6.5 (4.2) • At follow-up: 4.5 (2.5); p<0.05 **Analysis:** Wilcoxon signed-rank test was used to compare of PbB at baseline and follow-up. SCr data were analyzed by log linear regression adjusted for age, age squared, BMI, hypertension, diabetes, smoking status, alcohol consumption, analgesic use, baseline serum creatinine, and serum creatinine squared.	No association was observed between PbB and longitudinal increases in SCr (mg/dL per ln µg Pb/dL): • β=0.009 (SE 0.005) At baseline, an association was observed between ln PbB and changes in SCr in participants with diabetes (n=26), but not in participants with hypertension (n=115). • β (diabetes): 0.076 (SE 0.023); p<0.05 • β (hypertension): 0.008 (0.010) At the follow-up assessment, an association was observed between ln PbB and changes in SCr in participants with hypertension (n=108), but not in participants with diabetes (n=24). • β (diabetes): 0.223 (SE 0.183) • β (hypertension): 0.352 (SE 0.097); p<0.05
Yu et al. 2004 A prospective longitudinal study of 121 patients (mean age 57 years, range 2,582 years) with chronic renal insufficiency (without diabetes) and no history of occupational exposure to Pb; progression of renal insufficiency was evaluated for 48 months; patients were divided into those with high-normal body Pb burden (≥80–<600 µg, n=63) and low-normal body Pb burden (<80 µg, n=58)	**PbB** At baseline, mean±SD (range) • All patients: 4.2±2.2 (1.0–13.4) • Low-normal body Pb burden <80 µg: 3.4±1.3 (1.2–6.3) • High-normal body Pb burden ≥80–<600 µg: 4.9±2.6 (1.0–13.4); p=0.0002 **Analysis:** Body Pb burden was estimated by EDTA mobilization. Cox proportional hazard model examined whether a predictor was associated with renal function including age, sex, BMI, hyperlipidemia, hypertension, smoking, use of ACE inhibitor, baseline serum creatinine, daily protein	During the study period, an increased in PbB of 1 µg/dL was associated with a reduction in GFR of 4.0 mL/minute/1.73 m^2 (p=0.0148). Baseline mean±SE • GFR: 36±9.8 mL/minute/1.73 m^2 • SCr: 2.1±0.5 mg/dL • CCr: 41.5±11.0 mL/minute/1.73 m^2 At end of study period mean±SE • GFR: 26.6±11.9 mL/minute/1.73 m^2 • SCr: 3.0±1.6 mg/dL • CCr: 31.0±13.6 mL/minute/1.73 m^2

Table 6. Epidemiology Studies Evaluating Renal Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes[a]
	excretion, daily protein intake, and underlying kidney disease.	

ACE = angiotensin-converting-enzyme; ACR = albumin-to-creatinine ratio; ANOVA = analysis of variance; BMI = body mass index; BUN = blood urea nitrogen; CCr = creatinine clearance; CI = confidence interval; CKD = chronic kidney disease; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration eGFR method; EDTA = ethylenediaminetetraacetic acid; F = female(s); GFR = glomerular filtration rate; HR = hazard ratio; IQR = interquartile range; M = male(s); MDRD = Modification of Diet in Renal Disease eGFR method; NHANES = National Health and Nutrition Examination Survey; NS = not statistically significant; OR = odds ratio; Pb = lead; Sβ2M = serum β2-microblobulin; SCr = serum creatinine concentration; SD = standard deviation; SE = standard error; UNAG = urine N-acetyl-β-D-glucosaminidase; UPHC = urine human complex-forming protein (α1-microglobulin)

[a]A variety of methods are used to estimate GFR (Chao et al. 2015). Each has limitations for application to both clinical evaluations and epidemiology. The preferred method is to measure the clearance of substance from plasma that is known to be eliminated solely by glomerular filtration and is not reabsorbed in the renal tubule. Typically, in the clinical setting, this is accomplished with intravenous administration of GFR markers, such as ^{125}I-iothalmate for the radiocontrast agent (e.g., iohexol). These procedures are feasible in the clinical setting, but not in epidemiology studies in which invasive procedures and administration of such agents is not practical or possible. Clearance of endogenous creatinine is an alternative that has had wide use in epidemiology. However, it requires concurrent measurements of serum creatinine and the rate of urinary excretion of creatinine, which can be accurately determined only with a carefully timed urine sample that can represent the amount of glomerular filtrate formed over a given time interval. Achieving an accurately timed urine sample requires a rigidly implemented and supervised collection protocol, which is not always feasible, in particular in large scale epidemiology studies. Alternatives to clearance methods are measurement of endogenous metabolites in plasma whose clearance approximates GFR. Typically, this is achieved with endogenous creatinine or cystatin C. The serum concentration of these two metabolites strongly correlates with GFR; however, the relationship between creatinine or cystatin C concentration and GFR is also affected by other variables including age, sex, race, and for creatinine muscle mass. Several approaches have been developed to improve estimates of GFR from serum creatinine that attempt to account for these co-variables. These methods rely on multiple variable regression models that relate GFR to serum creatinine and other significant of determinants of GFR (Cockcroft and Gault 1976; Levey et al. 1999, 2009). An evaluation of two of the more commonly used methods for estimating GFR from serum creatinine, the CKD-EPI and MDRD equations, found that both achieved a median difference between calculated and measured GFR (from clearance measurements) that ranged from 2 to 6 mL/minute per 1.73 m^2 (Levey et al. 2009). The interquartile range in the difference was approximately 18 mL/minute per 1.73 m^2 in a validation dataset consisting of data for 3,986 study subjects. This suggests that approximately 25% of the GFR estimates from these methods are expected to be in error of true GFR by more than 18 mL/minute (or approximately 15% of the GFR in a healthy adult, 120 mL/minute).

Table 7. Epidemiology Studies Evaluating Endocrine Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Thyroid		
Abdelouahab et al. 2008 Cross-sectional study of 211 adults (124 men and 87 women; ages 18–74 years) in Canada; data collection period: March–August 2003	**PbB:** Median (maximum): • Men: 3.10 (20.9) • Women: 1.74 (12.5) (p<0.0001 compared to men) **Analysis:** Beta estimates were obtained from multiple regression analysis, adjusted for age, smoking and alcohol consumption, medications, and PCB congeners. PbB was log-transformed for parametric analyses.	A negative association was observed between PbB and TSH in women, but not men. No associations were observed between PbB and T3 or T4 in men or women. β per log µg/L: • Total T3 o Men: 0.12 o Women: 0.15 • Total T4 o Men: -1.93 o Women: -0.36 • TSH o Men: -0.05 o Women: -0.32 (p<0.05)

Table 7. Epidemiology Studies Evaluating Endocrine Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Chen et al. 2013 Cross-sectional study of 1,009 adolescents (ages 12–19 years) and 4,409 adults (≥20 years) participating in NHANES 2007–2008	**PbB:** Mean (range) • Adolescents: 0.93 (0.18, 9.20) • Adults: 1.75 (0.18, 33.1) **Analysis:** Data were analyzed by regression models with PbB and outcomes ln-transformed. Models were adjusted for age, sex, race/ethnicity, creatinine-adjusted urinary iodine, BMI *z*-score (adolescents only), BMI score (adults only), and serum cotinine level.	No associations between PbB and thyroid hormones were observed in adolescents or adults, Regression coefficients per 1 ln µg/dL (95% CI): Adolescents: • Ln-total T4: 0.01 (-0.02, 0.04) • Ln-FT4: 0.01 (-0.01, 0.04) • Ln-total T3: 0.01 (-0.01, 0.04) • Ln-FT3: 0.02 (-0.002, 0.04) • Ln-TSH: -0.05 (-0.18, 0.07) • Ln-Tg: 0.05 (-0.13, 0.24) Adults: • Ln-total T4: -0.01 (-0.02, 0.01) • Ln-FT4: 0.01 (-0.01, 0.02) • Ln-total T3: -0.0004 (-0.02, 0.02) • Ln-FT3: 0.01 (-0.001, 0.02) • Ln-TSH: -0.01 (-0.06, 0.04) • Ln-Tg: 0.01 (-0.03, 0.06)

Table 7. Epidemiology Studies Evaluating Endocrine Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Dundar et al. 2006 Cohort study of 42 Pb-exposed adolescent auto repair workers (mean age 16.5 years) and 55 controls (mean age 16.2 years) from Turkey; data collection period not reported	**PbB:** Mean (SD): • Workers: 7.3 (2.92); p<0.05 compared to controls • Controls: 2.08 (1.24) **Analysis:** Comparison between groups were made using Student's t test. Data were analyzed using Spearman correlation analysis and nonlinear multivariable regression analysis.	Comparison of hormone levels between groups, mean (SD) • FT4 (ng/mL): o Control: 1.12 (0.14) o Workers: 1.02 (0.18); p<0.05 • FT3 (ρg/mL) o Control: 3.70 (0.29) o Workers: 3.68 (0.41) • TSH (mU/L) o Control: 1.90 (0.73) o Workers: 1.97 (1.13) • Thyroid volume (mL): o Control: 12.3 (5.10) o Workers: 11.36 (3.12) Negative correlations were found between PbB levels and FT4 levels. • Spearman correlation analysis: r: -0.20; p=0.044 • nonlinear multivariable regression analysis: r: -0.27; p=0.048
Iijima et al. 2007 Cross-sectional study of 24 mother-infant pairs in Japan; data collection period: January–December 2005	**PbB:** Umbilical mean (SD): 6.3 (3.4) Range: 0.23–12 **Analysis:** Associations between PbB and FT4 and TSH were analyzed using Spearman rank correlation coefficients. No adjustments for potential confounding factors were reported.	No associations (p>0.05) were observed between PbB and FT4 or TSH levels. Spearman rank correlation coefficient: • FT4: 0.263 • TSH: 0.174

Table 7. Epidemiology Studies Evaluating Endocrine Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Luo and Hendryx 2014 Cross-sectional study of 6,231 adults (≥20 years) from the NHANES 2007–2010	**PbB:** Mean: 1.82 Range: 0.18–33.10 Tertiles: • T1: 0.18–1.09 • T2: 1.10–1.88 • T3: 1.89–33.10 *Note reporting inconsistency for T1 and T2 ranges (ranges for T1 and T2 also reported as 0.18–1.26 and 1.27–1.88, respectively). **Analysis:** Data were analyzed using multiple linear regression models, adjusted for age, sex, race/ethnicity, serum cotinine, BMI, and creatinine-adjusted urinary iodine.	A positive association was observed between PbB and FT3, but not other thyroid hormones. Regression coefficient β (95% CI) per tertile, with T1 as the reference: • FT4 (ng/dL): o T2: 0.001 (-0.16, 0.14) o T3: -0.09 (-0.28, 0.11) • FT3 (ρg/mL): o T2: 0.03 (0.001, 0.07) o T3: 0.04 (0.01, 0.08); p<0.01 • Ln-TSH (uIU/mL): o T2: 0.01 (-0.05, 0.07) o T3: 0.02 (-0.06, 0.09) • Ln-Tg (ng/mL): o T2: 0.04 (-0.04, 0.13) o T3: 0.02 (-0.07, 0.12)
Mendy et al. 2013 Cross-sectional study of 4,652 adults (≥20 years; mean 51 years) from the NHANES 2007–2008	**PbB:** Mean±SE (range): 1.52±1.20 (0.18–33.12) **Analysis:** Relationships between ln-PbB were analyzed by linear regression adjusted for age, sex, race/ethnicity, smoking, alcohol consumption, BMI, physical activity, medications, and bone density.	Increased ln-PbB was associated with decreased total T4, but not total T3, FT3, FT4, or TSH. Linear regression coefficient β (95% CI) for ln µg/dL: • Total T4: -0.22 (-0.34, -0.09); p<0.01 • FT4: 0.00 (-0.01, 0.02) • Total T3: -1.05 (-3.08, 0.98) • FT3: 0.02 (-0.01, 0.05) • TSH: 0.02 (-0.12, 0.16)

Table 7. Epidemiology Studies Evaluating Endocrine Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Ngueta et al. 2018 Cross-sectional study of 65 adults (51% male, 49% female), aged 50–57 years from Canada	**PbB:** Low PbB mean: 1.65 (all <2.48 (n=30) Higher PbB mean: 3.60 (range: >2.48–8.5) (n=35) **Analysis:** Relationships between PbB and basal salivary cortisol and acute cortisol stress response were evaluated by linear regression mixed models. Adjustments included sex, age, waist:hip ratio, family income levels, and current smoking status.	No differences were observed between the low and high PbB groups and cortisol levels evaluated at several time points from awakening to bedtime. No association was observed between PbB and basal cortisol levels or cortisol levels under stress. Adjusted regression coefficient β (SE): • Basal cortisol: -0.01 (0.02); p=0.26 • Stress cortisol: -0.01 (0.1); p=0.43
Nie et al. 2017 Cross-sectional study of 5,628 Chinese adults (2,278 men, mean age 53 years; 3,350 women, mean age 54 years; data collection period: February–June 2014	**PbB:** Men Gmean (GSD): 4.1 (0.20) Tertiles • T1: <3.4 • T2: 3.4–5.5 • T3: >5.5 Women: Gmean (GSD): 3.5 (0.20) Tertiles • T1: <2.9 • T2: 2.9–4.8 • T3: >4.8 Analysis: Relationships between PbB and TSH and thyroid antibodies were analyzed by linear and logistic regression models, adjusted for Cd, age, BMI, smoking status (men only), and alcohol consumption.	An association was observed between PbB and thyroid peroxidase antibodies and TSH for women, but not men. No association was observed for thyroglobulin antibodies for men or women. ORs (95% CI) for lnPbB by thyroid peroxidase antibodies (TPOAb) tertile: Men • TPOAb T1: 1 (reference) • TPOAb T2: 1.02 (0.87, 1.29) • TPOAb T3: 1.11 (0.95, 1.29) Women • TPOAb T1: 1 (reference) • TPOAb T2: 1.38 (1.21, 1.59); p<0.001 • TPOAb T3: 1.35 (1.20, 1.53); p<0.001 ORs (95% CI) for lnPbB by thyroglobulin antibodies (TGAb) tertile: Men • TGAb T1: 1 (reference) • TGAb T2: 1.07 (0.86, 1.32)

Table 7. Epidemiology Studies Evaluating Endocrine Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		• TGAb T3: 0.89 (0.77, 1.03) Women • TGAb T1: 1 (reference) • TGAb T2: 1.09 (0.95, 1.24) • TGAb T3: 1.05 (0.93, 1.18) β (95% CI) for TSH • Men: -0.020 (-0.059, 0.020); p=0.324 • Women: 0.047(0.012, 0.081); p=0.008
Yorita Christensen 2013 Cross-sectional study of 1,587 adults (mean 51 years) from the NHANES 2007–2008	**PbB:** Median (25th, 75th percentiles): 1.3 (0.9, 2.1) **Analysis:** Multivariate linear regression was used to model the association between thyroid hormone levels and PbB, adjusted for age, sex, race/ethnicity, BMI, total serum lipids, serum cotinine, pregnancy and menopausal status, and use of medications potentially affecting thyroid function.	β (SE) for association with ln µg/dL • Ln-Total T4: -0.028 (0.013); p<0.05 • Ln-FT4: -0.004 (0.012) • Ln-Total T3: 0.003 (0.012) • Ln-FT3: 0.011 (0.007) • Ln-TSH: 0.014 (0.043)

Table 7. Epidemiology Studies Evaluating Endocrine Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Cortisol		
Braun et al. 2014 Cross-sectional study of 918 pregnant Women (18–44 years; mean age 27.8 years) from Mexico City; data collection period: 2007–2011	**PbB:** Mean (SD): 3.7 (2.7) Range: 0.5–23 Quintiles: • Q1: 0–<1.8 • Q2: 1.8–<2.4 • Q3: 2.4–<3.4 • Q4: 3.4–<5.1 • Q5: ≥5.1 • Continuous: per 2.5 µg/dL Maternal tibia Pb concentration (µg/g); mean (SD): 2.7 (8.4) Maternal patella Pb concentration (µg/g); mean (SD): 4.6 (8.6) **Analysis:** PbB was measured during the 2nd trimester of pregnancy. Cortisol salivary levels were assessed using 10 timed collections. Cortisol awakening response was by change in the cortisol concentration between the first and second saliva samples of each day. Cortisol levels were log_{10}-transformed and data were analyzed by linear mixed models, adjusted for maternal age, education, BMI, marital status, gestational age at time of cortisol collection, parity (1, 2, 3, or 4+), and maternal smoking status during pregnancy.	Salivary cortisol AUC concentrations did not vary with blood or bone Pb concentrations. Percent difference in cortisol AUC per PbB quintiles, nmol-hour (95% CI): • Q1: 1 (reference) • Q2: 8 (-1, 18) • Q3: 9 (0, 19) • Q4: 8 (-1, 18) • Q5: 2 (-6, 12) • Continuous: -1 (-4,1) Cortisol awakening response was decreased in Q5, compared to Q1, β (SE): • Q1: 1 (reference) • Q2: 0.00 (-0.06, 0.06) • Q3: 0.01 (-0.05, 0.07) • Q4: -0.04 (-0.11, 0.02) • Q5: -0.06 (-0.12, 0.00) • Continuous: -0.02 (-0.04, 0.00)

Table 7. Epidemiology Studies Evaluating Endocrine Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Gump et al. 2008 Prospective study of 169 children from Oswego, New York; data collection period not reported	**PbB:** Prenatal quartiles: • Q1: ≤1 • Q2: 1.1–1.4 • Q3: 1.5–1.9 • Q4: 2.0–6.3 Postnatal quartiles: • Q1: 1.5–2.8 • Q2: 2.9–4.1 • Q3: 4.2–5.4 • Q4: 5.5–13.1 **Analysis:** Umbilical cord blood was used as the measure of prenatal PbB. Postnatal PbB was measured at 2–3 years of age. Cortisol response to stress (to cold challenge), measured by salivary cortisol levels, was assessed at 9.5 years of age. Regression analysis was conducted with adjustments for SES-related factors, HOME score, pregnancy health, and maternal substance abuse.	Associations were observed between increased salivary cortisol response to stress and PbB for prenatal PbB Q2–Q4 and postnatal PbBQ4, compared to respective Q1. No numeric data for quartiles were reported; data were presented graphically.

Table 7. Epidemiology Studies Evaluating Endocrine Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Vitamin D		
Kemp et al. 2007 Cross-sectional study of 142 urban African-American (n=91) and Hispanic (n=51) children (ages 1–8 years) from New Jersey; data collection periods were December 2001–March 2002 for winter and July–September 2002 for summer	**PbB:** Mean (SE) • 1–3 year-old children (n=78): o Winter: 4.94 (0.45) o Summer: 6.54 (0.82); p=0.0019 compared to winter PbB • 4–8 year-old children (n=64): o Winter: 3.68 (0.31) o Summer: 4.16 (0.36); p<0.0001 compared to winter PbB **Analysis:** This study evaluated relationships to seasonal increased PbB and vitamin D nutrition, age, and race. Data comparing groups were analyzed by paired t-tests.	An increase (approximately 45%; p<0.05; data presented graphically) in 25-OH-D in summer compared to winter was observed in African-American children ages 4–8 years, but not in African-American children ages 1–3 years or in Hispanic children of any age. Study authors concluded that "higher summertime increase in serum 1,25-(OH)2D3 levels in children between ages 4 and 8 years is most likely due to increased sunlight-induced vitamin D synthesis and may contribute to the seasonal increase in blood lead."
Diabetes		
Moon 2013 Cross-sectional study of 1,588 men and 1596 women (age ≥30 years) participating in the Korea National Health and Nutritional Examination Surveys 2009–2010	**PbB:** Mean (SE), quartiles: • Q1 (<25th percentile): 1.43 (1.01) • Q2 (25th–<50th percentile): 2.13 (1.00) • Q3 (50th–<75th percentile): 2.74 (1.00) • Q4 (≥75th percentile): 4.08 (1.01) **Analysis:** Diabetes was defined as fasting plasma glucose levels ≥126 µg/dL, currently on diabetes treatment, or reported history of physician diagnosed diabetes. Prevalence of diabetes was analyzed by logistic regression, adjusted for age, sex, region (rural or urban), smoking, alcohol consumption, and regular exercise.	Risk of diabetes was not associated with PbB. ORs (95% CI) for diabetes: • Q1: 1 (reference) • Q2: 0.908 (0.641, 1.288) • Q3: 0.759 (0.531, 1.086) • Q4: 0.745 (0.516, 1.077) • p-trend=0.336

Table 7. Epidemiology Studies Evaluating Endocrine Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Insulin-like growth factor		
Fleisch et al. 2013 Prospective study of 394 boys (age at initial visit: 8–9 years) from Russia; initial visit: 2003–2005	**PbB:** Median (range): 3 (0.5–31) Quartiles: • Q1 (n=109): ≤2 • Q2 (n=176): 3–4 • Q3 (n=97): 5–9 • Q4 (n=12): ≥10 **Analysis:** PbB was obtained at ages 8–9 years and IGF-1 levels were measured at ages 10–11 and 12–13 years. Repeated measures analysis to estimate the association between baseline PbB and serum IGF-1 concentrations at ages 10–11 and 12–13 years. Adjusted for parental education, birth weight, nutritional intake, and baseline and follow-up age and BMI.	PbB was associated with decreased serum IGF-1 (ng/mL) levels Q3 and Q4 compared to Q1 at the age 10–11-year assessment. Mean serum IGF-1 (95% CI): • Q1: 1 (reference) • Q2: -12.8 (-29.9, 4.4); p=0.15 • Q3: -34.5 (-53.1, -16.0); p>0.001 • Q4: -60.4 (-90.9, -29.9); p<0.001 Each unit increase in ln-PbB was associated with a 22.2 g/mL decrease in mean serum IGF-1 (95% CI: -33.9, -10.6).

AUC = area under the salivary cortisol concentration-time curve; BMI = body mass index; CI = confidence interval; Cd = cadmium; FT3 = free T3; FT4 = free T4; Gmean = geometric mean; GSD = geometric standard deviation; HOME = Home Observation for Measurement of the Environment; IGF-1 = insulin-like growth factor-1; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PCB = polychlorinated biphenyl; SD = standard deviation; SE = standard error; SES = socio-economic status; T3 = triiodothyronine; T4 = thyroxine; Tg = thyroglobulin; TSH = thyroid stimulating hormone

Table 8. Selected Epidemiology Studies Evaluating Immunological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Susceptibility to infections		
Krueger and Wade 2016 Cross-sectional study of 5,994 subjects (age ≥3 years) from NHANES, 1999–2012	**PbB:** Gmean (95% CI): 1.50 (1.43, 1.57) **CdB (µg/dL):** Gmean (95% CI): 0.33 (0.31, 0.36) **Analysis:** Seropositivity for *Heliobacter pylori, Toxoplasma gondii*, and *Hepatitis B* virus. Multiple logistic regression. Adjustments made for age, sex, race/ethnicity, country of birth origin, family income, self-reported general health condition, tap water source, household crowding, and use of illicit/street injected drugs.	Trend (p<0.0001) for increasing OR with increasing PbB or CdB. No interaction between PbB and CdB on OR. Adjusted OR (95% CI) for a doubling of PbB: • *H. pylori:* 1.22 (1.12, 1.34), p<0.05 • *T. gondii*: 1.19 (1.12, 1.28), p<0.05 • *Hepatitis B* virus: 1.19 (1.08, 1.32), p<0.05
Park et al. 2019 Cross-sectional study of 2,625 adults (mean age: 52.3 years; 1,752 men; 873 women) from South Korea; data collection period: 2014–2016	PbB: Mean (SD): 2.83 (1.31) Range: 0.13–9.87 **Analysis:** Gastrointestinal endoscopy was performed and histopathological assessments were conducted to determine the prese or absence of *H. pylori*. PbB data were natural log transformed. ORs were determined by multiple regression analysis adjusted for age, smoking, alcohol use, BMI, hypertension, diabetes mellitus, and exercise.	The risk of *H. pylori* infection increased with PbB. OR (95% CI): 1.143 (1.068, 1.223), p<0.001

Table 8. Selected Epidemiology Studies Evaluating Immunological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Sensitization		
Jedrychowski et al. 2011 Prospective study of 224 children (at 5 years of age) of women recruited in the 2nd trimester of pregnancy (2001–2004, Poland)	**PbB:** Gmean (95% CI): Cord: 1.16 (0.12, 1.22) Maternal: 1.60 (1.52, 1.67) **Analysis:** Atopic status evaluated at age 5 years for reaction to airborne allergens. Logistic regression. Adjustments made for sex, parity, maternal age, maternal education, maternal atopy, and ETS variables.	Increased risk of atopy in association with increasing cord PbB. Adjusted RR (95% CI): • Cord PbB: 2.28 (1.12, 4.62) • Maternal PbB: 1.72 (0.98, 3.00)
Pizent et al. 2008 Cross-sectional study of 216 adults (age range 19–67 years)	**PbB** median (range): • Male: 3.17 (0.99, 7.23) • Female: 2.16 (0.56, 7.35) **Analysis:** Skin prick test to common aeroallergens. Logistic regression with log_{10} transformed PbB. Adjustments made for age, smoking, alcohol use, log PbB, log CdB, SCu, SZn, SSe, GPx, and SOD.	Increasing PbB was associated with decreasing adjusted OR for positive skin prick test (95% CI): 0.92 (0.86, 0.98)
Humoral immunity		
Karmaus et al. 2005 Cross-sectional study of 671 children (age 7–10 years) in Germany	**PbB** Gmean (95% CI): • Males: 2.78 (1.48, 4.82) • Females: 2.54 (1.10, 4.38) **Analysis:** Serum IgA, IgE, IgG and IgM and B-cell abundance. ANOVA and multiple linear regression. Adjustments made for age, sex, ETS, number of infections during the last 12 months, lipid concentration, and breastfeeding.	Mean serum IgE levels were higher in PbB strata >2.84 and >3.41 µg/dL. B-cell abundance was lower (p≤0.05) in PbB stratum 2.21–2.83 compared to <2.2 µg/dL. No dose-response relationship was observed between PbB and B-cell abundance.

Table 8. Selected Epidemiology Studies Evaluating Immunological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Min and Min 2015 Cross-sectional study of 4,287 adults (age ≥22 years) from NHANES 2005–2006	**PbB** Gmean (95% CI): • 1.46 (1.44, 1.50) **Analysis:** Serum total IgE and antigen-specific IgEs. Multiple linear regression with log_{10} transformed PbB. Adjustments made for age, sex, race/ethnicity, family income, cigarette smoking, the presence of allergic disease, and BMI.	An association was observed between increasing serum IgE and increasing PbB. β for 1 log10 increase in IgE per 1 log_{10} increase in PbB (95% CI): • Q2 (1.1–1.69 µg/dL): 0.20 (0.05, 0.34) • Q3 (1.7–2.6 µg/dL): 0.26 (0.10, 0.42) • Q4 (2.61–26.4 µg/dL): 0.35 (0.20, 0.51)
Pizent et al. 2008 Cross-sectional study of 216 adults (age range 19–67 years)	**PbB** median (range): • Male: 3.17 (0.99, 7.23) • Female: 2.16 (0.56, 7.35) **Analysis:** Serum IgE. Multiple linear regression with log_{10} transformed PbB. Adjustments made for age, smoking, alcohol use, log PbB, log CdB, SCu, SZn, SSe, GPx, and SOD.	In females not taking oral contraceptives or hormone replacement therapy, increasing PbB was associated with increasing serum IgE. β log increase in IgE per log increase in PbB µg/L (SE): 0.600 (0.298), p=0.046
Sarasua et al. 2000 Cross-sectional study of 1,561 residents of communities with elevated levels of cadmium or Pb in soil and 480 residents of comparison communities (age range 6 months–75 years) (1991)	**PbB** mean (5^{th}–95^{th} percentile range) for combined resident and comparison communities: • Age 6–35 months: 7.0 (1.7, 16.1) • Age 36–71 months: 6.0 (1.6, 14.1) • Age 6–15 years: 4.0 (1.1, 9.2) • Age 16–75 years: 4.3 (1.0, 9.9) **Analysis:** B-cell abundance and serum IgA, IgG, and IgM. Multiple linear regression. Adjustments made for age (continuous), sex, study site, and smoking.	A positive association was observed between increasing PbB and serum IgA, IgG, and IgM, and B-cell abundance. β per 1 µg/dL PbB: Age 6–35 months: • IgA (mg/dL): 0.8, p<0.01 • IgG (mg/dL): 4.8, p<0.01 • IgM (mg/dL): 1.0, p=0.03 • B-cell count: 16.9, p<0.01 • B-cell%: 0.19, p=0.02 Age 6–15 years: • IgG (mg/dL): 7.5, p=0.02

Table 8. Selected Epidemiology Studies Evaluating Immunological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Wang et al. 2017a Cross-sectional study of 930 children (mean age: 5.74 years; 469 boys and 461 girls)	**PbB** Gmean (GSD) • All: 1.86 (1.21) • Boys: 1.88 (1.22) • Girls: 1.83 (1.20) **Analysis:** lgE data were ln-transformed analyzed by linear regression, adjusted for age, maternal age, maternal history of atopy, maternal nationality, parental education and occupation, family income, number of siblings, breast feeding, environmental tobacco smoke, incensing at home, dehumidifier at home, new paintings of houses, and residence using groundwater	For all participants and boys (but not girls), a one ln-unit increase in PbB (equal to 2.72 µg/dL) was positively associated with serum lgE. Regression coefficient β (95% CI): • All: 0.26 (0.009, 0.50); p=0.042 • Boys: 0.40 (0.03, 0.76); p=0.036 • Girls: 0.02 (-0.35, 0.40); p=0.901
Wells et al. 2014 Cross-sectional study of 1,788 children (age 2–12 years) from NHANES 2005–2006	**PbB** Gmean (95% CI): • 1.13 (1.04, 1.22) **Analysis:** Percent eosinophils. Multiple linear regression. Adjustments made for season, age, sex, race/ethnicity, education, passive smoke exposure, BMI, cockroaches, and avoidance/removal of pets.	An association was observed between increasing serum lgE and increasing PbB. β for percent increase per 1 µg/dL (95% CI): 10.27 (3.52, 17.47)
Xu et al. 2015 Cross-sectional study of 590 children (age 3–7 years) evaluated 2011–2012	**PbB** Gmean (SD of log PbB): • Total exposed: 6.76 (0.18) • Male: 6.61 (0.19) • Female: 6.16 (0.18) **Analysis:** Hepatitis B virus surface antibody titers following immunization at birth and age 6 months and 1 year. Multiple linear and mixed effects regression. Adjustments made for age and sex.	Hepatitis B virus surface antibody titers decreased with increasing PbB β signal to cutoff ratio per 1 µg/dL (SE) at two assessment dates: • 2011: -0.4467 (0.0225), p<0.001 • 2012: 0.3661 (0.0193), p<0.001

Table 8. Selected Epidemiology Studies Evaluating Immunological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Cell-mediated immunity		
Boscolo et al. 2000 Cross-sectional study of 30 atopic women (age range 19–49 years) and 30 non-atopic women in Italy	**PbB:** median (25^{th}–75^{th} percentile range: • Atopic: 6.4 (4.9, 7.9) • Control: 5.5 (4.4, 6.7) **Analysis:** Abundances of CD4+, CD3+, CD8+, CD45+, and HLA-DR+. Spearman correlation. No adjustments.	Positive correlation between PbB and T-cell abundances in non-atopic subjects (r for cell count): • CD4+ CD45RO-: 0.464, p<0.05 • CD3+ CD8+: 0.430 p<0.05 • CD3- HLA-DR+>: 0.435, p<0.05
Conterato et al. 2013 Cross-section study of battery manufacture workers (59), automobile painters (23), and control workers (36), age 15–61 years, in Brazil	**PbB** mean (SE): • Battery workers: 49.8 (4.0) • Painters: 5.4 (0.4) • Controls: 1.5 (0.1) **Analysis:** Abundances of lymphocytes, neutrophils, eosinophils. ANOVA and Spearman's rank correlation. No adjustments.	Neutrophil abundance was lower in Pb workers comparted to controls, mean (SE), $10^3/mm^3$: • Battery workers: 2.87 (0.27), p<0.05 • Painters: 3.07 (0.13), p<0.05) • Controls: 3.75 (2.49) Neutrophil abundance was negatively correlated with PbB.
Hsiao et al. 2011 Cross-sectional study of 214 children, enrolled in primary school grades 5–6, China	**PbB** Mean (SD): • Allergic and residing near oil refinery: 8.80 (0.45) • Non-allergic and residing near oil refinery: 5.23 (0.36) • Other rural or urban groups, allergic or not: 3.16–3.83 **Analysis:** Serum T-helper cell cytokines: IFN-γ, interleukins IL 4, IL-5, and IL-12. Unspecified comparison of means. No adjustments.	Compared to all other groups, the allergic group residing near the refinery (mean PbB 8.80 ± 0.45 SD µg/dL) had (p<0.05) lower serum IFN-γ and IL-12 (>96% decrease) and higher serum IL-4 and IL-25 (>500% increase).

Table 8. Selected Epidemiology Studies Evaluating Immunological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Karmaus et al. 2005 Cross-sectional study of 67 children (age 7–10 years) in Germany	**PbB** Gmean (95% CI): • males: 2.78 (1.48, 4.82) • females: 2.54 (1.10, 4.38) **Analysis:** T-cell abundance ANOVA and multiple linear regression. Adjustments made for age, sex, ETS, number of infections during the last 12 months, lipid concentration, and breastfeeding.	Total T-cell and T_C abundances were lower (p≤0.05) in PbB stratum 2.21–2.83 µg/dL compared to <2.2 µg/dL. No differences in T_H or NK cell abundances were observed. No dose-response relationship was observed between PbB and total T-cell abundances.
Sarasua et al. 2000 Cross-sectional study of 1,561 residents of communities with elevated levels of cadmium or Pb in soil and 480 residents of comparison communities (age range 6 months–75 years) (1991)	**PbB** mean (5^{th}–95^{th} percentile range) for combined resident and comparison communities: • age 6–35 months: 7.0 (1.7, 16.1) • age 36–71 months: 6.0 (1.6, 14.1) • age 6–15 years: 4.0 (1.1, 9.2) • age 16–72 years: 4.3 (1.0, 9.9) **Analysis:** T-cell and NK-cell abundances. Multiple linear regression. Adjustments made for age (continuous), sex, study site, and smoking.	An inverse association between increasing PbB and decreasing T-cell abundance β per 1 µg/dL PbB: Age 6–35 months: • T-cell%: -0.18, p=0.03 • T-cell count: 7.2, p=0.59 • NK-cell%: 0.00, p=0.99 • NK-cell count: 1.3, p=0.60
Wells et al. 2014 Cross-sectional study of 1,788 children (age 2–12 years) from NHANES 2005–2006	**PbB** Gmean (95% CI): • 1.13 (1.04, 1.22) **Analysis:** Eosinophil abundance. Multiple linear regression. Adjustments made for 6-month season, age, sex, race/ethnicity (non-Hispanic white/non-Hispanic black/other), parental educational status (<high school, high school, some college, 4-year college degree), presence of smokers in the home (IgE only) or prenatal smoke exposure (asthma only), BMI, cockroaches, and avoidance/removal of pets.	An association between increasing percent eosinophils in blood and increasing PbB was observed. β for % increase per 1 µg/dL (95% CI): 4.61 (2.44, 6.83)

Table 8. Selected Epidemiology Studies Evaluating Immunological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Inflammation		
Kim et al. 2007 Cross-sectional study of 300 adults (mean age 24±2 years) recruited in 2002 in Korea	**PbB** mean (range): • Q1: 1.46 (0.337,1.885) • Q2: 2.22 (1.886, 2.511) • Q3: 2.77 (2.513, 3.103) • Q4: 3.93 (3.110, 10.470) **Analysis:** Serum TNFα and IL-6, GSTM1 and TNFα genotypes, and WBC. Comparison of means (Chi-square, ANOVA) and multiple linear regression. Adjustments made for age, BMI, and smoking.	In male subjects, increased PbB was associated with increasing serum TNFα and WBC in the PbB stratum >2.51 µg/dL. β % increase per µg/dL (95% CI): • TNFα: 23 (4, 55), p=0.015 • IL-6: 26 (0, 55), p=0.082 • WBC: 15 (0, 35), p=0.004 When stratified by genotype, the effect of PbB was associated only in the TNFα GG and GSTM1-null genotypes.
Sirivarasai et al. 2013 Cross-sectional study of 924 male adults (mean age 43±25 years) enrolled in EGAT 1 study of cardiovascular disease conducted in 2009, Thailand	**PbB:** Mean (range): • 5.45 (1.23, 24.63) **Analysis:** Human serum CRP and GST genotypes. ANOVA for CRP, logistic regression for effect of GST genotype on CRP. Adjustments made for age, BMI, smoking, alcohol use, and blood pressure.	CRP was higher in upper quartile PbB stratum compared to Q1 and Q2 (p<0.001). In Q4 stratum, adjusted OR was elevated for GSTM1 and GSTT1 null genotypes (95% CI): • -GSTM1-/- and GSTT1-/-: 1.98 (1.47, 2.55) • -GSTM1-/-: 1.32 (1.03, 1.69) • -GSTT1-/-: 1.65 (1.17, 2.35)

Table 8. Selected Epidemiology Studies Evaluating Immunological Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Songdej et al. 2010 Cross-sectional study of 9,145 adults (age >40 years) from NHANES 1999–2004	**PbB:** Gmean: 1.89 **Analysis:** WBC and serum CRP and fibrinogen. Logistic regression. Adjustments made for age, BMI, smoking status, income, physical activity, ethnicity, education, and a history of inflammatory conditions, cardiovascular disease, and diabetes.	Adjusted ORs for elevated CRP were elevated in males, with no trend increasing PbB. ORs for fibrinogen or WBC were not elevated. OR (95% CI) for <1.16 versus >3.09 µg/dL: CRP • Males: 2.85 (1.49, 5.45) • Females: 0.57 (0.43, 0.76) Fibrinogen: • Males: 1.15 (0.61, 2.16) • Females: 0.87 (0.57, 1.33) WBC: • Males: 1.55 (0.96, 2.49) • Females: 0.84 (0.62, 1.13)

ANOVA = analysis of variance; BMI = body mass index; CdB = blood cadmium; CI = confidence interval; CL = confidence limit; CRP = C-reactive protein; EGAT 1 = Electric Generating Authority of Thailand study; ETS = environmental tobacco smoke; Gmean = geometric mean; GPx = glutathione peroxidase; GST = glutathione-s-transferase; GSTM1 = glutathione S-transferase mu 1; GSTT1 = glutathione S-transferase theta 1; IFN = interferon; Ig = immunoglobulin antibody; IL = interleukin; NHANES = National Health and Nutrition Examination Survey; NK = natural killer; OR = odds ratio; RR = relative risk; SCu = serum copper; SD = standard deviation; SE = standard error; SOD = superoxide dismutase; SSe = serum selenium; SZn = serum zinc; TNFα = tumor necrosis factor-alpha; WBC = white blood cell

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Intellectual deficits		
Baghurst et al. 1992 Prospective cohort of 494 children followed from birth (1979–1982) to age 7 years; Port Pirie, South Australia	**PbB**: Quartile range: • Birth: 4.3, 15.0 • Mean 0–2 years: 11.6, 27.1 • Mean 0–3 years: 12.2, 28.2 • Mean 0–4 years: 12.2, 27.7 • Lifetime average:10.8, 24.8 **Analysis:** Cognitive function (IQ) was assessed at age 7–8 years using WISC-R. Multiple linear regression with log-transformed PbB. Adjustments made for sex, birth weight, birth order, feeding method (breast, bottle, or both), duration of breastfeeding, parents' level of education, maternal age at delivery, parents' smoking status, SES, quality of home environment, maternal IQ, and whether the child's natural parents were living together.	Associations between increasing PbB and decreasing FSIQ measured at age 7–8 years. Adjusted changes in IQ for each lnPbB increase. β (SE) for PbB metrics: • Prenatal: 0.6 (1.4), p=0.68 • Mean 0–2 years: -4.6 (2.1), p=0.03 • Mean 0–3 years: -4.8 (2.3), p=0.04 • Mean 0–4 years: -4.6 (2.4), p=0.05 • Lifetime average: -3.7 (2.5), p=0.14
Bellinger et al. 1992; Bellinger and Needleman 2003 Prospective cohort 148 children followed from birth (1979–1981) to age 10 years; Boston, Massachusetts	**PbB:** Mean (SE): • 6 months: 6.7 (7.0) • 1 years: 7.7 (6.5) • 2 years: 6.5 (4.9) **Analysis:** Cognitive function was assessed at age 5–10 years using WISC-R. Multiple linear regression. Adjustments made for HOME57, HOME120, child stress, race, maternal IQ, SES, sex, birth order, marital status, and number of residence changes prior to age 57 months.	Associations between increasing PbB at age 2 years and decreasing FSIQ measured at age 10 years. Adjusted changes in IQ for each 1 µg/dL increase in PbB. β (SE) for PbB metrics: • Prenatal: -2.55 (2.56), p=0.57 • 6 months: -0.13 (0.15), p=0.39 • 2 years: -0.58 (0.21), p<0.007 • Peak <10 µg/dL: -1.56 (p=0.03) • Peak >10 µg/dL: -0.58 (p=NA)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Blackowicz et al. 2016 Retrospective study of 12,319 3rd grade Hispanic children (Chicago); data collection period: 1996–2006	**PbB:** Mean (SD) 4.16 (2.03) **Analysis:** Educational performance was based on scores on 3rd grade ISAT. Linear and log binomial regression. Adjustments were made for gender, mother's education, low-income, small for gestational age, preterm birth, age at time of blood lead, exam type, and Hispanic subgroup (Mexican American, Puerto Rican, other Hispanic).	Increased PbB was associated with lower ISAT score in each Hispanic subgroup Adjusted β (SE) for µg/dL (All Hispanic group): • Reading ISAT: -0.55 (0.06), p<0.001 • Math ISAT: -0.48 (0.06), p<0.001 Increased PbB was associated with increased risk of failure on ISAT in each Hispanic subgroup. Adjusted RR (95% CI) for All Hispanic group: • Reading ISAT: o 1 µg/dL increase: 1.07 (1.05, 1.10) o 5 µg/dL increase: 1.43 (1.25, 1.63) • Math ISAT o 1 µg/dL increase: 1.09 (1.06, 1.12) o 5 µg/dL increase: 1.53 (1.32, 1.78)
Boucher et al. 2014 Prospective cohort of 94 infants from the Canadian Arctic (Nunavik); data collection period was 1995–2001	**PbB:** Umbilical cord PbB • Mean (SD): 4.8 (3.5) • Range: 0.5–17.8 **Analysis**: Neurodevelopmental assessments (FTII, A-not-B test, BSID-II) were conducted at ages 6.5 and 11 months. Adjustments made for infant sex, infant age at testing, birth weight, maternal age, parity, social environment, maternal consumption of cigarettes, alcohol, and/or marijuana during pregnancy, cord plasma DHA, and cord blood Se.	Fixation duration (not specified if assessment time was 6.5 or 11 months) was associated with umbilical cord (ln) PbB, indicating slower information processing time. β (95% CI): 0.21 (0.07, 0.35); p≤0.01.

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Braun et al. 2012 Prospective cohort of 1,035 mother-infant pairs from Mexico City; child PbB was collected from four cohorts (data collection period: 1994–2004)	**PbB:** Median (5^{th}, 95^{th} percentile) at age: • 1 years: 4.2 (1.3, 10.6) • 2 years: 4.6 (1.5, 13.4) • 3 years: 5.5 (2.3, 13.8) • 4 years: 5.9 (2.5, 12.8) **Analysis:** PbB was collected at ages 1–4 years. Cognitive abilities (GCI) were conducted at age 4 years. Multiple linear regression. Adjustments made for maternal IQ, education, marital status, child sex, breastfeeding duration, and cohort.	Associations between increasing PbB and decreasing GCI assessed at age 4 years. Coefficient (95% CI) for change in GCI per 10 µg/dL increase in PbB for PbB measured at each year: • PbB at 1 years: -2.5 (-5.6, 0.5) • PbB at 2 years: -3.8 (-6.3, -1.4) • PbB at 3 years: -0.7 (-3.1, 1.6) • PbB at 4 years: -2.5 (-5.1, 0.1)
Canfield et al. 2003 Prospective cohort of 172 children (born 1994–1995), followed from age 24–40 months to 5 years; from Rochester, New York	**PbB:** Mean (SD): Lifetime average at age 5 years: 7.4 (4.3) Peak: 11.1 (7.1) Concurrent with FSIQ: 5.8 (4.1) **Analysis:** PbB data collected at ages 6 months–5 years. Cognitive function was assessed by S-BIS at ages 3 and 5 years. Multiple linear and nonlinear regression. Adjustments made for maternal IQ, race, level of education, use of tobacco during pregnancy, household income, and HOME, and the child's sex, birth weight, and iron status.	Associations between increasing PbB and decreasing FSIQ measured at age 3 and/or 5 years, with largest coefficients at age 5 years. Adjusted changes in IQ for each 1 µg/dL increase in PbB. β (95% CI) for PbB metrics and FSIQ age 5 years. Full cohort (n=172) • Lifetime average: -0.57 (-0.93, -0.20); p=0.003 • Peak: -0.26 (-0.47, -0.05); p=0.02 • Concurrent: -0.61 (-0.99, -0.24); p<0.001 Peak PbB <10 (n=101) • Lifetime average: -1.52 (-2.94, -0.09); p=0.04 • Peak: -1.44 (-2.55, -0.33); p=0.01 • Concurrent: -1.79 (-3.00, -0.60); p=0.004 Relationship between PbB and IQ was nonlinear. FSIQ change for lifetime average PbB: 1–10 µg/dL: -7.4 points 10–20 µg/dL: -2.5 points

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Chandramouli et al. 2009 Prospective study of 488 children followed from age 4 months (born 1992) to age 7 years in Avon, United Kingdom	**PbB:** • Mean (SD) at age 30 months: 4.22 (3.12) • Participants with PbB >10: 6% **Analysis:** PbB assessed at 30 months. Academic performance was assessed by SATs at ages 7–8 years. Adjustments made for gender, child's IQ, maternal education, home ownership, maternal smoking, a home facilities score at 6 months, paternal SES at the time of pregnancy, Family Adversity index, and parenting attitudes at 6 months.	OR (95% CI) for standard assessment test grades for PbB categories Reading • PbB 2–5 µg/dL: 0.88 (0.54, 1.43); p=0.608 • PbB 5–10 µg/dL: 0.51 (0.32, 0.82); p=0.006 Writing • PbB 2–5 µg/dL: 1.08 (0.69, 1.71); p=0.729 • PbB 5–10 µg/dL: 0.49 (0.31, 0.78); p=0.003 A 2-fold increase in PbB was associated with a 0.3 point (95% CI -0.5, -0.1) decrease in standard assessment test scores.
Chiodo et al. 2004 Prospective study of 237 children, age 7.5 years; Detroit, Michigan	**PbB:** Mean (SD, range): 5.4 (3.3, 1–25) **Analysis**: FSIQ measured at 7.5 years using WISC-III. Multiple nonparametric regression. Adjustments made for SES, education level, number of children <18 years old, HOME score, PPVT-R, gender, parity, FES, prenatal alcohol exposure, crowding, life stress of the child and caretaker, child's age, prenatal exposure to cocaine and marijuana, conflict tactics, and prenatal smoking.	Association between increasing concurrent PbB and decreasing FSIQ, β (SE): • <3 µg/dL: -0.10, p ≤0.1 • <5 µg/dL: -0.12, p ≤0.1 • <7.5 µg/dL: -0.14, p ≤0.05 • <10 µg/dL: -0.18 p ≤0.01 • Cohort: -0.20, p≤0.01

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Desrochers-Couture et al. 2018 Prospective study of 609 mother-infant pairs (recruited 2008–2011) with follow-up at age 3–4 years; Canada (Maternal-infant Research on Environmental Chemicals Study)	**PbB:** Gmean (SD) • 1st trimester 0.62 (1.6) • 3rd trimester: 0.59 (1.7) • Cord: 0.76 (1.7) • Child (3–4 years): 0.70 (1.7) **Analysis:** Cognitive assessments (WPPSI-III) were conducted at age 3–4 years. Adjustments made for cord blood models were child age, child sex, maternal education, evaluation site, cord mercury; and for child blood models were child age, child sex, evaluation site, marital status, family income, HOME score, parenting stress index, and cord blood lead.	FSIQ, verbal IQ, performance IQ, or general language composite were not associated with cord or child PbB, β per 1 SD PbB (95% CI) • Cord PbB o FSIQ: -0.070 (-0.143, 0.003, p=0.115 • Child PbB o FSIQ: 0.014 (-0.071, 0.098), p=0.791 Increasing cord PbB interacting with gender was associated with decreasing FSIQ: • Cord PbB o Male: -2.65 (-4.66, -0.48) p=0.04 o Female: -0.18 (-1.63, 1.21) p=0.83 • Child PbB o Male: -0.07 (-2.10, 2.17), p=0.96 o Female: 0.52 (-1.23, 2.40) p=0.63

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Dietrich et al. 1986 Prospective study of 280 mother-infant pairs from Cincinnati, Ohio (infants born 1979–1984)	**PbB:** Prenatal (maternal) • Mean (SD): 8.0 (3.8) • Range: 1–27 Neonatal (age 10 days) • Mean (SD): 4.5 (2.9) • Range: 1–22 **Analysis:** Neurodevelopmental assessments (MDI of the BSID) were conducted at age 6 months. Multiple linear regression with ln transformed PbB. Adjustments made for birth weight, gestational age by examination, obstetrical complications, postnatal complications, tobacco and alcohol consumption during pregnancy, maternal age at birth of child, gravidity, parity, maternal total iron binding capacity, race of child, sex of child, SES, HOME, and number of children in the home.	Associations with maternal PbB (n=245), β per 1 lnPbB (SE): • MDI: -14.978 (6.114); p<0.02 Associations with neonatal PbB (n=280), β per lnPbB (SE): • MDI: -15.110 (5.083); p<0.003 In males (but not females, data not reported), each unit increase in lnPbB was associated with a 5.7-point decrease in MDI: F (1,122): 4.95; p=0.03

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Dietrich et al. 1987 Prospective study of 185 mother-infant pairs from Cincinnati, Ohio (infants born 1979–1984)	**PbB:** Mean (SD, range) • Prenatal (maternal): 8.3 (3.8, 1–27) • Neonatal (10 days): 4.9 (3.3, 1–24) • Neonatal (3 months): 6.3 (3.8, 1–22) • Neonatal (6 months): 8.1 (5.2, 1–36) **Analysis:** Neurodevelopmental assessments (MDI of the BSID) were conducted at age 6 months. Multiple linear regression with ln transformed PbB. Adjustments made for obstetrical complications, postnatal complications, total iron binding capacity, birth weight, gestational age at examination, composite index of tobacco and alcohol use during pregnancy (CITAC), home environment (HOME), SES, and infant race (white/nonwhite).	Associations with 3-month PbB, β per lnPbB (SE): • MDI: -12.113 (4.727); p=0.01 • PDI: -13.248 (4.250); p=0.002 • Motor maturity: -0.570 (0.260); p=0.03 Associations with 6-month PbB, β per ln PbB (SE): • MDI: -2.117 (0.916); p=0.02

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Dietrich et al. 1989 Prospective study of 192 mother-infant pairs from Cincinnati, Ohio (infants born 1979–1984)	**PbB:** Mean (SD, range) • Prenatal (maternal): 8.2 (3.6, 1–27) • Neonatal (10 days): 4.8 (3.1, 1–23) • Neonatal (3 months): 6.0 (3.5, 1–20) • Neonatal (6 months): 7.9 (4.8, 1–35) • Neonatal (9 months): 11.5 (6.9, 2–57) • Neonatal (12 months): 14.2 (7.3, 4–47) **Analysis:** Neurodevelopmental assessments (MDI of the BSID) were conducted at age 12 months. Multiple linear regression and SEM. Adjustments made for obstetrical complications, postnatal complications, birth weight, gestational age, child race, child sex, CITAC, maternal age, gravidity, parity, maternal total iron binding capacity, child health variables (number of infections during the last year, current illness, iron status), HOME, SES, maternal IQ, and number of children in the home.	SEM indicated associations between increasing prenatal PbB and 12-month MDI through decreasing birth weight. Standardized regression coefficients: • Prenatal PbB --> birth weight: -0.15, p≤0.05 • Birth weight --> 12-month MDI: 0.18, p≤0.05
Dietrich et al. 1991 Prospective study of 258 4-year-old children (born 1979–1984) from Cincinnati, Ohio	**PbB:** Mean (SD, range) (based on Dietrich et al. 1992) • Maternal (6–7 months): 8.2 (3.8, 1–27) • Neonatal (10 days): 4.8 (3.3, 1–26) **Analysis:** Neurodevelopmental assessments (K-ABC) at 4 years. Multiple linear regression. Adjustments made for birth weight, maternal cigarette and alcohol use during pregnancy, maternal marijuana use during pregnancy, child race, HOME score, maternal IQ, and preschool attendance.	Associations between increasing neonatal (but not maternal or post-natal average) PbB and decreasing K-ABC scores. Coefficients per µg/dL neonatal PbB: Mental processing composite: -0.63 p<0.01 Sequential processing: -0.68, p<0.01 Simultaneous processing: -0.50, p<0.05 Nonverbal: -0.63, p<0.01 Achievement: -0.28, p<0.05

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Dietrich et al. 1992 Prospective study of 259 5-year-old children (born 1979–1984) from Cincinnati, Ohio	**PbB:** Mean (SD, range) • Maternal (6–7 months): 8.2 (3.8, 1–27) • Neonatal (10 days): 4.8 (3.3, 1–26) • Postnatal (5 years): 11.9 (6.4, 3–38) **Analysis:** Neurodevelopmental assessments (FWS, AFGS) at 5 years. Multiple linear regression. Adjustments made for hearing screen, social class, HOME score, birth weight, gestational age, obstetrical complications, and alcohol consumption.	Associations between increasing neo-natal and postnatal PbB and decreasing FWS scores. Coefficients per µg/dL neonatal PbB: FWS(T): -0.26 p<0.1 FWS(L): -0.20, p<0.01 FWS(R) -0.13, p<0.1 Coefficients per µg/dL concurrent PbB: FWS(T): -0.11 p<0.1 FWS(L): -0.06, p<0.1 FWS(R) -0.08, p<0.05
Dietrich et al. 1993a Prospective study of 253 6–7-year-old children (born 1979–1984) from Cincinnati, Ohio	**PbB:** Mean (SD) • Maternal: 8.3 (3.7) • Birth: 5 (3.4) • 4–5 years: 11.8 (6.3) **Analysis:** Cognitive function was assessed at age 6.5 years using WISC-R. Multiple linear regression. Adjustments made for birth weight, gestational age, obstetrical complications, postnatal complications, maternal age at birth, maternal IQ, and HOME score.	Associations between increasing PbB and decreasing FSIQ measured at age 6.5 years. Adjusted changes in IQ for each 1 µg/dL increase in PbB. β (SE) for PbB metrics: • Prenatal: 0.15 (0.21), p>0.1 • Lifetime average: -0.13 (0.11), p≤0.01 • Concurrent: -0.33 (0.14), p≤0.05
Emory et al. 2003 Retrospective study of 79 African-American mother-infant pairs from Atlanta, Georgia; data collection period: April–May 2000	**PbB:** Mean (SD; range) • Maternal: 0.72 (0.86; 0.05–3.3) **Analysis:** Memory assessment using FTII at 7 months. Chi-square test of score category (low, medium, high) versus mean maternal blood lead. No adjustments.	Lower FTII scores (Scaled Novelty Risk [risk of mental retardation later in life]) associated with higher maternal PbB (p<0.05). Score: PbB (±SD): Low risk: 0.65 µg/dL (0.80) Medium risk: 0.89 µg/dL (0.88) High risk: 1.01 µg/dL (0.126)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
EPA 2014e (re-analysis of cohorts in Lanphear et al. 2005) Prospective; pooled-analysis; 1,333 children (4.8–6 years of age) from seven prospective studies conducted in Boston, Massachusetts (Bellinger et al. 1992, n=116); Cincinnati, Ohio (Dietrich et al. 1993a, n=221); Cleveland, Ohio (Ernhart et al. 1989, n=160); Mexico City, Mexico (Schnaas et al. 2000, n=99); Port Pirie, Australia (Baghurst et al. 1992, n=324); Rochester, New York (Canfield et al. 2003; n=182); and Yugoslavia (Wasserman et al. 1997, n=231)	**PbB:** Mean (95% CI): Lifetime average: 12.4 (4.1, 34.8) Peak: 18.0 (6.2, 47.0) Concurrent with FSIQ: 9.7 (2.5, 33.2) **Analysis.** Cognitive function (FSIQ) was assessed at age 5–10 years using various instruments. Multiple linear regression with log-transformed PbB and spline function. Adjustments made for HOME score, birth weight, maternal IQ, and maternal education.	Regression analysis showed associations between increasing PbB and declines in FSIQ: β coefficient for FSIQ per ln PbB (µg/dL) increase in PbB (95% CI): • 6–24 months: -2.21 (-3.38, -1304) • Lifetime average: -3.14 (-4.39, -1.88) • Peak: -2.86 (-4.10, -1.61) • Concurrent: -2.65 (-3.69, -1.61) FSIQ change for concurrent PbB range: • 2.4–10 µg/dL: -3.8 points (-2.3, -5.3) • 10–20 µg/dL: -1.8 points (-1.1, -2.6) • 20–30 µg/dL: -1.1 (-0.7, -1.5)
Evens et al. 2015 Population-based retrospective cohort study of 47,168 3rd grade children (born 1994–1998) in Chicago, Illinois; data collection period for educational performance was 2003–2006	**PbB:** Mean (SD): 4.81 (2.22) Participants with PbB <10: 100% **Analysis.** Educational performance data (ISAT scores) in children in 3rd grade were linked to Chicago Blood Lead Registry data (collected birth–72 months of age). Multiple linear regression with log-transformed PbB. Adjustments made for sex of child, mother's education, low-income, very low birth weight/preterm, child's age at time of testing, and child race.	Regression analysis showed that ISAT reading and math scores were inversely associated with PbB. Regression coefficient (SE): • Reading: -0.60 (0.03); p<0.0001 • Math: -0.50 (0.03); p<0.0001 Adjusted RR (95% CI) for reading and math failure for increases in PbB of: Reading: • 1 µg/dL: 1.06 (1.05, 1.07) • 5 µg/dL: 1.32 (1.26, 1.39) Math: • 1 µg/dL: 1.06 (1.05, 1.07) • 5 µg/dL: 1.32 (1.26, 1.39)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Geier et al. 2017 Cross-sectional study of 1,411 children (age 6–15 years) from NHANES 2003–2004	**PbB:** Mean (SD): 1.32 (0.95) Percentiles, range: • 0–50th: 0.2–1.007 • 50th–75th: 1.007–1.53 • 75th–100th: 1.530–13.50 **Analysis:** Logistic regression of PbB and diagnosis of a learning disability, adjusted for gender and race.	Increasing PbB was associated with OR for diagnosis of a learning disability (95% CI): OR per µg/dL: 1.19 (1.00, 1.40) p=0.044 OR for upper quartile PbB relative to <50th percentile (<P50) as reference: • P50–P75: 1.46 (1.11, 1.92), p=0.0017 • P75–P100: 1.95 (1.16, 3.29), p=0.0033
Gomaa et al. 2002 Prospective study of 197 children followed from birth to age 2 years in Mexico City (data collection period not specified)	**PbB:** Umbilical cord mean (SD): 6.7 (3.4) Participants with PbB ≥10: 15.7% **Analysis:** Neurodevelopment (MDI of the BSID-II) was assessed at age 24 months. Adjustments made for maternal IQ, maternal age, child sex, maternal years of education, paternal years of education, marital status, duration of breastfeeding, and child hospitalization during the first 6 month of life, and Pb biomarkers (umbilical blood lead, tibia bone Pb, and patella bone Pb).	Linear regression showed a negative association between umbilical cord PbB and MDI score. β per lnPbB (SE): -4.48 (2.04); p=0.03 A doubling of umbilical cord PbB from 5 to 10 µg/dL was associated with a 3.1-point decrement in MDI score.

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Hong et al. 2015 Cross-sectional study of 1,001 children (ages 8–11 years) in South Korea; data collection period not reported	**PbB:** Gmean (GSD): 1.80 (1.40) 5^{th}–95^{th} percentile range: 0.53–6.16 **Analysis:** PbB and cognitive function (assessed by KEDI-WISC) were assessed at ages 8–11 years. Multiple linear regression with log_{10}-transformed PbB. Adjustments made for age, sex, residential region, paternal education level, and yearly income, ADHD-RS and CPT scores, log_{10}-transformed environmental chemical concentrations (Hg, Mn), creatinine-standardized urine concentrations of cotinine, phthalate metabolites (MnBP, MEOHP, MEHP), and bisphenol A.	PbB was associated with a decrease in IQ scores. Regression coefficients (95% CI): per 10-fold increase in PbB • Verbal IQ: -2.64 (-4.98, -0.30); p=0.027 • Full-scale IQ: -7.23 (-13.39, -1.07); p=0.021

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Hu et al. 2006 Prospective study of 146 mother-child pairs (birth dates: 1997–1999) followed prenatally to age 2 years in Mexico City	**PbB:** Mean±SD (range) • Umbilical cord: 6.20±3.88 (0.9–20.0) • Child 12-month: 5.22±3.41 (0.9–20.4) • Child 24-month: 4.79±3.71 (0.8–36.8) • Maternal 1st trimester: 7.07±5.10 (1.49–43.6) • Maternal 2nd trimester: 6.08±3.15 (1.58–22.4) • Maternal 3rd trimester: 6.86±4.23 (1.53–33.1) **Analysis:** Cognitive function (MDI of the BSID-II) was assessed at 24 months. Multiple linear regression with ln-transformed PbB. Adjusted for infant's concurrent blood lead (24 months of age), sex, maternal age, current weight, height-for-age Z-score, and maternal IQ.	Regression analysis showed a negative association between 1st trimester (but not 2nd or 3rd trimester) maternal PbB and MDI score. No association was observed for cord PbB or child PbB at 12 or 24 months. β (95% CI), per 1 SD change in lnPbB: • Umbilical cord: -0.35 (-4.72, 4.03); p=0.88 • Child 12-month: -2.38 (-6.24, 1.49); p=0.23 • Child 24-month: -1.00 (-3.93, 1.94); p=0.50 • Maternal 1st trimester: -4.13 (-8.10, -0.17); p=0.04 • Maternal 2nd trimester: -4.08 (-8.29, 0.12); p=0.06 • Maternal 3rd trimester: -2.42 (-6.38, 1.54); p=0.23

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Jedrychowski et al. 2009 Prospective study of 444 children (born 2001–2004) followed prenatally to age 3 years in Krakow, Poland	**PbB:** Umbilical cord PbB • Gmean: 1.29 • Range: 0.44–6.90 **Analysis:** Cognitive function (MDI of the BSID-II) was assessed at 12, 24, and 36 months. Multiple linear regression with log_{10}-transformed PbB. Adjustments made for maternal education, birth order, sex of child, and prenatal ETS exposure.	Regression analysis showed a negative association between log PbB (<5 µg/dL) and MDI scores at 24 and 36 months (but not at 12 months). β per log cord PbB±SE (95% CI): • 12 Months: -5.419±2.935 (-11.188, 0.3495); p=0.066 • 24 Months: -7.653±3.577 (-14.684, -0.623); p=0.033 • 36 Months: -6.717±2.964 (-12.546, -0.889); p=0.024 • For participants with PbB <5 (combination of all testing times): -6.618±2.499 (-11.517, -1.719); p=0.008 A 1 log unit increase of cord PbB was associated with a 6-point reduction in MDI scores.

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Jusko et al. 2008 Prospective study of 174 children (born 1994–1995) recruited at age 24–30 months and evaluated for FSIQ at 6 years in Rochester, New York	**PbB:** lifetime average: • Mean (SD): 7.2 (4.1) • Range: 1.4–27.1 • Participants <10: 77% **Analysis:** Cognitive function (by WPPSI-R) was assessed at 6 years. Multiple linear and nonlinear regression. Adjustments made for child's sex, birth weight, transferrin saturation, mother's race, IQ, and education level; HOME-SF total score, family income, and maternal prenatal smoking.	Associations between increasing PbB and decreasing FSIQ measured at age 6 years (p=0.003). Comparison of children with PbB of 5–9.9 (high) to those with PbB <5 (low) showed a 4.9-point decrease in FSIQ score (low: 91.3; high 86.4; p=0.04) Adjusted changes in IQ for each 1 µg/dL increase in peak lifetime PbB (p-value not reported): 2.1–10 µg/dL: -1.2 10–20 µg/dL: -0.32 20–30 µg/dL: -0.15
Kim et al. 2013b Prospective birth cohort (MOCEH study; 2006–2010); 884 mother infant pairs; South Korea	**PbB:** Gmean (GSD) Early pregnancy: 1.4 (1.5) Late pregnancy: 1.3 (1.5) **Analysis:** Mental performance evaluated at age 6 months using MDI using the BSID-II. Multiple linear regression. Adjustments made for infant birth weight, infant sex, maternal age, maternal education level, family income, breastfeeding status, residential area, Pb, and Cd.	Association between increased PbB in late pregnancy and decreasing MDI score (β) per 1 µg/dL change in PbB (95% CI): -1.94 (-3.60, -0.29); p=0.02

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Kordas et al. 2011 Prospective study of 186 children followed prenatally (1994–1995) to age 4 years in Mexico City	**PbB:** Mean (SD) • Umbilical cord: 6.6 (3.3) • 24 months: 8.1 (4.4) • 48 months: 8.1 (3.6) **Analysis:** Cognitive function was assessed at 24 months by BSID-II and 48 months by MSCA. Multiple linear regression. Adjustments made for birth weight, gestational age, child sex, maternal age, years of schooling, IQ, smoking status (ever), marital status at enrollment, crowding in the house, and type of floor in the house.	Associations between increasing cord PbB and concurrent PbB with decreasing scores on various assessments of cognitive function assessed at 24 and 48 months. β (SE): • 24-Month MDI o Cord PbB: -0.7 (0.3); p<0.05 o Concurrent PbB: -0.1 (0.2) • 24-Month PDI o Cord PbB: -0.4 (0.2); p≥0.05 o Concurrent PbB: -0.2 (0.2) • 48-Month GCI o Cord PbB: -0.2 (0.3) o Concurrent PbB: -0.6 (0.2); p<0.05 • Memory score o Cord PbB: 0.1 (0.1) o Concurrent PbB: -0.3 (0.1)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Lanphear et al. 2000a Cross-sectional study of 4,853 children (ages 6–16 years; birth year: 1972–1988) from NHANES III (1988–1994).	**PbB:** Gmean: 1.9 Participants with PbB ≥5: 9.7% Participants with PbB ≥10: 2.1% **Analysis:** Cognitive function was assessed by WRAT-R and WISC-R. Adjustments made for sex, race/ethnicity, Poverty Index Ratio, educational level of reference adult, serum ferritin level, and serum cotinine level.	Inverse relationships were observed between PbB and scores for arithmetic, reading, block design (non-verbal reasoning), and digit span (short-term and working memory). Regression coefficients (SE): • Arithmetic: o PbB <2.5: -1.28 (0.98), p=0.20 o PbB <5.0: -1.06 (0.48); p=0.03 o PbB <7.5: -1.06 (0.39); p=0.01 o PbB <10: -0.89 (0.32); p=0.008 • Reading: o PbB <2.5: -1.71 (0.93); p=0.07 o PbB <5.0: -1.66 (0.36); p<0.001 o PbB <7.5: -1.53 (0.31); p<0.001 o PbB <10: -1.44 (0.30); p<0.001 • Block design: o PbB <2.5: -0.08 (0.22); p=0.72 o PbB <5.0: -0.05 (0.07); p-0.45 o PbB <7.5: -0.11 (0.06); p=0.04 o PbB <10: -0.13 (0.06); p=0.03 • Digit span: o PbB <2.5: -0.25 (0.17); p=0.17 o PbB <5.0: -0.09 (0.07), p=0.20 o PbB <7.5: -0.09 (0.05); p=0.11 o PbB <10: -0.08 (0.04); p=0.03

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		For every 1 µg/dL increase in PbB, there were decreases of approximately 1 point in mean reading score, 0.7 points in mean arithmetic score, 0.1 points in mean score of nonverbal reasoning (block design), and 0.05 points in mean digital span score.
Lanphear et al. 2005 (same cohorts used for Budtz-Jorgensen et al. 2013) Prospective; pooled-analysis; 1,333 children (4.8–6 years of age) from seven prospective studies conducted in Boston, Massachusetts (Bellinger et al. 1992, n=116); Cincinnati, Ohio (Dietrich et al. 1993a, n=221); Cleveland, Ohio (Ernhart et al. 1989, n=160); Mexico City, Mexico (Schnaas et al. 2000, n=99); Port Pirie, Australia (Baghurst et al. 1992, n=324); Rochester, New York (Canfield et al. 2003; n=182); and Yugoslavia (Wasserman et al. 1997, n=231)	**PbB**: Mean (96% CL): • Lifetime average: 12.4 (4.1, 34.8) • Peak: 18.0 (6.2, 47.0) • Concurrent with FSIQ: 9.7 (2.5, 33.2) **Analysis:** Cognitive function was assessed at age 5–10 years using various instruments. Multiple linear regression with log-transformed PbB and spline function. Adjustments made for HOME score, birth weight, maternal IQ, and maternal education.	Associations between increasing PbB and decreasing FSIQ measured at age 5–10 years. Adjusted changes in IQ for each ln PbB (µg/dL) increase in PbB. β (95% CI) for PbB metrics: • 6–24 months: -2.04 (-3.27, -0.81) • Lifetime average: -3.04 (-4.33, -1.75) • Peak: -2.85 (-4.10, -1.60) • Concurrent: -2.70 (-3.74, -1.66) Relationship between PbB and IQ was nonlinear. FSIQ change for lifetime average PbB (95% CI): 2.4–10 µg/dL: -3.9 points (-2.4, -5.3) 10–20 µg/dL: -1.9 points (-1.2, -2.6) 20–30 µg/dL: -1.1 (-0.7, -1.5)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Lanphear et al. 2019 (re-analysis of data reported in Lanphear et al. 2005; same cohorts used for Budtz-Jorgensen et al. 2013) Prospective; pooled-analysis; 1,333 children (4.8–6 years of age) from seven prospective studies conducted in Boston, Massachusetts (Bellinger et al. 1992, n=116); Cincinnati, Ohio (Dietrich et al. 1993a, n=221); Cleveland, Ohio (Ernhart et al. 1989, n=160); Mexico City, Mexico (Schnaas et al. 2000, n=99); Port Pirie, Australia (Baghurst et al. 1992, n=324); Rochester, New York (Canfield et al. 2003; n=182); and Yugoslavia (Wasserman et al. 1997, n=231)	**PbB**: Median (95% CI): • Lifetime average: 11.9 (3.6, 34.5) • Peak: 18.0 (6.0, 47.0) • Concurrent with FSIQ: 9.7 (2.5, 33.2) **Analysis:** Cognitive function was assessed at age 5–10 years using various instruments. Multiple linear regression with log-transformed PbB and spline function. Adjustments made for HOME score, birth weight, maternal IQ, and maternal education.	Associations between increasing PbB and decreasing FSIQ measured at age 5–10 years. Adjusted changes in IQ for each ln PbB (µg/dL) increase in PbB. β (95% CI) for PbB metrics: • 6–24 months: -2.21 (-3.38, -1.04) • Peak: -2.86 (-4.10, -1.61) • Lifetime average: -3.25 (-4.51, -1.99) • Concurrent: -2.65 (-3.69, -1.61) Relationship between PbB and IQ was nonlinear. FSIQ change for concurrent PbB (95% CIL): • 2.4–10 µg/dL: -3.8 points (-2.3, -5.3) • 10–20 µg/dL: -1.8 points (-1.1, -2.6) • 20–30 µg/dL: -1.1 points (-0.7, -1.5)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Lin et al. 2013 Prospective (Taiwan Birth Panel Study; birth dates: April 2004–January 2005) of 230 mother-infant pairs from Taipei, Taiwan; followed until age 2 years	**PbB:** Umbilical cord • Mean (SD): 1.30 (0.75) • Range: 0.016–4.32 **Analysis:** Cognitive function was assessed by CDIIT at age 2 years. Adjustments made for maternal age, maternal education, fish intake ≥2 times/week during pregnancy, infant sex, ETS during pregnancy and after delivery, and HOME.	Regression analysis comparing PbB ≥1.645 (75th percentile) and PbB <1.645. Adjusted β (SE): • Total score: -4.23 (1.82); p<0.05 • Cognitive: -5.35 (2.19); p<0.05 • Language: -2.53 (1.89)
Liu et al. 2014b Prospective study of 243 infants followed from birth to age 3 years (birth years 2009–2010) from Pearl River Delta, Guangdong, China	**PbB:** Umbilical cord mean (SD) • Low PbB group: 1.35 (0.26) • High PbB group: 5.63 (0.32) **Analysis:** Neurodevelopmental assessments (MDI and PDI of the BSID-II) were conducted at ages 6, 12, 24, and 36 months. Adjustments made for birth weight, sex, blood umbilical cord Pb levels, maternal age, hemoglobin, IQ, tobacco use, parents' occupation, educational level, and yearly household income.	Increasing umbilical cord PbB (low to high group) was associated with decreasing MDI measured at 6, 12, 24, or 36 months, and decreasing PDI measured at age 36 months when adjusted for confounders. Regression coefficients (95% CI): • MDI o 6 months: -1.647 (-2.094, -1.200); p=0.016 o 12 months: -1.458 (-1.832, -1.084); p=0.023 o 24 months: -1.385 (-1.683, -1.087); p=0.033 o 36 months: -1.291 (-1.550, -1.032); p=0.036 • PDI at 36 months: -1.302 (-1.572, -1.031); p=0.041 Increasing PbB at age 24 and 36 months was associated with decreasing MDI scores measured at 24 and 36 months, respectively; β: • 24 Months: -1.403; p=0.026 • 36 Months: -1.382; p=0.032

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Mazumdar et al. 2011 A prospective of 43 adults followed from birth (1979–1981) to age 28–30 years; participants were from the Boston cohort (Bellinger et al. 1992)	**PbB:** Mean (SD) • Cord: 6.5 (5.3) • 6 months: 8.0 (5.3) • 12 months: 10.0 (6.7) • Age 2 years: 7.7 (4.0) • Age 4 years: 6.7 (3.6) • Age 10 years: 3.0 (2.7) **Analysis:** FSIQ was assessed using WASI at age 28–30 years. Adjustments made for sex, race, birth weight, birth order, gestational age at delivery, mother's marital status at delivery, highest educational level of mother at delivery, maternal IQ, maternal tobacco use during pregnancy, maternal alcohol use during pregnancy, subject's history of concussion or head trauma, and alcohol use.	Childhood PbB was associated with a decrease in FSIQ in adults examined at age 28–30 years. Changes in FSIQ per 1 µg/dL increase in PbB. β (95%CL) for average late childhood PbB (mean of 4 and 10 years PbB): • Unadjusted: -1.89 (-3.30, -0.47), p<0.01 • Adjusted for maternal IQ: -1.11 (-2.29, 0.06) • Other adjustments made for 95% UCLs for β <0
McLaine et al. 2013 Population-based retrospective cohort study of 3,406 children enrolled in kindergarten during 3 school years (2004–2005, 2005–2006, and 2006–2007) in Providence, Rhode Island	**PbB:** Median: 4.2 Interquartile range: 2.6–6.0 **Analysis:** Kindergarten reading readiness scores (PALS-K test) were linked to state health department data on PbB collected at birth and PbB screening data (collected 9–72 months of age). Multiple linear regression. Adjustments made for geometric mean BLL category (0–≥10 µg/dL), sex, year, age at time of test, race, child language, and free/reduced lunch status.	PbB was associated with a decrease in PALS-K scores. Mean differences (95% CI) in PALS-K scores (85% CL), compared to PbB <5 µg/dL: • PbB 5–9 µg/dL: -4.51 (-6.61, -2.85); p>0.182 • PbB ≥10 µg/dL: -10.13 (-13.30, -6.96); p>0.182 Prevalence ratio (95% CI) for falling below the PALS-K benchmark, compared to PbB <5 µg/dL: • PbB 5–9 µg/dL: 1.21 (1.19, 1.23); p<0.001 • PbB ≥10 µg/dL: 1.56 (1.51, 1.60); p<0.001

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Min et al. 2009 Prospective study of 267 children followed prenatally (1994–1996) to age 11 years in Cleveland, Ohio	**PbB:** Mean (SD) • 4 years: 7.0 µg/dL (4.1) **Analysis:** Cognitive function was assessed at 4 years (WPPSI-R), 9 years (WISC-IV) and 11 years (WISC-IV). Multiple linear regression. Adjustments made for prenatal cocaine, marijuana, tobacco, and alcohol exposure, SES, maternal age, marital status at birth, mother's education level, number of prenatal care visits, parity, child's race, child's sex, infant head circumference, HOME score, biological and current caregiver GSI, and iron deficiency anemia status.	Associations between increasing concurrent PbB with decreasing FSIQ score. Regression coefficient (SE): • 4 Years: -0.50 (0.20), $p<0.05$ • 9 Years: -0.41 (0.19), $p<0.05$ • 11 Years: -0.54 (0.19) $p<0.01$

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Miranda et al. 2009 Population-based retrospective cohort study of 57,678 4th grade children from North Carolina (all counties)	**PbB:** Mean: 4.8 Median: 4 Range: 1–16 Interquartile range: 3.0–6.0 **Analysis:** Reading EOG test scores of 4th grade students were linked to PbB screening data collected at ages 6–36 months. Adjustments made for race, household income, prenatal education, and BLL.	A negative association was observed between PbB and reading EOG test scores. Regression coefficients (95% CI): • PbB 2 µg/dL: -0.30 (-0.58, -0.01); p<0.0001 • PbB 3 µg/dL: -0.46 (-0.73, -0.19); p<0.0001 • PbB 4 µg/dL: -0.52 (-0.79, -0.24); p<0.0001 • PbB 5 µg/dL: -0.80 (-1.08, -0.51); p<0.0001 • PbB 6 µg/dL: -0.99 (-1.29, -0.68); p<0.0001 • PbB 7 µg/dL: -1.07 (-1.40, -0.74); p<0.0001 • PbB 8 µg/dL: -1.35 (-1.73, -0.97); p<0.0001 • PbB 9 µg/dL: -1.20 (-1.64, -0.75); p<0.0001 • PbB ≥10 µg/dL: -1.75 (-2.09, -1.41); p<0.0001

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Polanska et al. 2018 Prospective study of 539 mother-child pairs, recruited in 2007, with follow-up of 303 children at age 2 years; Polish Mother and Child Cohort (REPRO_PL), Poland	**PbB:** Gmean (SD) (range) • 2nd trimester: 0.99 (0.15) (0.29, 2.63) • Cord: 0.96 (0.16) (0.24, 5.65) **Analysis:** Cognitive function was assessed at age 2 years using BSID III. Linear regression. Adjustments made for parental age and education, SES and marital status, child sex, pregnancy complications, delivery type, week of pregnancy, anthropomorphic measures at birth, breastfeeding, number of children at home, daycare attendance, cotinine levels in saliva, alcohol consumption during pregnancy, and environmental exposure of child to tobacco smoke.	Increasing cord PbB was associated with decreasing cognitive scores in males. β score per µg/dL (95% CI): Cognitive score: • Females: 0.34 (-1.30, 1.98), p=0.68 • Males: -2.07 (-4.07, -0.06), p=0.04 Language score: • Females: -0.29 (-2.23, 1.65), p=0.77 • Males: -0.43 (-2.81, 1.95), p=0.72
Rodrigues et al. 2016 Prospective study with cross-sectional analysis of PbB and fine motor score; n=524 children, 20–30 months; Sirajdikhan and Pabna, Bangladesh	**PbB:** Median (P24, P75, Maximum) • Sirajdikhan: 7.6 (5.5, 10.4) • Pabna: <LOD (<LOD, 3.8, 13.8) **Analysis:** Cognitive function was assessed at age 2–3 years using BSID III. General linear model regression. Adjustments made for maternal age and education, exposure to environmental tobacco smoke, child sex, HOME score, maternal Raven score, and child hematocrit.	Child PbB was associated with decreasing cognitive scores β score per lnPbB µg/dL (SE) in Pabna: Cognitive score: • Sirajdikhan: -0.17 (0.09), p=0.05 • Pabna: 0.02 (0.12), p=0.87

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Rooney et al. 2018 Longitudinal study of 330 children age 8–12 years at recruitment (1997) with follow-up at age 12 and 17 years, Casa Pia Clinical Trial of Dental Amalgams in Children, Lisbon, Portugal	**PbB:** Mean (SD) at age 8–12 years • Females: 4.42 (2.19) • Males: 5.26 (2.73) **Analysis:** Cognitive function was assessed at ages 12 and 17 years using the Ray auditory Verbal Learning Test, WAdSI III, Wechsler Memory Scale for Adults III, Standard Reaction Time, finger tapping, Trailmaking A and B, Wisconsin Card Sorting Test and Stroop tests. Genetic variants of N-methyl-D-aspartate receptors (NMDAR subunits GRIN2A and GRIN2B) were evaluated at the start of the study. Bayesian mixed regression models. Adjustments made for age, race, nonverbal IQ at baseline, and urinary mercury. Other factors were considered to be sufficiently uniform to not require adjustments (e.g., SES, home environment, medical histories)	GRINA2A and GRIN2B variants were effect modifiers on associations between increasing PbB (at age 8–12 years) and decreasing performance on learning and memory and executive functions assessed at age 17 years. The associations were stronger and more consistent across tests in males.
Ruebner et al. 2019 Cross-sectional study of 412 children (median age 15.4 years) from prospective study of CKD in children; United States	**PbB:** Median (P24, P75) 1.2 (0.8, 1.8) **Analysis:** Cognitive function was assessed at various ages ranging from 1 to 18 years using a variety of tests (MSEL, WASI, WPPSI, CPT, CPTI). Linear regression. Adjustments made for age, sex, race, poverty, maternal education, CKD stage, CKD duration, glomerular CKD diagnosis, abnormal birth history, proteinuria, hypertension, and anemia.	Increasing child PbB was associated with poorer cognitive performance. β score per µg/dL (95% CI): FSIQ: • PbB: -2.1 (-3.9, -0.2), p=0.029 CPT variability score: • PbB: 1.8 (0.2, 3.5), p=0.033

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Schnaas et al. 2006 Prospective study of 150 children in Mexico City, followed from birth (1987–1992) to age 10 years	**PbB:** Maternal during full pregnancy • Gmean (range): 8.0 (1–33) Maternal PbB during pregnancy weeks 28–36 • Gmean (95% CI): 7.3 (1.5–17.4) Child 1–5 years • Gmean (range): 9.8 (2.8–36.4) Child 6–10 years • Gmean (range): 6.2 (2.2–18.6) **Analysis:** Cognitive function was assessed at ages 6–10 years using WISC-II. Multiple linear regression with log-transformed PbB and mixed effects. Adjustments made for maternal IQ, SES, birth weight, and an indicator variable of first FSIQ application at 6, 7, or 8 years.	Association between increasing maternal and child PbB and decreasing FSIQ assessed at age 6–10 years. β (95% CI): • Ln maternal PbB 28 weeks of pregnancy: -4.00 (-6.37, -1.65); p=0.001 • Ln child PbB (6–10 years): -2.45 (-4.09, -0.81); p=0.003

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Shadbegian et al. 2019 Retrospective study of 560,624 children born in the period 1990–2004 with PbB measured at ages 0–5 years and cognitive assessments during school grades 3–8, North Carolina	**PbB:** Mean (SD) • Full <10µg/dL: 3.66 (1.90) • Full ≤5 µg/dL: 2.89 (1.18) • CEM ≤5 µg/dL: 2.40 (1.24) (CEM is coarsened exact matching of potential co-variables to ≤1 µg/dL stratum) **Analysis:** Cognitive function was assessed during school grades 3–8 using standard achievement tests. General linear model of change in percentile score compared to children whose PbB was ≤1 µg/dL. Strata matched (CEM) to ≤1 µg/dL stratum for race/ethnicity, SES, mother's marital status, enrollment in Medicaid at time of blood test, school, school grade, year of assessment, mother's age at time of birth, and parent education.	Increasing child PbB was associated with decreasing percentile of academic performance score. Percentile score change relative to ≤1 µg/dL CEM stratum (SE) for children who had geometric mean PbB >1 and ≤5 µg/dL: Math percentile for PbB strata: • 2 µg/dL: -0.38 (0.19), p>0.05 • 3 µg/dL: -0.56 (0.20), p<0.01 • 4 µg/dL: -0.96 (0.23), p<0.001 • 5 µg/dL: -0.51(0.30), p>0.05 Reading percentile for PbB strata • 2 µg/dL: -0.55 (0.19), p<0.01 • 3 µg/dL: -1.02 (0.20), p<0.001 • 4 µg/dL: -1.31 (0.23), p<0.001 • 5 µg/dL: -0.97 (0.30), p>0.001
Sobin et al. 2015 Cross-sectional; 252 children; age 5.1–11.8 years; El Paso Texas	**PbB:** Mean (SD): • Females: 2.7 (1.5) • Males: 2.4 (1.0) • 96% <5.0 µg/dL **Analysis:** Memory performance assessed using CANTAB at ages 5–12 years. Multiple linear regression. Adjustments made for sex, age, mother's level of education, and site.	Association between increasing concurrent PbB and working memory misses. β (SE): 0.11 (0.03), p<0.01

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Taylor et al. 2017 Prospective study of 14,062 mother-infant pairs, followed from birth (recruited 1991–1992), with follow-up of a random subset of children at age 4 years (n=404) and 8 years (n=2,127) from 4,316 births; Avon, United Kingdom	**PbB:** Mean (SD): • Maternal (11 weeks): 3.67 (1.46) • Child (30 months): 4.22 (3.12) **Analysis:** Cognitive performance evaluated at age 4 years (WPPSI) and 8 years (WISC-III). Linear and logistic regression. Adjustments made for family adversity index, housing age, household crowding, first trimester tobacco smoking and alcohol consumption, maternal age at birth, parity, maternal education, residence in Avon, child sex, child age at testing, and weighted life events score.	Increasing maternal PbB was associated with increasing FSIQ of females, but not males, at age 8 years. β for score per µg/dL (95% CI): Females: • Verbal: 0.71 (0.11, 1.32), p=0.021 • Performance: 0.57 (-0.11, 1.24), p=0.099 • Total: 0.73 (0.13, 1.33), p=0.017 Males: • Verbal: -0.15 (-0.90, 0.60), p=0.72 • Performance: -0.42 (-1.19, 0.35), p=0.29 • Total: -0.29 (-1.02, 0.44), p=0.44 OR for low IQ (lowest IQ quartile) at age 8 years (95% CI) for children with PbB >5 µg/dL relative to ≤5 µg/dL (reference): • Verbal: 0.73 (0.51, 1.05), p=0.090 • Performance: 1.09 (0.78, 1.51), p=0.62 • Total: 0.86 (0.60, 1.22), p=0.39
Tellez-Rojo et al. 2006 Prospective study of 294 children followed from birth (1994–1995, 1997–1999) to age 2 years; Mexico City	**PbB:** Mean (SD): • Cord: 4.85 (3.0) • 12 months: 4.27 (2.14) • 24 months: 4.28 (2.25) **Analysis:** Motor performance (MDI) evaluated at ages 6 and 12 using the BSID II. Multiple linear regression with ln-transformed PbB. Adjustments made for sex, birth weight, and maternal IQ.	Association between increasing concurrent PbB and MDI score at age 24 months (β) per lnPbB: 12 Months: • <10 µg/dL: -0.15, p=0.57 • ≥10 µg/dL: -0.71, p=0.17 24 Months: • <10µg/dL: -1.04, p<0.01 • ≥10 µg/dL: 0.07, p=0.84

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Vigeh et al. 2014 Prospective study of 174 mother-child pairs (mothers enrolled 2006–2011) in Tehran, Iran; followed from birth to 36 months	**PbB:** Mean±SD (range) • 1st Trimester: 4.15±2.43 (1.6–20.5) • 2nd Trimester: 3.44±1.28 (1.1–7.5) • 3rd Trimester: 3.78±1.40 (1.5–8.0) • Umbilical cord: 2.86±1.09 (1.2–6.9) **Analysis:** Cognitive development was assessed at children up to 36 months of age by HIECDI and ECDI tests. Adjustments made for hematocrit, child mental development, mother's age, maternal educational level, BMI, length of pregnancy (weeks), passive tobacco exposure, mother's education level, age of child, birth weight, sex of child, and first born.	Low cognitive development scores were "low" in 8/174 children. 1st Trimester PbB was higher (p=0.01) in children with low scores (mean±SD: 6.31±1.95) than children with "normal" scores (mean±SD: 4.05±2.40). An inverse relationship was observed between 1st trimester PbB and ECDI scores. Pearson correlation coefficient: -0.173; p<0.05. OR for low ECDI scores based on 1st trimester PbB: 1.74 (95% CI 1.18, 2.57); p=0.005.
Wasserman et al. 1994, 1997, 2003 Prospective; 332 children age 4 years, 261 children age 7 years, 167 children age 10–12 years; Kosovska, Mitrovica, Kosovo, Yugoslavia; and Pristina, Kosovo, Yugoslavia	**PbB:** Mean (SD) Age 4 years: 9.6, Pristina 39.9, K. Mitrovica 10–12 years: 6.1 (1.9), Pristina 30.9 (9.6), K. Mitrovica **Analysis:** Cognitive function was assessed at age 4, 7, and 10–12 years using McCarthy GCI, WISC-III, and WISC-III, respectively. Multiple linear regression with log-transformed PbB. Adjustments made for sex, sibship size, birthweight, language spoken in the home, HOME score, years of maternal education, maternal age, and maternal RAVEN score.	Associations between increasing PbB and decreasing FSIQ measured at age 4, 7, and 10–12 years. Adjusted changes for each lnPbB increase in β (SE) for PbB metrics: 4 years: -9.43 (2.44), p=0.000 Lifetime AUC 7 years: -8.59 (1.89), p<0.05 Lifetime average 10–12 years: -5.31 (1.98), p<0.05

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Zhang et al. 2013 Population-based retrospective cohort study of 8,831, 7,708, and 4,742 students in grades 3, 5, and 8, respectively, from Detroit, Michigan; academic achievement data was collected 2008–2010	**PbB:** Mean (SD): 7.12 (7.26) **Analysis:** Educational testing (MEAP tests) data from Detroit public schools for grades 3, 5, and 8 was linked to state health department data surveillance PbB collected at birth and PbB screening data (collected birth–6 years of age). Adjustments made for grade level, sex, race, language, maternal education, and SES as implied by school lunch status.	An association was observed between PbB and decreased academic achievement. ORs (95% CI) for scoring "less than proficient" on MEAP tests (reference PbB ≤1) (p<0.05 for all ORs): • Mathematics: o PbB 1–5 (µg/dL): 1.42 (1.24, 1.63) o PbB 6–10 (µg/dL): 2.00 (1.74, 2.30) o PbB >10: 2.40 (2.07, 2.77) • Science: (µg/dL) o PbB 1–5 (µg/dL): 1.33 (1.10, 1.62) o PbB 6–10 (µg/dL): 2.22 (1.82, 2.72) o PbB >10 (µg/dL): 2.26 (1.84, 2.78) • Reading: o PbB 1–5 (µg/dL): 1.45 (1.27, 1.67) o PbB 6–10 (µg/dL): 2.21 (1.92, 2.55) o PbB >10 (µg/dL): 2.69 (2.31, 3.12)
Zhou et al. 2017 Prospective study of 139 mother-infant pairs recruited in 2010 and followed from birth to 24–36 months, Shanghai, China	**PbB:** Gmean (95% CI) Mid-late pregnancy: 3.30 (3.05, 3.57) **Analysis:** Neurobehavioral evaluations were conducted at age 24–36 months using Gesell Development Scale. Maternal prenatal stress was evaluated using the SSCL-90-R. Linear regression. Adjustments made for maternal age at enrollment, maternal education, gestational week, child sex, birth weight, age and family economic status.	Maternal PbB was not associated with child development quotient in complete cohort. β (95% CI) for development quotient per µg/dL: • Adaptive behavior: 3.60 (-3.64, 10.83) • Language: -6.76 (-17.29, 3.77) • Social behavior: -6.45 (-15.55, 2.65) Maternal PbB was associated with child development in subset of mothers who demonstrated high prenatal stress (Global Severity Index in upper quartile). β (95% CI) for development quotient per µg/dL: • Adaptive behavior: -17.93 (-35.83, -0.03) • Language: -33.82 (-60.04, -7.59) • Social behavior: -41.00 (-63.11, -18.89)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Mood and behavior		
Arbuckle et al. 2016 Cross-sectional study of 2,097 children (ages 6–19 years); data collection period: 2007–2009 (Cycle 1 of Canadian Health Measures Survey)	**PbB:** Gmean (95% CI) age 6–11 years: 0.91 (0.81, 0.99) age 12–19 years: 0.80 (0.74, 0.85) **Analysis:** Behavioral problems were assessed by weighted random population survey. Adjustments made for smoking at home, gender, income, education, hours slept, and fasted.	Increased PbB was associated with increased risk of behavior problems. Adjusted ORs (95% CI) for ln(PbB): • ADD/ADHD: 2.39 (1.32, 4.32) • Emotional symptoms: 1.08 (0.68, 1.71) • Hyperactivity/inattention: 2.33 (1.59, 3.43) • Total difficulties: 2.16 (1.33, 3.51) Pb interaction with other risk factors: • Learning disability (higher income): 2.78 (1.40, 5.51) • Prescribed psychotropic medication (non-fasting sample): 4.20 (1.92, 9.17)
Boucher et al. 2012 Prospective study of 272 children (mean age 11.3 years) from the Canadian Arctic (Nunavik); data collection period: 2005–2010	**PbB:** Mean±SD (range) • Umbilical cord: 4.7±3.3 (0.8–20.9) • Current: 2.7±2.2 (0.4–12.8) • Tertiles: o T1 (reference): 0.4–1.6 o T2: 1.6–2.7 o T3 2.7–12.8 **Analysis:** Behavior was assessed in children ages 8.5–14.5 years by the TRF child behavior checklist and Disruptive Behavior Disorders Rating Scale. Adjustments made for child age, child gender, SES, age of the biological mother at birth, maternal tobacco use during pregnancy, birth weight, cord Hg, and child Pb.	Child current PbB was associated with increased risk of behavior problems. Adjusted ORs (95% CI) for current PbB p<0.20 for all ORs): • ADHD-inattentive type: o T2 (n=94): 1.06 (0.42, 2.66) o T3 (n=91): 1.01 (0.38, 2.64) • ADHD-hyperactive-impulsive type: o T2(n=94): 4.01 (1.06, 15.23) o T3(n=91): 5.52 (1.38, 22.12) • Oppositional defiant disorder and/or conduct disorder: o T2 (n=94): 1.90 (0.88, 4.11) o T3 (n=91): 1.53 (0.67, 3.49) Umbilical cord PbB was not associated with behavior problem scores (data not reported).

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Braun et al. 2006 Cross-sectional study of 4,704 children (ages 4–15 years) from NHANES 1999–2002 study	**PbB:** Quintiles: • Q1 (reference): ND–0.7 • Q2: 0.8–1.0 • Q3: 1.1–1.3 • Q4: 1.4–2.0 • Q5: ≥2.0 **Analysis:** ADHD was defined as having current stimulant medication use and parent report of ADHD diagnosed by a doctor or health professional. Adjustments made for age, sex, race, prenatal ETS exposure, postnatal ETS exposure, blood lead levels, preschool or childcare attendance, health insurance coverage, and ferritin levels.	Child PbB was associated with increased risk of ADHD. Adjusted ORs (95% CI) for ADHD: • Q2: 1.1 (0.4, 3.4); p=0.804 • Q3: 2.1 (0.7, 6.8); p=0.195 • Q4: 2.7 (0.9, 8.4); p=0.086 • Q5: 4.1 (1.2, 14.0); p=0.026 • p-trend: 0.012
Braun et al. 2008 Cross-sectional study of 3,082 children (ages 8–15 years; born 1986–1996) from the NHANES 2001–2004 study	**PbB:** Quartiles: • Q1 (reference): 0.2–0.7 • Q2: 0.8–1.0 • Q3: 1.1–1.4 • Q4: >2.0 **Analysis:** Conduct disorder was assessed by DISC. Adjustments made for child's age in years, PIR, maternal age at child's birth, child's sex, child's race, prenatal tobacco smoke exposure, cotinine levels, and blood lead levels.	Child PbB was associated with increased risk of conduct disorder. Adjusted ORs (95% CI) for meeting conduct disorder criteria: • Q2: 7.24 (1.06, 49.47) • Q3: 12.37 (2.37, 64.56) • Q4: 8.64 (1.87, 40.04)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Choi et al. 2016 Longitudinal study of 2,159 children (ages 7–9 years) from 10 South Korean cities; participants did not have symptoms of ADHD at the baseline survey; data collection period: 2006–2010	**PbB:** Gmean (GSD): • All participants >7 years: 1.62 (1.52) • Boys: 1.65 (1.75) • Girls: 1.47 (1.76); p<0.001, compared to boys **Analysis:** Time of PbB measurement was not reported. Follow-up ADHD survey was conducted 2 years after the baseline assessment. Adjustments made for age, sex, residential area, monthly income, parental marital status, family history of psychiatric disorders (anxiety disorder, ADHD, autism and schizophrenia), preterm birth, and birth weight.	RR (95% CI) for development of ADHD symptoms: • PbB ≥2.17 (compared to PbB <2.17): 1.552 (1.002, 2.403)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Desrochers-Couture et al. 2019 Longitudinal study of 212 Inuit children followed from birth and evaluated at mean age 11.4 years (2005–2010) and 18.5 years (2013–2016); Canada (Nunavik Child Development Study)	**PbB:** Gmean (GSD) • Cord: 3.80 (1.84) • Child: 2.34 (1.86) • Adolescent: 1.63 (2.00) **Analysis:** Behavior assessments were conducted at age 9–14 years (child) and age 16–22 years (adolescent). Behavior outcomes assessed included externalizing (Youth Self-Report), hyperactivity-impulsivity (Barkley Adult ADHD-IV Rating Scale), conduct disorder (Diagnostic Interview Schedule for Children), and substance use (Detection of alcohol and drug problems in adolescents, Version 3.2). Adjustments made for age, sex, birth weight, SES, age of biological mother, maternal tobacco use during pregnancy, and cord blood Hg.	Child PbB was not associated with adolescent externalizing behavior score, β per $\log_2$ µg/dL PbB (95% CI) • Externalizing: 0.61 (-0.63, 1.96) • Hyperactivity-impulsivity: 0.11 (-0.14, 0.37) • Oppositional defiant/conduct disorder: 0.02 (-0.20, 0.21) Child PbB was indirectly associated with adolescent externalizing score through child externalizing score, β per $\log_2$ µg/dL PbB (95% CI): • Externalizing score: 0.32 (0.08, 0.72) Child PbB was not associated with any category of substance use; however, child PbB was indirectly associated with adolescent binge drinking and cannabis use through child externalizing score, β per $\log_2$ µg/dL PbB (95% CI): • Binge drinking: 0.09 (0.02, 0.23) • Cannabis use: 0.05 (0.002, 0.14)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Dietrich et al. 2001 Prospective study of 195 subjects 15–17 years of age (born 1979–1984) from Cincinnati, Ohio	**PbB:** Categories: Lowest: <10 Low: 10–15 Medium: 16–20 High: >20 **Analysis:** Delinquency evaluated based on SRBDS and PRDBS. Multiple linear regression. Adjustments made for HOME scores, SES, parental IQ, and birth weight.	Associations between increasing PbB and SRDBS scores (β ± SE): • Prenatal PbB: 0.192 (0.076); p=0.002 • 78-month PbB: 0.193 (0.061); p=0.002 • Average child PbB: 0.101 (0.047); p=0.036 When PbB was treated categorically, increasing SRSBS scores were associated with prenatal (p≥0.02) and 78 months (p≥0.0007) blood lead categories.
Froehlich et al. 2009 Cross-sectional study of (NHANES 2001–2004); 2,588 children, ages 8–15 years (born 1986–1996)	**PbB:** Tertiles: T1: 0.2–0.8 T2: 0.9–1.3 T3: >1.3 **Analysis:** ADHD was diagnosed based on 4th Edition of DSMMD. Logistic regression. Adjustments made for child sex, household income/poverty line ratio, race/ethnicity, mother's age at child's birth, NICU admission, postnatal secondhand tobacco smoke exposure, and preschool attendance.	Child PbB was associated with increased risk of ADHD. Adjusted ORs (95% CI) for ADHD (T1 reference): • T2: 1.7 (0.97, 2.9); p=0.06 • T3: 2.3 (1.5, 3.8); p=0.001 Risks associated with blood lead and exposure to tobacco smoke were greater than additive.

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Fruh et al. 2019 Prospective study of 1,006 mother-child pairs (pregnancies recruited 1999–2002); children evaluated at age 8 years; Massachusetts (Project Viva)	**PbB (erythrocyte Pb):** Median:1.1 25th–75th % range: 0.6 **Analysis:** Behavior was assessed using parent-rated and teacher-rated BRIEF and SDQ at mean age 7.8 (±0.8 SD) years. Adjustments for age, sex, race/ethnicity, maternal IQ, maternal smoking during pregnancy, nulliparity, parental education, prenatal Hg, prenatal Mn, child race/ethnicity, HOME score, and household income category.	Erythrocyte Pb was associated with parent-rated SDQ emotional problems score, β for change in score for an IQR increase in maternal 2nd trimester erythrocyte Pb (95% CI): Parent-rated: • Total difficulties: 0.36 (-0.04, 0.77) • Emotional problems: 0.18 (0.03, 0.33) Teacher-rated: • Total difficulties: 0.38 (-0.15, 0.91) • Emotional problems: 0.04 (-0.13, 0.21) Erythrocyte Pb was associated with parent-rated BRIEF plan/organize subscale, β for change in score for IQR increase in maternal 2nd trimester erythrocyte Pb (95% CI): Parent-rated: • Behavioral Regulation Index: 0.69 (-0.13, 1.51) • General Executive Composite: 0.73 (-0.06, 1.52) • Plan Organize: 0.85 (0.12, 1.59) Teacher-rated: • Behavioral Regulation Index: 0.46 (-0.34, 1.26) • General Executive Composite: 0.42 (-0.39, 1.23) • Plan Organize: 0.67 (-0.22, 1.57)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Geier et al. 2018 Cross-sectional study of 2,109 children (age 10–19 years) from the NHANES (2003–2004)	**PbB** Mean (SD): 1.16 (1.27) Quartiles, range: • 0–50th: 0.2–0.88 • 50th–75th: >0.88–<1.26 • 75th–100th: 1.26–34.8 **Analysis:** Logistic regression of PbB and diagnosis of ADD (mean age 14.5±1.8 SD years), adjusted for gender, race, age, and SES.	Increasing PbB was associated with OR for diagnosis of ADD (95% CI): OR for total sample (per µg/dL): 1.292 (1.025, 1.545) p=0.0301 Prevalence ratio for upper quartile PbB relative to 0–50th percentile as reference: • 50–75th %: 1.28 (0.82, 2.00), p=0.2466 • 75–100th %: 1.59 (1.05, 2.39), p=0.0130
He et al. 2019 Meta-analysis of seven studies of associations between PbB and risk of ADHD diagnosis	**PbB** Range of study means: 0.73, 8.77 **Analysis:** Pooled mean differences in risk or odds ratios.	Increasing PbB was associated with increase in risk of diagnosis of ADHD. Mean risk difference (95% CI): • All studies (7): 0.59 (0.50, 0.68), p<0.0001 • PbB <3 µg/dL: 0.47 (0.39, 0.56), p<0.0001 • Age 5–12 years compared to age >12 years: 1.35 (0.28, 2.41), p<0.0001

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Hong et al. 2015 Cross-sectional study of 1,001 children (age 8–11 years) in South Korea	**PbB:** Mean (SD): 1.80 (1.40) Range: 0.53–6.16 **Analysis:** Behavior was assessed using the ADHD Rating Scale. Multiple linear regression with log-transformed blood lead. Adjustments made for age, sex, residential region, paternal education level, yearly income, Full-Scale IQ, and environmental chemical concentrations (Hg, Mn, Cotinine, MnBP, MEOHP, bisphenol A, Pb)	PbB (log-transformed) was associated with increases in teacher-rated hyperactivity/ impulsivity and total ADHD score. Regression coefficients (95% CI): • Hyperactivity/impulsivity: 3.66 (1.18, 6.13); p=0.004 • Inattention: 2.72 (-0.12, 5.56); p=0.060 • Total score: 6.38 (1.36, 11.40); p=0.013 PbB (log-transformed) was associated with increases in parent-rated hyperactivity/ impulsivity score. Regression coefficients (95% CI): • Hyperactivity/impulsivity: 1.99 (0.17, 3.81); p=0.032 • Inattention: 0.94 (-1.27, 3.16); p=0.402 • Total score: 2.90 (-0.86, 6.68); p=0.131
Huang et al. 2016 Prospective study of mother infant pairs recruited 1997–2001 with follow-up of 578 children at age 6–13 years; Mexico.	**PbB** Mean (SD): 3.4 (3.1) **Analysis:** ADHD symptoms were assessed using the Connors' Rating Scales at mean age 9.1±1.3 years. Segmented regression with adjustments for maternal marital status, age educational years, SES, maternal smoking during pregnancy; child age at testing, sex, and birth weight.	PbB was associated with hyperactivity, restless-impulsivity and hyperactivity-impulsivity scores; regression slope per 1 µg/dL (95% CI): • Hyperactivity: 1.2 (0.3, 2.0), p=0.01 • Restless-impulsive: 1.2 (0.3, 2.0), p=0.007 • Hyperactive-impulsive: 1.1 (0.2, 2.0), p=0.02

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Ji et al. 2018 Prospective study of mother-infant pairs recruited beginning 1998 with follow-up of 1,479 children at median age 9.6 years; Boston Birth Cohort	**PbB** Mean (SD): • All: 2.2 (1.6) • ADHD: 2.4 (1.9) • No neurodevelopmental disorder: 2.1 (1.5) **Analysis:** Early child PbB was assessed in a group of children diagnosed with ADHD (n=299) and a control group of neurotypical children (n=1,180). Logistic regression with adjustments for maternal age, race/ethnicity, education, maternal smoking during pregnancy, intrauterine infection, parity, child sex, mode of delivery, preterm birth, and birth weight.	Increased PbB was associated with increased OR for ADHD diagnosis. Males and females: OR per ln PbB (µg/dL): 1.25 (1.01, 1.56) p=0.045 OR relative to <2 µg/dL reference: • 2–4 µg/dL: 1.08 (0.81, 1.44) p=0.622 • 5–10 µg/dL: 1.73 (1.09, 2.73) p=0.019 OR relative to <5 µg/dL reference: • 5–10 µg/dL: 1.66 (1.08, 2.56) p=0.020 Association was stronger for males: OR 5–10 µg/dL relative to <5 µg/dL reference: • Males: 2.49 (1.46, 4.26) p=0.001 • Females: 0.68 (0.27, 1.69) p-0.401 Joint effects of sex and PbB: OR 5–10 µg/dL relative to <5 µg/dL reference: • Males: 7.48 (4.29, 13.02) p <0.001 • Females 0.69 (0.28, 1.71) p=0.426
Joo et al. 2017 Case-control study of 214 child ADHD cases and 214 controls (age range 6–10 years), age recruited 2008–2019; South Korea	**PbB** Gmean (SD): Cases: 1.65 (1.45) Controls: 1.49 (1.48) **Analysis:** Odds ratio for ADHD adjusted for maternal education, family history of ADHD, and exposure to second-hand smoke.	Increased PbB was associated with increased OR for ADHD diagnosis; OR per µg/dL: • All AHDH: 1.28 (0.89, 1.83) • Inattention: 1.63 (1.03, 2.58), p<0.05 • Hyperactivity/impulsivity: 1.04 (0.53, 2.07)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Joo et al. 2018 Prospective study of 1,751 mother-infant pairs recruited beginning 2006 with follow-up of 575 children at age 5 years; South Korea	**PbB** Gmean (SD): Early pregnancy: 1.28 (1.48) Late pregnancy: 1.24 (1.57) Cord: 0.90 (1.57) 2 years: 1.55 (1.49) 3 years: 1.43 (1.44) 5 years: 1.29 (1.38 **Analysis:** Behavior assessed using the Korean version of the child behavior checklist. Linear regression with adjustments for maternal age at child's birth, parity, maternal education, household income, residential area type, and duration of breast feeding	Increased PbB was associated with increased total score for behavioral problems in females; β for score per µg/dL (95% CI): PbB at age 2 years: • Females: 3.82 (1.25, 3.69) • Males: 0.22 (-1.87, 2.32) PbB at age 3 years: • Females: 2.43 (-1.00, 5.87) • Males: 0.48 (-2.17, 3.12) PbB at age 5 years: • Females: 5.72 (0.44, 10.99) • Males: 1.37 (-2.06, 4.80)
Kim et al. 2016 Prospective study of 2,473 children (enrolled at age 7–8 years) with no history of development disorders, in South Korea (10 cities)	**PbB:** Mean (95% CI) • Age 7–8 years: 1.64 (1.60, 1.68) • Age 9–10 years: 1.58 (1.55, 1.61) • Age 11–12 years: 1.58 (1.55, 1.61) **Analysis:** Autistic behavior was assessed in children at ages 11–12 years by ASSQ and SRS. Multiple binomial regression. Adjustments made for sex, fetal and environmental tobacco smoke exposure, paternal and maternal education levels, family income, low birth weight, breastfeeding, gestational week at delivery, children's fish intake, and blood Hg concentration.	PbB (log transformed) at ages 7–8 years, but not ages 9–10 and 11–12 years, was associated with increased autistic behaviors. β (SE): ASSQ o PbB at 7–8 years: 0.151 (0.061, 0.242) o PbB at 9–10 years: -0.023 (-0.143, 0.097 o PbB at 11–12 years: 0.054 (-0.061, 0.170) SRS • PbB at 7–8 years: 2.489 (1.378, 3.600) • PbB at 9–10 years: 1.295 (-0.235, 2.825) • PbB at 11–12 years: 0.724 (-0.727, 2.176)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Liu et al. 2014a Prospective study of 332 mother-infant pairs from Shenzhen, Guangdong, China	**PbB:** Mean (SD) • Low PbB group o 1st Trimester: 1.22 (0.28) o 2nd Trimester: 1.01 (0.19) o 3rd Trimester: 1.19 (0.23) o Delivery: 1.26 (0.25) • High PbB group o 1st Trimester: 6.49 (0.62) o 2nd Trimester: 5.63 (0.43) o 3rd Trimester: 6.31 (0.51) o Delivery: 6.65 (0.55) **Analysis:** Infant behavior was assessed at 3 days of age by NBNA. Multiple and multivariate linear regression. Adjustments made for maternal IQ, hemoglobin, tobacco use, educational level, and parent's occupation.	A negative association was observed between 1st trimester PbB and NBNA scores but not 2nd trimester, 3rd trimester, and delivery PbB. β (95% CI): • 1st Trimester: -4.86 (-8.831, -0.889); p=0.03 • 2nd Trimester: -3.98 (-8.180, 0.220); p=0.07 • 3rd Trimester: -3.65 (-6.609, 1.309); p=0.21 • Delivery: -3.39 (-7.531, 0.751); p=0.11
Liu et al. 2015b Prospective study of 665 children (enrolled at ages 3–13 years) in Jintan City, China	**PbB:** Mean (SD): 6.26 (2.54) **Analysis:** PbB was measured at ages 3–5 years. Sleep was assessed at ages 9–13 years by parents using the CSHQ and by children using an adolescent sleep questionnaire. Multiple logistic regression. Adjustments made for age, sex, parental education, and school district.	Positive associations were observed between PbB and sleep onset delay. β (95% CI): 0.033 (0.009, 0.056); p=0.006

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Park et al. 2016 Case-control study of child (mean age 9 years) ADHD cases (n=114) and controls (n=114) identified in 2013 in Busan, Korea	**PbB:** Gmean ± SD (range): Cases: 1.90±0.86 (0.37, 5.35) Controls: 1.59±0.68 (0.18, 3.41) Q1: 0.18, 1.12 Q2: 1.13, 1.71 Q2: 1.72, 2.29 Q4: 2.30, 5.35 **Analysis:** ADHD assessed with CPT and parental ADHD-RS at age 9 years. Multiple logistic regression and linear regression. Adjustments made for age, sex, gestational age, birth weight, economic status, parental education, and parent smoking behavior.	Increasing PbB was associated with diagnosis of ADHD. OR (95% CI): All subjects: 1.60 (1.04, 2.25), p=0.03 Relative to Q1: Q2: 1.26 (0.56, 2.84), p=0.39 Q3: 1.26 (0.55, 2.87), p=0.61 Q4: 2.54 (1.09, 5.94), p=0.03 No association between scores on ADHD-RS or CPT. β (SE) for score per log-transformed PbB: ADHD-RS score: 1.74 (1.29), p=0.18 CPT score: Omission errors: 0.05 (2.29), p=0.99 Commission errors: -0.72 (2.08), p=0.72 Response time: 2.48 (2.60), p=0.12 Response time variability: 2.26 (2.23), p=0.31
Sioen et al. 2013 Prospective study of 270 children enrolled in the birth cohort from the Flemish Environment and Health Study (2002–2006); followed birth to 8 years	**PbB:** Umbilical cord mean (25^{th}–75^{th} percentiles): 1.43 (0.73–2.53) **Analysis:** Child behavior was assessed at ages 7–8 years by SDQ. Multiple logistic regression. Adjustments made for BMI of the parents, age of the mother at pregnancy, weight increase of the mother during pregnancy, smoking during pregnancy, current smoking habits of parents, smoking behavior of the maternal grandmother before the birth of the mother, highest education level of both parents, sex of the child, and serious infections of the child since birth.	Umbilical cord PbB was associated with an increased risk of hyperactivity. OR (95% CI): 2.940 (1.172, 7.380); p=0.022

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Stroustrup et al. 2016 Prospective study of 948 mother-infant pairs, followed from birth (recruited 2007–2011), with follow-up of 500 children at age 24 months; Mexico City	**PbB:** Median (IQR): 2nd trimester: 2.8 (2.7) **Bone Pb** Median (SD) • postpartum tibia: 2.6 (8.6) • postpartum patella: 4.9 (8.9) **Analysis:** Child temperament was evaluated at age 24 months using the TTS. Logistic regression. Adjustments made for postnatal depression (EPDS)	Increasing PbB and tibial Pb were associated with increasing probability of child demonstrating more difficult temperament score. OR (95% CI) for TTS score (easy, intermediate or difficult), easy score as reference: EPDS: Intermediate: 1.23 (0.78, 1.93) Difficult: 2.53 (1.69, 3.77) OR corresponding to 1 unit change of ln(maternal PbB µg/dL): Intermediate: 0.88 (0.59, 1.3) Difficult: 1.52 (1.03, 2.26) Tibia Pb OR corresponding to 1 unit change per 10 µg/g change in tibia Pb: Intermediate: 1.25 (0.95, 1.65) Difficult: 1.32 (1.01, 1.73) Probability of demonstrating difficult TTS score was approximately doubled if EPDS score was high.

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Wang et al. 2008 Case-control study of 630 children with ADHD and 630 matched controls without ADHD in China; children were assessed at ages 4–12 years; data collection period: 2003–2007	**PbB:** Means (SE) • ADHD cases: 8.77 (3.89) • Controls: 5.76 (3.36) • Cases versus control: p<0.05 Tertiles: • T1 (reference): ≤5 • T2: 5–10 • T3: ≥10 **Analysis:** ADHD was diagnosed based on 4th Edition of DSMMD Multiple logistic regression. Adjustments made for BLLs, household composition, birth weight, twin, family history of ADHD, labor complications, cesarean, premature labor, NICU, mother's age, father's age, parents' education, prenatal tobacco exposure, and prenatal alcohol exposure.	PbB was associated with an increased risk of ADHD. OR (95% CI): • T2: 4.92 (3.47, 6.98); p<0.01 • T3: 6.00 (4.11, 8.77); p<0.01
Winter and Sampson 2017 Prospective study of birth cohort (n=1,255) recruited in 1995–1997, with follow-up from birth to age 18 years (n=208), Chicago	**PbB:** Means (SD) at age <6 years: 6.14 (4.58) **Analysis:** Impulsivity and anxiety or depression was evaluated using the Child Behavior Checklist. Linear regression with and without CEM. Adjustments made for child age at testing, gender, race/ethnicity; and primary caregiver immigrant generational status, marital status, education, Temporary Assistance for Needy Families receipt; proportion of child's residential neighborhood that is non-Hispanic Black, Hispanic and below poverty line; and proportion of child's residential neighborhood that was tested for Pb exposure.	Increasing PbB was associated with increasing impulsivity and anxiety or depression scores. β for score per µg/dL (95% CI): Ordinary least squares: • Impulsivity: 0.06 (0.01, 0.12) • Anxiety or depression: 0.09 (0.03, 0.16) Course exact matching: • Impulsivity: 0.08 (0.01, 0.16) • Anxiety or depression: 0.11 (0.01, 0.21)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Neuromotor neurosensory function		
Chiodo et al. 2004 Prospective study of 237 children, age 7.5 years; Detroit, Michigan	**PbB:** Mean (SD, range): 5.4 (3.3, 1–25) **Analysis**: Neurobehavioral test battery administered at 7.5 years. Multiple nonparametric regression. Adjustments made for SES, education level, number of children <18 years, HOME score, PPVT-R, sex, parity, FES, prenatal alcohol exposure, crowding, life stress of the child and caretaker, child's age, prenatal exposure to cocaine and marijuana, conflict tactics, and prenatal smoking.	Association between increasing child PbB and decreasing performance on tests battery: Tests with declines (p≤0.05), β at <3, <5, <7.5, or <10 µg/dL: • Block design: <10, <5 • Digit span backwards: <7.5 • Beery visual-motor integration: <10, <5 • Matching familiar figures (number correct): <5 • Attention-TRF: <3 • Barkley-inattention: <5 <3 • Withdrawn-TRF: <7.5, <3 • Barkley off-task: <10, <5 • Sternberg reaction time "Yes": <5, <3 • Color naming: <5 • CPT visual (number correct): none • Seashore rhythm: <3 • Mental rotation RT "forward": <10, <5

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Dietrich et al. 1987 Prospective study of 185 mother-infant pairs from Cincinnati, Ohio (infants born 1979–1984)	**PbB:** Mean (SD, range) • Prenatal (maternal): 8.3 (3.8, 1–27) • Neonatal (10 days): 4.9 (3.3, 1–24) • Neonatal (3 months): 6.3 (3.8, 1–22) • Neonatal (6 months): 8.1 (5.2, 1–36) **Analysis:** Neurodevelopmental assessments (PDI of the BSID) were conducted at age 6 months. Adjustments made for obstetrical complications, postnatal complications, mother's iron status during pregnancy, gestational age by examination, birth weight, CITAC, HOME score, SES, and race of infant.	Associations with 3-month ln PbB, β (SE): • PDI: -13.248 (4.250); p=0.002 • Motor maturity: -0.570 (0.260); p=0.03 Associations with 6-month ln PbB, β (SE): • PDI: -2.117 (0.916); p=0.02 • Motor maturity: -0.092 (0.056); p=0.11
Dietrich et al. 1989 Prospective study of 192 mother-infant pairs from Cincinnati, Ohio (infants born 1979–1984)	**PbB:** Mean (SD, range) • Prenatal (maternal): 8.2 (3.6, 1–27) • Neonatal (10 days): 4.8 (3.1, 1–23) • Neonatal (3 months): 6.0 (3.5, 1–20) • Neonatal (6 months): 7.9 (4.8, 1–35) • Neonatal (9 months): 11.5 (6.9, 2–57) • Neonatal (12 months): 14.2 (7.3, 4–47) **Analysis:** Neurodevelopmental assessments (PDI of the BSID) were conducted at age 12 months. Multiple linear regression and SEM. Adjustments made for obstetrical complications, postnatal complications, birth weight, gestational age, child race, child sex, CITAC, maternal age, gravidity, parity, maternal total iron binding capacity, child health variables (number of infections during the last year, current illness, iron status), HOME, SES, maternal IQ, and number of children in the home.	Associations between increasing prenatal PbB and decreasing 12-month PDI score β (SE): • PDI: -14.09 (7.26); p=0.054 SEM indicated significant associations between increasing prenatal PbB and race and 12-month PDI. • Prenatal PbB --> 12-month PDI: -0.47, p≤0.05 • Prenatal PbB x race --> birth weight: 0.97, p≤0.05 • Race --> 12-month MDI: -0.72, p≤0.05

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Dietrich et al. 1993b Prospective study of 245 children (age 6 years, born 1979–1984) from Cincinnati, Ohio	**PbB:** Mean (SD) • Prenatal (maternal): 8.4 (3.8) • Neonatal: 4.8 (3.1) • Life average • 6 years: 10.1 (5.6) • Lifetime average quartile range: 7–22 **Analysis:** Motor function assessed with test battery at age 6.5 years using BOTMP. Multiple linear regression. Adjustments made for maternal age at birth, birth weight, gestational age, 5-minute Apgar, race, SES, HOME score, maternal IQ, marital status, and parents' education level.	Associations between increasing PbB and decreasing motor performance measured at age 6 years. Tests with significant (p≤0.05) declines (β) associated with neonatal (N), mean lifetime (L) or concurrent (C) PbB: • Bilateral coordination: N, M • Visual motor control: C • Upper limb speed and dexterity: C, M, N • Fine motor composite: C, M, N Bilateral coordination score exhibited trend for decreasing score with increasing PbB.
Ethier et al. 2012 Prospective longitudinal; 149 children; age 10–13 years; Canadian Arctic (Nunavik)	**PbB:** Mean (SD, range) • Cord: 4.6 (3.1, 0.8–19.5) • 11 years: 2.6 (2.3, 0.4–12.8) **Analysis:** VEPs were assessed at age 10 and 13 years. Multiple linear regression. Adjustments made for smoking during pregnancy, marijuana and alcohol use during pregnancy, sex, cord DHA, current DHA, and cord and current child blood levels of Se, Hg, and PCB-153.	Association between increasing cord PbB and delay of N150 latency of VEP at multiple contrast levels. Mean latency (estimated from reported bar plot): • ≥4.15 µg/dL: ~160 ms, p<0.05 • <4.15 µg/dL: ~153 ms (reference)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Fraser et al. 2006 Prospective study; 101 children (2000–2002); age 5 years; Canadian Arctic (Nunavik)	**PbB:** Mean (SD): Cord: 4.9 (3.7) Child: 5.3 (4.9) **Analysis:** Motor function was assessed at age 5 years (tremor, sway, reaction time). Multiple linear regression with log-transformed PbB. Adjustments made for binge drinking during pregnancy, child's weight at testing time, and blood PCB153 concentration at testing time.	Associations between increasing concurrent PbB and fine motor function (β): • Hand movements: 0.30, p≤0.01 • Sway velocity: 0.28, p≤0.01 • Transversal sway: 0.24, p≤0.05
Kim et al. 2013b Prospective birth cohort (MOCEH study; 2006–2010); 884 mother-infant pairs; South Korea	**PbB:** Gmean (GSD) Early pregnancy: 1.4 (1.5) Late pregnancy: 1.3 (1.5) **Analysis:** Motor performance (PDI) evaluated at age 6 months using the BSID II. Multiple linear regression. Adjustments made for infant birth weight, infant sex, maternal age, maternal education level, family income, breastfeeding status, residential area, and Pb and Cd concentrations.	Maternal PbB was not associated with PDI score (β) per 1 µg/dL change in PbB (95% CI): -1.69 (-3.65, -0.27); p=0.09

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Liu et al. 2018b Cross-sectional study of 234 children (age 3–7 years) in evaluated in 2014; China.	**PbB:** Median (SE) e-waste location: 4.94 (0.20) reference location: 3.85 (1.81) **Analysis:** Hearing was evaluated (pure-tone air conduction) in 146 children who resided near an e-waste site and 88 children from a reference location. Logistic regression of hearing loss and PbB. Adjustments made for age, sex, body weight and height, BMI, parent education, family member smoking, family income, distance to road, noise (from various sources), and earphone use.	Increasing PbB (but not urinary cadmium) was associated with hearing loss (pure-tone air conduction score >25 dB); OR per µg/dL (95% CI): • Hearing loss 1.24 (1.029, 1.486) p<0.05 • Low frequency loss: 1.02 (0.869, 1.190) • High frequency: 1.08 (0.839, 1.379)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Osman et al. 1999 Retrospective study of longitudinal cohort of 155 children, age 4–14 years; Katowice region of Poland	**PbB:** Median (range) • 7.2 (1.9–28.1) **Analysis:** Hearing thresholds and BAEP evaluated at age 4–14 years. Multiple linear regression. Adjustments made for age, sex, BLL, Apgar score, ears without pathologies at inspection, nasopharynx without pathologies at inspection, ear diseases, frequent colds, mumps, gentamycin, environmental noise, and maternal smoking during pregnancy.	β per 1 change in PbB for right ear (95% CI) for full cohort: • 0.5 kHz: 0.054 (0.035, 0.074) • 1 kHz: 0.044 90.026, 0.062) • 2 kHz: 0.048 (0.029, 0.066) • 4 kHz: 0.060 (0.039, 0.081) • 6 kHz: 0.068 (0.044, 0.092) • 8kHz: 0.072 (0.050, 0.094) β per 1 change in PbB for left ear (95% CI): • **0.5 kHz: 0.051 (0.026, 0.075)*** • **1 kHz: 0.032 (0.014, 0.050)*** • **2 kHz: 0.036 (0.019, 0.053)*** • **4 kHz: 0.039 (0.020, 0.059)*** • **6 kHz: 0.004 (0.044, 0.049)*** • **8 kHz: 0.047 (0.024, 0.080)*** Association ($p<0.05$) between increasing PbB and increasing hearing threshold in stratum <10 µg/dL (thresholds not reported). No association between PbB and BAEPs.

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Polanska et al. 2018 Prospective study of 539 mother-child pairs, recruited in 2007, with follow-up of children at age 2 years; 280 blood and 303 cord blood samples were randomly chosen for analysis; Polish Mother and Child Cohort (REPRO_PL), Poland	**PbB:** Gmean (SD) (range) • 2nd trimester: 0.99 (0.15) (0.29, 2.63) • Cord: 0.96 (0.16) (0.24, 5.65) **Analysis:** Cognitive function was assessed at age 2 years using BSID III. Linear regression. Adjustments made for person who conducted child examination, mother's age, mother's education, sex of the child, age of the child, and mother's cotinine levels.	Increasing cord PbB was associated with decreasing cognitive scores in males. β score per µg/dL (95% CI): Motor score: • Females: 0.48 (-1.55, 2.52), p=0.64 • Males: -0.70 (-2.90, 1.51), p=0.53
Rodrigues et al. 2016 Prospective study with cross-sectional analysis of PbB and fine motor score; n=524 children, 20–30 months; Sirajdikhan and Pabna Bangladesh	**PbB:** Median (P25, P75, Maximum) • Sirajdikhan: 7.6 (5.5, 10.4) • Pabna: <LOD (<LOD, 3.8, 13.8) **Analysis:** Cognitive function was assessed at age 2–3 years using BSID. General linear model regression. Adjustments made for maternal age and education, exposure to environmental tobacco smoke, child sex, HOME score, maternal Raven score, and child hematocrit.	Child PbB was associated with decreasing cognitive scores β score per lnPbB µg/dL (SE): Fine motor score: • Sirajdikhan: 0.07 (0.11), p=0.50 • Pabna: -0.07 (0.11), p=0.50

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Silver et al. 2016 Prospective study; infants assessed for hearing at 2 days and vision at 6 weeks. Maternal blood Pb collected at mid pregnancy and late pregnancy and in cord blood; Hebei Province, China	<u>Exposure for infants with hearing data:</u> Gmean (SD) Mid-pregnancy: 2.4 (2.5) (n=343); Late-pregnancy: 2.7 (2.3) (n=362); Cord: <LOQ (n=321) <u>Exposure for infants with vision data:</u> Gmean (SD) Mid-pregnancy: 2.4 (2.6) (n=1,038); Late-pregnancy: 2.9 (2.2) (n=1,058); Cord: <LOQ (n=949) **Analysis:** Data were analyzed by general linear model. Adjustments made for age at testing, sex, cord blood iron status, gestational age, birth weight, and head circumference.	Increasing late-pregnancy PbB was associated with decreasing visual acuity score and increasing ABR central-peripheral response time ratios (ABR-C-P ratio); percent change in score relative to <2 µg/dL reference group (95% CI): Visual acuity score for PbB strata: • >3.8 µg/dL: -8.5 (-14.7, -2.4) • **2–3.8 µg/dL: -7.2 (-13.3, -1.1)*** ABR C-P ratio for PbB strata: • >3.8 µg/dL: 4.6 (1.8, 7.4) • **2–3.8 µg/dL: 3.2 (0, 5.9)***
Taylor et al. 2018 Prospective study of 14,541 mother-infant pairs, followed from birth (recruited 1991–1992) with follow-up of 1,558 children at age 7 years; Avon, United Kingdom	**PbB:** Mean (SD) at gestation week 11 Mean (SD) 3.66 (1.55) Range: 0.20, 19.14 **Analysis:** Motor skills were evaluated using the Movement Assessment Battery at age 7 years. Logistic regression. Adjustments made for maternal education, smoking in pregnancy, alcohol in pregnancy, age, parity, and sex of child.	PbB was not associated with scores on motor skill tests. OR for scores per µg/dL prenatal PbB (95% CI): Heal to toe: 0.99 (0.74, 1.33), p=0.93 Beanbag: 0.88 (0.58, 1.32), p=0.54 Threading lace: 1.12 (0.83, 1.50), p=0.47 Peg board (preferred hand): 1.19 (0.88, 1.60), p=0.26 Peg board (non-preferred hand): 1.14 (0.85, 1.54), p=0.37

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Tellez-Rojo et al. 2006 Prospective study of 294 children followed from birth (1994–1995, 1997–1999) to age 2 years; Mexico City	**PbB:** Mean (SD): • Cord: 4.85 (3.0) • 12 months: 4.27 (2.14) • 24 months: 4.28 (2.25) **Analysis:** Motor performance (PDI) evaluated at ages 6 and 12 years using the BSID II. Multiple linear regression with ln-transformed PbB. Adjustments made for sex, birth weight, and maternal IQ.	Association between increasing concurrent PbB and PDI score at age 24 months (β) per 1 ln change in PbB: 12 Months: • <10 µg/dL: -0.01, p=0.98 • ≥10 µg/dL: -1.19, p=0.01 24 Months: • <10µg/dL: -1.18. p<0.01 • ≥10 µg/dL: 0.04, p=0.89
Zhou et al. 2017 Prospective study of 139 mother-infant pairs recruited in 2010 and followed from birth to 24–36 months, Shanghai, China	**PbB:** Gmean (95% CI) Mid-late pregnancy: 3.30 (3.05, 3.57) **Analysis:** Neurobehavioral evaluations were conducted at age 24–36 months using Gesell Development Scale. Maternal prenatal stress was evaluated using the Symptom Checklist-90-Revised scale (SCL-90-R). Linear regression. Adjustments made for maternal age at enrollment, maternal education, family monthly income, gestational week, child sex, birth weight, age, and family economic status.	Maternal PbB was not associated with child development quotient in complete cohort. β (95% CI) for development quotient per µg/dL: • Gross motor: 3.31 (-6.11, 12.73) • Fine motor: 0.49 (-11.27, 12.24)

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Altered brain structure and chemistry		
Cecil et al. 2008 (Brubaker et al. 2010) Prospective study of 157 adults, age 19–24 years from a birth cohort born 1979–1984 from Cincinnati, Ohio	**PbB:** Mean (SD, range): • 6 months–6.5 years: 13.3 (5.9, 4.6–37.2) **Analysis:** Brain volume evaluated at ages 19–24 years using MRI. Multiple linear regression with ln-transformed PbB. Adjustments made for age at time of scanning, and birth weight.	Association (p≤0.001) between increasing childhood mean PbB and decreasing brain volume affecting 1.2% of the total gray matter. Effects were greater in males than females. Largest effects were in the anterior cingulate cortex. The association was strongest for PbB measured at age 5–6 years.
Cecil et al. 2011 Prospective study of 159 adults, age 19–24 years from a birth cohort born 1979–1984 from Cincinnati, Ohio	**PbB:** Mean (SD, range): • 6 months–6.5 years: 13.3 (6.1, 4.7–37.2) **Analysis:** Brain metabolites were imaged at ages 19–24 years using proton magnetic resonance spectroscopy. Multiple linear regression with ln-transformed PbB. Adjustments made for age at time of imaging, FSIQ.	Association (p<0.05) between increasing childhood mean PbB and decreasing regional levels of gray matter N-acetyl aspartate, glutamate-glutamine, creatine, and phosphocreatine, and white matter cholines. Areas affected include the basal ganglia, cerebellum vermis, parietal white matter, and frontal white matter.

ABR = Brainstem Auditory Response; ADD = attention deficit disorder; ADHD = attention deficit/hyperactivity disorder; ADHD-RS = ADHD-rating scale; AFGS = Auditory Figure-Ground Subtest; ASSQ = Autism Spectrum Screening Development Questionnaire; AUC = area under the curve; BAEP = Brainstem Auditory Evoked Potentials; BLL = blood lead level; BOTMP = Bruininks-Oseretsky Test of Motor Proficiency; BRIEF = Behavior Rating Inventory of Executive Function; BSID = Bayley Scales of Infant Development; CANTAB = Computer-based Tests of Working Memory; Cd = cadmium; CDIIT = Comprehensive Developmental Inventory for Infants and Toddlers; CEM = Coarsened Exact Matching; CI = confidence interval; CITAC = Composite Index of Tobacco and Alcohol Consumption; CKD = chronic kidney disease; CL = confidence limit; CPT = Continuous Performance Test; CSHQ = Children's Sleep Habits Questionnaire; DHA = docosahexaenoic acid; DISC = Diagnostic Interview Schedule for Children-Caregiver Module; DSMMD = Diagnostic and Statistical Manual of Mental Disorders; ECDI = Early Child Development Inventory; EOG = End of Grade; EPDS = Edinburgh Postnatal Depression Scale; ETS = Environmental Tobacco Smoke; FES = Family Environmental Scale; FSIQ = full-scale IQ; FTII = Fagan Test of Infant Intelligence; FWS = filtered word subtest; GCI = General Cognitive Index; Gmean = geometric mean; GSD = geometric standard deviation; GSI = Global Severity Index; Hg = mercury; HIECDI = Harold Ireton Early Child Development Inventory; HOME = The Home Observation for Measurement of the Environment Inventory; HOME57 = HOME at age 57 months; HOME120 = HOME at 10 years; HOME-SF = HOME Short Form; IQ = intelligence quotient; IQR = interquartile range; ISAT = Illinois Standard Achievement Tests; K-ABC = Kaufman Assessment Battery for Children; KEDI-WISC = Korean Educational Development Institute's WISC; LOD = limit of detection; MDI = Mental Development Index; MEAP = Michigan Educational Assessment Program; MEHP = mono-2-ethylhexyl phthalate; MEOHP = mono-2-ethyl-5-oxohexyl phthalate; Mn = manganese; MnBP = mono-n-butyl phthalate; MOCEH = Mothers and Children's Environmental Health; MRI = magnetic resonance imaging; MSCA = McCarthy Scales of Children's Abilities; MSEL = Mullen Scales of Early Learning; NA = not available; NBNA = Neonatal Behavioral

Table 9. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Children at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes

Neurological Assessment; ND= not detected; NHANES = National Health and Nutrition Examination Survey; NICU = neonatal intensive care unit; OR = odds ratio; PALS-K = Phonological Awareness Literacy Screening-Kindergarten; Pb = lead; PCB-153 = 2,2',4,4',5,5'-hexachlorobiphenyl; PDI = Psychomotor Development Index; PIR = poverty-to-income ratio; PPVT-R = Peabody Picture Vocabulary Test Revised; PRDBS = Parental Report of Predelinquent and Delinquent Behavior Survey; RAVEN = standard progressive matrices; a nonverbal group test typically used in educational settings; RR = relative risk; SAT = Standardized Assessment Test; S-BIS = Stanford-Binet Intelligence Scale; SCL-90-R = Symptom Checklist-90-Revised scale; SD = standard deviation; SDQ = Strengths and Difficulties Questionnaire; Se = selenium; SE = standard error; SEM = structural equation modeling; SES = socioeconomic status; SRBDS = Self-Reported Delinquent Behavior Survey; SRS = Social Responsiveness Scale; TRF = Teacher Report Form from the Child Behavior Checklist; TTS = Toddler Temperament Scales; UCL = upper confidence limit; VEP = visual evoked potential; WAdSI = Wechsler Adult Scale of Intelligence; WASI = Wechsler Abbreviated Scale of Intelligence; WISC = Wechsler Intelligence Scale for Children; WISC-R = WISC-Revised; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence, Revised; WRAT-R = Wide Range Achievement Test-Revised

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Cognitive abilities		
Krieg et al. 2005 Cross-sectional study of 5,662 adults, age 20–59 years (from NHANES III, 1988–1994).	**PbB**: • Gmean (range): 2.51 (0.7, 41.8) • Percent <10: 96% **Analysis:** Cognitive function was assessed at age 20–59 years using the NBES. Multiple linear regression with log-transformed PbB. Adjustments made for sex, age, education, family income, race/ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase.	No associations between PbB and performance scores for: • Simple visual reaction time: o Mean reaction time: p=0.24 • Symbol-digit substitution o Mean total latency: p=0.27 o Number of errors: p=0.82 • Serial digit learning o Trials to criterion: p=0.26 o Total score: p=0.24

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Muldoon et al. 1996 Cross-sectional, mean age 70±4 (SD) years study of 530 adult women recruited from the Study of Osteoporotic Fractures (1990)	**PbB:** Mean (SD): • All: 4.8 (0.4) • Rural: 4.5 (0.4) • Urban: 5.4 (0.4) • Low: <4 • Medium: 4–7 • High: >7 **Analysis:** Cognitive function was assessed at age ≥65 years using a modification of the MMSE, WASI-R, and IMT. Analysis of variance and covariance. Adjustments made for age, education, smoking, and alcohol consumption.	Difference in mean test scores between PbB categories (ANOVA). OR (95% CI) for poor performance (low PbB reference): Rural • Trailmaking B: ANOVA, p=0.03: o Medium PbB: 2.05 (1.05, 4.02) o High PbB: 2.60 (1.04, 6.49) • Digit symbol (correct): ANOVA, p=0.03 o Medium PbB: 2.03 (1.06, 3.88) o High PbB: 3.73 (1.57, 8.84) • Incidental memory: ANOVA, p=0.70 o Medium PbB: 1.37 (0.77, 2.41) o High PbB: 1.89 (0.83, 3.41) Urban • Trailmaking B: ANOVA, p=0.70 o Medium PbB OR: 0.97 (0.40, 2.40) o High PbB OR: 0.79 (0.20, 3.04) • Digit symbol (correct): ANOVA, p=0.20 o Medium PbB OR: 0.61 (0.25, 1.50) o High PbB OR: 0.64 (0.16, 2.47) • Incidental memory: ANOVA, p=0.25 o Medium PbB OR: 0.50 (0.22, 1.16) o High PbB OR:0.99 (0.28, 1.16)

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Payton et al. 1998 Longitudinal study 141 males, mean age 67±6.8 (SD) years (from Normative Aging Study, 1988–1994)	**PbB:** Mean (SD): • 5.5 (3.5) • Q1: 1.4 • Q2: 3.5 • Q3: 5.4 • Q4: 9.8 **Analysis:** Cognitive function was assessed at age 67 years using NBES, WASI-R, and CERAD. Multivariate linear regression. Adjustments made for age and education.	Association between increasing PbB and performance on various cognitive tests; coefficient (SE): • Pattern recognition: 0.074 (0.032), p=0.02 • Vocabulary: -0.841 (0.20), p=0.0001 • Word list memory: -0.182 (0.086), p=0.036 • Boston naming test: -0.036 (0.016), p=0.028 • Verbal fluency: -0.230 (0.120), p=0.09
Power et al. 2014 Longitudinal study 584 adult females, mean age 61±6 (SD) years (from Nurses' Health Study 2002–2008)	**PbB:** Mean (SD): • 2.9 (1.9) **Tibia Pb (µg/g):** Mean (SD): • 10.5 (9.7) **Patella Pb (µg/g):** Mean (SD): • 12.6 (11.7) **Analysis:** Cognitive function was assessed using a telephone interview (TICS). Linear mixed model regression. Adjustments made for variables for time, data source (cognitive and lead), alcohol consumption, smoking status, education, husband's education, menopausal status/hormone replacement therapy use, aspirin use, physical activity, ibuprofen use, aspirin use, vitamin E supplementation, percent of residential census tract of white race/ethnicity, and median income of residential census track, including both main effects and interactions with change in age from baseline cognitive test and a marker for second or subsequent interview.	No associations between PbB (or bone Pb) and performance on various cognitive tests; β for 1-age year change in score per 1 SD PbB (95% CI): • Overall cognition: -0.013 (-0.044, 0.017) • Verbal memory: 0.006 (-0.037, 0.050)

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Przybyla et al. 2017 Cross-sectional study 498 adults (age 60–84 years) from NHANES 1999–2002, United States	**PbB:** Gmean (range): 2.17 (0.4, 16.4) **Analysis:** Cognitive function was assessed using the DST of the WAdSI. Path analysis. Adjustments made for sex, age, race/ethnicity, education, smoking, and lipids.	Increasing PbB was associated with lower DST scores. β for DST score per lnPbB µg/dL (95% CI): • -0.10 (-0.20, -0.006), p=0.04
Seo et al. 2014 Cross-sectional study of 31 retired female Pb workers, mean age 60.4±5.5 (SD) years, and 34 sex and age-matched controls in South Korea (date not reported)	**PbB:** Mean (SD): **PbB:** Gmean (range): • Exposed: 4.07 (0.88–13.5) • Controls: 2.00 (1.24–6.47) **Analysis:** Verbal working memory was assessed using the N-back test with concurrent brain MRI. T-test for means of memory test scores; multiple linear regression with log-transformed PbB for MRI. Adjustment made for educational level.	Lower mean score on verbal working memory test in retired workers compared to controls: Accuracy % (SD), exposed versus control: • 1-Back test: 55.9 (19.8) versus 65.4 (19.4), p=0.056 • 2-Back test: 61.4 (20.1) versus 77.2 (15.6), p=0.001 Decreased activation of DLPFC, IPC, and IFC; β per log-PbB (95% CI): • Left DLPFC: -0.125 (-0.232, -0.018), p<0.05 • Right DLPFC: -0.120 (-0.241, 0.0001) p≥0.05 • Right IPC: -0.094 (-0.172, -0.015), p<0.05 • Right IFC: -0.087 (-0.152, -0.022), p<0.05

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Shih et al. 2006 Cross-sectional study of 985 adults, mean age 59.4±6.0 (SD) years (from Baltimore Memory Study)	**PbB:** Mean (SD): • 3.46 (2.23) **Tibia Pb (µg/g):** Mean (SD): • 18.72 (11.24) **Analysis:** Cognitive performance evaluated with various (20) tests of language, eye-hand coordination, processing speed, executive function, verbal memory and learning, visual memory, and visuoconstruction. Multiple linear regression. Adjustments made for age, sex, technician (categorical), and presence of APOE-ε4 allele (ε2ε4, ε3ε4, ε4ε4 versus noε4 allele).	Performance on cognitive tests declined ($p<0.05$) with increasing tibia Pb, but not PbB; β per 1 µg/g tibia Pb (SE): • Language: -0.0083 (0.0023), $p\leq0.01$ • Processing speed: -0.0042 (0.0021), $p<0.01$ • Eye-hand: -0.0079 (0.0020), $p\leq0.01$ • Executive function: -0.0075 (0.0019), $p\leq0.01$ • Verbal memory and learning: -0.0078 (0.0024), $p\leq0.01$ • Visual memory: -0.0067 (0.0023), $p\leq0.01$ • Visuoconstruction: -0.0122 (0.0027), $p\leq0.01$ The above associations were attenuated ($p\geq0.05$) in models that included race/ethnicity and years of education.

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Weisskopf et al. 2007 Longitudinal study cohort 1089 males, mean age 68.7±7.4 (SD) years (from Normative Aging Study, 1991–2001)	**PbB:** Median (IQ range): • 5 (3–6) **Tibia Pb (µg/g):** Median (IQ range): • 20 (13–28) **Patella Pb (µg/g):** Median (IQ range): • 25 (17–37) **Analysis:** Cognitive performance (attention/working memory/executive function, short-term memory, visuospatial, verbal, language) evaluated using NES2, WASI-R, CERAD, MMSE, and VMI. Linear regression and nonlinear spline regression. Adjustments made for age, age squared, education, smoking, alcohol intake, years between bone Pb measurement and first cognitive test, and years between the cognitive tests.	Cross-sectional analysis: association between lower score on vocabulary test with increasing PbB; β per 3 µg/dL increase in PbB (95% CI): • Vocabulary: -1.26 (-2.08, -0.44), p=0.003 No associations between PbB or bone Pb on other performance domains. Longitudinal analysis (two tests): Association between change in test scores and increasing bone Pb; β per IQR (95% CI): Patella Pb: • Visuoconstruction: -0.067 (-0.11, -0.02), p=0.0041 Tibia Pb: • Pattern comparison latency (ms): 0.079 (0.04, 0.12), p=0.0004

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Weuve et al. 2006 Longitudinal study cohort of 915 males, mean age 68.7±7.4 (SD) years (from Normative Aging Study, 1991–1997)	**PbB:** Median (IQ range): • 5.2 (2.9) • 94% <10 **Tibia Pb (µg/g):** Median (IQ range): • 19 (13–28) **Patella Pb (µg/g):** Median (IQ range): • 27 (18–39) **Analysis:** Cognitive performance using MMSE. Nonlinear spline regression. Adjustments made for age, age squared, education, experience with computers, time between Pb assessment and cognitive assessment and for the blood analyses, and time between cognitive measures.	Association between increasing PbB and decreasing scores of cognitive function tests among ALAD-2 carriers (but not wild-type). Change in MMSE score per IQR in PbB, 3 µg/dL (95% CI): • ALAD-2: -0.29 (-0.56, -0.02) • ALAD wildtype: -0.05 (-0.16, 0.06) No association with bone Pb.
Weuve et al. 2009 Longitudinal study cohort 587 females, mean age 61 (range 47–74) years (from Nurses' Health Study, 2000–2005)	**PbB:** Mean (SD): • 2.9 (1.9) **Tibia Pb (µg/g):** Median (SD): • 10.5 (9.7) **Patella Pb (µg/g):** Median (SD): • 12.6 (11.6) **Analysis:** Cognitive function was assessed using a telephone interview (TICS). Multiple linear regression. Adjustments made for education, husband's education, Pb substudy source, and cognitive substudy source.	Association between increasing PbB and decreasing scores of cognitive function tests (excluding test of letter fluency). Change in score per 1 SD in PbB or bone Pb (95% CI): • Tibia Pb: -0.051 (-0.099, -0.003), p=0.04 • Patella Pb: -0.033 (-0.080, 0.014), p=0.17 • PbB: -0.016 (-0.071, 0.039), p=0.57 The Pb effect was greater than for age (years between repeated tests): • -0.017 (-0.028, -0.007), p=0.002.

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Wright et al. 2003b Longitudinal study cohort of 736 males, mean age 68.2±6.9 (SD) years (from Normative Aging Study, 1991–1997)	**PbB:** Mean (SD): • All: 4.5 (2.5) • Q1: 2.5 • Q2: 4.0 • Q3: 5.9 • Q4: 8.9 **Tibia Pb (µg/g):** Median (SD): • 22.4 (15.3) **Patella Pb (µg/g):** Median (SD): • 29.5 (21.2) **Analysis:** Cognitive performance using MMSE. Logistic regression. Adjustments made for age, education, and alcohol intake.	Adjusted OR for low MMSE score (<24) associated with 1 µg/dL increase in PbB or 1 µg/g increase in bone Pb (95% CI): • PbB: 1.21 (1.07, 1.36) • Patella Pb: 1.02 (1.00, 1.03) • Tibia Pb: 1.02 (1.00, 1.04) Interaction between age and PbB and bone Pb with increasing β for age with increasing Pb, age β for PbB quartile (95% CI): • Q1: -0.04 (-0.07, -0.02) • Q2: -0.04 (-0.08, -0.01) • Q3: -0.09 (-0.13, -0.06) • Q4: -0.12 (-0.17, -0.02)

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Yu et al. 2019b Cross-sectional study of 339 males, mean age 28.6 years, newly hired lead workers recruited in 2015–2017 (SPHERL longitudinal study), United States	**PbB:** Gmean (IQR): 2.47 (2.00, 3.00) **Analysis:** Cognitive performance assessed using Stroop test MRT, DST, and MTL. Linear and logistic regression. Adjustments made for age, ethnicity, waist-to-hip ratio, heart rate, smoking, alcohol consumption, education, serum insulin levels, and total-to-HDL cholesterol ratio.	PbB was not associated with cognitive performance. β per log_{10} PbB (95%CI): • Stroop MRT incongruent trials (%): 5.1 (-4.5, 15.6), p=0.30 • Stroop MRT congruent trials (%): -1.2 (-10.4, 9.0), p=0.81 • Stroop interference effect (%): 23.0 (-15.4, 78.9), p=0.28 • DST MTL (%): 5.4 (-0.4, 11.5), p=0.066 OR for cognitive performance scores not significant (95% CI): • Stroop error score incongruent trials: 1.48 (0.63, 3.47), p=0.37 • Stroop interference score: 0.79 (0.33, 1.89). p=0.59 • Digit symbol error score: 0.58 (0.31, 1.10), p=0.096

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Mood and behavior		
Bouchard et al. 2009 Cross-sectional study of 1987 adults (age 20–39) years from the NHANES (1999–2004)	**PbB:** Gmean (range) • 1.24 (1.96) • 99% ≤10 • Q1: 0.6 • Q2: 0.9 • Q3: 1.2 • Q4: 1.3 • Q5: 3.0 **Analysis:** Psychiatric disorders (major depressive, panic, generalized anxiety) were assessed based on the WHO CIDI and the DSM-IV. Logistic regression. Adjustments made for age, sex, race/ethnicity, education, and poverty to income ratio.	Adjusted ORs (95% CI) for PbB relative to Q1: • Major depressive disorder o Q5: 2.32 (1.13, 4.75); p=0.05, trend • Panic disorder o Q5: 4.94 (1.32, 18.48); p=0.02, trend • Generalized anxiety disorder o Q5: 1.53 (0.39, 5.96); p=0.78, trend Eliminating current smokers from the analysis strengthened the effect size (smoking was correlated with higher PbB): • Major depressive disorder o Q5: 2.93 (1.24, 6.92); p=0.03, trend • Panic disorder o Q5: 9.57 (1.28, 71.43); p=0.01, trend • Generalized anxiety disorder o Q5: 1.59 (0.19, 13.31); p=0.44, trend

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Buser and Scinicariello 2017 Cross-sectional study of 3,905 adults (age ≥20 years) from NHANES 2011–2012	**PbB:** Gmean (GSD) • Males: 1.29 (0.04) • Females: 0.93 (0.03) • All: 1.09 (0.03) • Q1: <0.7 • Q2: 0.70–1.06 • Q3: 1.07–1.67 • Q4: >1.67 **Analysis:** Depression symptoms scored from self-administered version of Prime MD (NHANES PHQ-9). Logistic regression. Adjustments made for sex, age, race/ethnicity, obesity, serum cotinine, poverty income ratio, smoking status, alcohol consumption, and education level.	Adjusted OR for depression symptoms associated with increasing PbB quartile in females age 20–47 years (95% CI): Q2: 1.23 (0.71, 2.13) Q3: 1.86 (1.01, 3.41); p<0.05 Q4: 2.97 (1.01, 8.74); p<0.05
Fan et al. 2020 Cross-sectional study of 994 adults (544 females), age >60 years, recruited in 2016; Anhui Province, China	**PbB:** Mean (SD): 3.229 (2.357) Q1: <2.027 Q2: 2.027, 2.677 Q3: 2.677, 3.058 Q4: ≥3.058 **Analysis:** Depression symptoms were assessed using a GDS. Logistic regression adjusted for age, gender, residence region, marital status, income, education, alcohol consumption, smoking, and BMI.	Increasing PbB was associated with higher depression scores on GDS. OR for depression for PbB quartiles relative to Q1 (95% CI): Q2: 1.28 (0.79, 2.08), p=0.315 Q3: 1.36 (0.84, 2.22), p=0.216 Q4: 2.03 (1.23, 3.35), p=0.006 p-trend =0.007

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Golub et al. 2010 Cross-sectional study of 4,195 adults (age ≥20 years) from NHANES 2005–2006	**PbB:** Mean (SE) • 1.75 (0.05) • Q1: ≤0.88 • Q2: 0.89–1.40 • Q3: 1.41–2.17 • Q4: 2.18–26.4 **Analysis:** Depression symptoms scored from self-administered version of Prime MD (NHANES PHQ-9). Logistic regression. Adjustments made for sex, age, ethnicity, poverty income ratio, and education level.	Adjusted OR for depression symptoms was elevated in PbB quartile 3 (95% CI): Q2: 1.22 (0.98, 1.51) Q3: 1.25 (1.07, 1.47) Q4: 1.18 (0.83, 1.68)
Li et al. 2017a Cross-sectional study of 1,931 pregnancies (age 13–42 years), recruited in 2010; Shanghai, China	**PbB:** Gmean (range): 3.99 (0.80, 14.84) **Analysis:** Depression, anxiety, and psychological stress symptoms were scored at gestation weeks 28–36 using LESPW, SCL-90-R, and GSI. Linear regression. Adjustments made for age, ethnicity, education, income, and residence time in Shanghai.	Increasing PbB was associated with depression or anxiety symptoms in PbB stratum ≤2.57 µg/dL. β per $\log_{10}$ PbB: Full cohort: • GSI: 0.01 (-0.05, 0.07), p=0.815 • Depression: 0.03 (-0.05, 0.10), p=0.466 • Anxiety: 0.01 (-0.06, 0.08), p=0.770 PbB ≤2.57: • GSI: 0.22 (0.05, 0.40), p=0.013 • Depression: 0.34 (0.12, 0.56), p=0.002 • Anxiety: 0.25 (0.04, 0.46), p=0.019 PbB >2.57: • GSI: -0.07 (-0.16, 0.01), p=0.100 • Depression: -0.09 (-0.19, 0.02), p=0.113 • Anxiety: -0.08 (-0.18, 0.02), p=0.136

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Opler et al. 2004 Case-control study of 44 schizophrenia cases and 75 matched controls from birth cohorts (1959–1966) from California	**PbB:** Cohort stratified into <15 or ≥15 µg/dL based on 2nd trimester ALA measurements **Analysis:** Mantel-Haenszel OR and logistic regression. Adjustments made for mother's age at delivery.	Adjusted OR for schizophrenia associated with high (≥15 µg/dL) prenatal PbB. OR (95% CI): • 2.43 (0.99, 5.96), p=0.051
Opler et al. 2008 Case-control study of 71 schizophrenia cases and 129 matched controls from birth cohorts (1959–1966) from California and New England	**PbB:** Cohort stratified into <15 µg/dL or ≥15 µg/dL based on 2nd trimester ALA measurements **Analysis:** Logistic regression. Adjustments made for maternal age and maternal education.	Adjusted OR for schizophrenia associated with high (≥15 µg/dL) prenatal PbB. OR (95% CI): • 1.92 (1.05, 3.87), p=0.03
Rajan et al. 2007 Longitudinal study cohort of 1,075 males, mean age 67.1±7.2 (SD) years (from Normative Aging Study, 1991–2002)	**PbB:** Mean (SD): • All: 6.2 (4.1) **Tibia Pb (µg/g):** Median (SD): • 22.1 (13.8) **Patella Pb (µg/g):** Median (SD): • 31.4 (19.6) **Analysis:** Psychiatric symptoms scored using Brief Symptom Inventory. Logistic regression. Adjustments made for age at bone scan, alcohol consumption (categorical), education (categorical), time between BSI assessments, and cumulative smoking (pack-years).	Association between increasing bone Pb and psychiatric symptoms (abnormal, responses to BSI). Adjusted OR (95% CI) for inter quartile increases in tibia Pb (14 µg/g) or patella Pb (20 µg/g): • Somatization, tibia Pb: 1.21 (1.01, 1.46) • Global severity index, patella Pb: 1.23 (1.02, 1.47) OR 95% CIs encompassed 1 for anxiety, depression, hostility, phobic anxiety, or total symptoms.

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Rhodes et al. 2003 Longitudinal study cohort of 526 males, mean age 67.1±7.2 (SD) years (from Normative Aging Study, 1991–1995)	**PbB:** Mean (SD): • 6.3 (4.2) **Tibia Pb (µg/g):** Median (SD): • 21.9 (13.5) **Patella Pb (µg/g):** Median (SD): • 32.1 (19.8) **Analysis:** Psychiatric symptoms scored using Brief Symptom Inventory. Logistic regression. Adjustments made for age, age squared, alcohol ingestions (g/day), education (four levels), and employment status (three levels).	Association between increasing bone Pb and psychiatric symptoms (abnormal, responses to BSI). Adjusted OR (95% CI) for inter-quintile increases in blood (8.9 µg/dL), tibia Pb (27 µg/g), or patella Pb (45 µg/g): • Phobic anxiety, patella Pb: 1.91 (1.01, 3.61) • Combined symptoms, PbB: 2.91 (1.39, 6.09) • Combined symptoms, tibia Pb: 2.08 (1.06, 4.07) • Combined symptoms, patella Pb: 3.62 (1.62, 8.08)
Scinicariello and Buser 2015 Cross-sectional study of 2,892 adults (age 20–39 years) from NHANES 2007–2010	**PbB:** Gmean (GSD) • 0.96 (0.02) **Analysis:** Depression symptoms scored from self-administered version of Prime MD (NHANES PHQ-9). Logistic regression. Adjustments made for sex, age, race/ethnicity, obesity, blood cadmium, serum cotinine, poverty income ratio, smoking status, alcohol consumption, and education level.	Adjusted OR for depression symptoms was not associated with increasing PbB (ORs were not reported).
Neuromotor neurosensory function		
Casjens et al. 2018 Longitudinal study of 1,188 males, age 55–86 years at follow-up (median age at baseline of 58 years), recruited in 2000–2003 with follow-up 2011–2014, Germany	**PbB:** Median (% >9) • Baseline: 3.29 (2.27%) • Follow-up: 2.59 (0.84%)	PbB was not associated with odor detection error. POR (95% CI) for impaired odor identification relative <5.0 µg/dL: Baseline: • 5.0–<9.0 µg/dL: 0.91 (0.65, 1.28) • ≥9.0 µg/dL: 1.96 (0.94, 4.11)

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
	Analysis: Olfaction and fine motor skills were assessed using an odor identification test and a Motor Performance Series (finger tapping, aiming, line tracing, steadiness). Logistic regression adjusted for age, occupation, smoking, alcohol consumption, and test time.	Follow-up: • 5.0–<9.0 µg/dL: 1.04 (0.55, 1.94) • ≥9.0 µg/dL: 1.57 (0.47, 5.19) PbB was associated with fine motor skills assessed by tapping test at 5.0–<9.0 µg/dL, but not other tests. OR (95% CI) for impaired performance compared to <5.0 µg/dL: Finger tapping hits: Baseline • 5.0–<9.0 µg/dL: 0.87 (0.53, 1.44) • ≥9.0 µg/dL: 1.35 (0.49, 3.70) Follow-up: • 5.0–<9.0 µg/dL: 2.63 (1.26, 5.94) • ≥9.0 µg/dL: 0.80 (0.14, 4.59) Aiming errors Baseline: • 5.0–<9.0 µg/dL: 1.07 (0.75, 1.53) • ≥9.0 µg/dL: 0.56 (0.22, 1.42) Follow-up: • 5.0–<9.0 µg/dL: 1.35 (0.73, 2.51) • ≥9.0 µg/dL: 0.42 (0.09, 2.08) Line tracing errors: Baseline: • 5.0–<9.0 µg/dL: 1.09 (0.68, 1.76) • ≥9.0 µg/dL: 0.93 (0.32, 2.74) Follow-up • 5.0–<9.0 µg/dL: 1.01 (0.41, 2.48) • ≥9.0 µg/dL: 0.59 (0.08, 4.11)

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		Steadiness errors: Follow-up: • 5.0–<9.0 µg/dL: 0.99 (0.62, 1.59) • ≥9.0 µg/dL: 1.36 (0.50, 3.66) Follow-up: • 5.0–<9.0 µg/dL: 1.16 (0.50, 2.69) • ≥9.0 µg/dL: 1.75 (0.41, 7.58)
Hwang et al. 2009 Cross-sectional study of 259 male steel workers, mean age 36.0±6.5 years; Taiwan, China	**PbB:** Mean (SD): 5.43 (3.46) **Analysis**: Hearing loss assessed. Logistic regression. Adjustments made for age and noise level.	Association between increasing PbB and hearing loss. Adjusted OR (95% CI) for hearing loss (>25 dB) in PbB categories relative to ≤4 µg/dL: Loss at 3,000 Hz: • 4–7 µg/dL: 0.75 (0.17, 3.29) • ≥7 µg/dL: 4.49 (1.28, 15.8); p<0.005 Loss at 4,000 Hz: • 4–7 µg/dL: 3.54 (1.40, 8.97); p-value not reported • ≥7 µg/dL: 6.26 (2.35, 16.6); p<0.005 Loss at 6,000 Hz: • 4–7 µg/dL: 2.11 (0.94, 4.47) • ≥7 µg/dL: 3.06 (1.27, 7.39); p<0.05 Loss at 8,000 Hz: • 4–7 µg/dL: 3.0 (0.78, 11.5) • ≥7 µg/dL: 6.16 (1.59, 23.9); p<0.05

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Huh et al. 2018 Cross-sectional study of 2,387 adults, age 19–85 years; KNHANES 2010–2012, Korea	**PbB:** Gmean (95% CI): 2.46 (2.41, 2.52) Q1: 0.515, 1.780 Q2: 1.780, 2.248 Q3: 2.248, 2.723 Q4: 2.273, 3.396 Q5: 3.396, 26.507 **Analysis**: Hearing loss assessed (pure tone average). Logistic regression. Adjustments made for age, sex, income, education, smoking, BMI, occupational noise exposure, loud noise exposure, firearm noise exposure, hypertension, and diabetes.	Increasing PbB was associated with high frequency hearing loss. OR per doubling of PbB (95% CI): • Low frequency: 0.91 (0.52, 1.61) • Speech frequency: 1.21 (0.72, 2.04) • High frequency: 1.88 (1.11, 3.17) Joint interaction blood cadmium on high frequency loss was in the negative direction. OR ratio (95% CI): • Joint (multiplicative) 0.55 (0.33, 0.92), p=0.023 OR for high frequency hearing loss for PbB quintile relative to Q1: • Q2: 1.07 (0.68, 1.68) • Q3: 1.16 (0.75, 1.82) • Q4: 1.51 (0.97, 2.36) • Q5: 1.44 (0.90, 2.31) • p-trend =0.035
Ji et al. 2013 Cross-sectional study of 1,795 males and 1,798 females, age >50 years (median 61.2 years) from NHANES (1999–2002)	**PbB:** Mean (SD): • Females: 2.17 (0.06) • Males: 3.18 (0.12) **Analysis**: Walking speed assessed. Multiple linear regression. Adjustments made for age, education, ethnicity, alcohol use, smoking status, height, and waist circumference.	Association between increasing PbB and walking speed in women. Mean change in walking speed (feet/second) for PbB quintile relative to Q1 (≤1.2 µg/dL): • 1.3–≤1.6: -0.024 (-0.112, 0.064), p=0.58 • 1.7–≤2.1: -0.027, (-0.118, 0.063), p=0.54 • 2.2–≤2.9: -0.104 (-0.187, -0.021), p=0.02 • 3.3–≤53.0: -0.114 (-0.191, -0.038), p=0.01 Trend, p=0.005

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Ji et al. 2015 Longitudinal study cohort of 807 males, mean age 69±7 years (from Normative Aging Study, 1991–ND)	**PbB:** Mean (SD): • 5.0 (2.7) • % <10: 96% **Tibia Pb (µg/g):** Median (SD): • 21.2 (13.3) **Patella Pb (µg/g):** Median (SD): • 28.0 (18.4) **Analysis:** Hand tremor assessed. Linear and logistic regression. Adjustments made for age, age squared, alcohol intake, cigarette pack-years, and education level.	No association between PbB or bone Pb and tremor. Adjusted OR (95% CI) for bone Pb or PbB quintiles relative to Q1 (3 µg/dL): • Q5 (8–28), PbB: 0.84 (0.38, 1.86), p=0.72 • Q5 (40–165), patella Pb: 0.83 (0.31, 2.19), p=0.41 • Q5 (30–126), tibia Pb: 1.08 (0.46, 2.53), p=0.60

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Kang et al. 2018 Cross-sectional study of 6,409 adults (50.4% female), age 20–87 years (mean age 57 years); KNHANES 2010–2013, Korea	**PbB:** Mean (SE) Females, weighted mean (SE) • Q1: 1.12 (0.01) • Q2: 1.61 (0.01) • Q3: 2.11 (0.01) • Q4: 3.03 (0.03) Males, weighted mean (SE) • Q1: 1.56 (0.01) • Q2: 2.22 (0.01) • Q3: 2.82 (0.01) • Q4: 4.22 (0.08) **Analysis**: Hearing loss assessed (pure tone average). Logistic regression. Adjustments made for age, BMI, education, smoking alcohol consumption, exercise, diabetes mellitus, hypertension, occupational noise exposure, loud noise exposure, and firearm noise exposure.	Increasing PbB was associated with high frequency hearing loss. OR for high frequency hearing loss for PbB quartile relative to Q1: Males: • Q2: 1.368 (1.006, 1.859) • Q3: 1.402 (1.005, 1.955) • Q4: 1.629 (1.161, 2.287) Females: • Q2: 0.947 (0.606 1.477) • Q3: 1.013 (0.698, 1.471) • Q4: 1.502 (1.027, 2.196)
Krieg et al. 2005 Cross-sectional study of 5,662 adults, age 20–59 years (from NHANES III, 1988–1994	**PbB**: • Gmean (range): 2.51 (0.7, 41.8) • Percent <0: 96% **Analysis:** Cognitive function was assessed at age 20–59 years using the NBES. Multiple linear regression with log-transformed PbB. Adjustments made for sex, age, education, family income, race/ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase.	No associations between PbB and performance scores for: • Simple visual reaction time: o Mean reaction time: p=0.24

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes

Muldoon et al. 1996
 	
Cross-sectional, mean age 70±4 (SD) years study of 530 adult women recruited from the Study of Osteoporotic Fractures (1990)
	PbB: Mean (SD):
	• All: 4.8 (0.4)
	• Rural: 4.5 (0.4)
	• Urban: 5.4 (0.4)
	• Low: <4
	• Medium: 4–7
	• High: >7
	
	Analysis: Sensorimotor function was assessed at age ≥65 years using grooved pegboard and reaction time. Analysis of variance and covariance. Adjustments made for age, education, smoking, and alcohol consumption.
		Difference in mean reaction time test scores between PbB categories (ANOVA). OR (95% CI) for poor performance (low PbB reference) in the rural cohort:
		• Pegboard: ANOVA, p=0.98
		  o Medium PbB: 1.37 (0.71, 2.65)
		  o High PbB: 1.16 (0.45, 3.01)
		• Upper extremity: ANOVA, p<0.01:
		  o Medium PbB: 1.39 (0.73, 2.65)
		  o High PbB: 2.43 (1.01, 5.83)
		• Lower extremity: ANOVA, p<0.01
		  o Medium PbB: 1.29 (0.68, 2.47)
		  o High PbB: 2.84 (1.19, 6.74)
		
		No difference in mean reaction time test scores between PbB categories (ANOVA) for poor performance (low PbB reference) were observed in the urban cohort.

Neurological disease		
Fang et al. 2010 Case-control study of 184 male ALS cases and 194 matched controls, mean age 63 years (range 34–84 years) from the National registry of U.S. veterans with ALS (2003–2006)	**PbB:** Mean (range): • Controls 1.76 (0.32–6.90) • Cases: 2.41 (0.72–7.58) **Analysis:** Logistical regression. Adjustments made for age (continuous; age at diagnosis for cases and age at interview for controls) and log_2-transformed CTX level.	Association between increasing PbB and ALS. Adjusted OR for ALS (95% CI) for doubling of PbB: • All cases (n=184): 1.9 (1.3, 2.7) • Excluding progressive muscular atrophy and primary lateral sclerosis (n=151): 1.8 (1.2, 2.5)

Table 10. Selected Epidemiology Studies Evaluating Neurodevelopmental Effects in Adults at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Kamel et al. 2002 Case-control study of 109 ALS cases and 256 matched controls, age 30–80 years from New England hospitals (1993–1996)	**PbB:** Mean (range): • Cases: 3 of 194 had PbB >10 • Controls: <10 µg/dL **Analysis:** Logistical regression. Adjustments made for age, sex, region, education, and inactivity,	Association between increasing PbB and ALS. Adjusted OR for ALS (95% CI) for a 1 µg/dL increase in PbB: • 1.9 (1.4, 2.6) Adjusted OR for ALS (95% CI) relative to <2 µg/dL: • 3–4 µg/dL: 14.3 (3.0, 69.3) • 5–14 µg/dL: 24.5 (4.3, 139.3)

ALA = aminolevulinic acid; ALAD-2 = delta-aminolevulinic acid dehydratase allele; ALS = amyotrophic lateral sclerosis; ANOVA = analysis of variance; BMI = body mass index; BSI = Brief Symptom Inventory; CERAD = Consortium to Establish Registry for Alzheimer's Disease; CI = confidence interval; CIDI = Composite International Diagnostic Interview; CL = confidence limit; CTX = C-terminal telopeptides of type 1 collagen; DLPFC = dorsolateral prefrontal cortex; DSM = Diagnostic and Statistical Manual; DST = Digit-Symbol Test; GDS = Geriatric Depression Scale; Gmean = geometric mean; GSD = geometric standard deviation; GSI = Global Severity Index; HDL = high-density lipoprotein; IFC = inferior frontal cortex; IMT = Incidental Memory Test; IPC = inferior parietal cortex; IQ = intelligence quotient; IQR = interquartile range; KNHANES = Korean National Health and Nutrition Examination Survey; LESPW = Life Event Stress Scale for Pregnant Women; MMSE = Mini-Mental Status Examination; MRI = Magnetic Resonance Imaging; MRT = mean reaction time; MTL = mean total latency; NBES = Neurobehavioral Evaluation System; NES2 = Neurobehavioral Evaluation System 2; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; PHQ = Public Health Questionnaire; POR = proportional odds ratio; SCL-90-R = Symptom Checklist 90 Revised; SD = standard deviation; SE = standard error; SPHERL = Study for Promotion of Health in Recycling Lead; TICS = Telephone Interview for Cognitive Status; VMI = Visual Motor Integration; WAdSI = Wechsler Adult Scale of Intelligence; WASI = Wechsler Abbreviated Scale of Intelligence; WHO = World Health Organization

Table 11. Epidemiology Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Chen et al. 2016 Cross-sectional study of 2,286 men (mean age: 54 years) in China	**PbB:** • Median (IQR): 4.40 (2.90–6.23) • Quartiles: o Q1: <2.9 (n=558) o Q2: 2.9–4.39 (n=572) o Q3: 4.4–6.2 (n=585) o Q4: >6.2 (n=571) **Analysis:** Data for blood levels of reproductive hormones (SHBG, T, FSH, LH, E) were log-transformed and analyzed by linear regression analysis, adjusted for age, current smoking status, BMI, systolic blood pressure, diabetes, and blood Cd concentration.	SHBG, T, FHS, and LH were positively associated with PbB in the Q4 group; no association was observed between PbB and E. β coefficients (SE): • SHBG: p-trend: <0.001 o Q1: 1 (reference) o Q2: < 0.001 (0.011) o Q3: 0.021 (0.011) o Q4: 0.038 (0.012); p<0.01 • T: p-trend=0.001. o Q1: 1 (reference) o Q2: 0.001 (0.010) o Q3: 0.010 (0.010) o Q4: 0.033 (0.010); p<0.01 • E: p-trend=0.794 o Q1: 1 (reference) o Q2: -0.008 (0.016) o Q3: 0.014 (0.017) o Q4: -0.003 (0.017) • FSH: p-trend=0.067 o Q1: 1 (reference) o Q2: 0.010 (0.014) o Q3: 0.004 (0.014) o Q4: 0.030 (0.015); p<0.05 • LH: p-trend=0.065 o Q1: 1 (reference) o Q2: 0.018 (0.013) o Q3: 0.015 (0.013) o Q4: 0.028 (0.013); p<0.05

Table 11. Epidemiology Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Famurewa and Ugwuja 2017 Cross-sectional study of 75 men (age range: 20–45 years) with infertility from Nigeria	**PbB:** Mean (SD) • Normospermic, n=36: 1.49 (0.59) • Azoospermic, n=15: 1.71 (0.98) • Oligospermic, n=22: 2.05 (0.97) **Analysis:** ANOVA was used to compare means for PbB. Semen parameters were evaluated using Pearson correlation analysis. No information on adjustments was reported.	PbBs were higher ($p<0.05$) in azoospermic and oligospermic groups compared to the normospermic group. A negative association between PbB and sperm count, but not for other parameters, in infertile men. Pearson correlation R value: • Semen volume (mL): -0.132; p=0.27 • Sperm count ($x10^6$ cells/mL): -0.280; p=0.02 • Total motility (%): -0.092; p=0.44 • Morphology (%): -0.081; p=0.50

Table 11. Epidemiology Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Hernandez-Ochoa et al. 2005 Cross-sectional study of 68 men (21–54 years of age) who resided in the Region Lagunera, Mexico (site of large smelter complex) for at least 3 years	**PbB:** Mean (SD): 9.31 • Range: 1.9–24.4 • Participants with PbB >10: 48% Other Pb measurements: • Seminal fluid: 2.02 µg/L (range 1.14–12.4 µg/L) • Spermatozoa: 0.047 ng/10^6 cells (range: 0.032–0.245 ng/10^6 cells) • No correlation was observed between PbB and Pb levels in seminal fluid or in spermatozoa **Analysis:** Semen parameters (volume, sperm concentration, motility, morphology, viability and viscosity) were analyzed by linear and multi-linear regression adjusted for age, BMI, days of sexual abstinence, smoking intensity, and consumption of alcohol and drugs.	No associations (p>0.05) were observed between PbB and sperm or semen quality. β coefficients per µg/dL: • Sperm motility: -0.006 • Sperm morphology: -0.001 • Sperm viability: -0.095 • Semen volume: -0.043 Sperm quality: concentration, motility, morphology, and viability were negatively associated with Pb in spermatozoa (β coefficients per ng/10^6 cells): • Log sperm concentration (10^6 cells/mL): -17.17 (p<0.05) • Motility (%): -2.12 (p<0.05) • Morphology (%): -1.42 (p<0.05) • Viability (%): -0.130 (p<0.05) Semen volume: negatively associated with Pb in seminal fluid (β coefficient mL per µg/L: • -0.183 mL; p<0.05).

Table 11. Epidemiology Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Li et al. 2015 Cross-sectional study of 154 male participants from a reproductive medical center; recruited May 2012–February 2013	**PbB:** Mean (SD): • All participants: 2.78 (1.85) • Low-quality semen group: 3.43 (2.47); n=59 • High-quality semen group: 2.38 (1.17); n=95 High-quality semen was defined as a sperm concentration ≥15x10^6/mL, semen volume ≥1.5 mL, number of sperm ≥39x10^6, total motility sperm ≥40% or progressive motility sperm ≥32%, and sperm with normal morphology ≥4%. **Analysis:** Semen parameters (volume, sperm concentration, sperm number, motility, and morphology) were analyzed by multiple logistic regression analysis and adjusted for age, BMI, education, smoking intensity, alcohol consumption, betel nut chewing, coffee intake, nutritional supplement consumption, chronic disease, and Pb-related occupation.	Mean PbB in the low-quality semen group was significantly higher (p=0.0391) than in the high-quality semen group. Adjusted ORs (95% CI) with PbB as a variable for: • Low-quality sperm: 1.040 (1.011, 1.069); p=0.0061 • Decreased sperm concentration: 1.046 (1.015, 1.078); p=0.0032 • Decreased sperm number: 1.041 (1.012, 1.071); p=0.0048 • Decreased motile sperm: 1.057 (1.026, 1.089; p=0.0003 • Decreased progressive motile sperm: 1.047 (1.014, 1.080); p=0.00043 • Decreased morphologically normal sperm: 1.071 (1.025, 1.118; p=0.0021

Table 11. Epidemiology Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Kresovich et al. 2015 Cross-sectional study of 869 men (aged >20 years) participating in three consecutive NHANES (1990–2000, 2001–2002, and 2003–2004) studies	**PbB:** • Median: 2.0 • Quartiles o Q1: ≤1.4 (reference) o Q2: 1.4–2.1 o Q3: 2.10–3.20 o Q4: >3.20 **Analysis:** Reproductive hormones (testosterone, free testosterone, estradiol, free estradiol, androstenedione, glucuronide, and SHBG) were analyzed by multiple linear regression adjusted for age, race, BMI, smoking, diabetes status, and alcohol consumption.	PbB was associated with an increase in serum testosterone (ng/mL) in Q3 and Q4. β coefficient per µg/dL (SE): • Q1: reference • Q2: 0.38 (0.23) • Q3: 0.54 (0.21); p<0.05 • Q4: 0.79 (0.22); p<0.05 • p-trend=0.0026 PbB was associated with an increase in serum free testosterone (ng/mL) in Q4. β coefficient per µg/dL (SE): • Q1: reference • Q2: 0.95 (0.50) • Q3: 0.70 (0.51) • Q4: 1.06 (0.51); p<0.05 • p-trend=0.1388
Lewis and Meeker 2015 Cross sectional study of 484 men (aged 18–55 years) participating in an NHANES (2011–2012) study	**PbB:** • Gmean: 1.06 • Quartiles: o Q1 (<25th percentile): <0.71 o Q2 (25th–50th percentile): 0.71–1.00 o Q3 (50th–75th percentile): 1.00–1.59 o Q4 (>75th percentile): 1.59–33.67 **Analysis:** Serum testosterone was analyzed by multiple linear regression adjusted for age, BMI, economic status, and serum cotinine.	Adjusted models showed that a doubling of PbB was associated with a 6.65% (95% CI: 2.09, 11.41; p<0.004) increase in serum testosterone. A positive trend (p=0.003) was observed across quartiles.

Table 11. Epidemiology Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Meeker et al. 2008 Cross-sectional study of 219 men (aged 18–55 years) recruited from two Michigan infertility clinics	**PbB:** • Median: 1.50 • Quartiles (Q): o Q1: <1.10 o Q2: 1.10–1.50 o Q3: 1.50–2.00 o Q4: 2.00–16.2 **Analysis:** Semen parameters (volume, sperm count, sperm concentration, percent motile, and sperm morphology) and semen quality were analyzed by multiple linear regression and adjusted for age, BMI, race, income, smoking status, and blood levels of Cd, Cu, Se, and Zn.	No association was observed for PbB and sperm concentration, sperm motility, morphologically abnormal sperm, or semen volume for Q2, Q3, or Q4, compared to Q1 (reference). Adjusted regression coefficients per µg/dL (95% CI): • ln-sperm concentration (10^6/mL) o Q2: -0.15 (-0.55, 0.25) o Q3: -0.25 (-0.67, 0.18) o Q4: 0.02 (-0.39, 0.43) o p-trend: 0.97 • Sperm motility: (% mobile) o Q2: 0.96 (-4.52, 6.45) o Q3: 2.00 (-3.87, 7.88) o Q4: 1.10 (-4.56, 6.75) o p-trend: 0.64 • Sperm morphology (% normal): o Q2: 0.71 (-0.69, 2.11) o Q3: -0.83 (-2.34, 0.67) o Q4: -0.16 (-1.58, 1.26) o p-trend: 0.64 • Semen volume (mL) o Q2: -0.43 (-0.99, 0.13) o Q3: -0.28 (-0.87, 0.31) o Q4: 0.17 (-0.41, 0.74) o p-trend: 0.92

Table 11. Epidemiology Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Meeker et al. 2010 Cross-sectional study of 219 men (aged 18–55 years) recruited from two Michigan infertility clinics	**PbB:** • Median: 1.5 • Quartiles o Q1: <1.1 (reference) o Q2: 1.1–1.5 o Q3: 1.5–2.0 o Q4: >2.0–16.2 **Analysis:** Reproductive hormones (serum FSH, LH, inhibin B, T, and SHBG levels) was analyzed by bivariate analysis using SAS (version 9.1) and adjusted for age, BMI, and smoking status.	Elevated serum testosterone (ng/dL) was associated with PbB for Q4. Regression coefficient Q4: 39.9 (3.32, 76.4). Trend analysis across quartiles was not statistically significant (p<0.07). No associations between PbB and serum levels of other hormone were observed (FSH, LH, inhibin B, SHBG, FAI) for Q2–Q4, compared to Q1. Adjusted regression coefficients per µg/dL (95% CI) for Q4 versus Q1, and p-trend: • FSH (IU/L): 0.07 (-0.18, 0.31); p-trend=0.65 • ln-LH (IU/L): 0.08 (-0.14, 0.29); p-trend=0.32 • Inhibit B (pg/mL): -7.79 (-29.0, 13.4); p-trend=0.52 • ln-SHBG (nmol/L): 0.07 (-0.10, 0.23); p-trend=0.34 • ln-FAI: 0.08 (-0.05, 0.21); p-trend=0.35

Table 11. Epidemiology Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Mendiola et al. 2011 Case-control study of 61 men (30 case subjects and 31 controls; average age 33.5 years) attending three infertility clinics in Southeastern Spain between 2005 and 2007	**PbB:** • Mean: 2.8 • Median: 2.9 • 95th percentile: 3.3 **Analysis:** Reproductive hormones (FSH, LH, and T) and serum samples (seminal plasma) were analyzed using multiple linear regression and adjusted for age, BMI, and smoking.	A significant association between Pb in seminal plasma and the % of immotile sperm was observed (β=1.5; 95% CI: 0.37, 1.9; p≤0.05). No association was observed between PbB and sperm concentration (10^6/mL), immotile sperm (%), and morphologically normal sperm (%), or serum levels of FSH, LH, or T. β per µg/L (95% CI): • ln-sperm concentration (10^6/mL): 0.08 (-4.1, 5.2) • % Immotile sperm: -0.49 (-1.8, 0.62) • % Morphologically normal sperm: -0.08 (-3.5, 3.4) • FSH (IU/L): -0.20 (-0.64, 0.25) • LH (IU/L): -0.07 (-0.49, 0.31) • T (ng/mL): -0.12 (-0.40, 0.14)

Table 11. Epidemiology Studies Evaluating Effects on the Male Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Telisman et al. 2007 Cross-sectional study of 240 Croatian men (aged 19–55 years) with no previous occupational exposure to metals; data collection period was October 2002–May 2005	**PbB:** • Median: 4.92 • 10^{th}–90^{th} percentile: 2.10–9.44 • Range: 1.13–14.91 **Analysis:** Reproductive parameters (semen volume, pH, percentage of leukocytes/erythrocytes, number of immature sperm cells, sperm concentration, sperm count, motility, viability, morphology, FSH, LH, prolactin, testosterone, and estradiol) were analyzed using linear multiple regression and adjusted for age, smoking and alcohol consumption, and body burden of cadmium, copper, zinc, and selenium.	Standardized regression coefficients for log PbB µg/L (β coefficients) for: • Effects on sperm o Immature sperm ($x10^6$/mL): 0.13 ($p<0.07$) o Pathologic sperm (%): 0.31 ($p<0.0002$) o Wide sperm (%): 0.32 ($p<0.0001$) o Round sperm (%): 0.16 ($p<0.03$) • Effects on hormone levels o Prolactin (IU/L): -0.18 ($p<0.007$) o T (nmol/L): 0.21 ($p<0.003$) o Estradiol (nmol/L): 0.22 ($p<0.0008$)

ANOVA = analysis of variance; BMI = body mass index; Cd = cadmium; CI = confidence interval; Cu = copper; E = estradiol; FAI = free androgen index; FSH = follicle-stimulating hormone; Gmean = geometric mean; Inhibin B = gonadal dimeric polypeptide hormone; IQR = interquartile range; LH = luteinizing hormone; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio; Pb = lead; SD = standard deviation; Se = selenium; SE = standard error; SHBG = sex hormone-binding globulin; T = testosterone; Zn = zinc

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Hormone levels		
Chang et al. 2006 Case control study of 147 women (64 cases and 83 controls aged 23–44 years) who attended a fertility clinic in Kaohsiung City, Taiwan August 2000–July 2001; controls consisted of women who delivered normal babies January–June 1999	**PbB:** • Control group mean (SD): 2.78 (2.05) • Infertile group mean (SD): 3.55 (1.39); p=0.007 compared to control **Analysis:** Hormone levels (FSH, LH) were analyzed using multivariate linear regression and adjusted for age, BMI, and smoking (active and passive).	No differences between control and infertile groups were observed for serum levels of LH (mIU/mL), FSH (mIU/mL), estradiol (ρg/mL), or progesterone (ng/mL). Means (SD) • LH: control: 4.38 (2.00); infertile: 4.47 (2.75); p=0.813 • LH: control: 7.13 (2.05); infertile: 6.64 (1.88); p=0.135 • Estradiol: control: 27.5 (12.65); infertile: 30.4 (13.74); p=0.181 • Progesterone: control: 0.44 (0.19); infertile: 0.44 (0.19); p=0.692 For women with PbB >2.5, an association was observed between PbB (per 1 µg/dL and estradiol (ρg/mL). β coefficient (SE): 1.18 (0.60); p=0.049

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Chen et al. 2016 Cross-sectional study of 1,571 postmenopausal women (mean age: 63 years) in Chirimina	**PbB:** • Median (IQR): 4.1 (2.7–6.0) • Quartiles: o Q1: <2.7 (n=382) o Q2: 2.7–4.09 (n=395) o Q3: 4.1–5.98 (n=401) o Q4: >5.98 (n=393) **Analysis:** Data for blood levels of reproductive hormones (SHBG, T, E, FSH, LH) were log-transformed and analyzed by linear regression analysis, adjusted for age, current smoking status, BMI, systolic blood pressure, diabetes, and blood cadmium concentration.	FSH was positively associated with PbB in the Q3 and Q4 groups; SHBG, LH were positively associated with PbB in the Q4 group; no association was observed between PbB and T or E. β coefficients (SE): • SHBG: p-trend: <0.002 o Q1: 1 (reference) o Q2: 0.010 (0.015) o Q3: 0.018 (0.015) o Q4: 0.048 (0.016); p<0.01 • T: p-trend=0.612 o Q1: 1 (reference) o Q2: -0.033 (0.019) o Q3: -0.017 (0.019) o Q4: -0.016 (0.020) • E: p-trend=0.201 o Q1: 1 (reference) o Q2: -0.001 (0.019) o Q3: -0.020 (0.019) o Q4: -0.021 (0.020) • FSH: p-trend=0.001 o Q1: 1 (reference) o Q2: 0.013 (0.015) o Q3: 0.047 (0.015); p<0.01 o Q4: 0.046 (0.016); p<0.01 • LH: p-trend=0.026 o Q1: 1 (reference) o Q2: 0.022 (0.015) o Q3: 0.027 (0.016) o Q4: 0.037 (0.016); p<0.05

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Jackson et al. 2011 Longitudinal Cohort of 252 healthy, pre-menopausal women (aged 18–44 years) with self-reported menstrual cycle length between 21 and 35 days, BMI >18 or <35 mg/m^3, no recent birth control use, and who were not planning on becoming pregnant and were not breastfeeding; the study was carried out at the University of Buffalo 2005–2007	**PbB:** • Mean: 0.87 **Analysis:** The correlation between Pb and reproductive hormone levels (FSH, LH, E, and progesterone) was analyzed using linear and logistic regression and adjusted for age, race, ethnicity, Pb, and Cd. Models were not adjusted for smoking status; however, subanalysis was restricted to nonsmokers.	No associations were observed between PbB and menstrual cycle length (days) or serum levels of FSH (mIU/mL), LH (mg/mL), E (ρg/mL), or progesterone (ng/mL). Percentage difference per unit change in PbB (µg/dL): • Cycle length: 0.2 (-2.8, 3.3) • FSH: -2.5 (-11.2, 7.0) • LH: 2.5 (-12.3, 19.9) • E: 4.9 (-5.0, 15.9) • Progesterone: 4.6 (-12.2, 24.6)

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Krieg 2007 Cross sectional study of 3,375 women (aged 35–60 years) participating in an NHANES III study 1998–1994	**PbB:** • Gmean: 2.2 • Range: 0.7–31.1 **Analysis:** Hormone levels (FSH and LH) were analyzed using linear regression and adjusted for age, total bone mineral density, log_{10} serum cotinine, alcohol use, current breastfeeding, hysterectomy, one ovary removed, Norplant use, radiation/ chemotherapy, hormone pill use, vaginal cream use, and hormone patch use.	Slopes (SE) for serum FSH (IU/L) and log_{10} PbB (µg/dL) by status: • Pre-menopausal: 8.3 (2.2); 95% CI: 3.8, 12.7; p=0.0006 • Post-menopausal: 22.2 (4.3); 95% CI: 13.5, 30.8; p=0.0000 • Both ovaries removed: 32.6 (11.2); 95% CI: 10.1, 55.1; p=0.0054 Slopes (SE) for serum LH (IU/L) and log_{10} PbB by status: • Pre-menopausal: 1.7 (1.2); 95% CI: -0.6, 4.1; p=0.1486 • Post-menopausal: 6.2 (1.6); 95% CI: 3.0, 9.5; p=0.0003 • Both ovaries removed: 10.0 (4.4); 95% CI: 1.1, 18.9; p=0.0279 Lowest PbB for at which a relationship for FSH was detected by status: • Pre-menopausal: 4.1; slope (SE): 5.5 (2.7); 95% CI: 0.1, 11.0; p=0.0475 • Post-menopausal: 2.4; slope (SE): 28.0 (13.0); 95% CI: 2.0, 54.1; p=0.0354 • Both ovaries removed: 1.7; slope (SE): 71.6 (32.1); 95% CI: 7.1, 136.2; p=0.0304

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		Lowest PbB for at which a relationship for LH was detected by status: • Pre-menopausal: NR • Post-menopausal: 2.8; slope (SE): 8.6 (3.3); 95% CI: 2.1, 15.2; p=0.0109 • Both ovaries removed: 4.2; slope (SE): 9.7 (4.5); 95% CI: 0.6, 18.8; p=0.0380
Pollack et al. 2011 Longitudinal Cohort of 252 healthy, pre-menopausal women (aged 18–44 years) with self-reported menstrual cycle length between 21 and 35 days, BMI >18 or <35 mg/m^3, no recent birth control use, and who were not planning on becoming pregnant and were not breastfeeding; the study was carried out at the University of Buffalo 2005–2007	**PbB:** • Gmean: 0.93 • Tertiles (T): o T1: 0.30–0.72 (reference) o T2: 0.73–1.10 o T3: 1.11–6.20 **Analysis:** Hormone levels (FSH, E, LH, progesterone, and cycle length) were analyzed using nonlinear mixed models with harmonic terms and weighted linear mixed models and adjusted for age, BMI, race, Cd, and Hg.	No associations were observed between PbB (µg/dL) and mean serum levels of E (ρg/mL), FSH (mIU/mL), LH (ng/mL), or progesterone (ng/mL). β-coefficient (95% CI): • E: 0.03 (-0.05, 0.11) • FSH: -0.01 (-0.07, 0.06) • LH: 0.02 (-0.06, 0.10) • Progesterone: 0.06 (-0.04, 0.17) OR for anovulation per 1 µg/dL increase in PbB: 1.20 (95% CI, 0.62–2.34). When examined by tertiles, an association was observed between PbB for mean progesterone (%) and progesterone amplitude for T2, but not for T3: • Mean (95% CI): o T2: 7.5 (0.1,15.4) o T3: 6.8 (-0.8, 14.9) • Amplitude (95% CI) o T2: 0.07 (0.01, 0.15) o T3: -0.06 (-0.13, 0.01)

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Fertility		
Bloom et al. 2010 Longitudinal cohort of 15 women who previously took part in a SMART study at the Center for Reproductive Health of the University of California at San Francisco September 2007–August 2008; women were referred to the center for infertility treatment and their first IVF procedure	**PbB:** • Mean (SD): 0.82 (0.32) • Range: 0.34–1.50 **Analysis:** Oocyte maturity was analyzed using multivariate log-binomial regression and adjusted for smoking status, race, and ethnicity. Adjustment was also made for cadmium in urine of male partners.	No association was observed between PbB and oocyte fertilization. RR (95% CI): 1.09 (0.72, 1.65).
Bloom et al. 2011 Longitudinal cohort of 80 women (aged 18–34 years) who previously participated in a fish consumption study in New York, 1991–1992; eligible women from this study (not currently pregnant) were re-contacted 1996–1997 and were followed for 12 menstrual cycles or until they became pregnant	**PbB:** • No positive pregnancy test group: o Mean (SD): 1.55 (0.16) o Range: 0.60–4.30 • Positive pregnancy test group: o Mean (SD): 1.54 o Range: 0.80–3.00 o p>0.05 (between group means) **Analysis:** Fecundity was analyzed using Cox proportional hazards and adjusted for baseline arsenic, cadmium, magnesium, nickel, selenium, and zinc, total serum lipids, age, parity, frequency of intercourse during fertility, alcohol consumption, and smoking habits.	No association was observed between PbB and achieving pregnancy over a 12-month observation period. Regression coefficient β probability of pregnancy per µg/L: -0.031 (95% CI: -1.066, 1.004); p=0.954

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Chang et al. 2006 Case control study of 147 women (64 cases and 83 controls aged 23–44 years) who attended a fertility clinic in Kaohsiung City, Taiwan August 2000–July 2001; controls consisted of women who delivered normal babies, January–June 1999	**PbB:** • Control group mean (SD): 2.78 (2.05) • Infertile group mean (SD): 3.55 (1.39); p=0.007 compared to control • Combined control and infertile groups o mean (SD): 3.12 (0.19) o range: 0.068–9.85 **Analysis:** Infertility was analyzed using multivariate linear regression and adjusted for age, BMI, and smoking (active and passive).	Adjusted OR for infertility for all participants for PbB >2.5 versus ≤2.5 µg/dL: 2.94 (95% CI: 1.18, 7.34); p=0.021
Pregnancy outcome		
Bloom et al. 2015 Case control study of 235 women (aged 18–40 years) from 16 counties in Michigan and Texas, 2005–2009, who had no use of injectable contraceptive within 12 months, and with self-reported menstrual cycle of 21–42 days	**PbB:** Mean (SD): 0.71 (0.30) Median: 0.55 Range: <0.25–2.23 Tertiles (mean): • T1: not reported • T2: 0.66 • T3: 0.73 **Analysis:** Pregnancy outcome was analyzed using multivariate linear regression and adjusted for maternal age, difference between maternal and parental ages, smoking habits, income, and race.	No association was observed between maternal PbB and duration of gestation. Linear regression coefficient, gestational age (weeks) per µg/L (95% CI): • T1: reference • T2: 0.43 (-0.48, 1.35) • T3: 0.14 (-0.81, 1.09) • p-trend: 0.671

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Garcia-Esquinas et al. 2014 Birth cohort study of infants born in the Madrid Autonomous region, October 2003–May 2004; participants included 100 pregnant women (mean age of 31.1 years) who had resided in the study area for >1 year and had attended childbirth classes in the public health care system	**PbB:** Gmean (95% CI): 1.83 (1.67, 2.01) **Analysis:** Pregnancy outcome (duration of gestation) was analyzed using multivariate linear regression and adjusted for district of residence (metropolitan or urban), maternal age, smoking habits, and newborn sex.	No associations were observed between PbB and duration of gestation. Adjusted mean difference per 2-fold increase in PbB: gestational age (weeks) per µg/L: 0.02 (95% CI: -0.44, 0.47)
Gundacker et al. 2010 Cross-sectional study of 30 women (8 with previous miscarriage; 22 with no previous miscarriage) recruited during their second trimester, May–November 2005 in Vienna, Austria	**PbB:** Maternal PbB: • Median: 2.5 • Range: 1.04–8.40 Placental Pb (µg/kg) • Median: 25.8 • Range: 10.7–75.4 **Analysis:** Pregnancy outcome (miscarriage) was analyzed using categorical regression (no confounders were applied).	The placental level of Pb (PbPl) in women with a history of miscarriage was higher (p=0.039) than in women with no history of miscarriage. • PbPl with history of miscarriage: 39 µg/kg, n=8 • PbPl with no history of miscarriage: 27 µg/kg, n=22

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Lamadrid-Figueroa et al. 2007 Cross-sectional study of 207 women (71 with previous miscarriage; 136 with no previous miscarriage) from Mexico City originally recruited for two cohorts, 1997–2004	**PbB:** Mean (SD) • All participants: 6.24 (4.48) • Controls (no miscarriages): 6.47 (4.95) • Cases (≥1 miscarriage): 5.79 (3.41) Plasma Pb (µg/dL) • All participants: 0.014 (0.013) • Controls: 0.013 (0.013) • Cases: 0.014 (0.013) Plasma/blood Pb ratio (%): mean (SD) • All participants: 0.22 (0.14) • Controls: 0.21 (0.13) • Cases: 0.25 (0.17) **Analysis:** Pregnancy outcome (miscarriage) was analyzed using Poisson regression and adjusted for age and education.	Adjusted IRR of miscarriage per 1 SD increase in: • PbB: 0.93; p=0.56 • Plasma Pb: 1.12; p=0.22 • Plasma/blood Pb ratio: 1.18; p=0.02 Adjusted IRRs for miscarriage for plasma/blood Pb ratio (values for tertiles were not reported): • T1: reference • T2: 1.161; p=0.612 • T3: 1.903; p=0.015
Li et al. 2017b Population-based birth cohort of 3,125 mother-infant pairs in China, enrolled in 2009	**PbB:** Mean (range): 1.5 (0.02–5.46) Stratified: • Low: <1.18 • Medium: 1.18–1.70 • High: ≥1.71 **Analysis:** Pre-term birth was defined as a live birth at less than 37 weeks of gestation. Data were analyzed using multiple logistic regression models, with data adjusted for maternal age, pre-pregnancy BMI, monthly income, gravidity, and parity.	Maternal serum Pb was positively associated with risk of preterm birth in the medium and high PbB groups. ORs (95% CI): • Low PbB: 1 (reference) • Medium PbB: 2.33 (1.49, 3.65); p<0.001 • High PbB: 3.09 (2.01, 4.76); p<0.001

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes

Perkins et al. 2014
 	
Birth cohort of 949 mother-infant pairs recruited at their first prenatal visit in Massachusetts 1999–2002
	PbB:
	RBC Pb concentration (µg/dL)
	• Mean (SD): 1.22 (0.59)
	• Quartiles (SD):
	  o Q1: 0.65 (0.15)
	  o Q2: 0.96 (0.09)
	  o Q3: 1.27 (0.12)
	  o Q4: 2.02 (0.60)
	PbB (estimated based on the assumption that the RBC Pb concentration is approximately 3-fold higher than PbB)
	• Mean: 0.4
	
	Analysis: Pregnancy outcome was analyzed using multiple linear regression and logistic regression and adjusted for maternal age, race, pre-pregnancy BMI, and smoking habits.
		No association was observed between RBC Pb concentration and gestational age (weeks). Adjusted linear regression, β estimates per µg/dL (95% CI):
		• Q1: reference
		• Q2: 0.04 (-0.28, 0.36)
		• Q3: -0.14 (-0.4, 0.18)
		• Q4: -0.17 (-0.51, 0.16)
		• p-trend=0.20

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Rabito et al. 2014 Birth cohort study of 98 women in their 16th and 28th week of gestation and (aged 16–40 years) participating in the CANDLE study in Shelby County, Tennessee study 2008–2011	**PbB:** Second trimester • Mean (SD): 0.42 (0.20) • Median: 0.43 • Range: 0.19–1.22 Third trimester • Mean (SD): 0.45 (0.28) • Median: 0.43 • Range: 0.19–2.10 Delivery • Mean (SD): 0.50 (0.35) • Median: 0.50 • Range: 0.21–2.47 **Analysis:** The association between maternal blood Pb and gestational age was analyzed using multiple linear regression. Models were adjusted for maternal age, smoking, calcium intake during pregnancy, race, gravidity (primigravida versus multigravida), insurance (Medicaid versus other insurance), marital status, education, and income.	OR (95% CI) for preterm birth: • Second trimester PbB: 1.66 (1.23, 2.23); p<0.01 • Third trimester PbB: 1.24 (1.01, 1.52); p=0.04
Taylor et al. 2013, 2015 Longitudinal cohort of 3,870 women enrolled in the ALSPAC in the Avon area of Bristol, United Kingdom, April 1991–December 1992	**PbB:** Mean (SD): 3.67 (1.47) Median: 3.42 Range: 0.41–19.14 **Analysis:** Pregnancy outcome (preterm birth) was analyzed using linear regression (continuous outcomes) and logistic regression (categorical outcomes) and adjusted for maternal height, smoking, parity, sex of infant, and gestational age.	Preterm birth (number observed/number examined) comparing PbB <5.0 and PbB ≥5.0. • <5.0: 186/3,330 (5.3%) (n=3,330) • ≥5.0: 52/540 (8.8%); p=0.001 (n=540) Adjusted OR (95% CI) for preterm birth: • <5.0: 1 (reference) • ≥5.0: 2.0 (1.35, 3.00); p=0.001

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Vigeh et al. 2010 Longitudinal cohort of 351 singleton pregnant women (15 with spontaneous abortion; 336 with no spontaneous abortion; aged 16–35 years) in Tehran, Iran 2006–2008	**PbB:** Mean (SD) • All participants: 3.8 (2.0); range: 1.0–20.5 • No spontaneous abortion: 3.83 (1.99) • Spontaneous abortion 3.51 (1.42) **Analysis:** Pregnancy outcome was analyzed using the t-test and logistic regression and adjusted for age, parity, hematocrit, and passive smoking exposure.	Mean PbB between the spontaneous abortion and no spontaneous abortion groups were not different (p=0.41). No association was observed between PbB and spontaneous abortion during gestational weeks 13–19. Adjusted OR (95% CI) for log PbB: 0.331 (0.011, 10.096); p=0.53.
Vigeh et al. 2011 Longitudinal cohort of 348 singleton pregnant women (44 with preterm birth; 304 with term birth; aged 16–35 years) referred for prenatal care during the first trimester of pregnancy in Tehran, Iran, 2006	**PbB:** Mean (SD) • All participants: 3.8 (2.0); range: 1.0–20.5 • Term birth: 3.72 (2.03) • Preterm birth: 4.52 (1.63) **Analysis:** Preterm birth was analyzed using logistic regression and adjusted for age, infant sex, education, passive smoking exposure, pregnancy weight gain, parity, hematocrit, and delivery type.	PbB for women with preterm birth were higher (p<0.05) than for women having full-term births. An association was observed between PbB and the risk of preterm birth. • Adjusted OR for preterm birth: 1.41 (95% CI: 1.08, 1.84)
Yin et al. 2008 Case control study in 80 women (40 cases of anembryonic pregnancies; 40 normal pregnancies; aged 25–35 years) enrolled at 8–12 weeks of gestation in the Shanxi Province, China, August 2004–December 2006	**PbB:** Mean (95% CI) • Controls (term birth): 4.5 (3.7, 5.0) • Cases of anembryonic pregnancy: 5.3 (5.3, 5.9) **Analysis:** Anembryonic pregnancy was analyzed using the t-test with no adjustment for confounding factors.	PbB was higher in cases of anembryonic pregnancy (with miscarriage or resorption during gestational weeks 8–13) compared to controls with term births (p=0.03).

Table 12. Epidemiology Studies Evaluating Effects on the Female Reproductive System at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Zhu et al. 2010 Retrospective cohort of 43,288 mother-infant pairs (3,519 preterm birth; 39,769 term birth; aged 15–49 years) with blood Pb <10 µg/dL registered in the New York State Heavy Metal Registry 2003–2005	**PbB** Mean: 2.1 Median: 2.0 Range: 0–9.9 Quartiles: • Q1: ≤1.0 • Q2: 1.1–2.0 • Q3: 2.1–3.0 • Q4: 3.1–9.9 **Analysis:** Birth outcome (birth weight, preterm delivery, and SGA) was analyzed using multiple linear regression with fractional polynomials and logistic regression and adjusted for timing of Pb test, maternal age, race, Hispanic ethnicity, smoking status, drug abuse, marital status, participation in special financial programs, parity, and infant sex.	Adjusted ORs did not show an increased risk of preterm birth for any quartile: • Q1 (n=1,069): reference • Q2 (n=1,036): 1.03 (0.93, 1.13) • Q3 (n=1,171): 1.01 (0.92, 1.10) • Q4 (n=243): 1.04 (0.89, 1.22)

ALSPAC = Avon Longitudinal Study of Parents and Children; BMI = body mass index; CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood; Cd = cadmium; CI = confidence interval; E = estradiol; FSH = follicle-stimulating hormone; Gmean = geometric mean; Hg = mercury; IRR = incidence rate ratio; IVF = *in vitro* fertilization; LH = luteinizing hormone; NHANES = National Health and Nutrition Examination Survey; NR = not reported; OR = odds ratio; Pb = lead; RBC = red blood cell; RR = relative risk; SD = standard deviation; SE = standard error; SGA = small for gestational age; SHBG = sex hormone binding globulin; SMART = Study of Metals and Assisted Reproductive Technologies; T = testosterone

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Birth outcome		
Al-Saleh et al. 2014 Cross-sectional study of 1,578 mother-infant pairs who delivered in Al-Kharj hospital, Saudi Arabia 2005–2006	**PbB:** Mean (SD): 2.897 (1.851) Median: 2.540 75th percentile: 3.314 Range: 0.073–25.955 **Analysis:** Univariate logistic regression analysis was performed to determine the odds of fetal growth outcomes in the >10th percentile per log unit change in metal level compared <10th percentile.	No associations were observed between maternal PbB (µg/dL) and neonatal head circumference, crown-heel length or birth weight, comparing PbB in the >10th percentile to the <10th PbB percentile. Unadjusted ORs (95% CI): • Birth weight: 1.107 (0.797, 1.538); p=0.545 • Birth height: 1.299 (0.945, 1.786); p=0.107 • SGA: 1.168 (0.837, 1.631); p=0.362 • Head circumference: 1.007 (0.724,1.400); p=0.968 • Crown-heel length: 1.061 (0.795, 1.415); p=0.689 • Apgar 5-minute score: 1.027 (0.787, 1.341); p=0.842

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Bloom et al. 2015 Case control study of 235 mother-infant pairs from 16 counties in Michigan and Texas, 2005–2009	**PbB:** Mean (SD): 0.71 (0.30) Median: 0.66 Range: <0.25–2.23 Tertiles: • T1: <0.55 (reference) • T2: 0.55–<0.73 • T3: 0.73–2.23 **Analysis:** Birth outcome (birth weight, birth length, head circumference) was analyzed using multivariate linear regression and adjusted for maternal age, difference between maternal and parental ages, smoking habits, income, and race.	No associations were observed between maternal PbB and birth weight, birth length or head circumference. Linear regression coefficients per µg/dL (95% CI): • Birth weight (g) o T2: 81.80 (-74.94, 238.55) o T3: -34.85 (-197.76, 128.06) o p-trend: 0.202 • Birth length (cm): o T2: 0.43 (-0.48, 1.35) o T3: 0.14 (-0.81, 1.09) o p-trend: 0.671 • Head circumference (cm) o T2: 0.03 (-0.68, 0.74) o T3: -0.33 (-1.07, 0.41) o p-trend: 0.132

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Bornschein et al. 1989 Prospective study of 202 mother-infant pairs for a birth cohort of 861 pairs in Cincinnati Ohio, recruited between January 1980 and May 1985	**PbB:** Mean (SD): 7.5 (1.6) Range: 1–27 **Analysis:** Multiple linear regression with natural log of PbB (ln PbB) adjusted for gestational age, alcohol and tobacco consumption, maternal age, maternal height, and number of prenatal visits.	A significant association between ln PbB and birth weight (with significant interaction with maternal age; p=0.0073) and length, but not head circumference. Decrease in birth weight (g) per lnPbB (µg/dL): • Maternal age 18 years: -58 • Maternal age 30 years: -601 In the complete birth cohort (n=861) the decrease was -114 g per ln PbB (p<0.001). Decreased birth length was associated with PbB. Regression coefficient (cm per ln PbB µg/dL): 2.5; p<0.019 No association between PbB and head circumference. Regression coefficient (cm per ln PbB µg/dL): 0.0; p=0.97
Garcia-Esquinas et al. 2014 Birth cohort with 100 mother-infant pairs in the Madrid Autonomous region from October 2003 to May 2004. Participants (mean age of 31.1 years) had resided in the study area for >1 year and had attended childbirth classes in the public health care system	**PbB:** Gmean (95% CI): 1.83 (1.67, 2.01) **Analysis:** Birth outcome (birth weight, birth length, abdominal diameter, and cephalic diameter) was analyzed using multivariate linear regression and adjusted for district of residence (metropolitan or urban), maternal age, smoking habits, and newborn sex.	No associations were observed between maternal PbB and neonatal birth weight, birth length, abdominal diameter or cephalic diameter. Adjusted mean difference (95% CI) for a 2-fold increase in PbB (µg/L): • Birth weight (g): 62.4 (-73.1, 197.8) • Birth length (cm): 0.17 (-0.56, 0.91) • Abdominal diameter (cm): 0.31 (-0.52, 1.15) • Cephalic diameter (cm): 0.15 (-0.21, 0.51)

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Gonzalez-Cossio et al. 1997 Birth cohort study of 272 mother-infant pairs from Mexico City, Mexico; examinations were conducted at delivery	**PbB:** • Maternal o Mean (SD): 8.9 (4.1) o Quartiles: ▪ Q1: ≤5.8 ▪ Q2: 5.9–8.0 ▪ Q3: 8.1–11.0 ▪ Q4: ≥11.1 • Umbilical cord o Mean (SD): 7.1 (3.5) o Quartiles ▪ Q1: ≤4.6 ▪ Q2: 4.7–6.1 ▪ Q3: 6.2–8.5 ▪ Q4: ≥8.6 **Bone Pb (mg Pb/g bone):** • Tibia Pb o Mean (SD): 9.8 (8.9) o Quartiles: ▪ Q1: ≤4.50 ▪ Q2: 4.51–9.59 ▪ Q3: 9.60–15.14 ▪ Q4: ≥15.15 • Patella Pb o Mean (SD): 14.2 (13.2) o Quartiles: ▪ Q1: ≤4.84 ▪ Q2: 4.85–13.75 ▪ Q3: 13.76–23.34 ▪ Q4: ≥23.35	Tibia Pb was negatively associated with birth weight. No association was observed between maternal or umbilical PbB and birthweight. Regression coefficient (SE): • Maternal PbB for Q4: -98.30 (59.55); p=0.100 • Umbilical cord PbB for Q4: -41.74 (64.04); p=0.514 • Tibia Pb for Q4: -155.55 (61.18); p=0.012 • Patella Pb for Q4: -57.37 (63.22); p=0.356 For tibia, an increase of 10 mg Pb/g bone was associated with a decrease in birth weight of 73 g.

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Kim et al. 2017b Longitudinal study of 280 mother-infant pairs (maternal age range: 23–46 years) enrolled in the Children's Health and Environmental Chemicals in Korea for the period January 2011–December 2012	**PbB:** Umbilical cord, mean (SE) • All: 1.31 (0.06) • Infant boys: 1.39 (0.09) • Infant girls: 1.21 (0.07) **Analysis:** Birth outcome parameters were assessed at birth. Log-transformed data were analyzed by linear regression, adjusted for maternal age, maternal BMI, gestational period, cesarean section, and smoking status.	PbB was positively associated with birth length and negatively associated with ponderal index in boys. No associations were observed for birth weight or head circumference in boys or any birth outcome measure in girls. Regression coefficient β (95% CI) for log-transformed PbB: • Boys o Birth weight: 0.010 (-0.014, 0.034); p=0.403 o Birth length: 0.017 (0.003, 0.031); p=0.019 o Head circumference: 0.010 (-0.001, 0.022); p=0.083 o Ponderal index: -0.055 (-0.103, -0.006); p=0.027 • Girls o Birth weight: 0.001 (-0.025, 0.027); p=0.950 o Birth length: 0.007 (-0.010, 0.025); p=0.410 o Head circumference: -0.007 (-0.016, 0.002); p=0.148 o Ponderal index: -0.009 (-0.062, 0.045); p=0.748

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Nishioka et al. 2014 Cohort study of 386 mother-infant pairs (maternal age ≥20 years) who visited Juntendo University Hospital in Tokyo, Japan December 2010–October 2012 during early gestational week 12	**PbB:** Mean (SD; range) at gestational week • 12 weeks: 0.98 (0.55; 0.10–3.99) • 25 weeks: 0.92 (0.63; >0.09–3.96) • 36 weeks: 0.99 (0.66; <0.09–3.96) **Analysis:** Birth weight was analyzed using multiple regression and adjusted for hematocrit, maternal age, maternal BMI, gestational age, and alcohol consumption.	A significant correlation was observed between log maternal PbB (µg/dL) at gestational week 12 and decreased birth weight (g) in male newborns (Spearman' coefficient=-0.145, p<0.05), but not female newborns. Regression coefficient for gestational week 12 and log PbB: • Males: -0.151 (p<0.05) • Females: -0.098 (p>0.05) No significant correlation was observed between maternal PbB at gestational weeks 25 and 36 in both male and females.
Odland et al. 1999 Cohort study of 262 mother-infant pairs from 3 Russian (n=148; mean age 25.0) and 3 Norwegian (n=144; mean age 28.2) hospital delivery departments April 1993–June 1994	**PbB:** Maternal, mean (range); p-values compare Russian and Norwegian cohorts • Russian cohort: 2.9 (0.83–13.5) • Norwegian cohort: 2.3 (0.41–3.9); p<0.001 • Combined cohort: not reported Cord PbB, mean (range) • Russian cohort: 2.1 (0.62–11.0) • Norwegian cohort: 1.0 (0.41–3.7); p<0.001 **Analysis:** Birth weight was analyzed using multivariate and univariate linear regression and adjusted for maternal age, BMI, height, serum zinc, urinary creatinine and MBPb, parity, pre-eclamptic condition, local food consumption, smoking, and gestational age.	A significant correlation was observed between maternal PbB and decreased birth weight for combined Russian and Norwegian cohorts. Regression coefficients (g per PbB µmol/L): -1,068 (95% CI: -2,134, -2); p<0.05)

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Perkins et al. 2014 Birth cohort of 829 mother-infant pairs recruited at their first prenatal visit in eastern Massachusetts 1999–2002	**PbB:** Mean: 0.4 (estimated based on the assumption that the maternal RBC Pb concentration is approximately 3-fold higher than PbB) **RBC Pb concentration (µg/dL):** mean (SD): 1.22 (0.59) • Quartiles for maternal RBC Pb; mean (SD): o Q1: 0.65 (0.15) o Q2: 0.96 (0.09) o Q3: 1.27 (0.12) o Q4: 2.02 (0.60) **Analysis:** Birth outcome (birth weight, birth weight for gestational age, birth length, and head circumference) was analyzed using multiple linear regression and logistic regression and adjusted for gestational weight gain, pre-pregnancy BMI, race, country of birth, 2nd trimester calcium intake, parity, smoking in pregnancy, maternal age, and child sex.	No associations were observed between maternal RBC Pb concentration (µg/dL) and birth weight, birth length or head circumference. Linear regression β coefficient (95% CI) across RBC quartiles: • Birth weight (g): o Q1: reference o Q2: -17 (-98, 63) o Q3: -15 (-95, 64) o Q4: -47 (-128, 35) o p-trend: 0.27 • Head circumference (cm): o Q1: reference o Q2: -0.06 (-0.29, 0.17) o Q3: -0.08 (-0.31, 0.15) o Q4: -0.08 (-0.33, 0.16) o p-trend: 0.56 • Birth length (cm): o Q1: reference o Q2: 0.03 (-0.33, 0.40) o Q3: 0.02 (-0.36, 0.39) o Q4: -0.15 (-0.54, 0.23) o p-trend: 0.37

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Rabito et al. 2014 Birth cohort of 98 mother-infant pairs (maternal age: 16–40 years) participating in the CANDLE study in Shelby County, Tennessee, 2008–2011	**PbB:** Second trimester • Mean (SD): 0.42 (0.20) • Median: 0.43 • Range: 0.19–1.22 Third trimester • Mean (SD): 0.45 (0.28) • Median: 0.43 • Range: 0.19–2.10 Delivery • Mean (SD): 0.50 (0.35) • Median: 0.50 • Range: 0.21–2.47 **Analysis:** Birth weight was analyzed using linear regression adjusted for maternal age, smoking, calcium intake during pregnancy, race, gravidity (Primigravida versus Multigravida), insurance (Medicaid versus other insurance), marital status, education, and income.	No association was observed (g) between maternal PbB and birth weight. Linear regression β coefficient (95% CI) µg/dL maternal PbB: • Second trimester: -43.21 (-88.6, 2.18); p=0.06 • Third trimester: β not reported; p=0.68 • Delivery: β not reported; p=0.83

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Rodosthenous et al. 2017 Prospective cohort study of 944 mother-infant pairs (mean maternal age: 27.2 years) in Mexico City; data collection period: 2007–2011	**PbB:** Maternal 2nd trimester • mean (SD): 3.7 (2.7) • range: 0.5–22.9 • Quartiles: o Q1: <1.93 o Q2: 1.93–2.79 o Q3: 2.80–4.53 o Q4: >4.53 **Analysis:** Evaluation for associations between PbB and birthweight-for-gestational age z-score were conducted using multivariable linear regression, adjusted for maternal age, BMI, SES, hemoglobin levels, and infant sex. ORs were determined using logistic regression.	No association was observed between maternal PbB and birthweight-for-gestational age z-score. β (95% CI) for a doubling of PbB: -0.06 (-0.13, 0.003); p=0.06. No trend for small-for gestational age infants was observed across PbB quartiles. OR (95% CI): • Q1: 1 (reference) • Q2: 1.30 (0.79–2.15) • Q3: 1.37 (0.83–2.25) • Q4: 1.62 (0.99–2.65) • p-trend: 0.06

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Taylor et al. 2013, 2015 Longitudinal cohort study of 4,285 mother-infant pairs enrolled in the ALSPAC in the Avon area of Bristol, United Kingdom April 1991–December 1992	**PbB:** Mean (SD): 3.67 (1.47) Median: 3.42 Range: 0.41–19.14 **Analysis:** Birth outcome (birth weights, head circumference, crown-heel length, and low birth weight) was analyzed using linear regression (continuous outcomes) and logistic regression (categorical outcomes) and adjusted for maternal height, smoking, parity, sex of infant, and gestational age.	Birth outcomes comparing PbB <5.0 and PbB ≥5.0 µg/dL. • Birth weight (g), mean (SD) o <5.0: 3,424 (567) (n=3,469) o ≥5.0: 3,334 (595); p=0.001 (n=583) • Head circumference (cm), mean (SD) o <5.0: 34.8 (1.5) (n=3010) o ≥5.0: 34.6 (1.8); p=0.031 (n=504) • Crown-heel length (cm) o <5.0: 50.7 (2.3) (n=2,970) o ≥5.0: 50.4 (2.6); p=0.011 (n=497) • Low birth weight (<2,500 g), n (%) o <5.0: 346/3,654 (9.5%) o ≥5.0: 74/615 (12.0%); p=0.048 Maternal PbB was associated with significant reductions in birth weight (g), head circumference (sc), and crown-heel length (cm). β coefficients per µg/dL (SE); 95% CI • Birth weight: -13.23 (5.37); -23.75, -2.70; p=0.014 • Head circumference: -0.04 (0.16); -0.07, -0.06 (as reported; β coefficient is outside of the 95% CI); p=0.021 • Crown-heel length: -0.05 (0.03); -0.10, -0.00; p=0.034

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Thomas et al. 2015 Prospective cohort of 1,835 mother-infant pairs (maternal age ≥18 years), recruited 2008–2011 and evaluated from their first trimester from 10 study sites across Canada	**PbB:** Median: 0.59 Range: 0.17–4.04 Tertiles: • T1: <0.52 • T2: 0.52–1.04 • T3: >1.04 **Analysis:** Birth outcome (length, weight at birth, gestational age) was analyzed using log binomial regression and adjusted for age, parity, ethnicity, country of origin, household income, education, smoking status, pre-pregnancy BMI, and marital status.	No association was observed between maternal PbB and SGA. Adjusted RR (95% CI): • T1: reference • T2: 1.33 (0.88,1.99) • T3: 1.19 (0.65, 2.18)

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Wang et al. 2017b Prospective cohort study of 3,125 mother-infant pairs (mean age of mothers: 27.5 years) participating in the China-Anhui Birth Cohort Study; data collection period not specified	**Serum Pb (maternal):** Mean: 1.50 Median: 1.43 Range: 0.02–5.46 Tertiles (for serum Pb measured in 1st and 2nd trimesters): • T1: <1.18 • T2: 1.18–1.70 • T3: ≥1.71 **Analysis:** Associations between serum Pb and birth outcome measures were analyzed by linear regression models. ORs for correlation of maternal Pb level with risk of SGA infants were analyzed by multivariate logistic regression. All models were adjusted for pre-pregnancy BMI, maternal age, gravidity, parity, time for collection serum, and monthly income.	A negative association was observed between serum Pb and SGA for all infants in T2 and T3, and for girl infants and boy infants in T3. OR (95% CI): • All infants: o T1: 1 (reference) o T2: 1.45 (1.04,2.02); p=0.03 o T3: 1.69 (1.22,2.34); p=0.002 • Boys: o T1: 1 (reference) o T2: 1.44 (0.83, 2.50) o T3: 1.75 (1.03, 2.99) • Girls: o T1: 1 (reference) o T2: 1.51 (0.99, 2.31) o T3: 1.68 (1.12, 2.54) A negative association was observed between serum Pb and birth weight, but not birth length, head circumference or chest circumference. Regression coefficient β (95% CI): • Birth weight: -2.74 (-5.17, -0.31); p=0.03 • Birth length: -0.013 (-0.026, 0.001); p=0.06 • Head circumference: -0.008 (-0.019, 0.004); p=0.18 • Chest circumference: -0.008 (-0.018, 0.002); p=0.13

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Wang et al. 2017c Cross-sectional study of 1,009 mother-infant pairs (537 boys and 472 girls) in Shanghai; data collection period: September 2008–October 2009	**PbB:** Cord PbB, Gmean (95% CI) All: 4.07 (3.98, 4.17) Infant boys: 4.07 (3.89, 4.17) Infant girls: 4.17 (3.98, 4.36) **Analysis:** PbB data were log-transformed. Data on birth outcome variables (birth weight, birth length, head circumference, and ponderal index) were analyzed by multiple linear regression adjusted for maternal age, gestational age, maternal BMI before delivery, parity, sex of baby, monthly household income per capita, mode of delivery, and diet.	A positive association was observed between cord PbB and birth weight in boys and negative association for ponderal index in girls. Regression coefficient β (95%), per 1-unit increase in log_{10}-transformed PbB: • Birth weight (g) o All: 60.78 (-66.30, 187.85); p=0.35 o Boys: 182.32 (15.24. 349.39); p=0.03 o Girls: -96.06 (-289.23, 97.10); p=0.33 • Birth length (cm) o All: 0.32 (-0.18, 0.82); p=0.21 o Boys: not reported o Girls: 0.30 (-0.46, 1.05); p=0.44 • Head circumference (cm) o All: -0.36 (-0.78, 0.06); p=0.09 o Boys: -0.50 (-1.09, 0.09); p=0.10 o Girls: -0.32 (-0.91, 0.27); p=0.29 • Ponderal index [(g/cm^3) x 100] o All: -0.01(-0.10, 0.09); p=0.94 o Boys: 0.10 (-0.03, 0.23); p=0.12 o Girls: -0.17 (-0.31, -0.02); p=0.02

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Xie et al. 2013 Birth cohort of 252 mother-infant pairs recruited from a rural area near the south coast of Laizhou Bay, China, 2010–2011	**PbB:** Mean (SD): 3.53 (1.51) Median: 3.20 Range: 1.00–11.91 **Analysis:** Birth outcome (birth weight, birth length, and head circumference) was analyzed using multiple linear regression and adjusted for infant sex, gestational age, maternal education, parity, maternal age, pre-pregnancy BMI, and weight gain during pregnancy.	A negative association was observed for maternal PbB for a square root unit increase and birth weight (g), but no association was found for birth length (cm) or head circumference (cm). β coefficients per square root increase in PbB µg/dL (95% CI): • Birth weight: -148.99 (-286.33, -11.66); p=0.03 • Birth length: -0.46 (-1.25, 0.34); p=0.26 • Head circumference: -0.37 (-0.78, 0.19); p=0.24 A 1-µg/dL increase in maternal PbB was associated with a decrease in birth weight of 39.10 g (95% C: -72.79, -5.41); p=0.02.

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Zhu et al. 2010 Retrospective cohort of 43,288 mother-infant pairs (3,519 preterm birth; 39,769 term birth; aged 15–49 years) with blood Pb <10 µg/dL registered in the New York State Heavy Metal Registry 2003–2005	**PbB** Mean: 2.1 Median: 2.0 Range: 0–9.9 Quartiles: • Q1: ≤1.0 • Q2: 1.1–2.0 • Q3: 2.1–3.0 • Q4: 3.1–9.9 **Analysis:** Birth outcome (birth weight, preterm delivery, and SGA) was analyzed using multiple linear regression with fractional polynomials and logistic regression and adjusted for timing of Pb test, maternal age, race, Hispanic ethnicity, smoking status, drug abuse, marital status, participation in special financial programs, parity, and infant sex.	A negative association was observed for maternal PbB (per 1 µg/dL increased in PbB) and birth weight (g). β coefficients (95% CI) for PbB of: 0: reference 1: -27.4 (-17.1, -37.8) 2: -38.8 (-24.1, -53.4) 3: -47.5 (-29.6, -65.4) 4: -54.8 (-34.2, -75.5) 5: -61.3 (-38.2, -84.4) 6: -67.2 (-41.8, -92.5) 7: -72.5 (-45.2, -99.9) 8: -77.6 (-48.3, -106.8) 9: -82.3 (-51.2, -113.3) 10: -86.7 (-54.0, -119.4) Adjusted ORs did not show an increased risk of small-for-gestational age for any quartile: • Q1 (n=1168): reference • Q2 (n=1268): 1.07 (0.98, 1.17) • Q3 (n=1353): 1.06 (0.98, 1.16 • Q4 (n=303): 1.07 (0.93, 1.23)

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Birth defects		
Brender et al. 2006 Case-control study of 184 Mexican-American women (age range not specified) with neural tube defect-affected pregnancies living in Texas counties boarding Mexico 1995–2000; controls (n=225) had normal live births	**PbB:** Control • Mean (SD): 2.5 (1.6) • Range: 0–8 Cases • Mean (SD): 2.4 (1.9) • Range: 0–8 **Analysis:** Birth defects (neural tube defect) was analyzed using logistical regression and adjusted for household income, proximity to industrial sites, and breastfeeding.	No difference was observed between maternal PbB in controls versus cases (p>0.05). The risk of neural tube defect was not increased in cases versus controls: OR (95% CI) for PbB ≥6 µg/dL: 1.5 (0.6, 4.3). Further adjustment for breastfeeding increased the OR (95% CI): 3.8 (0.8, 19.5).

Liu et al. 2018a
 	
Case-control study for congenital heart disease for gestational ages 14–40 weeks in 97 cases and 201 controls in China; data collection period: February 2010–October 2011
	PbB:
	• Umbilical cord Pb median (median)
	  o Controls: 0.740
	  o Cases: 0.791
	• Tertiles
	  o T1: <0.696
	  o T2: 0.696–<0.826
	  o T3: ≥0.826
	
	Analysis: ORs for congenital heart defects were calculated by logistic regression adjusted for maternal age, maternal BMI, maternal education level, use of folic acid supplement, and parental smoking status.
		The risk of all congenital heart disease (including septal defects, conotruncal defects, right- or left-sided outflow tract deformity, anomalous pulmonary venous return, and any other structural abnormalities) ORs (95% CI):
		• T1: 1.00 (reference)
		• T2: 1.46 (0.77, 2.77)
		• T3: 1.67 (0.88, 3.17)

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Needleman et al. 1984 Case-control study of 4,354 mother-infant pairs (maternal age 16–35 years) delivering at least 20 weeks gestation age at the Boston Hospital for Woman, April 1979–March 1980	**Cord blood Pb** Quartiles: mean (percentage of neonates with cord blood Pb >mean) • Q1: 0.7 (98.7) • Q2: 6.3 (50.0) • Q3: 15 (1.7) • Q4: 24 (0.2) **Analysis:** Birth defects (hemangiomas, lymphangiomas, hydrocele, minor skin irritations, and undescended testicles) were analyzed using logistic regression and adjusted for gestational age, birth weight, history of spontaneous or induced abortion, maternal parity, and age.	The following minor congenital anomalies were observed: hemangiomas, lymphangiomas, hydrocele, minor skin irritations (e.g., skin tags, papillae), and undescended testicles. No association with Pb was observed for any single malformation (summary statistics not reported). RR (95% CI) of all anomalies: • Q1: 1 (reference) • Q2: 1.87 (1.44, 2.42) • Q3: 2.38 (1.66, 3.43) • Q4: 2.73 (1.80, 4.16)

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Anthropometric measures in children		
Afeiche et al. 2011 Cross-sectional study of 999 children (522 boys; 477 girls; aged 0–5 years) previously enrolled in one of three birth cohorts for other longitudinal studies in Mexico City 1994–2005	**PbB:** • Child PbB, mean (SD): 3.8 (2.9) • Maternal PbB not reported **Maternal bone Pb, mean (SD), µg/g** • Patella: 10.4 (11.8) • Tibia: 8.7 (9.7) **Analysis:** Birth weight was analyzed using Univariate and bivariate regression and adjusted for birth cohort, maternal age, maternal calf circumference, maternal height, education, parity, breast feeding, gestational age, height at birth, and repeated concurrent child blood Pb measures.	A lower weight (g) trajectory was observed in females at 1–5 years of age, but not males, in association with maternal patella Pb. β coefficients (95% CI) for a 1-SD increase in maternal patella Pb (µg/g): Females • 12 months: -70.9 (-147.9, 6.0) • 24 months: -96.1 (-170.4, -21.8) • 36 months: -121.3 (-200.0, -42.6) • 48 months: -146.4 (-235.5, -57.4) • 60 months: -171.6 (-275.2, -68.0) Males • 12 months: 29.4 (-42.1, 100.8) • 24 months: 27.8 (-43.5, 99.1) • 36 months: 7.9 (-67.3, 83.1) • 48 months: -13.6 (-97.9, 70.8) • 60 months: -35.0 (-132.4, 62.3)

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Alvarez-Ortega et al. 2019 Cross-sectional study of 554 children (ages 5–16 years; 53.1% female) from Columbia; data collection period: January–August 2015	**PbB:** Mean (SE): 3.5 (0.2) Median: 1.9 Range: 0.1–50.1 **Analysis:** The relationship between PbB and anthropometric measures were analyzed by Spearman correlation analysis. No information on adjustments was reported.	Negative correlations were observed between PbB and weight, height, and BMI for all participants, females, and children ages 12–16 years: Spearman correlations: • Weight o All participants: -0.152; p<0.001 o Females: -0.226; p<0.001 o Males: -0.056; p=0.380 o Age 5–11 years: -0.069; p=0.010 o Age 12–16 years: -0.385; p<0.001 • Height o All participants: -0.101; p=0.019 o Females: -0.153; p=0.009 o Males: -0.037; p=0.567 o Age 5–11 years: -0.137; p=0.418 o Age 12–16 years: -0.206; p=0.009 • BMI o All participants: -0.172; p<0.001 o Females: -0.273; p<0.001 o Males: -0.040; p=0.536 o Age 5–11 years: -0.056; p=0.295 o Age 12–16 years: -0.384; p<0.001

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Dallaire et al. 2014 Prospective cohort study of 290 children (aged 8–14 years) born from Inuit mothers (n=233) who were recruited at their first prenatal visit, Arctic Québec 1993–1998	**Cord blood Pb:** • Mean (SD): 4.8 (3.3) • Range: 0.8–20.9 **Child blood Pb:** • Mean (SD): 2.7 (2.1) • Range: 0.4–12.8 **Analysis:** Pubertal state (head circumference, height, weight) was analyzed using multiple regression and adjusted for: (1) child characteristics (sex of child, duration of gestation, duration of breastfeeding, child age at testing, concentrations of mercury, vitamin, and hemoglobin in child blood), (2) maternal parameters (pre-pregnancy weight, height, age at delivery, parity, education, marital status, SES, food insecurity of the family, cord plasma levels of the omega-3 fatty acid docosahexaenoic acid, and (3) other prenatal exposures (cord mercury, maternal smoking, alcohol use, and illicit drug use).	Cord blood Pb: significant associations were observed between cord blood Pb and child head circumference (cm) and height (cm), but not child weight (kg) or BMI (kg/m^2), in children 8–14 years of age. β coefficients per µg/dL; 95% CI not reported: • Height: -1.57 (p=0.004) • Head circumference: -0.005; p=0.04 • Weight: β not reported; p=0.70 • BMI: -0.07; p=0.23

Deierlein et al. 2019
 	
Prospective longitudinal study of 683 girls (enrolled at ages 6–8 years) from three locations (New York, Cincinnati, and San Francisco); data collection period: 2004–2007
	PbB:
	• All participants (n=683)
	  o Mean (SD): 1.16 (0.67)
	  o Range: 0.18–5.40
	• New York (n=30)
	  o Mean (SD): 1.29 (0.63)
	  o Range: 0.44–3.20
	  o <1 µg/dL: n=12
	  o ≥1 µg/dL: n=18
	• Cincinnati (n=326)
	  o Mean (SD): 1.28 (0.79)
	  o Range: 0.34–5.40
		Regression analysis predicted lower anthropometric measures were lower in girls with PbB ≥1 µg/dL compared to <1 µg/dL at all ages. Predicted mean differences (95% CI) for PbB ≥1 µg/dL compared to <1 µg/dL at ages 7–14 years:
		• Height (cm) at ages
		  o 7: -2.0 (-3.0, -1.0); p<0.001
		  o 8: -1.9 (-2.8, -0.9): p<0.001
		  o 9: -1.7 (-2.7, -0.8); p<0.001
		  o 10: -1.6 (-2.6, -0.7): p=0.001
		  o 11: -1.6 (-2.5, -0.6): p=0.002

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
	o <1 µg/dL: n=153 o ≥1 µg/dL: n=173 • San Francisco (n=327) o Mean (SD): 1.04 (0.51) o Range: 0.18–3.73 o <1 µg/dL: n=177 o ≥1 µg/dL: n=150 **Analysis:** PbB was measured at enrollment and anthropometry measurements (height, BMI, waist circumference, and percent body fat) were measured at ≥3 biannual or annual follow-up visits. Participants were stratified into two groups: <1 and ≥1 µg/dL. Linear mixed effects regression analysis was used to estimate associations between PbB and anthropometric measures from ages 7 to 14 years, adjusting for age, age squared, race, interaction between age and PbB, interaction between age squared and PbB, and interaction between race and age.	o 12: -1.5 (-2.5, -0.5): p=0.004 o 13: -1.5 (-2.5, -0.5): p=0.004 o 14: -1.5 (-2.5, -0.4): p=0.01 • BMI (kg/m^2) at ages o 7: -0.7 (-1.2, -0.2); p=0.005 o 8: -0.8 (-1.3, -0.3); p=0.001 o 9: -0.9 (-1.4, -0.4) p=0.001 o 10: -0.9 (-1.4, -0.4); p=0.001 o 11: -0.9 (-1.5, -0.3); p=0.002 o 12: -0.9 (-1.5, 0.3); p=0.005 o 13: -0.8 (-1.5, -0.2); p-0.02 o 14: -0.8 (-1.5, -0.02); p=0.05 • Waist circumference (cm) at ages o 7: -2.2 (-3.8, -0.6); p=0.01 o 8: -2.5 (-3.8, -1.1); p<0.001 o 9: -2.7 (-4.0, -1.4); p<0.001 o 10: -2.9 (-4.3, -1.4) p<0.001 o 11: -3.0 (-4.5, -1.4); p<0.001 o 12: -3.0 (-4.7, -1.3); p=0.001 o 13: -3.0 (-4.8, -1.1); p=0.002 o 14: -2.9 (-4.8, -0.9); p=0.005 • Body fat (%) at ages o 7: -1.8 (-3.2, -0.4); p=0.01 o 8: -2.0 (-3.3, -0.7); p=0.003 o 9: -2.1 (-3.4, -0.8); p=0.001 o 10: -2.2 (-3.4, -0.9); p=0.001 o 11: -2.1 (-3.4, -0.9); p=0.001 o 12: -2.1 (-3.4, -0.8); p=0.002 o 13: -1.9 (-3.2, -0.6); p=0.003 o 14: -1.7 (-3.1, -0.4); p=0.01

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Hauser et al. 2008 Cross-sectional study of 489 healthy boys (aged 8–9 years) residing in Chapaevsk Russia, May 2003–May 2005	**Child PbB:** Mean (25^{th}–75^{th} percentile): 3 (2–5) Number of children with PbB >10: 3 **Analysis:** Pubertal state (height and weight) was analyzed using multivariate logistic regression and adjusted for gestational age, height, BMI, and age at exam.	Associations were observed for PbB (natural log transformation, µg/dL) and height (cm), but not weight (kg) or BMI (kg/m^2), in 8–9-year-old boys. Adjusted regression coefficient (95% CI): • Height: -1.439 (-2.25, -0.63); p<0.001 • Weight: -0.761 (-1.54, 0.02); p=0.067 • BMI: -0.107 (-0.44, 0.23); p=0.53
Hong et al. 2014 Cross-sectional study of 1,150 mother-infant pairs (546 girls; 604 boys; aged 6–24 months) previously enrolled in a prospective birth cohort, South Korea May 2006–December 2010	**Maternal PbB:** Early pregnancy, • Mean (SD): 1.25 (1.46) • Range: 0.25–2.63 Late pregnancy • Mean (SD): 1.25 (1.52) • Range: 0.26–2.52 **Cord blood Pb:** Mean (SD): 0.91 (1.57) Range: 0.11–1.90 **Analysis:** Pubertal state (weight and height) was analyzed using multivariate linear regression and adjusted for child sex, maternal age, maternal education, pre-pregnancy maternal BMI, and gestational age.	Associations between maternal PbB (log transformed, µg/dL) in late pregnancy, but not for maternal PbB in early pregnancy or cord blood Pb, and z scores for weight (g) and height (cm) were observed in children at 24 months of age. β coefficients (95% CI): • Late pregnancy PbB: o Weight z score: -0.28 (-0.48, -0.09); p<0.05 o Height z score: -0.28 (-0.49, -0.06); p<0.05 • Early pregnancy PbB: o Weight z score: -0.05 (-0.22, 0.11) o Height z score: -0.15 (-0.34, 0.04) • Cord blood PbB: o Weight z score: -0.1 (-0.21, 0.17) o Height z score: 0.02 (-0.19, 0.24)

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Ignasiak et al. 2006 Cross-sectional study of 899 school children (463 boys, 436 girls; aged 7–15 years) residing near copper smelters and refineries, South-Western Poland, 1995	**PbB:** Mean: 7.7 Range: 2.0–33.9 **Analysis:** Pubertal state (weight and height, BMI, trunk length, leg length, arm length, and trunk-length ratio) was analyzed using stepwise multiple regression analysis and adjusted for mother's education and two age terms (age, age^2).	Associations were observed between PbB and several anthropometric measures. Slope per $\log_{10}$ µg/dL (SE): • Weight (kg) o Boys: -4.00 (2.45); p=0.10 o Girls: -6.59 (2.09); p=0.001 • Height (cm) o Boys: --6.26 (1.40); p=0.002 o Girls: -5.54 (2.05); p=0.007 • BMI (kg/m^2) o Boys: -0.39 (0.82); p=NS o Girls: -1.86 (0.75); p=0.01) • Trunk length (cm) o Boys: -2.21 (0.97); p=0.02 o Girls: -1.47 (1.00); p=NS • Leg length (cm) o Boys: -4.05 (1.27); p=0.002 o Girls: -4.08 (1.27) p=0.0001 • Arm length (cm) o Boys: -3.20 (0.97); p=0.0001 o Girls: -2.61 (0.98); p=0.008 • Trunk-length ratio o Boys: 0.71 (0.34): p=0.04 o Girls: 1.03 (0.34); p=0.003

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Kim et al. 2017b Prospective longitudinal study of 280 children enrolled in the Children's Health and Environmental Chemicals in Korea recruited during January 2011–December 2012	**PbB:** Umbilical cord, mean (SE): 1.31 (0.06) • All: 1.31 (0.06) • Boys: 1.39 (0.09) • Girls: 1.21 (0.07) **Analysis:** Anthropogenic measures were assessed during a 27-month period. All data were log-transformed data associations between PbB and outcome measures were analyzed by linear regression, adjusted for child gender, maternal age, maternal BMI, gestational period, cesarean section, and smoking status.	Positive associations were observed between PbB and body weight and BMI at 24 months, no associations were observed at 18 or 27 months. Regression coefficient β (95% CI): • Weight: o 18 months: 0.897 (-0.171, 1.965); p=0.092 o 24 months: 0.717 (0.195, 1.239); p=0.009 o 27 months: 0.316 (-0.345, 0.977); p=0.333 • Height: o 18 months: 0.909 (-0.222, 2.040); p=0.101 o 24 months: 0.138 (-0.530, 0.806); p=0.675 o 27 months: 0.354 (-0.497, 1.205); p=0.394 • BMI: o 18 months: 0.157 (-1.266, 1.580) p=0.806 o 24 months: 0.695 (0.077, 1.313); p=0.029 o 27 months: 0.409 (-0.398, 1.216); p=0.300

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes

Lamb et al. 2008
 	
Population-based prospective cohort study of 309 mother-child pairs (children aged 1–10 years) who previously participated in the Yugoslavia Study of Environmental Lead Exposure, Pregnancy Outcomes, and Childhood Development, Mitrovica and Pristina, Yugoslavia 1985–1986
	Maternal PbB:
	Mid-pregnancy, mean (SD), for town of:
	• Pristina: 5.60 (1.99)
	• Mitrovica: 20.56 (7.38)
	
	Analysis: Pubertal state (height and BMI at birth) was analyzed using linear regression and adjusted for infant sex, ethnicity, parity, maternal height or BMI, maternal education, gestational age at blood sample, gestational age at birth, and quality of home environment.
		No associations were observed between maternal PbB and child height (cm) or BMI (kg/m^2) at 1, 4, 6.5, or 10 years of age.
		β coefficients per log µg/dL (95% CI) for ages 1 and 10 years for attained height/BMI:
		• Pristina:
		  o 1 years: -0.61 (-2.24, 1.03)
		  o 10 years: -0.09 (-3.69, 3.52)
		• Mitrovica:
		  o 1 years: -0.30 (-2.55, 1.96)
		  o 10 years: -2.87 (-6.21, 0.47)

Little et al. 2009 Cross-sectional study of 360 children (aged 2–12 years), from two cohorts studied in 1980–1989 (n=191) and 2002 (n=169), Dallas, Texas	**Child PbB:** Mean (SE) • 1980 cohort: 23.6 (1.3) • 2002 cohort: 1.6 (0.2) • Pooled cohort PbB not reported **Analysis:** Pubertal state (height, weight, and BMI) was analyzed using MANOVA/MANCOVA and regression models and adjusted for child's sex, cohort effect, and two age terms (age, age^2).	Study authors concluded that "male and female children ages one to 12 years old in 2002 were significantly ($p<0.0001$) taller and heavier with higher BMI and lower blood lead than children measured in the 1980s." For the pooled cohort, a decrease in PbB of 10 µg/dL was associated with increased height (cm), weight (kg), and BMI (kg/m^2). • Height: 2.1 (95% CI: 1.9, 2.3); $p<0.0001$ • Weight: 1.9 (95% CI: 1.7, 2.1); $p<0.0001$ • BMI: 0.5 (0.4, 0.7); $p<0.0001$.

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Min et al. 2008b Cross-sectional study of 108 children (62 boys, 46 girls; aged 5–13 years), Seoul South Korea (study dates not reported)	**Child PbB:** Mean (SD): 2.4 (0.7) Range: 0.8–5.2 Number of children with PbB >10: 14 **Analysis:** Pubertal state (height, weight, BMI, and total arm length) was analyzed using multiple linear regression and adjusted for child's age, child's sex, and father's education.	PbB was negatively associated with height (cm) and total arm length (cm), but not weight (kg) or BMI (kg/m^2). Regression coefficient per µg/dL (SE) • Height: -1.449 (0.639); p=0.026 • Weight: -0.646 (0.718); p=0.370 • BMI: -0.006 (0.272); p=0.982 • Total arm length: -1.804 (0.702); p=0.012
Olivero-Verbel et al. 2007 Cross-sectional study of 189 children (99 boys, 90 girls; aged 5–9 years) from 10 primary schools, Cartagena Columbia, June–August 2004	**Child PbB:** Mean (SE): 5.53 (0.23) Range: <1.0–21.0 **Analysis:** Pubertal state (height and weight) was analyzed using univariate and bivariate statistics and Spearman correlation without adjustment for confounding factors.	An association was observed between PbB and height (cm), but not weight (kg). Correlation coefficients: • Height: -0.224;p=0.002 • Weight: -0.126; p=0.087
Raihan et al. 2018 Cross-sectional study of 729 children (<2 years of age; mean age: 12.6 months; 50.3% males) in Bangladesh; data collection period: November 2009–December 2012	**Child PbB:** Mean (SD): 8.25 (3.64) 95% CI: 7.98, 8.51 "Normal" PbB: <5 "Elevated" PbB: ≥5 **Analysis:** ORs for "elevated" PbB (relative to "normal" PbB) and stunting (defined as length-for-age z score <-2), wasting (defined as weight-for-length z-score <-2), and underweight (defined as weight-for-age z-score <-2) were analyzed by multiple logistic regression. Adjustment variables included gender, age, weight, maternal education, BMI, average household income, and Household Food Insecurity Access Scale categories.	For PbB ≥5 µg/dL (compared to PbB <5 µg/dL) increased risks were observed for stunting and underweight, but not wasting. Adjusted ORs (95% CI): • Stunting: 1.78 (1.07, 2.99); p=0.028 • Wasting: 1.18 (0.64, 2.19); p=0.581 • Underweight: 1.63 (1.02, 2.61); p=0.043

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Renzetti et al. 2017 Prospective study of 513 mothers and their children who returned for assessments at ages 4–6 years in Mexico City; data collection period: 2007–2011; PROGRESS cohort	**PbB:** Gmean (range) • Maternal o 2nd trimester: 3.0 (0.8–17.8) o 3rd trimester: 3.1 (0.3–28.3) o At delivery: 3.5 (0.7–21.9) • Umbilical cord: 2.8 (0.4–18.5) **Analysis:** Maternal PbB was collected during the 2nd and 3rd trimesters of pregnancy and within 12 hours of delivery; umbilical cord PbB was also measured. Anthropometric measures in children were assessed at ages 4–6 years. PbB data were log2-transformed and associations between PbB and anthropometric measures were analyzed by linear regression, adjusted for mother's age, BMI, education, gestational age, primiparity, cigarette smoke exposure, delivery mode, breastfeeding, sex of the child, parity, total dietary intake, childhood blood lead, and child's age.	Negative associations between PbB and weight-for-age z-score and height-for-age z-score in the 3rd trimester. No associations were observed for any other PbB measurements. β coefficient (95% CI) for: BMI z-score • 2nd trimester: 0.04 (-0.07, 0.15); p=0.51 • 3rd trimester: -0.01 (-0.12, 0.10); p=0.81 • At delivery: -0.03 (-0.08, 0.14); p=0.58 • Cord PbB: 0.05 (-0.08, 0.17); p=0.46 Percentage body fat • 2nd trimester: -0.13 (-0.75, 0.49); p=0.68 • 3rd trimester: -0.21 (-0.82, 0.41); p=0.52 • At delivery: -0.12 (-0.74, 0.50); p=0.70 • Cord PbB: 0.31 (-0.37, 0.99); p=0.37 Weight-for-age z-score • 2nd trimester: -0.02 (-0.13, 0.09); p=0.68 • 3rd trimester: -0.11 (-0.22, -0.003); p=0.04 • At delivery: -0.03 (-0.13, 0.08); p=0.58 • Cord PbB: -0.03 (-0.15, 0.09); p=0.64 Height-for-age z-score • 2nd trimester: -0.04 (-0.13, 0.04); p=0.32 • 3rd trimester: -0.10 (-0.19, -0.01); p=0.03 • At delivery: -0.04 (-0.13, 0.05); p=0.39 • Cord PbB: -0.04 (-0.14, 0.06); p=0.39

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Schell et al. 2009 Longitudinal cohort study of 244 mother-child pairs (mean maternal age 22.7 years; children aged 3–12 months) receiving first-time prenatal care in Albany New York, 1986–1992 and 1992–1998 (study was conducted in two phases)	**Maternal PbB:** (measured in the 2nd trimester) • Mean (SD): 2.8 (2.63) • Range: 0.4–13 **Analysis:** Pubertal state (length, weight for age, weight for length, head circumference, and upper arm circumference) was analyzed using multiple linear regression and adjusted for infant sex, infant birth weight, infant nutrition, maternal age, marital status, employment, race, height, parity, 2nd trimester smoking, and education.	Associations were observed between maternal PbB and length (positive) and head circumference (negative), but not for weight, weight for length, or upper arm circumference. Regression coefficients per log µg/dL (SE): • Length (cm) o 6 months: 0.149 (0.076); p=0.05 o 12 months: 0.073 (0.083); p=0.38 • Weight-for-age (kg) o 6 months: 0.013 (0.098); p=0.89 o 12 months: 0.124 (0.107); p=0.25 • Weight for length (kg): o 6 months: -0.158 (0.111); p=0.16 o 12 months: 0.084 (0.111); p=0.45 • Head circumference (cm) o 6 months: -0.242 (0.094); p=0.01 o 12 months: -0.220 (0.109); p=0.05 • Upper arm circumference (cm) o 12 months: -0.132 (0.114); p=0.25

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
		When stratified by maternal PbB <3 and ≥3 µg/dL, no associations were observed at PbB <3 µg/dL. For PbB ≥3 µg/dL, significant associations were observed for weight for length at 6 months and head circumference at 6 and 12 months. Regression coefficients (SE): • Weight (kg) o 6 months: -0.771 (0.344); p=0.03 • Weight for length (kg): o 6 months: -1.461 (0.404); p<0.01 • Head circumference (cm) o 6 months: -0.846 (0.338); p=0.01 o 12 months: -1.163 (0.376); p<0.01 • Upper arm circumference (cm) o 12 months: -1.063 (0.436); p=0.02
Yang et al. 2013a Cross sectional study of 246 children (aged 3–8 years) attending kindergarten near an electronic waste processing area, Guiyu China (dates are not reported)	**Child PbB** Mean: 7.30 5th–95th percentile: 4.33–15.43 **Analysis:** Pubertal state (height, weight, BMI, and biochemical markers related to bone metabolism) was analyzed using multiple linear regression and Spearman correlation coefficients and adjusted for child age and sex.	Linear regression analysis showed negative associations between PbB and height (cm) and weight (kg), but not BMI (kg/m^2). β coefficients per µg/dL: • Height: -0.10; p=0.02 • Weight: -0.14; p=0.01 • BMI: -0.08; p=0.24 Spearman correlation coefficients: • Height: -0.119; 0.05<p<0.01 • Weight: -0.128; 0.05<p<0.01 • Osteocalcin: 0.020; p>0.05 • bALP: 0.087; p>0.05 • uDPD: 0.239; p<0.01

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Onset of puberty in females		
Den Hond et al. 2011 Cross-sectional study of 792 girls (aged 14–15 years) attending their 3rd year of secondary education and living in the study area for at least 5 years, Flanders Belgium 2003–2004	**PbB:** Median: 1.81 10th–90th percentile: 0.88–3.81 **Analysis:** Puberty onset (pubic hair growth and breast development) was analyzed using logistic regression and adjusted for age, BMI, smoking, and oral contraception use.	A 2-fold increase in PbB was associated with 35% lower odds of reaching stage P4 for pubic hair development. Adjusted OR (95% CI): 0.65 (0.45, 0.93); p=0.020. No association was observed between PbB and breast development (data not reported).
Denham et al. 2005 Cross-sectional study of 138 Akwesasne Mohawk Nation girls (aged 10–16.9 years), territory spanning New York, Ontario and Quebec, Canada (dates are not reported)	**PbB:** Mean (SD): 0.49 (0.905) Range: 0.07–4.40 Median: 1.2 75th percentile: 1.66 **Analysis:** Puberty onset (attainment of menarche) was analyzed using probit and logistic regression and adjusted for age, SES, and BMI.	PbB was associated with a decreased likelihood of attaining menarche. β coefficient (SE) predicting menarcheal status based on PbB (ln µg/dL): • Mean PbB: -1.29 (0.494); p=0.01 • 75th percentile PbB: -3.75 (1.822); p=0.04 For PbB ≥1.2, the predicted age at menarche for girls was 10.6 months later than for girls with PbB <1.2. Predicted age of menarche (95% CI): • PbB <1.2: 11.8 years (9.9. 12.8) • PbB ≥1.2: 12.7 years (12.2, 13.1) A doubling of PbB was associated with decreased odds of reaching menarche (data presented graphically): • PbB increase from 0.49 to 0.98: 72% decrease • PbB increase from 1.66 to 3.32: 98% decrease

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Gollenberg et al. 2010 Cross-sectional study of 705 girls (aged 6–11 years) who previously participated in the NHANES III study 1988–1994	**PbB:** Median: 2.5 Range: 0.07–29.4 Participants with PbB >10: n=32 (5%) Tertiles • T1: <1.0 • T2: 1–4.99 • T3: ≥5.00 **Analysis:** Reproductive hormones (luteinizing hormone and inhibin B) were analyzed using survey logistic regression and adjusted for age, race/ethnicity, BMI, census region, and poverty income ratio.	Decrease in the likelihood of exceeding the inhibin B (a marker of follicular development) pubertal cutoff value (35 ρg/mL) was observed for a 1 unit increase in PbB (log-transformed). Adjusted OR (95% CI):0.51 (0.34, 0.78). Adjusted ORs (95% CI) for exceeding the inhibin B pubertal cutoff value by tertile: • T1: reference • T2: 0.38 (0.12, 1.15) • T3: 0.26 (0.11, 0.60) No association was observed between PbB and serum LH levels (data not shown).

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Naicker et al. 2010 Cross-sectional and longitudinal study of 682 girls (aged 13 years) of black or mixed ancestry who were previously enrolled in the Birth to Twenty cohort and living in the study area for at least 6 months after birth, South Africa	**PbB:** Mean (SD): 4.9 (1.9) Range: 1.0–16.3 Participants with PbB >10: n=5 (1%) **Analysis**: Puberty onset (breast development and attainment of menarche) was analyzed using logistic regression and adjusted for BMI.	Higher PbB was associated with delays in the onset of puberty. Trend analysis for Tanner breast development associated and mean PbB (SD): • Stage 1 (n=9): 7.3 (2.47) • Stage 2 n=82: 5.6 (1.74) • Stage 3 (n=283): 5.0 (1.83) • Stage 4 (n=262): 4.8 (1.92) • Stage 5 (n=46): 4.5 (1.69) • p-trend=<0.001 Trend analysis for pubic hair and mean PbB (SD): • Stage 1 (n=16): 5.5 (1.67) • Stage 2 n=86: 5.4 (1.87) • Stage 3 (n=322): 5.0 (2.04) • Stage 4 (n=230): 4.7 (1.59) • Stage 5 (n=28): 4.6 (2.18) • p-trend=<0.001 Trend analysis for attainment of menarche associated and mean PbB (SD) for age: • 9 (n=5): 3.8 (0.87) • 10 (n=15): 4.2 (1.31) • 11 (n=91): 4.9 (2.04) • 12 (n=186): 4.8 (2.01) • 13 (n=220): 4.8 (1.75) • 14 (n=115): 5.5 (1.66) • 15 (n=33): 5.6 (2.04) • 16 (n=9): 5.9 (2.73) • p-trend=<0.001

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Selevan et al. 2003 Cross-sectional study of 2,186 girls (aged 8–18 years) who had previously participated in the NHANES III study, 1988–1994	**PbB:** Gmean (95% CI) • Non-Hispanic White (NHW): 1.4 (1.2, 1.5) • Non-Hispanic African-American (NHAA): 2.1 (1.9, 2.3) • Mexican-American (MA): 1.7 (1.6, 12.4) **Analysis:** Puberty onset (breast development, pubic hair development, and age of menarche) was analyzed using ordinal logistic regression and Cox proportional hazards and adjusted for age, age^2, smoking, dietary Ca2+, dietary iron, dietary vitamin C, dietary total fat, anemia, urban residence, and family income.	Adjusted ORs (95% CI) for the likelihood of reaching a successive stage of pubertal development for girls for PbB (log-transformed) of 3 µg/dL compared to 1 µg/dL: • Breast development o NHW: 0.82 (0.47, 1.42) o NHAA: 0.64 (0.42, 0.97); p<0.05 o MA: 0.76 (0.63, 0.91); p<0.05 • Pubic hair development: o NHW: 0.75 (0.37, 1.51) o NHAA: 0.62 (0.41, 0.96); p<0.05 o MA: 0.70 (0.54, 0.91); p<0.05 • Age of menarche 8–16-year-old girls (hazard ratio [95% CI]) o NHW: 0.74 (0.55, 1.002) o NHAA: 0.78 (0.63, 0.98); p<0.05 (age at menarche delayed 3.6 months) o MA: 0.90 (0.73, 1.11)
Wolff et al.2008 Cross-sectional study of a multiethnic group of 192 girls (aged 9 years) residing in New York City, New York 1996–1997	**PbB:** Median: 2.4 **Analysis:** Puberty onset (breast development, pubic hair stage, attainment of menarche) was analyzed using Poisson multivariate regression with robust error variance. Adjustments for breast development included age, BMI, and race and adjustments for hair stage included height, private clinic, and race.	No association was observed between ln PbB and delay of sexual maturation as measured by Breast development stage and public hair development stage. Prevalence ratios (95% CI): • Breast stage ≥2 versus stage 1: 1.01 (0.79,1.30) • Pubic hair stage ≥2 versus stage 1: 1.25 (0.83, 1.88)

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Wu et al. 2003b Cross-sectional study of 1,706 girls (aged 8–16 years) who had previously participated in the NHANES III study, 1988–1994	**PbB:** Mean (SD): 2.5 (2.2) Range: 0.7–21.7 Tertiles: • T1: 0.7–2.0 (reference) • T2: 2.1–4.9 • T3: 5.0–21.7 **Analysis:** Puberty onset (breast development, pubic hair stage, attainment of menarche) was analyzed using logistic regression with weighted and adjusted for race/ethnicity, age, family size, residence, poverty income, ratio, and BMI.	PbB was associated with delayed pubic hair development and attainment of menarche and, but not with breast development. Adjusted ORs (95% CI): • Breast development: o T2: 1.51 (0.90, 2.53) o T3: 1.20 (0.51, 2.85) • Pubic hair development: o T2: 0.48 (0.25, 0.92) o T3: 0.27 (0.08, 0.93) • Attainment of menarche: o T2: 0.42 (0.18, 0.97) o T3: 0.19 (0.08, 0.43)
Onset of puberty in males		
Den Hond et al. 2011 Cross-sectional study of 887 boys (aged 14–15 years) attending their 3rd year of secondary education and living in the study area for at least 5 years, Flanders, Belgium 2003–2004	**PbB:** Median: 2.50 10th–90th percentile: 1.20–5.12 **Analysis:** Puberty onset (risk of gynecomastia, sexual maturation) was analyzed using logistic regression and adjusted for age, parental education, age, BMI, and smoking status.	A 2-fold increase in PbB was associated with increased risk of gynecomastia. Adjusted OR (95% CI): 1.84 (1.11–3.05); p=0.018 No association was observed between PbB and sexual maturation (data not reported).

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Hauser et al. 2008 Cross-sectional study of 489 peripubertal boys (aged 8–9 years) residing in Chapaevsk, Russia 2003–2005	**PbB:** Median: 3 5th –95th percentile: 2–5 Participants with PbB ≥5: n=137 (28%) Participants with PbB >10: 3% **Analysis:** Puberty onset (odds of having entered genitalia stage G2) was analyzed using multivariate logistic regression and adjusted for gestational age, height, BMI, and age at exam.	Reduced OR of having entered genitalia stage G2 were reduced at PbB ≥5 compared to PbB <5. OR (95% CI): 0.57 (0.34, 0.95); p=0.03
Williams et al. 2010 Longitudinal cohort of 489 peripubertal boys (aged 8–9 years) who had two follow-up evaluations residing in Chapaevsk, Russia 2003–2008	**PbB:** Median: 3 Participants with PbB ≥5: 28% Participants with PbB >10: 3% **Analysis:** Puberty onset was analyzed using Cox proportional hazards and adjusted for birth weight, gestational age, energy intake, proportion of fat consumption, proportion of protein consumption, maternal alcohol consumption during pregnancy, height at study entry, BMI at study entry, household income, and parental education.	Onset of puberty occurred 6–8 months later for boys with PbB ≥5 µg/dL compared to boys with PbB <5 µg/dL. A reduced risk of pubertal onset was observed in boys with PbB ≥5 µg/dL compared to those with PbB <5 µg/dL, based on testicular volume and genitalia stage. HRs (95% CI): • Testicular volume <3 mL: 0.73 (0.55, 0.97); p=0.03 • Genitalia stage ≥2: 0.76 (0.59, 0.98); p=0.04 • Pubic hair stage ≥2: 0.69 (0.44, 1.07); p=0.10

Table 13. Epidemiology Studies Evaluating Developmental Effects at Mean Blood Lead Concentrations (PbB) ≤10 µg/dL

Reference and study population	PbB (µg/dL) and analysis	Outcomes
Williams et al. 2019 Longitudinal cohort study of 481 boys (enrolled at ages 8–9 years) residing in Chapaevsk, Russia; enrollment period: 2003–2005; assessment period: through 2017	**PbB:** Median: 3 Range: 0.5–31 <5: n=347 ≥5: n=134 (28%) **Analysis:** PbB measurements were made at enrollment; PbB was stratified as <5 and ≥5 µg/dL. Puberty and sexual maturity were assessed at 12-month intervals and measured by genitalia and pubic hair development and testicular volume. To determine difference between the <5 and ≥5 µg/dL groups for ages of onset of puberty and sexual maturity, data were analyzed by interval-censored regression models. Adjustments for puberty onset were high caloric intake for genitalia, pubic hair, and testicular volume; low maternal education for genitalia; no biological father residing in household for genitalia, pubic hair, and testicular volume; and birth weight for genitalia and testicular volume. Adjustments for sexual maturity were high caloric intake for genitalia; mother <20 years old at birth for genitalia, no biological father residing in household for public hair and testicular weight; low income level for public hair; and low maternal education level for testicular volume.	Age at pubertal onset (shift in mean age in months) (95% CI) based on: • Genitalia: 8.40 (3.70,13.10); p<0.001 • Pubic hair: 8.12 (3.46,12.78); p<0.001 • Testicular volume: 7.68 (3.46,11.90); p<0.001 Age at sexual maturity (shift in mean age in months) (95% CI) based on: • Genitalia: 4.20 (0.56, 7.84); p=0.024 • Pubic hair: 4.23 (-0.31, 8.77); p=0.068 • Testicular volume: 5.14 (1.70, 8.58); p=0.003

ALSPAC = Avon Longitudinal Study of Parents and Children; bALP = bone alkaline phosphatase; BMI = body mass index; CANDLE = Conditions Affecting Neurocognitive Development and Learning in Early Childhood; CI = confidence interval; Gmean = geometric mean; HR = hazard ratio; LH = luteinizing hormone; MA = Mexican Americans; MANCOVA = multivariate analysis of covariance; MANOVA = multivariate analysis of variance; MBPb = maternal whole blood lead; NHW = non-Hispanic whites; NHAA = non-Hispanic African Americans; NHANES = National Health and Nutrition Examination Survey; NS = not statistically significant; OR = odds ratio; Pb = lead; PROGRESS = Programming Research in Obesity, Growth, Environment and Social Stressors; RBC = red blood cell; RR = relative risk; SD = standard deviation; SE = standard error; SES = socioeconomic status; SGA = small for gestational age; uDPD = urine deoxypyridinoline

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
PbB ≤10 µg/dL				
Van Larebeke et al. 2004 Flemish women with no previous occupational exposure (n=99; age 50–65 years) in Antwerp and Antwerp peer	Mean • Antwerp: 3.3 • Peer: 2.9	Peripheral blood lymphocytes	Gene mutation (HPRT)	+ Higher PbB level (10^{th}–90^{th} percentile: 1.6–5.2 µg/dL; p=0.033) was associated with greater HPRT mutation frequency than found in the total population.
Akram et al. 2019 100 construction workers and 100 matched controls	Mean: • Workers: 8 • Controls: 3.5 (estimates; data displayed graphically)	Peripheral blood lymphocytes	DNA damage	+
Al Bakheet et al. 2013 Heavy metal exposed male workers (n=40, age 20–42 years; n=20 age-matched controls) in Saudi Arabia	Mean (SE): • Workers: 2.1 (0.251) • Controls: 1.1 (0.062)	Peripheral blood lymphocytes	DNA damage/repair	–
Hengstler et al. 2003 Occupational exposure (n=78 workers and n=22 controls); co-exposure to cadmium, cobalt, and lead	Mean: 4.41	Mononuclear blood	DNA damage/repair	–
Jasso-Pineda et al. 2012 Children (4–11 years) in three Mexican communities (n=A: 48; B: 12; C: 25) co-exposed to arsenic and lead	Mean, community: A: 11.4 B: 7.3 C: 5.3	Peripheral blood mononuclear cells	DNA damage/repair	+ Compared to Community C, Communities A and B had increased (p<0.05) DNA damage.
Zota et al. 2015 Adults (n=6,796) participating in NHANES (1999–2002)	Mean (95% CI):1.67 (1.63, 1.70)	Leukocytes	Telomere length	–

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Pawlas et al. 2015 Children (n=99); 8 years of age, from Poland	Gmean (range): 3.28 (0.90–14.2)	Whole blood	Telomere length	+ PbB was associated with decreased telomere length (β: -0.13, p=0.029)
Hanna et al. 2012 Women (n=43, mean age 36 years) undergoing IVF	Low: <0.73 High: >0.73	Whole blood	DNA methylation	+ Reduced methylation was detected in the COL1A2 promoter in women with higher exposure to lead (p=0.004), and an inverse correlation was observed (r:-0.45, p=0.03).
Li et al. 2016b Adults (n=105; 64 females, 41 males) with PbB obtained from birth to 78 months from the Cincinnati Lead Study	Mean: 1.36	Peripheral blood lymphocytes	DNA methylation	+ Mean PbB from birth to 78 months was associated with decreased DNA methylation (p=0.002) at some differentially methylated regions, and increased DNA methylation (p=0.01) at other regions in adults.
Pilsner et al. 2009 Umbilical cord blood samples (n=103) (Mexico)	Mean (SD): 6.6 (2.7)	Umbilical cord leukocytes	DNA methylation	+ Prenatal Pb exposure was inversely associated with genomic DNA methylation in cord blood (p=0.01).
Wu et al. 2017 Mother-infant pairs (n=268) in Massachusetts	Mean (SD) maternal erythrocyte Pb, 2nd trimester: 1.22	Umbilical cord blood (all cell types)	DNA methylation	+ Prenatal Pb exposure was associated with decreased epigenome-wide DNA methylation in cord blood (-1:4% per doubling of PbB; $p=2:3x10^{-7}$)
Mielzyńska et al. 2006 Children (n=74; age 5–14 years) in Silesia, Poland	Mean (SD): 7.69 (4.29) Range: 2.7–23.0	Peripheral blood lymphocytes	SCE	–

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Wu et al. 2002 Occupational exposure in 57 storage battery workers (high exposure n=23; low exposure n=34) and 30 controls in Taiwan	Mean (SD): • High exposure: 32.5 (14.5) • Low exposure: 9.3 (2.9) • Control: 4.2 (1.4)	Peripheral blood lymphocytes	SCE	– No increase in SCE for the low exposure group.
Mielzyńska et al. 2006 Children (n=74; age 5–14 years) in Silesia, Poland	Mean (SD): 7.69 (4.29) Range: 2.7–23.0	Peripheral blood lymphocytes	MN	– No increase in MN in children below the threshold value of 10 µg/dL.
PbB >10 µg/dL				
Chinde et al. 2014 Occupational exposure (n=200 storage battery workers; n=200 controls)	Mean (SD) • Workers: 30.1 (4.13) • Controls: 6.71 (0.97)	Peripheral blood lymphocytes	DNA damage (Comet assay)	+ Increased ($p<0.01$) mean percent tail DNA compared to controls.
Danadevi et al 2003 Occupational exposure (n=45 Pb recovery unit workers; 36 controls) in India	Mean (SD) • Workers: 25 (14.7) • Controls: 2.7 (1.5)	Peripheral blood lymphocytes	DNA damage (Comet assay)	+ • Percentage of cells with DNA damage (44.58%) in exposed works was increased compared to controls (21.14%). • A positive correlation was observed between PbB and DNA damage ($p<0.01$).
de Restrepo et al. 2000 Occupational exposure (n=43 electric battery factory workers; n=13 controls) in Bogotá, Colombia	Mean: • Workers: 98.5 • Controls: 5.4	Peripheral blood lymphocytes	DNA damage/repair (comet assay)	+ Increased DNA damage ($p=0.05$) in workers with PbB >120 µg/dL compared to workers with PbB >40 µg/dL.

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Fracasso et al. 2002 Occupational exposure (n=37 battery plant workers; n=29 controls)	Workers: • Mean (SE): 39.63 (7.56) • Control mean (SE): 4.4 (1.7)	Peripheral blood lymphocytes	DNA damage (comet assay)	+ Elevated levels of DNA breaks in workers compared to controls (p<0.00001).
Grover et al. 2010 Occupational exposure (n=90 male Pb recovery unit workers; n=90 controls) in India	Mean (SD) • Workers: 30.33 (2.085) • Controls: 3.21 (0.26)	Peripheral blood lymphocytes	DNA damage (comet assay)	+ Increased comet tail length in workers compared to controls (p<0.05).
Jannuzzi and Alpertunga 2016 Occupational exposure (n=25 male storage battery workers; n=25 controls) in Turkey	Mean (SE) • Workers: 28.58 (3.78) • Controls: 3.58 (0.08)	Peripheral blood lymphocytes	DNA damage/repair (comet assay)	+ • Increased percentage of DNA in tail than controls (p<0.05). • In challenge assay, mean DNA% repair capacity was reduced (p<0.01).
Kasuba et al. 2012 Occupational exposure (n=30 pottery-glaze workers; n=30 controls; age 18–57 years)	Workers • Mean (SE): 22.04 (1.775) Range: 4.168–40.477 Controls: • Mean (SE): 3.04 (0.24) Range: 1.2–5.2	Peripheral blood lymphocytes	DNA damage (Comet assay and DNA diffusion assay)	+ • Increased tail intensity in workers compared to controls (p<0.0001). • Poisson regression analysis showed a correlation between PbB and increased primary DNA damage (p<0.0001).
Kayaalti et al. 2015a Pb workers (n=61, mean age 38.27 years) in Turkey	Mean (SD) • Workers: 12.56 (12.17) • Controls: not reported	Peripheral blood lymphocytes	DNA damage (Comet assay)	+ Statistically significant positive correlation (p<0.01) between PbB and including tail intensity, tail moment, and DNA tail.

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Méndez-Gómez et al. 2008 Cross-sectional study in children from schools in three locations in Mexico based on distance from a smelter: distant (n=21); intermediate (n=22); and near (n=22)	Mean • Distant: 4.6 • Intermediate: 19.5 • Near: 28.6	Peripheral blood lymphocytes	DNA damage/repair (Comet assay)	+ Tail length and cells with long tails were increased ($p<0.05$) in the nearest location group, compared to the intermediate and distant groups.
Shaik and Jamil 2009 Pb battery workers (n=113) and controls (n=102) in India	Range: • Workers: 21.8–88.0 • Controls: 0.6–3.4	Peripheral blood lymphocytes	DNA damage (Comet assay)	+ Workers had increased DNA damage, compared to controls, for mean comet tail length ($p<0.05$) and basal DNA damage ($p<0.01$).
Al-Hakkak et al. 1986 Occupational exposure (n=19 storage battery workers; n=9 controls) in Baghdad city	Workers • Mean: 64 • Range: 38–96 Controls: • Mean: 24 • Range: 6–30	Peripheral blood lymphocytes	CAs	+ Higher frequencies of chromatid and chromosome aberrations were observed in workers compared to controls ($p<0.05$).
Anwar and Kamal 1988 Occupational exposure (n=28 traffic policemen with exposure to automobile exhaust for over 10 years; n=15 controls) in Cairo	Mean (SD): • Workers: 30.1 (8.7) • Controls: 18.2 (1.2)	Peripheral blood lymphocytes	CAs	+ CAs were increased in workers compared to controls ($p<0.05$).
Bauchinger et al. 1977 Study of children (n=30) living in a town with a lead plant	Range: 12–33	Peripheral blood lymphocytes	CAs	–

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Chinde et al. 2014 Occupational exposure (n=200 storage battery workers; n=200 controls)	Mean (SD): • Workers: 30.1 (4.13) • Controls: 6.71 (0.97)	Peripheral blood lymphocytes	CAs	+ CAs were increased ($p<0.01$) in workers compared to controls.
Forni et al. 1976 Occupational exposure (n=10 storage battery plant workers; n=11 controls)	Range: • Workers: 45–64 • Controls: 34	Peripheral blood lymphocytes	CAs	+ Rate of abnormal metaphase approximately doubled after 1 month of work ($p<0.05$).
Grover et al. 2010 Occupational exposure (n=90 male Pb recovery unit workers; n=90 controls) in India	Mean (SD) • Workers: 30.33 (2.085) • Controls: 3.21 (0.26)	Peripheral blood lymphocytes	CAs	+ Aberrant metaphase in workers was elevated compared to controls ($p<0.05$).
Huang et al. 1988 Occupational exposure (n=21 battery plant workers; n=7 controls	Mean (SD): • Low Pb group: 33.7 (5.9) • Medium Pb group: 52.1 (7.3) • High Pb group: 86.9 (16.5) • Controls: 7.8 (2.3)	Peripheral blood lymphocytes	CAs	+ • Significant increase in CA percentage in medium and high exposure groups compared to controls ($p<0.01$). • CA percentage increased with PbB ($p<0.01$).
Maki-Paakkanen et al. 1981 Occupational exposure (n=18 male Finnish smelter workers; n=12 controls)	Mean: • Workers: 49 • Controls: <10	Peripheral blood lymphocytes	CAs	–

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Nordenson et al. 1978 Occupational exposure (n=6 for high exposure; n=16 for medium exposure; n=4 for low exposure) in Northern Sweden	Mean: • High exposure: 64.7 • Medium exposure group: 39.2 • Low exposure group: 22.9 • Controls: not reported	Peripheral blood lymphocytes	CAs	+ • CA frequency was increased in Pb-exposed workers compared to controls ($p<0.001$). • Frequency of aberrations correlated with PbB.
Pinto et al. 2000 Occupational exposure (n=25 male outdoor painters; n=25 controls) in Mexico	Mean (SE) • Workers: 10.48 (3.13) • Controls: 7.10 (2.79)	Peripheral blood lymphocytes	CAs	+ Elevated CAs in workers compared to controls ($p<0.05$).
Schwanitz et al. 1970 Occupational exposure (n=8 Pb oxide factory workers)	Range • Workers: 60–90	Peripheral blood lymphocytes	CAs	+ Increased proportion of mitoses with secondary CAs in workers compared to controls (p-value not reported).
Schwanitz et al 1975 Occupational exposure (n=105 workers)	Mean: • Workers: 38	Peripheral blood lymphocytes	CAs	–
Shaik and Jamil 2009 Pb battery workers (n=113) and controls (n=102) in India	Range: • Workers: 21.8–88.0 • Controls: 0.6–3.4	Peripheral blood lymphocytes	CAs	+ Increased number of aberrant cells, satellite associations, and CAs in workers compared to controls (Chi-square test; $p<0.01$).

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Anwar and Kamal 1988 Occupational exposure (n=28 traffic policemen with exposure to automobile exhaust for over 10 years; n=15 controls) in Cairo	Mean (SD): • Workers: 30.1 (8.7) • Controls: 18.2 (1.2)	Peripheral blood lymphocytes	SCEs	– Increased SCEs on workers compared to controls ($p<0.05$); however, increase in SCEs was not correlated with PbB.
Dalpra et al. 1983 Children (n=19 exposed; n=12 controls, age 3–14 years) living in a contaminated area near a smelting plant	Mean: 29.3–62.7	Peripheral blood lymphocytes	SCEs	–
Duydu et al. 2001 Occupational exposure (n=31 battery plant workers; n=20 controls) in Turkey	Mean (SD) • Workers: 36.31 (8.28) • Controls: 11.1 (2.13)	Peripheral blood lymphocytes	SCEs	+ SCEs were increased in workers compared to controls ($p<0.05$).
Duydu et al. 2005 Occupational exposure (n=50 storage battery plant workers; n=50 controls) in Turkey	Workers • Mean (SE): 40.14 (9.99) • Range: 22.24–63.11 Controls: • Mean: 9.77 (1.67) • 7.92–13.51	Peripheral blood lymphocytes	SCEs	+ Increased SCE in exposed workers compared to controls ($p<0.001$).
Grandjean et al. 1983 Occupational exposure study (n=10 long-term Pb exposed men at a battery plant; n=18 newly employed workers; each subject served as his own control)	Range: • Workers: 29–75	Peripheral blood lymphocytes	SCEs	–

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Huang et al. 1988 Occupational exposure: n=21 battery plant workers; n=7 controls	Mean (SD): • Low exposure group: 33.7 (5.9) • Medium exposure group: 52.1 (7.3) • High exposure group: 86.9 (16.5) • Controls: 7.8 (2.3)	Peripheral blood lymphocytes	SCEs	+ • SCEs were increased in the high-exposure group compared to controls ($p<0.001$). • No correlation between PbB and SCEs was observed.
Maki-Paakkanen et al. 1981 Occupational exposure (n=18 male Finnish smelter workers; n=12 controls)	Mean: • Workers: 49 • Controls: <10	Peripheral blood lymphocytes	SCEs	–
Pinto et al. 2000 Occupational exposure (n=25 male outdoor painters; n=25 controls) in Mexico	Mean (SE) • Workers: 10.48 (3.13) • Controls: 7.10 (2.79)	Peripheral blood lymphocytes	SCEs	+ Elevated SCEs in workers compared to controls ($p<0.05$).
Wiwanitkit et al. 2008 Occupational exposure (n=32 volunteer male Thai police officers, 24 in high-exposure group, and 6 in low-exposure group); no controls were included	Mean: • Total for all subjects: 43.5 • High exposure group: 68.3 • Low exposure group: 31.1	Peripheral blood lymphocytes	SCEs	+ The average SCE was increased ($p<0.05$) in the high-exposure group compared to those with low-metal exposure.

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Wu et al. 2002 Occupational exposure (n=57 storage battery workers; n=30 controls) in Taiwan	Mean (SD): • High exposure group (n=23): 32.5 (14.5) • Low exposure (n=34): 9.3 (2.9) • Controls: 4.2 (1.4)	Peripheral blood lymphocytes	SCEs	+ Significant increase in SCEs in high Pb group ($p<0.01$).
Chinde et al. 2014 Occupational exposure (n=200 storage battery workers; n=200 controls)	Mean (SD): • Workers: 30.1 (4.13) • Controls: 6.71 (0.97)	Peripheral blood lymphocytes	MN	+ MN increased in workers compared to controls ($p<0.01$).
Grover et al. 2010 Occupational exposure (n=90 male Pb recovery unit workers; n=90 controls) in India	Mean (SD) • Workers: 30.33 (2.085) • Controls: 3.21 (0.26)	Peripheral blood lymphocytes and buccal mucosa cells	MN	+ Significant increase in frequency of MN in workers compared to controls ($p<0.05$).
Hamurcu et al. 2001 Occupational exposure (n=31 male workers at a metal powder-producing plants; n=20 controls)	Mean (SD) • Workers: 40 (18) • Controls: 12 (4)	Peripheral blood lymphocytes	MN	+ Exposed workers had higher MN mean values than controls ($p<0.01$).
Khan et al. 2010b Occupational exposure (n=30 male painters; n=30 controls) in India	Mean (SD) • Workers: 21.56 (6.43) • Controls: 2.84 (0.96)	Buccal epithelial cells	MN	+ • Elevation in MN frequencies and nuclear changes (karyorrhexis, karyolysis, broken egg, and binucleate) in buccal epithelial cells in workers compared to controls ($p<0.01$). • Association of PbB observed between MN frequency and PbB.

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Kasuba et al. 2012 Occupational exposure (n=30 pottery-glaze workers; n=30 controls; age 18–57 years)	Workers • Mean (SE): 22.04 (1.775) • Range: 4.168–40.477 Controls: • Mean: 3.04 (0.24) • Range: 1.2–5.2	Peripheral blood lymphocytes	MN	+ Frequency of MN was increased in workers compared to controls (p<0.03).
Mielzyńska et al 2006 Genotoxic effects in children (n=74, age 5–14 years), living in two cities in Upper Silesia Poland	Mean: 7.69 Range 2.7–23.0	Peripheral blood lymphocytes	MN	+ MN was increased in children with PbB >10 µg/dl compared to children with PbB <10 µg/dL.
Minozzo et al. 2004 Occupational exposure (n=26 male workers of a recycling automotive battery industry; n=29 controls) in Brazil	Mean • Workers: 35.40 • Controls: 1.95	Peripheral blood lymphocytes	MN	+ MN frequency was higher in workers compared to controls (p<0.0001).
Pinto et al. 2000 Occupational exposure (n=25 male outdoor painters; n=25 controls) in Mexico	Mean (SE) • Workers: 10.48 (3.13) • Controls: 7.10 (2.79)	Peripheral blood lymphocytes	MN	+ Elevated MN was observed in workers compared to controls (p<0.05).
Shaik and Jamil 2009 Occupational exposure (n=113 battery workers; n=102 controls) in India	Range • Workers: 21.8–88.0 • Controls: 0.6–3.4	Buccal epithelial cells	MN	+ MN formation was increased in workers compared to controls (p<0.01).

Table 14. Epidemiological Studies Assessing Genotoxicity

Reference and study population	PbB (µg/dL)	Cell type	Test type	Result
Singh et al. 2013 Occupational exposure (n=30 battery workers; n=30 controls)	Workers • Mean (SD): 57.17 (18.4) • Range: 22.45–95.45 Controls • Means: 5.43 (1.94) • Range: 2.45–8.77	Buccal mucosal cells	MN	+ • Increased MN frequency was observed in workers compared to controls ($p<0.001$). • A positive association was observed between PbB and MN frequency ($p<0.001$).
Vaglenov et al. 1998 Occupational exposure (n=22 exposed workers; n=19 unexposed workers from the same plant; n=19 external unexposed workers)	Mean (SE): • Workers: 60.9 (3.1) • External controls: 18.2 (0.62) • Internal controls: 27.5 (1.66)	Peripheral blood lymphocytes	MN	+ An increased incidence of MN was observed in workers compared to controls ($p<0.001$).
Vaglenov et al. 2001 Occupational exposure (n=103 exposed workers; n=78 controls) (follow-up study to Vaglenov et al. 1998)	Mean (SE): • Workers: 55.9 (2.1) • Controls: 18.8 (0.83)	Peripheral blood lymphocytes	MN	+ PbB >25 µg/dL was associated with increased MN frequency ($p<0.001$).

– = negative test result; + = positive test result; ± = equivocal result; CA = chromosomal aberration; CI = confidence interval; DNA = deoxyribonucleic acid; Gmean = geometric mean; IVF = *in vitro* fertilization; MN = micronuclei; NHANES = National Health and Nutrition Examination Survey; Pb = lead; PbB = blood lead concentration; SCE = sister chromatid exchange; SD = standard deviation; SE = standard error

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