NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

June 13, 2012

APPENDICES A - E:
HUMAN STUDIES CONSIDERED IN DEVELOPING CONCLUSIONS

Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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APPENDIX A:
HUMAN STUDIES OF NEUROLOGICAL EFFECTS OF LEAD CONSIDERED IN DEVELOPING CONCLUSIONS

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Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional Al-Saleh, (2001) Saudi Arabia	533 Saudi Arabian girls (6-12 yrs of age) enrolled in 33 public schools in Riyadh. Year not stated Male=0%	7.8 (0.9) yrs	8.11 (3.50) Measured at time of testing.	Standardized tests of cognitive, visual-motor, visual-perceptual functions (the Test of Non-Verbal Intelligence (TONI), and the Beery Visual Motor Integration (Beery VMI) and class rank as a measure of academic achievement	Spearman rank correlation analysis; Kruskal-Wallis one way analysis of variance; multiple regression analysis Sociodemographic variables, early developmental milestones and child health status.	Multiple regression on blood Pb levels and neuropsychological and academic achievement scores <u>Beery VMI Saudi-based Standard scores</u> **log Pb β(SE)= -5.16 (2.09); p=0.014** <u>Rank percentile scores</u> **log Pb β(SE)= -12.31 (2.85); p=0.0015** New text - Authors state that Pb had no effect on TONI scores for the entire population In regression analysis of girls with blood Pb ≤9, only class rank was associated with blood Pb levels (<0.02). In regression analysis of girls with blood Pb >9, class rank, VMI, and TONI scores were all associated with blood Pb levels (<0.05)	Blood Pb was significantly associated lower neurocognition scores and academic achievement in 6 to 12 year old girls.
Prospective Al-Saleh (2009) Al-Kharj, Saudi Arabia	Children of healthy Saudi mothers delivering at King Khalid Hospital Year= 2004; % male not stated	Cord n = 119 6 mon n = 107 12 mon n = 79 18 mon n = 56 24 mon n = 43	Prenatal: Cord: 2.73 (2.52) Postnatal 6 mon: 3.36 (2.38) 12 mon: 3.27 (2.02) 18 mon: 3.98 (1.06) 24 mon: 4.45 (2.31) Exposure measured at birth (cord), and at 6, 12, 18, 24 months when outcome was assessed	Early cognitive development assessed using the Bayley Scale of Infant Development (BSID-I), consisting of a Mental Developmental Index (MDI) and a Psychomotor Development Index (PDI).	Univariate analyses; Student's *t*-test, ANOVA, multiple regression analyses Infants age, weight, height, number of people living in the house, gestational age, head circumference, 1- and 5-minute Apgar scores, sibling rank, total number of siblings, total number of half-siblings	<u>Effects of prenatal Pb exposure:</u> **MDI at 6 months, β = -0.24; p=0.02** **PDI at 6 months, β= -0.23; p=0.02** MDI at 12 months, PDI at 12 months, MDI at 18 months, PDI at 18 months, and MDI at 24 months: not reported PDI at 24 months, β = -0.36; p=0.09 <u>Effects of postnatal Pb exposure (at 6 months):</u> MDI at 12 months, PDI at 12 months, MDI at 18 months, PDI at 18 months, and MDI at 24 months: not reported **PDI at 24 months, β = -0.57 (p=0.005)** Only β's and p-values for significant effects were reported.	Cord blood Pb was significantly associated with lower MDI and PDI at 6 months. Blood Pb at 6 months was significantly associated with lower PDI at 24 months.
Cross-sectional Altmann (1998) Germany	384 children in Duisburg (n=120), Leipzig (n=191), and Gardelegen (n=73) examined during regular medical examination for school entrance. Year =1994; Male = 52%	6.2 (0.425) Range: 5.0-7.8	Duisburg: 3.784 (0.140) Leipzig: 5.098 (0.153) Gardelegen: 3.206 (0.141)	Visual function assessed by neurophysiological measures of visual-evoked potentials (VEP) of three different checkerboard patterns (VEP1, VEP2 and VEP3) by peak latencies (N75, P100, N150), amplitude (Amp) and interpeak	Linear regression. Latencies adjusted for area, age, birth weight, head circumference, visual acuity, quality of fixation, and weight. Amplitudes adjusted for gender, head circumference, weight, quality of fixation	<u>Multiple regression for neurophysiological outcomes and log blood Pb (µg/L)</u>: Reg. Coeff. (SE), *p*-value VEP1N75 (n=336): 0.086 (0.059), *p*=0.144 VEP1P100 (n=336): -0.094 (0.058), *p*=0.107 VEP1N150 (n=329): -0.108 (0.059), *p*=0.070 VEP1Amp (n=324): -0.015 (0.051), *p*=0.768 VEP2N75 (n=335): 0.091 (0.059), *p*=0.123 VEP2P100 (n=332): 0.020 (0.059), *p*=0.743 VEP2N150 (n=321): -0.065 (0.060), *p*=0.277 VEP2Amp (n=314): 0.002 (0.052), *p*=0.976 VEP3N75 (n=329): 0.043 (0.060), *p*=0.469 VEP3P100 (n=328): -0.010 (0.060), *p*=0.873 VEP3N150 (n=326): 0.065 (0.060), *p*=0.283	Concurrent blood Pb was significantly associated with decreased interpeak latencies in a neurophysio-logical measure of a visually evoked potential in 6 year old

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				latencies and psychophysical measures of contrast sensitivity (CS) measurements. Visual acuity measurements used as a control for other measurements. Urine Hg also measured.		VEP3Amp (n=319): 0.043 (0.053), *p*=0.417 VEP1:N150-P100 (n=329): -0.081 (0.059), *p*=0.086 **VEP1:P100-N75 (n=336): -0.174 (0.059), *p*=0.002** **VEP1:N150-N75 (n=329): -0.156 (0.058), *p*=0.004** VEP2:N150-P100 (n=321): -0.083 (0.059), *p*=0.080 VEP2:P100-N75 (n=332): -0.048 (0.059), *p*=0.207 VEP2:N150-N75 (n=321): -0.096 (0.059), *p*=0.053 VEP3:N150-P100 (n=325): 0.068 (0.060), *p*=0.129 VEP3:P100-N75 (n=328): -0.042 (0.060), *p*=0.241 VEP3:N150-N75 (n=325): 0.037 (0.060), *p*=0.270 The two results with p < 0.05 remained significant after Bonferoni correction for multiple testing (data not shown) Blood Pb was not significantly associated with psychophysical outcomes. Urine Hg was not associated with neurophysiological measures but was significantly associated with psychophysical outcomes.	children.
Prospective Baghurst (1992) Port Pirie, Australia *Population may overlap with Wigg (1988) and others*	494 7-year old children living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; re-evaluated at age 7; Year = 1979-1982 (at baseline) % male not stated	7 years (median age: 186 days after 7th birthday)	Means by quartile: (Q1 low - Q4 high) Maternal 6.2, 8.7, 10.6, 14.3 Cord (mean 8.9) 4.3, 7.4, 9.9, 15.0 Lifetime 0-15 months 9.9, 14.3, 18.0, 23.8 Lifetime 0-2 years 11.6, 16.6, 20.5, 27.1 Lifetime 0-3 years 12.2, 17.4, 21.7, 28.2 Lifetime 0-5 years 11.8, 17.0, 21.1, 26.9 Lifetime 0-7 years 10.8, 15.7, 19.7, 24.8	IQ as measured by the Wechsler Intelligence Scale for Children-Revised (WISC-R)	Multiple regression analysis Sex, parents' level of education, maternal age at delivery, parents' smoking status, socioeconomic status, quality of home environment, maternal IQ, birth weight, birth order, feeding method, duration of breast feeding, and whether child's natural parents were living together	Adjusted Multiple regression of log blood Pb and lifetime averages with Full Scale IQ at age 7: *β*(SE) Maternal blood Pb: -1.4 (2.0); p=0.48 Cord blood Pb: 0.60 (1.4); p=0.68 **Blood Pb 0-15 months: -4.0 (2.0); p=0.04** **Blood Pb 0-2 years: -4.6 (2.1); p=0.03** **Blood Pb 0-3 Years: -4.8 (2.3); p=0.04** **Blood Pb 0-4 Years: -4.6 (2.4); p=0.05** Blood Pb 0-7 Years: -3.7 (2.5); p=0.14 Verbal IQ had larger effect sizes and similar significance levels at full scale IQ. Performance IQ was not related to blood Pb at any age Estimated regression coefficients for subscale scores and lifetime average blood Pb 0-3 years: *β*(SE) **Information: -1.45 (0.57), *p* = 0.01** Similarities: -0.90 (0.62), *p* = 0.14 Arithmetic: -0.51(0.63), *p* = 0.42 Vocabulary: -0.44 (0.51), *p* = 0.40 Comprehension: -0.88 (0.54), *p* = 0.10 Picture Completion: -0.15 (0.45), *p* = 0.74 Picture Arrangement: -0.34 (0.60), *p* = 0.56 **Block Design: -1.61 (0.62), *p* = 0.01** Object Assembly: -0.08 (0.50), *p* = 0.86 Coding: -0.22 (0.53), *p* = 0.66	Blood Pb levels sampled from birth to 4 years were significantly associated with lower full scale and verbal IQ, but not performance IQ, at 7 years of age. Average lifetime blood Pb from 0-3 years was significantly associated with the Information and Block Design subscales.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Baghurst (1995) Port Pirie, Australia *Population may overlap with Wigg (1988) and others*	494 children (48.2% male) living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; re-evaluated at age 7; Year = 1979-1982 (at baseline) % male not stated	7-8 years	Maternal: 9.5 Cord: 8.4 6 months: 14.4 2 years: 21.2 (peak) 7 years: 11.6 SD not reported (Pb levels declined from age 2 to 7 with intermediate values included in a figure)	Developmental status assessed at age 7 with the Beery Developmental Test of Visual-Motor Integration (VMI)	Multiple regression models All models included: gender, birth order, months at school, age at testing, maternal IQ, parental smoking, SES and HOME scores. Some models included: Mother's education (maternal, cord, 6 mo), infant feeding style (maternal, cord, 6 mo), duration of breast-feeding (maternal, cord, 6 mo), whether parents live together (cord and 36 mo), father's education (15, 24, 72 and 0-84 mo)	Regression of Visual-Motor Integration Score on Log Blood Pb Concentration: β (SE) Maternal: Simple: -1.80 (0.41); Partial: -0.93 (0.46) Cord: Simple: -0.61 (0.30); Partial: -0.01 (0.33) 6 months: Simple: -1.41 (0.33); Partial: -0.75 0.35) 15 months: Simple: -1.59 (0.33); Partial: -0.83 (0.36) 24 months: Simple: -1.82 (0.38) ; Partial: -0.94 (0.42) 36 months: Simple: -2.10 (0.37); Partial: -1.36 (0.42) 48 months: Simple: -1.84 (0.36) ; Partial:-1.40 (0.39) 60 months: Simple: -1.58 (0.35) ; Partial: -0.81 (0.39) 72 months: Simple: -1.81 (0.35) ; Partial:-0.83 (0.41) 84 months: Simple: -1.85 (0.33) ; Partial:-1.30 (0.37) 0-84 months: Simple: -2.39 (0.51) ; Partial: -1.47 (0.60) *Statistical significance of these results not reported.* For an increase in lifetime average blood Pb from 10 to 30 µg/dL the significant estimated deficit in children's visual-motor performance was **1.6 points (95% CI = 0.3-2.9**)	Pre and postnatal blood Pb levels were associated with lower visual-motor performance at age 7.
Prospective Bandeen-Roche (2009) Baltimore, MD, USA *Population may overlap with Shih (2006) and others*	964 adults from the Baltimore Memory Study, aged 50 – 70 years, residing in Baltimore for at least 5 years. Year not stated Male= 34.3%	59.3 (6.0) years at baseline	Tibia Pb: 18.8 (11.6) µg/g at first follow-up 18.5 (11.6) µg/g at second follow-up Exposure measured at first and second follow-up visits	Cognitive function assessed by a 90-minute battery of 20 standardized tests covering 6 cognitive domains: *language* (Boston naming test, letter fluency, category fluency); *processing speed* (inverse or reaction time); e*ye-hand coordination* (Purdue pegboard hands and trail-making test A); *executive functioning* (Purdue pegboard assembly Stroop C minus A form, trail making test B minus A); *Verbal memory and learning* (Rey auditory verbal learning test); *Visual memory* (Rey	Marginal longitudinal linear regression, Q-normal plots, regression models, Age, sex, neurobehavioral testing technician, race/ethnicity, educational attainment, household wealth Adjusted for age, sex, interviewer, SES, and race (if applicable)	Tests of changing effect hypothesis: Eye-hand coordination (p=0.0035) **low-level Pb: β = -0.036 (-0.075, 0.004)** **high-level Pb: β = 0.020 (-0.027, 0.068)** **p=0.0035** An African-Americans only analysis retained a significant association with eye-hand coordination (p=0.0062), but whites were not significantly associated with any domain. Race and SES adjusted Domain Score Difference per 12.7 µg/g tibia Pb mean (95% CI): Baseline eye-hand coordination = -0.005 (-0.052, 0.042) Yearly difference amplification = -0.019 (-0.031, -0.007) No cognitive function domains were significantly associated in African Americans before or after adjusting for SES, or in the total sample after adjusting for race and SES. In White subjects only, adjusted domain score difference with a 12.7 (IQR) of tibia Pb: Mean (95% CI) Language: -0.0241 (-0.0764, 0.0281), p = 0.33 Processing Speed: -0.0241 (-0.1162, 0.068), p = 0.83	Tibia Pb was significantly associated with decreased hand eye coordination in adults, particularly in African-Americans, while other cognitive function domains were only significantly associated in white subjects.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				complex figure)		**Eye-hand coordination: -0.0635 (-0.1183, -0.0087),** p = 0.071 **Executive functioning: -0.0635 (-0.1158, -0.0112),** p = 0.053 **Verbal memory and learning**: -0.0762 (-0.1534, 0.001), ***p* = 0.034** Visual memory: -0.0648 (-0.1544, 0.0248), p = 0.31	
Prospective Bellinger (1984) Boston, MA, USA *Population may overlap with Bellinger (1986) and others*	249 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year= born between 1979-1981 % male not stated	6 months	Cord (mean) 6.6 (3.2) Cord blood Pb by categories (mean) Low: 1.8 Mid: 6.5 High: 14.6	Development as assessed by the Mental Development Index (MDI) and Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development	Multiple regression analyses, Spearman rank-order correlation Length of gestation, total HOME score PDI: additionally adjusted for presence of a problem being followed by an infant's pediatrician at 6 months	<u>Adjusted Regression of MDI and cord blood Pb</u> -2.891 (SE 0.210), p = 0.0019 95% CI for mean decrease in MDI score: -1.1, -4.7 <u>Correlation of cord blood Pb and MDI</u>: -0.11, p = 0.10 <u>Scores on item clusters from MDI Bayley Scales of Infant Development by cord blood Pb</u>: Low, mid, high, p-value Gross Motor: 8.3, 8.1, 8.2; p = 0.215 **Fine Motor: 9.6, 9.7, 9.2; *p* = 0.022** **Social Responsiveness: 6.9, 6.8, 6.7; *p* = 0.014** Goal Directedness: 3.2, 3.3, 3.1; p = 0.188 **Visually Directed Reaching: 8.2, 8.1, 7.9; *p* = 0.016** Secondary Circular Reactions: 1.8, 1.9, 1.8; p = 0.928 Object Permanence: 2.4, 2.4, 2.4; p = 0.794 Vocalization/Language: 4.0, 3.9, 3.9; p = 0.276 Log of 6 month blood Pb was not significantly associated with MDI PDI measures were not significantly associated with cord blood Pb or log 6 month blood Pb.	Cord blood Pb was significantly associated with lower scores on the MDI, but not the PDI, at 6 months. Concurrent blood Pb was not associated with MDI or PDI scores at 6 months.
Prospective Bellinger (1986) Boston, MA, USA *Population may overlap with Bellinger (1984) and others*	249 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year= born between 1979-1981 % male not stated	6, 12, 18, 24 months	Cord: 6.6 (3.2) Categorized into: Low <3 Mid 6-7; High >=10 6 months: 6.2 (7.1) Range 0-48.6 12 months: 7.7 (6.5) Range 0-30.6	Development as assessed by the Mental Development Index (MDI) of the Bayley Scales of Infant Development at 6 and 12 months	Simple bivariate regression without adjustment for confounding Stepwise/simultaneous multivariate regression Length of gestation, and total HOME score	<u>Bivariate associations between MDI and Pb</u>: est. (SE) 6 mon. MDI, Cord blood Pb: -1.49 (1.01), p = 0.14 6 mon. MDI, 6 mon. blood Pb: 0.65 (0.94), p = 0.49 12 mon. MDI, Cord blood Pb: -2.04 (1.11), p = 0.07 12 mon. MDI, 6 mon. blood Pb: -0.74 (1.04), p = 0.48 12 mon. MDI, 12 mon. blood Pb: -0.41 (1.08), p = 0.71 <u>Adjusted multivariate regression for MDI scores and Cord blood Pb:</u> β (95% CI) **6 mon. MDI: -2.89 (-1.09, -4.69); p=0.0019** **12 mon MDI: -3.63 (-1.43, -5.83); p=0.0015** <u>Adjusted multivariate regression MDI Scores at 12 months and Cord blood Pb</u>: mean (SD) **Fine motor: p=0.0004** **Low: 4.3 (1.6); Mid: 4.3 (1.6); High: 3.3 (1.7);** **Imitation: p=0.011**	Cord blood Pb was significantly associated with lower MDI scores at 6 and 12 months, but postnatal blood Pb was not associated with MDI scores.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Low: 4.2 (1.0); Mid: 4.1 (1.0); High: 3.7 (1.2); Object permanence: p=0.74 Low: 3.8 (0.5); Mid: 3.8 (1.0); High: 3.9 (0.4); **Language: p=0.018** **Low: 4.6 (1.5); Mid: 4.9 (1.8); High: 4.0 (1.2);** Spatial: p=0.064 Low: 0.8 (0.8); Mid: 0.6 (0.8); High: 0.6 (0.8); Goal directed: p=0.25 Low: 2.4 (1.2); Mid: 2.3 (1.1); High: 2.3 (1.0);	
Prospective Bellinger (1987) Boston, MA, USA *Population may overlap with Bellinger (1984) and others*	249 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year= born between 1979-1981 Male=59.3%	6, 12, 18, 24 months	Cord: 6.6 (3.2) Categorized into: Low, <3; Medium, 6-7; High, >=10	Development as assessed by the Mental Development Index (MDI) of the Bayley Scales of Infant Development	Least Squares Regression Mother's age, race, IQ, education, years of smoking, and 3rd trimester alcoholic drinks per week; mean family social class during the study, quality of the care-giving environment, gender, birth weight, gestational age, and birth order	<u>Infants' adjusted MDI Scores by Cord-Blood Pb Group</u>: 6 months (N=201) p=0.095 Low: 110.2 (1.3); Med: 108.0 (1.3); High: 105.9 (1.4) **12 months (N=199) p=0.020** **Low: 114.7 (1.6); Med: 114.4 (1.5); High: 108.9 (1.6)** **18 months (N=187) p=0.049** **Low: 116.2 (1.9); Med: 114.8 (1.9); High: 109.5 (2.0)** **24 months (N=182) p=0.006** **Low: 118.9 (1.8); Med: 117.8 (1.7); High: 111.1 (1.8)** Estimated difference between: Low and high groups **4.8 points (95% C.I. 2.3, 7.3)** Medium and high groups **3.8 (95% C.I. 1.3, 6.3).**	Cord blood Pb level was significantly associated with lower MDI scores at 12, 18, and 24 months, while postnatal blood Pb was not significantly associated with MDI scores.
Prospective Bellinger (1990) Boston, MA, USA *Population may overlap with Bellinger (1984) and others*	170 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year= born between 1979-1980 % male not stated	Blood measured from birth through 57 months Median age at final assessment: 57.8 months	Exposure measured at birth (umbilical cord), 6, 12, 18, 24, and 57 months Categorized into: Low < 3µg/dL Medium 3-10µg/dL High ≥ 10µg/dL *No mean, SD, range, or number in each category reported here*	Change in cognitive performance (Δz): an index of a child's developmental trajectory between 24 and 57 months. Calculated as the difference in z-scores (Δz) from measures: cognitive function as assessed by the Mental Development Index (MDI) scores from the Bayley Scales of Infant Development at 24 months and by the General Cognitive Index (GCI) score from the McCarthy	Multiple regression analysis; stratified analyses Adjusted for MDI at 24 months, HOME score at 57 months, social class, maternal IQ, maternal age, gender, and ethnicity	<u>Adjusted regression coefficients for change in cognitive performance (Δz) and blood Pb:</u> β(SE) **Cord blood Pb: 0.03 (0.01); p=0.016** 6 months blood Pb: 0.00 (0.07); p=0.96 12 months blood Pb: -0.08 (0.07); p=0.23 **18 months blood Pb: -0.21 (0.08); p=0.007** **24 months blood Pb: -0.22 (0.08); p=0.005** **57 months blood Pb: -0.23 (0.10); p=0.028** <u>Regression coefficients β(SE) for predictors of Δz in each cord blood Pb stratum</u>: Low cord blood (< 3µg/dL) Cord blood Pb: 0.04 (0.11); p=0.72 6 months blood Pb: -0.01 (0.10); p=0.94 12 months blood Pb: -0.18 (0.09); p=0.063 18 months blood Pb:-0.13 (0.09); p=0.16 24 months blood Pb: -0.16 (0.08); p=0.057 57 months blood Pb:-0.16 (0.14); p=0.26 Medium cord blood (3-10µg/dL) Cord blood Pb: 0.10 (0.29); p=0.74 6 months blood Pb: 0.02 (0.12); p=0.88 12 months blood Pb: 0.03 (0.13); p=0.84	Postnatal blood Pb levels were significantly associated with greater declines in scores on cognitive tests between age 2 and age 5.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				Scales of Children's Abilities at 57 months		**18 months blood Pb:-0.34 (0.150; p=0.028** 24 months blood Pb: -0.31 (0.16); p=0.065 57 months blood Pb: -0.14 (0.22); p=0.52 High cord blood (≥ 10µg/dL) Cord blood Pb: 0.07 (0.04); p=0.07 6 months blood Pb: 0.01 (0.13); p=0.95 12 months blood Pb: -0.18 (0.14); p=0.20 18 months blood Pb:-0.16 (0.16); p=0.33 24 months blood Pb: -0.28 (0.16); p=0.079 **57 months blood Pb: -0.46 (0.18); p=0.013**	
Prospective Bellinger (1991) Boston, MA, USA *Population may overlap with Bellinger (1984) and others*	170 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year=1979-1981 Male=51.2%	Children enrolled at birth Cognitive assessment at 57 months Median age (days): Session 1: 1777 Session 2: 1796	Cord: 6.8 (6.3) 6 months: 6.8 (7.3) 12 months: 7.8 (6.4) 18 months: 8.0 (5.7) 24 months: 7.0 (6.6) 57 months: 6.4 (4.1) 57 months tooth Pb: 2.8 (1.7) µg/g *abstract states that 24 month mean is 6.8 (6.3)µg/dL	General Cognitive Index (GCI) at 57 months; The McCarthy Scales of Children's Abilities, five subscale scores: verbal, perceptual-performance, quantitative, memory, and motor	Multiple regression Family social class, maternal IQ, marital status, preschool attendance, HOME total, hours per week of "out of home" care, number of family residence changes, recent medication use, number of adults in household, gender, race, birth weight, and birth order	<u>Adjusted mean change in GCI at 57 months for each natural log increase in Pb at one age</u>: β(95% CI), *P* value 6 month Pb: 0.28 (-2.3, 2.8); p=0.83 12 month Pb: -1.43 (-3.9, 1.0); p=0.25 18 month Pb: -1.62 (-4.3, 1.1); p=0.25 **24 months Pb: -2.95 (-5.7, -0.2); p=0.040** 57 month Pb: -2.28 (-6.0, 1.4); p=0.23 Dentine Pb: -2.51 (-10.2, 5.2); p=0.52 <u>Adjusted mean change in GCI at 57 months for each natural log increase in Pb level over age spans</u>: β(SE), *P* value Birth-57mo: -2.76 (2.41), *P* = 0.25 6-57mo: -2.33 (2.22), *P* = 0.30 12-57mo: - 2.17 (1.98), *P* = 0.28 18-57mo: - 2.94 (1.19), *P* = 0.13 24-57mo: - 2.80 (1.59), *P* = 0.08 <u>Adjusted mean change in 57 month Subscale Scores for each natural log increase in blood Pb at 24 or 57 months</u>: β(SE), *P* value Verbal 24 months: -0.41 (1.04); p=0.69 57 months: -1.06 (1.38); p=0.44 **Perceptual-Performance** **24 months:-2.58 (0.88); p=0.004** **57 months:-2.33 (1.13); p=0.042** Quantitative 24 months:-1.45 (0.85); p=0.09 57 months:0.13 (1.13); p=0.91 Memory 24 months:-0.66 (0.94); p=0.49 57 months: 0.49 (1.25); p=0.70 Motor 24 months:-0.90 (0.92); p=0.33 57 months:-1.89 (1.15); p=0.10 Cord blood Pb levels were not significantly associated	Blood Pb at 24 months was significantly associated with lower GCI scores at age 57 months. Blood Pb at 24 and 57 months were significantly associated with decreased perceptual performance at age 57 months.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						with GCI scores at 57 months of age unless concurrent Pb levels were above 10µg/dL	
Prospective Bellinger (1992) Boston, MA, USA *Population may overlap with Bellinger (1984) and others*	148 middle and upper-middle class children delivered at the Brigham and Women's Hospital from the Boston Lead Study of child development; Year= born between 1979-1980 Male=50.7%	10 years	6 months: 6.7 (7.0) 12 months:7.7 (6.5) 18 months: 7.8 (5.7) 24 months: 6.5 (4.9) 57 months: 6.3 (3.8) 10 years: 2.9 (2.4) Cord blood Pb ≥10µg/dL: 28.6%	Wechsler Intelligence Scale for Children-Revised (WISC-R) and the Kaufman Test of Educational Achievement (K-TEA)	Multiple regression Adjustments include HOME at age 10 and 57 months, family stress, child stress, maternal age, race, birth weight, maternal IQ, SES, sex, birth order, and marital status number of residence changes prior to 57 months, family balance, and parent's sense of competence,	<u>Adjusted regression of WISC-R and K-TEA at age 10 and a 10µg/dL increase in blood Pb at 24 months</u>: coefficient (SE), *P* **Full-Scale IQ: -0.58 (0.21), *P* = 0.007** **Verbal IQ: -0.63 (0.22), *P* = 0.004** Performance IQ: -0.396 (0.23), *P* = 0.091 **K-TEA Battery Composite: -0.89 (0.24), *P* = 0.0003** **Mathematics Composite: -0.91 (0.29), *P* = 0.002** Reading Composite: -0.38 (0.21), *P* = 0.078 **Spelling: -0.97 (0.28), *P* = 0.0008** Blood Pb at birth (Cord: low and med vs. high), 6, 12, 18, and 57 months, and 10 years were not associated with any of the cognitive test scores (all p > 0.05).	Blood Pb at 24 months was significantly associated with lower cognitive test scores at age 10. Cord blood Pb and 5 postnatal blood Pb measures were not significantly associated with any of the cognitive measures.
Prospective Bellinger (1994b) Boston, MA, USA *Population may overlap with Leviton (1993)*	1,782 children born at the Lying-In Division of the Boston Hospital for Women; Year = 1979-1980 Male=50%	8 years	Cord: 6.8 (3.1) Deciduous tooth dentin Pb (µg/g): 3.4 (2.4)	Children's behavior measured using the Teacher Report Form (TRF) of the Child Behavior Profile	Multiple logistic regression Adjustments include pre-pregnant weight, birth weight, race, cesarean section, parental education, sex, parents living together in child's first year, aspirin use in week before delivery, urinary tract infection during pregnancy, current medication use by child, mother smoking during pregnancy, mother married at time of delivery, mother on public assistance at time of delivery, prenatal care begun after first trimester, colic, and sibship size	<u>Adjusted regression for summary T scores associated with each log unit increase in Pb</u>: estimate (95% CI), *p* Cord blood Pb: Total problem behaviors: -0.02 (-1.21, 1.17); *p*=0.98 Internalizing: -0.27 (-1.30, 0.75); *p*=0.60 Externalizing: 0.08 (-0.92, 1.09); *p*=0.87 **Tooth Pb:** **Total problem behaviors: 2.06 (0.93, 3.18) *p*=0.0003** **Internalizing: 1.61 (0.62, 2.60); *p*=0.002** **Externalizing: 1.57 (3.64, 2.50); *p*=0.001** <u>Adjusted Odds Ratio for extreme summary scores associated with a log unit increase in Pb</u>: OR (95% CI) Cord blood Pb: Total problem behaviors: 0.94 (0.63, 1.42), *p*=0.78 Internalizing: 1.06 (0.74, 1.53), *p*=0.74 Externalizing: 0.95 (0.63, 1.43), *p*=0.79 Tooth Pb: Total problem behaviors: 1.42 (0.95, 2.13), *p*=0.092 Internalizing: 1.39 (0.98, 1.97), *p*=0.064 Externalizing: 1.41 (0.94, 2.12), *p*=0.099	Pb levels in primary teeth was significantly associated with internalizing, externalizing and total problem behaviors, but cord blood Pb was not associated. An association between tooth Pb and an extreme problem behavior score was not statistically significant.
Prospective Bellinger (1994a)	79 subjects who were a portion of a	19-20 years	Blood Pb: ≤5	Neuropsychological tests for Children: 1)	Multiple regression analyses	Association with attention factors: *F* (d.f.), *p*-value or coefficient (SE), *p* for individual task results	Dentin Pb levels were

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Boston, MA, USA	cohort of adolescents recruited as first and second graders; Year=dentine collected 1975-1978, blood and bone Pb collected 1989-1990 Male= 43%		Dentin Pb: 13.7 (11.2) µg/g Tibia Pb: 5.4 µg/g Patella Pb: 9.2 µg/g	Encode factor: Digit span subtest of the Wechsler Intelligence Scale for Adults-revised and arithmetic subtest of the Wechsler Intelligence Scale for Adults-revised; 2) Focus-execute factor: Talland Letter Cancellation test, Stroop Color-Word interference Test, digit-symbol subtest of the Wechsler Intelligence Scale for Adults-revised, and Trail-making Test; 3) Sustain factor: A visual Continuous performance Test (CPT); 4) Shift factor: number of errors on the Wisconsin Card Sorting Test, ALA-D isozyme phenotype	Parent IQ, mother's age at the time of child's birth, maternal education, family social class, sex, birth order, current cigarette smoker, current illicit drug use, and current alcohol use	Dentin Pb levels: **Focus-execute factor: 3.15 (4, 53), *p*=0.022** **Shift factor: 8.82 (1, 57) *p*=0.004** Encode factor: 1.26 (2, 56), *p*=0.29 Sustain factor: 1.38 (3, 47), *p*=0.26 Tibia Pb levels: **Focus-execute factor: *p*=0.037** Shift factor: not significant Encode factor: not significant Sustain factor: not significant Patella Pb levels: No significant association with any of the attention factors 5 individuals with the 1-2 ALA-D phenotype (all others 1-1) had mean dentin Pb of 8.0 ppm (vs. 14.1), tibia Pb levels below 6 µg/g (vs. 19.9 % in 1-1), yet all had patella Pb levels above 6µg/g (vs. 43% in 1-1). After adjusting for dentin Pb, the 5 subjects with the 1-2 phenotype had more optimal scores on almost every endpoint, but p-values are not reported due to the limited sample size.	significantly associated with lower scores on two of four attention factors: focus-execute and shift; tibia Pb levels were significantly associated with lower focus-execute factor scores; but patella Pb levels were not associated with any attention factors. A rare ALA-D isozyme phenotype may modify Pb stores and the relationship between tooth Pb and attention.
Cross-sectional Bellinger (2005) Chennai, India	54 children aged 4 to 14 from a rural primary school; Year not stated Male=74.2%	6.7 (2.1) years	11.1 (5.6) µg/dL	Neurobehavioral function: the Binet-Kamath IQ test, the Wide Range Assessment of Visual Motor Activity (WRAVMA), Connor's Behavioral Rating Scale (both parents and teachers).	Linear regression Maternal age, father and mother living together, parents' education, parents' occupation, family income, child's gender, age, class (grade), early feeding method, and birth order.	Regression coefficient for IQ and concurrent blood Pb: Unadjusted: -0.62 (95% CI -1.84, 0.59), *p* = 0.31 Adj. for maternal age: -1.10 (-2.63, 0.44), *p* = 0.16 Adj. for paternal educ.: -0.47 (-1.70, 0.76), *p* = 0.21 [other adjustments were between the 2 above] After adjustment for all covariates: Median value= -0.76 Mean (SD) IQ in highest quartile: 95.6 (12.3) Mean (SD) IQ in lowest quartile: 102.0 (22.5) Regression coefficient for WRAVMA and concurrent blood Pb: Unadjusted: -0.44 (95% CI -1.76, 0.88), *p* = 0.51 [Adjustments ranged between -1.18 (-2.7, 0.34), p=0.12 and -0.32 (-1.64, 0.99), *p* = 0.62] After adjustment for all covariates: Median value= -0.88 Behavior Ratings were not associated with blood Pb.	Concurrent blood Pb was not significantly associated with IQ or WRAVMA composite scores in children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional Bouchard (2009) USA *Population may overlap with Braun (2006)*	1987 adults from NHANES 1999-2004; Year= 1999-2004 Male= 44%	Range = 20 – 39 years	1.61 (1.72) µg/dL Range = 0.3 – 37.3 µg/dL Current blood Pb level measures	Psychiatric Outcomes were assessed using three diagnostic modules of WHO's Composite International Diagnostic Interview: Major Depressive Disorder, Panic Disorder and Generalized Anxiety Disorder.	Linear trend analysis and logistic regression models using $\log_{10}$ transformed blood Pb values. Sex, age, race/ethnicity, education status, poverty to income ratio,	Logistic Regression Analyses by blood Pb quintile: **Major Depressive Disorder (p=0.05 for trend)** 1st (≤7 µg/dL), OR = reference 2nd (0.71-1.0 µg/dL), OR =1.39 (0.71, 2.72) 3rd (1.01-1.4 µg/dL), OR =1.28 (0.69, 2.38) 4th (1.41-2.1 µg/dL), OR =1.41 (0.76, 2.60) **5th (≥2.11 µg/dL), OR =2.32 (1.13, 4.75)** **Panic Disorder (p=0.02 for trend)** 1st (≤7 µg/dL), OR = reference 2nd (0.71-1.0 µg/dL), OR=2.88 (0.72, 11.49) 3rd (1.01-1.4 µg/dL), OR =1.80 (0.44, 7.44) 4th (1.41-2.1 µg/dL), OR =3.13 (0.78, 12.57) **5th (≥2.11 µg/dL), OR = 4.94 (1.32, 18.48)** Generalized Anxiety Disorder (p=0.78 for trend) 1st (≤7 µg/dL), OR = reference 2nd (0.71-1.0 µg/dL), OR =1.26 (0.47, 3.36) 3rd (1.01-1.4 µg/dL), OR =2.25 (0.75, 6.70) 4th (1.41-2.1 µg/dL), OR =2.16 (0.76, 6.09) 5th (≥2.11 µg/dL), OR =1.53 (0.39, 5.96)	Blood Pb was significantly associated with major depression disorder and panic disorder but not generalized anxiety disorder
Prospective Boucher (2009) Quebec, Canada *Population may overlap with Despres (2005)*	104 Inuit children were assessed at 5 years and 201 children were assessed at 11 years from whom umbilical cord blood samples had been obtained in the Cord Blood Monitoring Program(80 children were assessed at both 5 and 11 years) Years=1993-1998 Male= 41% at 5 yrs Male= 45% at 11 yrs	5.4 years (range = 4.8 – 6.2 years) 11.3 years (range = 10.2 – 12.9 years)	Cord blood levels in children assessed at 5 years: 4.9 µg/dL (range = 0.8 – 27.1 µg/dL) Cord blood levels in children assessed at 11 years: 4.8 µg/dL (range = 0.8 – 20.9 µg/dL)	A visual oddball paradigm was used to elicit the P3b wave at 5 years, and an auditory oddball paradigm was used to elicit the P3b wave at 11 years.	Pearson correlations and multiple regression analyses. Maternal non-verbal intelligence, breastfeeding status, Hg levels, hemoglobin, PCB-153 levels, and age at testing, socio-economic status.	Cord blood Pb and P3b parameters: P3b Amplitude at 5 years **Pearson r = -0.38; p≤0.05** **Standardized β = -0.38; p≤0.05** P3b Amplitude at 11 years Pearson *r*= -0.06; p=NS Standardized β= -0.04; p=NS Blood Pb at 5 years and P3b parameters: P3b Latency at 5 years Pearson r =-0.25; p=NS Standardized β = 0.08; p=NS P3b Latency at 11 years Pearson r= 0.07; p=NS Standardized β= 0.00; p=NS	Cord blood Pb was significantly associated with a decrease in P3b amplitude at age 5 years but not at 11 years or P3b latency
Cross-sectional Braun (2006) USA *Population may overlap with Bouchard (2009)*	4,704 participants from NHANES 1999-2002 Years=1999-2002 Male=48%	mean not reported Range = 4 – 15 years 4-6, n=1018 7-9, n=1003	mean not reported 3rd quintile: 1.1-1.3	ADHD: Parent reported previous diagnosis of ADHD use of stimulant medication, prenatal and postnatal tobacco smoke	Logistic regression analysis, Chi-square, multivariable main effects model. Child's age, sex, race, prenatal ETS exposure,	Logistic regression analysis, adjOR (95% CI) for parent-reported ADHD with prescription stimulant use Blood Pb quintiles (µg/dL): 1st quintile (ND-0.70): referent 2nd quintile (0.8-1.0): 1.1 (0.4, 3.4); p=0.804 3rd quintile (1.1-1.3): 2.1 (0.7, 6.8); p=0.195 4th quintile (1.4-2.0): 2.7 (0.9, 8.4); p=0.086	Blood Pb was significantly associated with a parent-reported diagnosis of ADHD in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
		10-12, n=1182 13-15, n=1501		exposure	postnatal ETS exposure, blood Pb levels, preschool or child care attendance, health insurance coverage, and ferritin levels	**5th quartile (>2): 4.1 (1.2, 14.0); p=0.026** Prenatal tobacco smoke exposure No – referent **Yes adjOR = 2.5(1.2,5.2); p=0.020** Postnatal tobacco smoke – smoker in home No – referent Yes adjOR = 0.6(0.3,1.3); p=0.224 Population attributable fraction for parent-reported ADHD and stimulant medication: Blood Pb >2.0 µg/dL: 27.9% exposed; OR=4.1; 21.1% attributable (95% CI 4.7-25.9) = 290,000 excess cases Prenatal tobacco: 30.7% exposed; OR=2.5; 18.4% attributable (95% CI 5.1-24.8) = 270,000 excess cases Blood Pb >2.0 µg/dL AND prenatal tobacco: 46.2% exposed; OR=3.3; 32.2% attributable (95% CI 4.2-41.3) = 480,000 excess cases	children aged 4-15.
Cross-sectional Braun (2008) USA *Population may overlap with Braun (2006)*	3,081 children ages 8-15 years from NHANES; Year=2001-2004; Male=49.2%	8-15 years	mean not reported 1st quartile (22.8%): 0.2-0.7 2nd quartile (23.4%): 0.8-1.0 3rd quartile (21.8%): 1.1-1.4 4th quartile (33%): 1.5-10.0	Conduct disorder (CD) measured by Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV)	Logistic regression Child's age in years, poverty-to-income ratio, maternal age at child's birth, child's sex, child's race, prenatal tobacco smoke exposure, cotinine levels, and blood Pb levels	Adjusted odds ratio for meeting DSM-IV CD criteria by blood Pb levels (quartiles): 1st (0.2-0.7 µg/dL): referent **2nd (0.8-1.0 µg/dL) Adj.OR= 7.24 (1.06-49.47)** **3rd (1.1-1.4 µg/dL) Adj.OR= 12.37 (2.37-64.56)** **4th (1.5-10.0 µg/dL) Adj.OR= 8.64 (1.87-40.04)** Poisson regression analysis for CD symptom count in past year by blood Pb levels (quartiles): 1st (0.2-0.7 µg/dL): referent **2nd (0.8-1.0 µg/dL) Adj.SR=1.55 (1.09, 2.22)** **3rd (1.1-1.4 µg/dL) Adj.SR=1.50 (1.04, 2.17)** **4th (1.5-10.0 µg/dL) Adj.SR (1.23, 2.43)** OR for meeting DSM-IV CD criteria and for CD symptom count in the past year was also significant for prenatal tobacco exposure and serum cotinine in the 4th and 5th quintiles.	Blood Pb was significantly associated with conduct disorder in children aged 8-15.
Prospective Brubaker (2009) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	91 children of participants of the Cincinnati Lead Study (CLS) were followed up as adults Year=1979-1984 Male=43%	22.9 (1.5) years Range = 20.0 – 26.1 years	12.9 (6.2) µg/dL Range = 4.8 – 37.3 µg/dL Exposure measured 23 times during first 6.5 years.	Adult white matter architecture was evaluated using Diffusion Tensor Imaging (DTI).	Multiple regression analysis using a general linear model; simple voxel-wise regressions. Maternal prenatal tobacco and alcohol use, maternal IQ, gestational age, adult marijuana use, age at imaging,	Statistics not reported; authors state the following conclusions: The fractional anisotropy (FA) map Inverse association between FA and blood Pb levels in diffusely scattered white matter regions. The mean diffusivity (MD) map Inverse (corpus callosum), and direct (superior corona radiate) correlations with blood Pb levels. The axial diffusivity (AD) map Inverse association between AD values and blood Pb levels within the anterior and superior corona radiata. The radial diffusivity (RD) map	Blood Pb in children under 6 years of age was associated with changes in white matter microstructure as quantified with diffusivity changes suggestive of altered

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Inverse (corpus callosum and internal capsule) and direct (superior corona radiate) correlations with blood Pb levels.	myelination and axonal integrity.
Prospective Burns (1999) Port Pirie, Australia *Population may overlap with Wigg (1988) and others*	322 children (49% male) living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; re-evaluated at 11-13 yrs of age. Year = 1979-1982 (at baseline)	11-13 years	Lifetime average (geom mean and 95%CI): Boys 14.3 (13.5-15.1) Girls 13.9 (13.2-14.6) Cord blood in this subset: 8.1µg/dL Blood levels at other ages reported in other papers on this cohort. All postnatal exposure measures were qualitatively similar to those reported for lifetime average exposures (data not shown).	Behavior: parents (mothers) completed the Achenbach Child Behavior Checklist and the General Health Questionnaire to assess the parent's psychological adjustment. Family adjustment assessed with the general functioning scale of the McMaster Family Assessment Device. Wechsler Intelligence Scale for Children-Revised (WISC-R) was used to assess each child's intelligence	Multiple linear regression stratified by gender, and multiple logistic regression with a binary outcome variable using the median behavior score Adjusted for maternal age, smoking during pregnancy, birth weight, type of feeding, length of breastfeeding, maternal education, maternal IQ, father's education, maternal psychopathology, birth order, family functioning, father's occupation, parents' smoking habits, marital status, HOME environment, and child's IQ.	Mean behavior problem scores stratified by gender and blood Pb level (µg/dL): ≤15 (SD); >15 (SD); *p* - value **Total, boys: 21.1 (1.9); 28.1 (2.1); *p* < 0.008** **Total, girls: 18.0 (1.7); 29.7 (2.3); *p* < 0.008** Internalizing, boys: 6.4 (0.6); 7.1 (0.7); *p* = 0.45 **Internalizing, girls: 6.1 (0.7); 9.0 (0.8); *p* < 0.008** **Externalizing, boys: 7.4 (0.8); 11.4 (0.8); *p* < 0.008** **Externalizing, girls: 5.8 (0.6); 10.4 (0.8); *p* < 0.008** Change in behavior problem scores from an increase in lifetime blood Pb from 10 to 30µg/dL (at age 11-13): adjusted estimate (95% CI); OR (95% CI) Boys (n=159) **Total problems: 5.2 (0.4, 10.1); 3.2 (1.4, 6.6)** Internalizing problems: 0.8 (-0.9, 2.4); 1.2 (0.6, 2.2) Externalizing problems: **3.5 (1.6, 5.4);** 1.7 (0.8, 3.3) Withdrawn: 0.1 (-0.4, 0.7); 1.5 (0.7, 3.1) Somatic complaints: -0.1 (-0.7, 0.4); 0.8 (0.3, 1.6) Anxious/depressed: 0.8 (-0.2, 1.8); 1.9 (0.9, 4.0) Social problems: 0.4 (-0.2, 1.1); 1.7 (0.8, 3.0) Thought problems: 0.0 (-0.2, 0.3); 1.8 (0.8, 4.0) Attention problems: 0.3 (-0.6, 1.3); 1.2 (0.6, 2.3) **Delinquent behavior: 0.9 (0.3, 1.4); 2.8 (1.4, 5.8)** **Aggressive behavior: 2.7 (1.3, 4.1); 1.9 (1.0, 4.3)** Girls (n=163) **Total problems: 6.2 (1.3, 11.1); 2.8 (1.0, 6.8)** **Internalizing problems: 2.1 (0.0, 4.2); 3.8 (1.4, 11.0)** Externalizing problems: 1.8 (-0.1, 3.7); 2.0 (0.8, 4.6) **Withdrawn: 0.6 (0.0, 1.1); 2.6 (1.0, 6.5)** Somatic complaints: 0.3 (-0.4, 0.9); 1.5 (0.6, 3.3) **Anxious/depressed: 1.3 (0.1, 2.5); 3.1 (1.2, 7.9)** Social problems: 0.3 (-0.3, 0.8); **3.3 (1.2, 9.3)** Thought problems: **0.3 (0.1, 0.5);** insufficient data Attention problems: **1.1 (0.3, 1.8);** 2.0 (0.8, 4.9) Delinquent behavior: 0.2 (-0.1, 0.6); **2.3 (1.0, 5.7)** Aggressive behavior: **1.6 (0.0, 3.2);** 1.9 (0.8, 4.5)	Lifetime average blood Pb in 11-13 year olds was significantly associated with increased total problem behavior scores, with boys having more externalizing behaviors and girls more internalizing behaviors.
Cross-sectional Caffo (2008) DE and NJ, USA	513 former organolead (tetraethyl Pb from 1923-1991; tetramethyl Pb from 1960 to 1983)	60.39 (7.93) in 2001-2003 Range 34.7-78.3	Mean peak tibia Pb: 23.99 (18.46) mg/g Mean time since occupational Pb exposure: 18.01,	Brain volumes were assessed using MRI images. Neurobehavioral and cognitive ability were assessed using: the	A novel statistical strategy was developed by condensing the unmanageable multivariate images with targeted, simpler,	Point estimates (95% CIs) for the association of peak tibia Pb with cognitive domain scores for every µg/g increase in peak tibia Pb: Visuo-construction Gray matter = -3.40 (-8.86, 1.88) White matter = -4.24 (-9.54, 1.06)	Cumulative tibia Pb dose was significantly associated with lower executive

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	manufacturing workers. Years=1994-1997 and 2001-2003 Male=100%		Range 1.5-48.3 years	vocabulary subtest from the Wechsler Adult Intelligence Scale–Revised (WAIS-R); the Rey Auditory Verbal Learning Test (RAVLT); the symbol digit paired associate learning test; the Rey-Osterrieth complex figure, delayed score; the Stroop test; the University of Pennsylvania Smell Identification Test (UPSIT); the finger tapping task; the Purdue pegboard; the Center for Epidemiologic Studies–Depression Scale (CES-D); and the Symptom CheckList-90 (SCL-90).	composite summaries. Adjusted for age, visit number, apolipoprotein E *ε4* allele, Pb exposure duration, education, testing technician, years since last exposure, smoking and alcohol drinking.	Verbal Memory and Learning Gray matter = -2.77 (-6.89, 1.36) White matter = -2.75 (-6.86, 1.35) Visual Memory Gray matter = -1.19 (-5.83, 3.44) White matter = -1.42 (-6.04, 3.19) Executive Function **Gray matter = -5.00 (-8.57, -1.42)** **White matter = -3.79 (-7.40, -0.18)** Eye-hand coordination Gray matter = -3.95 (-8.07, 0.17) White matter = -3.63 (-7.71, 0.45) Processing Speed Gray matter = -1.87 (-5.80, 2.05) White matter = -1.62 (-5.50, 2.26) <u>Estimated proportion of the total effect for the Pb-derived association volumes</u>: Indirect [bootstrap (1,000) estimate±SE (95% CI)]; Direct proportion estimate **Visuo-construction** **Gray matter = 0.31±0.12 (0.16, 0.62); 0.03** **White matter = 0.18±0.06 (0.08, 0.32); 0.01** **Executive Function** **Gray matter = 0.24±0.08 (0.14, 0.44); 0.02** **White matter = 0.15±0.05 (0.07, 0.29); 0.01** **Eye-hand coordination** **Gray matter = 0.19±0.07 (0.09, 0.36); 0.01** **White matter = 0.15±0.05 (0.07, 0.27); 0.01**	function score.
Prospective Canfield (2003a) Rochester, NY, USA Population may overlap with Canfield (2003b) and others	172 children born between July 1994 and January 1995, enrolled when they were 24-30 months old. Year not stated Male=47%	60.6 (1.0) months	Lifetime average = 7.4 (4.3) µg/dL Peak = 11.1 (7.1) µg/dL Concurrent = 5.8 (4.1) µg/dL Exposure measured at 6, 12, 18, 24, 36, 48 and 60 months of age	IQ measured by the Stanford-Binet Intelligence Scale at ages 3 and 5 years	Linear, polynomial, and semi-parametric models; mixed models with regression diagnostics. Childs' sex, birth weight and iron status; mother's IQ, education, race, tobacco use during pregnancy; yearly household income, HOME score.	Changes in IQ for each increase in blood Pb concentration of 1 µg/dL: <u>Lifetime average Pb</u> **at 3 years: β(SE)= -0.35 (0.17); p=0.05** **at 5 years: β(SE)= -0.57 (0.18); p=0.003** **Overall: β(SE)= -0.46 (0.15); p=0.004** <u>Peak Pb</u> At 3 years: β(SE)= -0.19 (0.10); p=0.06 **At 5 years: β(SE)=-0.26 (0.11); p=0.02** **Overall: β(SE)=-0.23 (0.09); p=0.01** <u>Concurrent Pb</u> **At 3 years: β(SE)=-0.31 (0.15); p=0.04** **At 5 years: β(SE)=-0.61 (0.19); p<0.001** **Overall: β(SE)=-0.46 (0.14); p=0.002** <u>Average Pb in Infancy (6-24 months)</u> At 3 years: β(SE)= -0.32 (0.20); p=0.10 **At 5 years: β(SE)= -0.53 (0.20); p=0.01**	Lifetime average and concurrent blood Pb was significantly associated with children's IQ scores at 3 and 5 years of age. Peak blood Pb and average Pb during infancy were significantly associated with overall IQ and IQ at 5 years,

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Overall: β(SE)=-0.43 (0.17); p=0.02	but not IQ at 3 years.
Prospective Canfield (2003b) Rochester, NY, USA Population may overlap with Canfield (2003a) and others	172 participants of an ongoing longitudinal study of the neurobehavioral effects of low-level Pb exposure, recruited as infants from lists of live births at urban hospitals. Year not stated Male= 52%	Tested at 48 months and/or 54 months.	At 48 months = 6.49 µg/dL Exposure measured when outcome assessed	Children performed the Shape School task at 48 and 54 months of age.	Bivariate correlations, general linear mixed model methods. Model covariates included: age, child's sex, birth weight, gestational age, birth order, race, maternal IQ, marital status, maternal education, prenatal smoking, household income, HOME score Model+: augmented base model including rating of attention/task orientation during the test phase and/or rating of color or shape knowledge for the practice phase Model+IQ: augmented base model with child's Stanford-Binet IQ	Efficiency Score – Control **Base Model: β = -0.017 (0.005); p< 0.01** **Model+: β = -0.008 (0.004); p< 0.05** Efficiency Score – Inhibit **Base Model: β = -0.019 (0.006); p< 0.01** Attention/task orientation – Control **Base Model: β = -0.024 (0.011); p< 0.05** Attention/task orientation – Completed Phases **Base Model: β = -0.159 (0.028); p< 0.001** **Model+: = -0.080 (0.021); p< 0.01** **Model+IQ: = -0.062 (0.022); p< 0.01** Attention/task orientation – Color knowledge **Base Model: β = -0.074 (0.014); p< 0.001** **Model+: = -0.027 (0.009); p< 0.01** **Model+IQ: β = -0.025 (0.009)** Attention/task orientation – Shape knowledge **Base Model: β = -0.057 (0.019); p< 0.01** Other models were not statistically significant.	Blood Pb at 48 months was significantly negatively associated with children's focused attention while performing the tasks, efficiency at naming colors, and inhibition of automatic responding
Prospective Canfield (2004) Rochester, NY, USA *Population may overlap with Canfield (2003b) and others*	174 children in an ongoing longitudinal study of the neurobehavioral effects of low-level Pb exposure, enrolled between 5 and 7 months from lists of live births at urban hospitals Year not stated Male = 49.4%	66.7 (1.2) months	6 months: 3.4 24 months: 9.7 60 months: 6.0 Lifetime average at 60 months: 7.2µg/dL Range = 1.4 – 19.9 Assessed semiannually from 6 to 24 months, and annually at 36, 48, and 60 months	Cognitive function as assessed by the Working Memory and Planning Battery of the Cambridge Neuropsychological Testing Automated Battery (CANTAB), tests of spatial working memory, spatial memory span, intradimensional and extradimensional shifts, and an analog of the Tower of London task.	General linear, logistic, and mixed model regressions. Child's IQ, NICU admission, maternal IQ, HOME scores, duration of breastfeeding, cigarette smoking during pregnancy, household income, average moves per year, sex of child, birth weight, maternal ethnicity, marital status, maternal education,	Associations between lifetime average blood Pb concentration and CANTAB outcomes: Big Little Circle task - % correct: **Pearson's *r* = -0.34; p≤ 0.001** **β(SE) = -0.619 (0.17); p≤ 0.001** Spatial Span task – Total non-target errors: **Pearson's *r* = 0.20; p≤ 0.01** **β(SE) = 0.145 (0.036); p≤ 0.001** Spatial Working Memory – Total errors – 6-box problems: **Pearson's *r* = 0.37; p≤ 0.05** **β(SE) = 0.456 (0.179); p = 0.016** Intradimensional and extradimensional shift task – Stages completed: **Pearson's *r* = -0.22; p≤ 0.01** **β (SE) = -0.112 (0.052); p = 0.025**	Children with higher lifetime average blood Pb showed impaired cognitive function on several measures.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
					average crowding in home, first prenatal visit.	Intradimensional and extradimensional shift task – Total trials **Pearson's *r* = 0.28; p≤ 0.01** **β (SE) = 1.40 (0.459); p = 0.003** Stocking of Cambridge task – Mean moves: **β (SE) = 0.050 (0.019); p = 0.009** Stocking of Cambridge task – Mean subsequent planning time – 2-move problems: **Pearson's *r* = 0.35; p≤ 0.001** **β (SE) = 0.142 (0.029); p < 0.001**	
Prospective Cecil (2008) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	157 participants of the Cincinnati Lead Study between the ages of 19 and 24 (1979-1984) Year=2003 Male= 53%	20.8 (0.9) years	Mean of 23 measurements = 13.3 (5.9) µg/dL Range = 4.65–37.2 µg/dL Blood Pb measured every 3 months from birth to first 5 years of life, then every 6 months from 6 to 6.5 years	Global and regional changes in brain tissue were assessed using whole-brain, 3-dimensional, high resolution MRI data.	statistical analysis not reported	Percent gray matter associated with mean childhood blood Pb concentration: **Total: 1.2%; p<0.001** **Male only: 1.7%; p<0.001** Female only: p=NS	Higher mean childhood blood levels were associated with significant decrements in gray matter volume for several cortical areas overall and in males but not females.
Prospective Chandramouli (2009) United Kingdom	582 children from the Avon Longitudinal Study of Parents and Children. Year=Random sample of children born Jun – Dec 1992. Male=57%	Blood Pb measure: 30 months Evaluation of behaviour: 7 and 8 years old	4.22 (3.12) µg/dL Exposure measured at 30 months of age.	Child behavior was assessed using the Strengths and Difficulties Questionnaire, the Development And Well-being Assessment, and the Anti-social Behavior Interview. Attention was measured using the Test of Everyday Attention for Children. The educational performance of the children was captured from the results of the	Regression analyses and ordinal regression. Child's gender and IQ, maternal educational qualification and smoking, paternal socio-economic status at the time of the pregnancy, home ownership, home facilities score at 6 months, Family Adversity Index, parenting attitudes at 6 months.	<u>Regression analyses of the effect of blood Pb levels on:</u> Strengths and Difficulties Questionnaire Teacher: Hyperactivity 2–5 µg/dL, OR = 0.84 (0.47, 1.52) 5–10 µg/dL, OR = 1.25 (0.67, 2.33) **>10 µg/dL, OR =2.82 (1.08, 7.35)(*p*=0.03)** Teacher: Total Difficulties 2–5 µg/dL, OR =1.02 (0.58, 1.79) 5–10 µg/dL, OR =1.30 (0.71, 2.37) **>10 µg/dL, OR =2.69 (1.06, 6.81)(*p*=0.04)** Parent: Hyperactivity 2–5 µg/dL, OR = 0.88 (0.58, 1.78) 5–10 µg/dL, OR = 1.24 (0.79, 1.97) >10 µg/dL, OR = 1.30 (0.62, 2.71) Parent: total difficulties 2–5 µg/dL, OR = 1.13 (0.74, 1.72) 5–10 µg/dL, OR = 1.27 (0.81, 2.01) >10 µg/dL, OR = 1.20 (0.57, 2.51) Development and Well-being Assessment	Blood Pb at 30 months was significantly associated with hyperactivity, as assessed by teachers, antisocial behavior and lower writing and reading scores at 7 to 8 years old.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				national Standard Assessment Tests (SATs).		Activity score 2–5 µg/dL, OR = 0.81 (0.50, 1.29) 5–10 µg/dL, OR = 1.24 (0.77, 2.01) >10 µg/dL, OR = 0.96 (0.44, 2.10) Attention score 2–5 µg/dL, OR = 0.83 (0.52, 1.32) 5–10 µg/dL, OR = 1.28 (0.79, 2.06) >10 µg/dL, OR = 1.15 (0.54, 2.47) Anti-social Behavior Interview Anti-social Activities 2–5 µg/dL, OR = 0.93 (0.47, 1.83) 5–10 µg/dL, OR = 1.44 (0.73, 2.84) **>10 µg/dL, OR = 2.90 (1.05, 8.03)(*p*=0.04)** Test of Everyday Attention for Children Selective attention 2–5 µg/dL, OR = 1.03 (0.66, 1.61) 5–10 µg/dL, OR = 0.99 (0.62, 1.57) >10 µg/dL, OR = 1.14 (0.54, 2.40) Dual attention 2–5 µg/dL, OR = 1.13 (0.66, 1.91) 5–10 µg/dL, OR = 1.22 (0.70, 2.14) >10 µg/dL, OR = 0.48 (0.20, 1.13) Same worlds 2–5 µg/dL, OR = 0.99 (0.64, 1.53) 5–10 µg/dL, OR = 1.31 (0.82, 2.08) >10 µg/dL, OR = 1.48 (0.69, 3.15) Opposite worlds 2–5 µg/dL, OR = 1.29 (0.83, 2.01) 5–10 µg/dL, OR = 1.26 (0.79, 2.03) >10 µg/dL, OR = 1.04 (0.49, 2.21) Standard Assessment Tests Reading 2–5 µg/dL, OR = 0.88 (0.54, 1.43) **5–10 µg/dL, OR = 0.51 (0.32, 0.82); p=0.006** >10 µg/dL, OR = 0.62 (0.28, 1.35) Writing 2–5 µg/dL, OR = 1.08 (0.69, 1.71) **5–10 µg/dL, OR = 0.49 (0.31, 0.78); p=0.003** **>10 µg/dL, OR = 0.44 (0.21, 0.93); p=0.031** Spelling 2–5 µg/dL, OR = 1.41 (0.78, 2.53) 5–10 µg/dL, OR = 0.76 (0.40, 1.42) >10 µg/dL, OR = not reported Mathematics 2–5 µg/dL, OR = 1.38 (0.86, 2.20)	

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						5–10 µg/dL, OR = 0.73 (0.46, 1.15) >10 µg/dL, OR = 0.86 (0.41, 1.81)	
Prospective Chen (2005) USA *Population may overlap with Chen (2007)*	780 children in the Treatment of Lead-exposed Children (TLC) Study who had blood Pb levels of 20-44 µg/dL at age 12-33 months; Year not stated % male not stated	2 to 7 years	Pre-treatment baseline (~age 2): 26.2 (5.1) Age 5: 12 (5.2) Age 7: 8.0 (4.0) Peak (2-7): 30.6 (6.6) Average (age 2 to 5): 17 (5) Average (age 2 to 7): 14.4(4.6) Up to 24 Pb measures: before randomization; on days 7, 28, and 42 after the beginning of each course of treatment; and every 3-4 months after treatment stopped	Intelligence assessed by Bayley Scales of Infant Development (BSID-II) at age 2; the Wechsler Preschool and Primary Scales of Intelligence Scale for Children (WPPSI-R) at 5 years old; and the Wechsler Intelligence Scale for Children at 7 years old.	Multiple linear regression models. Clinical center, race, gender, language, parent's education, parent's employment, single parent, caregiver's IQ, and exact age at both blood Pb measurements.	<u>Adjusted estimates (95% CI) of a 10 µg/dL increase in Pb on change on IQ test scores:</u> **Age 2 Pb and MDI at baseline: - 2.9 (-4.7, -1.0)** **Age 2 Pb and IQ at 5: -2.3 (-4.1, -0.5)** **Age 5 Pb and IQ at 5: -3.5 (-5.3, -1.7)** **Aver. (2-5) Pb and IQ at 5: -2.9 (-4.8, -1.0)** Age 2 Pb and IQ at 7: -1.1 (-2.9, 0.7) **Age 5 Pb and IQ at 7: -2.9 (-4.8, -1.1)** **Age 7 Pb and IQ at 7: -5.4 (-7.8, -2.9)** Peak Pb and IQ at 7: -0.7 (-2.1, 0.7) **Aver. (2-7) Pb and IQ at 7: -3.3 (-5.4, -1.1)** <u>Adjusted estimates (95% CI) of a 10 µg/dL increase in prior and concurrent Pb on change on IQ test scores:</u> Age 2 and Age 5 Pb with IQ at 5: No score adj: 2=-1.2 (-3.1, 0.7); **5=-2.9 (-4.9, -0.9)** Base MDI adj: 2=-0.1 (-1.8, 1.5); **5=-2.4 (-4.1, -0.7)** Age 2 and Age 7 Pb with IQ at 7: No score adj: 2=0.1 (-1.8, 2.0); **7=-5.0 (-7.6, -2.4)** Base MDI adj: 2=-0.4 (-1.4, 2.1); **7=-3.8 (-6.2, -1.4)** Age 5 and Age 7 Pb with IQ at 7: No score adj: 5=-1.2 (-4.1, 1.7); **7=-3.9 (-7.4, 0.0)** Age 5 IQ adj: 5=1.7 (-0.3, 3.6); **7=-3.7 (-6.3, -1.1)** <u>Adjusted estimates of regression coefficients(95% CI) of categorical blood Pb in models for IQ scores</u>: mean; est. IQ at age 5, blood Pb at ages 2 and 5: 2 (Pb<24.9), 5 (Pb<11.4): 83.7; Referent **2 (Pb<24.9), 5 (Pb≥11.4): 78.8; -2.9 (-5.8, 0.1)** 2 (Pb≥24.9), 5 (Pb<11.4): 82.4; 0.4 (-2.5, 3.3) **2 (Pb≥24.9), 5 (Pb≥11.4): 77.6; -4.0 (-6.6, -1.5)** IQ at age 7, blood Pb at ages 2 and 7: 2 (Pb<24.9), 7 (Pb<7.2): 89.3; Referent **2 (Pb<24.9), 7 (Pb≥7.2): 84.6; -3.6 (-6.4, -0.7)** 2 (Pb≥24.9), 7 (Pb<7.2): 88.9; 0.0 (-2.8, 2.7) **2 (Pb≥24.9), 7 (Pb≥7.2): 84.0; -3.7 (-6.2, -1.3)** IQ at age 7, blood Pb at ages 5 and 7: 5 (Pb<11.4), 7 (Pb<7.2): 89.4; Referent 5 (Pb<11.4), 7 (Pb≥7.2): 85.9; -2.3 (-5.9, 1.3) 5 (Pb≥11.4), 7 (Pb<7.2): 88.2; 0.3 (-3.1, 3.7) **5 (Pb≥11.4), 7 (Pb≥7.2): 83.9; -3.8 (-6.0, -1.6)**	Concurrent blood Pb levels were significantly associated with lower intelligence test scores at ages 2, 5, and 7 with the estimates increasing with age. Age 5, but not age 2, blood Pb was significantly associated with lower intelligence test scores at age 7. The authors conclude that peak blood Pb does not fully account for the observed association in older children between their lower blood Pb concentrations and IQ

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Chen (2007) USA *Population may overlap with Chen (2005)*	780 children in the Treatment of Lead-exposed Children (TLC) Study who had blood Pb levels of 20-44 µg/dL at age 12-33 months; Year not stated Male=56%	7 (0.5) years	26 (5.1) µg/dL at baseline (age 2) 12 (5.2) µg/dL at 5-year follow-up 8.0 (4.0) µg/dL at 7-year follow-up Measured at age 2 (baseline), age 5 and age 7	The Connors Parent Rating Scale (CPRS-R) and the Wechsler Preschool and Primary Scales of Intelligence Scale for Children (WPPSI-R) at 5 years old; the Behavior Assessment System for Children teacher rating and parent rating scales (BASC-TRS and BASC-PRS), and the Wechsler Intelligence Scale for Children at 7 years old.	Path (regression) analysis, logistic regression analysis, spline regression. Clinic center, race, sex, language, parent's education, parent's employment, single parent, exact age at blood Pb concentration measurement, caregiver's IQ, (and 7-year IQ in direct effect models only)	Indirect effects of 10 µg/dL blood Pb concentration at age 5 on behavioral test scores (CPRS-R) at age5, adjOR (95% CI): **Oppositional Index: 0.35 (0.02, 0.68); p<0.05** **Hyperactivity Index: 0.34 (0.05, 0.63); p<0.05** ADHD Index: 0.61 (-0.39, 1.61); NS Behavioral Index: 0.44 (-0.46, 1.34); NS After controlling for IQ (direct effect), the none of the associations were significant Indirect effects of 10 µg/dL blood Pb concentration at age 2 on behavioral test scores (CPRS-R) at age5, adjOR (95% CI): **ADHD Index: 0.90; p<0.05** **Behavioral Index: 0.64 (0.23, 1.05); p<0.05** There was no association with Oppositional Index and Hyperactivity Index. After controlling for IQ (direct effect), the none of the associations were significant AdjOR (95% CI) for BASC scores $\geq$ 60 per 10 µg/dL blood Pb concentration at age 7: BASC-TRS Behavioral symptoms = 1.25 (0.90, 1.73); NS **Externalizing problems = 1.42 (1.03, 1.97); p<0.05** Internalizing problems = 1.07 (0.76, 1.52); NS **School problems = 1.39 (1.05, 1.86); p<0.05** BASC-PRS **Behavioral Symptoms = 1.52 (1.13, 2.05); p<0.05** Externalizing problems = 1.27 (0.96, 1.68); NS Internalizing problems = 0.98 (0.69, 1.40); NS Authors state that at age 7 there were no statistically significant direct or indirect effects of blood Pb concentration at age 2 [data not shown].	Concurrent blood Pb was significantly associated with Oppositional and Hyperactivity Indexes at age 5 and Externalizing Problems, School Problems and Behavioral Symptoms at age 7. Blood Pb at age 2 was associated with ADHD and Behavioral Indexes at age 5, but no measures at age 7.
Cross-sectional Chiodo (2004) Detroit, MI, USA *Population may overlap with (Chiodo et al. 2007)*	246 African American inner-city children of mothers recruited while pregnant; Year not stated Male=60%	7.8 (0.3) years (range = 7.2 – 8.9 years).	5.4 (3.3) µg/dL (range = 1 – 25 µg/dL Blood Pb measured at 7.5 years of age	Intelligence was assessed by (WISC-III IQ), reaction time, visual–motor integration (Grooved Pegboard Test), fine motor skills, attention (Mirsky's Attention Battery), and teacher-reported withdrawn behaviors	Nonparametric regression plots, multiple regression analysis, Pearson correlation. Primary caregiver's socioeconomic status, age, marital status, vocabulary, level of depression,	Relation of blood Pb levels to neurobehavioral measures at age 7.5: WISC-III IQ **Full IQ: β = -0.20; p$\leq$ 0.01** **Verbal IQ: β = -0.14; p$\leq$ 0.05** **Performance IQ: β = -0.21; p$\leq$ 0.001** Mirsky's Attention Battery: **CPT – visual, number correct** **β = -0.14; p$\leq$ 0.05** **Working Memory – Seashore rhythm** **β = -0.15; p$\leq$ 0.05**	Blood Pb was significantly associated with lower IQ and multiple other measurements of neuro-behavioral deficits at age 7.5 years.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				(Achenbach Child Behavior Checklist and Barkley-DuPaul Attention Deficit Hyperactivity Disorder Scale).	psychological symptoms (anxiety and hostility); number of children in the household, HOME score, crowded living conditions, disruption in care-giving, Family Environment Scale (FES), Life Events Scale for the primary caregiver (LES) and for the child (LES-C); child's gender and parity.	**Working Memory – WISC-III digit span** **β = -0.13; p≤ 0.05** **Executive Function – Conceptual Level** **β = -0.31; p≤ 0.05** **Executive Function – Conceptual Level** **β = -0.30; p≤ 0.05** Beery Visual – motor integration: **β = -0.20; p≤ 0.01** Matching Familiar Figures – number correct: **β = -0.19; p≤ 0.01** Peg Board – Number of pegs dropped: **β = 0.17; p≤ 0.01** *Mental Rotation – Backward reaction time:* **β = 0.14; p≤ 0.05** Magnitude Est. – Numbers reaction time **β = 0.15; p≤ 0.05** Barkley – DuPaul ADHD Scale: ADHD score **β = 0.16; p≤ 0.05** Inattention factor **β = 0.18; p≤ 0.05** Child Behavior Checklist: Attention **β = 0.15; p≤ 0.05** Thought Problems **β = 0.18; p≤ 0.05** Barkley Direct Observation - Off Task: **β = 0.14; p≤ 0.05**	
Cross-sectional (Chiodo *et al.* 2007) Detroit, MI, USA *Population may overlap with (Chiodo et al. 2004)*	506 African American inner-city children of mothers recruited while pregnant; Year=births between 1989 and 1991 Male=50.8%	7 years	5.0 (3.0) Measured at the 7-year follow-up	Wechsler Primary and Preschool Scale of Intelligence-Revised (WPPSI-R) and the Test of Early Reading Ability; total reading and math scores measured by the Metropolitan Achievement Test; sustained attention by the Conner's Continuous Performance Test (CPT); PROBS-14; Teacher Report Form (TRF); Test of Early	Regression analyses Prenatal drug exposures	Relation between child outcome and Pb (β): PROBS-14 **Central Processing: β=0.18; p<0.001** **Hyperactivity: β=0.13; p<0.01** TRF **Attention problems: β=0.13; p<0.01** Social problems: β=0.10; p<0.10 Delinquent behavior: β=0.09; p<0.10 Total behavior problems: β=0.09; p<0.10 Appropriate behavior: β=-0.09; p<0.10 Hard working: β=-0.10; p<0.10 **Math performance: β=-0.12; p<0.01** Reading performance: β=-0.10; p<0.10 CPT **Reaction time: β=0.15; p<0.001** Conner's Teacher Rating Scale: Attention factor: β=0.12; p<0.10	Blood Pb was significantly associated with neurobehavioral deficits including lower IQ, math scores, and early reading ability and higher central processing, hyperactivity, reaction time, and more attention problems.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				Reading Ability		Impulsivity factor: β= 0.04; NS **Test of early reading ability: β=-0.14; p<0.001** MAT **Math: β=-0.17; p<0.001** Reading: β=-0.06; NS WPPSI **Verbal IQ: β=-0.17; p<0.001** **Performance IQ: β=-0.16; p<0.001** **Full IQ: β=-0.19; p<0.001**	
Cross-sectional Cho (2010) Korea *Second phase of Kim(2009)*	639 third and fourth grade children from schools in each town: Seoul, Ulsan, Incheon, Seongnam, and Yeoncheon; Year = 2008 Male = 52.1%	9.05 (0.72) Range: 8-11	1.9 (0.67)µg/dL Range: 0.53-6.16 Boys: 2.02µg/dL Girls: 1.82µg/dL	Inattention-hyperactivity and neurocognitive profiles: teachers and parents completed the Korean version of the ADHD Rating Scales, and the children performed the Korean Educational Development Institute–Wechsler Intelligence Scales (KEDI-WISC) and a neurocognitive battery consisting of the continuous performance test (CPT), the Children's Color Trails Test (CCTT), and the Stroop Color–Word Test *Also measured urinary cotinine (mean = 5.8ng/mL)*	Linear regression Adjusted for age, gender, paternal education, maternal IQ, child IQ, residential area, and birth weight *Additionally adjusted for urinary cotinine*	<u>Association of ADHD, neurocognition and blood Pb</u>: *ß*, *p* ADHD rating scale **Inattention, teacher: 0.157, *p* < 0.001** **Hyperactivity, teacher: 0.179, *p* < 0.001** **Total, teacher: 0.176, *p* < 0.001** Inattention, parent: 0.056, *p* = 0.249 Hyperactivity, parent: 0.073, *p* = 0.132 Total, parent: 0.067, p = 0.165 Continuous Performance Test Omission errors: 0.035, *p* = 0.457 **Commission errors: 0.093, *p* = 0.044*** ***Adjusted for cotinine: 0.077, *p* = 0.101 Response time: -0.020, *p* = 0.679 Response time variability: 0.055, *p* = 0.239 *When Stroop Word and Color Test Word reading: : 0.037, *p* = 0.421 Color naming: : 0.021, *p* = 0.651 Color−word: : -0.003, *p* = 0.947 Interference: : -0.037, *p* = 0.461 Children's Color Trail Test CCTT-1 total time: : 0.021, *p* = 0.663 CCTT-2 total time: : -0.021, *p* = 0.650 Difference interference: : 0.050, *p* = 0.301 *Adjustment for urinary cotinine did not significantly change Pb results other than CPT commission errors.* *Cotinine was associated with several neurocognitive functions (but not ADHD) after adjustment for blood Pb.*	Concurrent blood Pb was associated with teacher reports of ADHD symptoms including inattention and hyperactivity, but an association with one neurocognition measure was confounded by urinary cotinine. Urinary cotinine was also significantly associated with poorer performance on several measures of cognitive performance after adjusting for blood Pb
Case-control Chuang (2007) Kaohsiung, Taiwan	294 male factory workers (121 with an average hearing threshold over 25 dB and 173 with	39.4 (9.8) years <u>Cases</u>: 44.3 (8.6) years	Geom mean (SD) <u>Cases</u>: 10.662 (0.370) Range: 0.18-96.3	Hearing threshold 16hrs after the end of the last working day	Mann-Whitney nonparametric test <u>Average hearing</u> threshold of each ear:	Pb was higher in the cases, p<0.001 <u>Average hearing threshold and logPb (µg/L)</u>: β (SE), p-value **Right (0.5k+1k+2k)/3: 6.14 (1.40), p<0.001**	Blood Pb levels were higher in cases with hearing loss and positively

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	normal hearing), selected from hospital-based occupational health examinations; Year =2003-2004 Male = 100%	Controls: 35.9 (9.2) years	Controls: 3.902 (0.203) Range: 0.80-47.1 *text and abstract have slightly different values than Table 3 shown here	*Also measured blood Mn, As, and Se*	multiple regression Hearing threshold: mixed regression model Adjusted for age, smoking, alcohol, years exposed to noise, logMn, logAs, and logSe. Mixed model also included left vs right ear and pure tone frequency	**Left (0.5k+1k+2k)/3: 7.99 (1.57) p<0.001** **Right (0.5k+1k+2k+3k+4k+6k)/6: 4.43 (1.54), p=0.004** **Left (0.5k+1k+2k+3k+4k+6k)/6: 6.06 (1.66) p<0.001** Age was significantly positively associated (p<0.001) and logSe was significantly negatively associated (p: 0.113-0.005) in the model Hearing threshold: β (SE), p-value **logPb (µg/L): 7.11 (1.33), p<0.001** **Age (yr): 0.47 (0.07), p<0.001** **logSe (µg/L): -10.83 (5.05), p=0.033**	associated with hearing threshold
Case control Coon (2006) Detroit, MI, USA	121 Parkinson's Disease (PD) patients and 414 age-, sex-, and race-frequency-matched controls from the Henry Ford Health System; Year=1995-1999 Male cases=62.8% Male cont.=54.8%	69.9 (8.2)	Blood Pb: mean not reported Environmental Pb exposure (% of time exposed while at work): High: 90% Moderate: 10-90% Low: <10% Tibia and calcaneal bone Pb (µg/g) Range: 0-200, Lifetime Pb exposure by model including blood and bone Pb	Parkinson's Disease: International Classification of Disease, 9th revision (ICD-9)codes 332 and 332.0	Multiple logistic regression; chi-square Age, sex, race, smoking, and coffee and alcohol consumption	Risk of PD: Adj.OR (95% CI) Whole body lifetime Pb exposure (quartiles) 1st: reference 2nd: 1.90 (0.97, 3.71); p=0.060 3rd: 1.71 (0.86, 3.41); p=0.125 **4th: 2.27 (1.13, 4.55); p=0.021** Tibia (quartiles) 1st: reference 2nd: 0.87 (0.43, 1.75); p=0.691 3rd: 1.33 (0.70, 2.52); p=0.387 4th: 1.62 (0.83, 3.17); p=0.160 Calcaneus (quartiles) 1st: reference 2nd: 1.71 (0.91, 3.20); p=0.094 3rd: 1.12 (0.57, 2.22); p=0.737 4th: 1.50 (0.75, 3.00); p=0.253	The risk of PD in individuals in the highest quartile for lifetime Pb exposure was significantly twices that of individuals in the lowest quartile. There was no association of PD with bone Pb.
Prospective Cooney (1989a) Sydney, Australia *Population may overlap with Cooney (1989b)*	N=215-274 from the Sydney Lead Study; Year=born between 1982-1983 % male not stated	6, 12, 24, and 36 months	Maternal at delivery: 9.1; Range 3-28 (70% ≤ 10µg/dL) Cord: 8.1; range 1-36 (80% ≤ 10µg/dL) Blood also measured in 6, 12, 18, 24, 30, and 36 month s	Development assessed by the Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores of the Bayley Scales of Infant Development at 6, 12 and 24 months, and General Cognitive Index (GCI) score from the McCarthy Scales of Children's Abilities	Multiple regression Maternal age, maternal verbal intelligence, maternal education, maternal smoking, maternal alcohol use, paternal age, paternal education, paternal occupation, birth-weight, gestational age, obstetrical complications, and postnatal factors, and current HOME score	Simple correlation with maternal and cord blood Pb and incremental effect of Pb: mat., cord corr; ΔR^2; *P* 6 months, BSID Mental: -0.044, -0.161; ΔR^2= 0.008; p>0.25 PDI: 0.035,0.025; ΔR^2=0.003; p>0.60 12 months, BSID MDI: 0.015; **0.153 (p<0.05)**; ΔR^2=0.008, p>0.30 PDI: 0.081; **0.167 (p<0.05)**; ΔR^2=0.019; p>0.05 24 months, BSID MDI: 0.006, 0.053; ΔR^2=0.001; p>0.70 PDI: 0.021, -0.060; ΔR^2= 0.013; p>0.20 36 months, MSC GCI: 0.040, 0.045; ΔR^2=0.001; p>0.70 Motor score: 0.015, 0.010; ΔR^2=0.001; p>0.90	Maternal blood and cord blood Pb were not significantly associated with mental or psychomotor developmental deficits at 6, 12, 24, or 36 months.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				and motor subscale at 36 months		No significant relationships were found when four birth outcomes (birth-weight, gestational age, obstetrical complications, and postnatal factors) were regressed on maternal and cord blood Pb levels	
Prospective; Sydney, Australia; Cooney (1989b) *Population may overlap with Cooney (1989a)*	207 children from the Sydney Lead Study Year=born between 1982 and 1983 % male not stated	48 months	Maternal: 9.1(1.3) Cord: 8.1(1.4) 6 months: 15.0 (1.6) 12 months: 15.4 (1.5) 18 months: 16.4 (1.5) 24 months: 15.2 (1.5) 30 months: 12.8 (1.8) 36 months: 12.0 (1.5) 42 months: 10.7 (1.5) 48 months: 10.1 (1.4) Prenatal includes maternal and cord	General Cognitive Index (GCI) score from the McCarthy Scales of Children's Abilities (MSCA) and motor subscale	Correlation, Regression Analysis of covariance (ANCOVA) Gestational age, verbal ability, education of mother, education and occupational status of father, and the HOME total score at 48 months	<u>Correlations between blood Pb and MSCA scores at 48 months:</u> Maternal: GCI r=-0.008; Motor r=-0.029 Cord: GCI r=0.109; Motor r=-0.025 6 months: GCI r=0.080; Motor r=-0.022 12 months: GCI r=0.130; Motor r=0.118 18 months: GCI r=0.050; Motor r=0.057 24 months: GCI r=-0.034; Motor r=-0.040 30 months: GCI r=0.095; Motor r=-0.067 36 months: GCI r=-0.060; Motor r=-0.131 42 months: GCI r=0.030; Motor r=-0.057 48 months: GCI r=-0.028; Motor r=0.005 None of the correlations are significant (p>0.05) Correlations between composite blood Pb levels and MSCA scores at 48 months: 1st yr: **GCI r^2=0.160; p<0.05**; Motor r^2=0.056 2nd yr: GCI r^2=0.016; Motor r^2=0.037 3rd yr: GCI r^2=0.029; Motor r^2=-0.097 4th yr: GCI r^2=-0.010; Motor r^2=-0.026 <u>Adjusted regression of MSCA scores at 48 months on current and previous blood Pb levels</u>: Prenatal: GCI r^2=0.009; p=0.14, Motor r^2=0.002; p=0.55 1st yr: GCI r^2=0.013; p=0.07, Motor r^2=0.001; p=0.67 2nd yr: GCI r^2=0.002; p=0.60, Motor r^2=0.004; p=0.33 3rd yr: GCI r^2=0.003; p=0.76, Motor r^2=0.006; p=0.26 4th yr: GCI r^2=0.001; p=0.76, Motor r^2=0.001; p=0.96 All: GCI r^2=0.0028; p=0.14, Motor r^2=0.018; p=0.56 <u>ANCOVA: Incremental effect of Pb on change in developmental outcome from 36 to 48 months</u>: Current Pb exposure (4th year): GCI r^2=0.004; p=0.36, Motor r^2=0.000; p=0.96 Current and Previous Pb exposure : GCI r^2=0.028; p=0.14, Motor r^2=0.018; p=0.56	Prenatal and postnatal blood Pb was not associated with lower developmental indices at 48 months of age.
Prospective Coscia (2003) Cincinnati, OH USA *Population may overlap with*	196 participants from the Cincinnati Lead Study (CLS) Year=1979-1984 Male= 47%	1st assessment 6.55 (0.12) years 2nd assessment 11.40 (1.04) years	Means over spans: Prenatal: 8.53 (3.90) 1st yr: 10.73 (5.13) 2nd yr: 17.03 (8.13) 3rd yr: 16.25 (7.31) 4th yr: 14.30 (12.02) 5th yr: 12.02 (6.20)	Cognitive development at ages 6.5, 11, and 15 measured by Vocabulary and Block Design and Wechsler Intelligence Scales	Backward Elimination Regression Analysis Fetal distress and growth, perinatal complications, and maternal IQ;	<u>Blood Pb at age 15 years and vocabulary scores at ages 6.5, 11, and 15 years (growth curve analysis)</u>: **Main effect: β (SE)= -4.01 (1.78)** **Linear Effect: β (SE)= 0.95 (0.35)** **Quadratic Effect: β (SE)= -0.05 (0.02)** Other statistically significant covariates retained in the models include: age, birthweight, SES after age 11,	Blood Pb at age 15 was significantly associated with lower verbal comprehension scores and a

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Dietrich (1987) and others		3rd assessment 15.5 (0.85) years	6th yr: 9.78 (5.18) Yrs 1-6: 13.46 (5.87) @ 6.5 yrs: 8.27 (4.67) @ 15 yrs: 2.80 (1.29)	for Children.	socioeconomic status, HOME inventory at 6, 12, 24 and 36 months.	maternal IQ, and HOME score. None of the other Pb measures were statistically significant. None of the Pb measures were statistically significantly related to Block Design Scores.	greater decline in vocabulary development at age 15; blood Pb (at any age) was not associated with perceptual organization test scores
Cross-sectional Counter (2008) Ecuador	166 children aged 6 – 16 years exposed to Pb in a ceramic glazing cottage industry in high altitude villages; Year not stated Male= 49%	[mean age not stated] Range = 6 – 16 years	Blood Pb = 18 (15.1) µg/dL Range 3-86 ZPP/heme ratio = 105.7 (100.9) µmol/mol (normal reference range = 30-69 µmol ZPP/mol heme) Current blood Pb levels	Auditory memory/attention was assessed using the Digit Span subtest of the Wechsler IV intelligence scale.	Student's *t*-test; regression analyses	Correlation between log blood Pb and Digit span scale score: **r = 0.251; p = 0.001** Correlation between logZPP/ heme ratio (a chronic measure of exposure) and Digit span scale score: **r = 0.246; p = 0.001**	Blood Pb and ZPP levels were significantly associated with poor performance on a test of auditory memory.
Cross-sectional Despres (2005) Quebec, Canada *Population may overlap with Boucher (2009)*	110 Preschool Inuit children aged 4 to 6 Nunavik, Quebec; follow-up of the Cord Blood Monitoring Program conducted (1993 – 1996) with no known neurological or developmental disorder, and no severe chronic disease; Year= 4-6 years after 1993-1996 program Male= 45%	5.4 (0.4) years	Cord = 5.0 (4.1) (range = 0.8 - 27.1) *sig. correlation with PCB153 Venous blood at testing = 5.4 (5.0) (range = 1.0 - 37.1) Correlation between cord and age 5 blood Pb: 0.23 (p<0.05)	Motor functions were assessed with quantitative tests for sub-clinical detection of movement disorders: Catsys system measured postural hand tremor, reaction time, and postural sway; the Sway Analysis Test System; Rapid pointing and alternating arm movements Neurological function measured with the Amiel-Tison and Gosselin examination and gross motor	Multiple hierarchical linear regression (p≤0.1 remained in model) Mother's age, socioeconomic status, reproductive history, education, psychological distress, nonverbal reasoning abilities; number of children and adults at home, intra-family violence, HOME Inventory; child's head circumference, height, weight, BMI, duration of breastfeeding, iron deficiency, prenatal exposure to alcohol, illicit drugs or tobacco.	Hierarchical linear regression for neuromotor variables and concurrent childhood Pb*:* Pearson *r*; *β*; Reaction Time (n=93): ***r* = 0.21, p≤ 0.05; *β* = 0.24, p≤ 0.01;** Model included age, HOME, maternal education, breastfeeding, and head circumference **Model *F* = 8.89, p≤0.001**; R^2 = 0.38 Sway (static) Velocity (n=96): ***r* = 0.24, p≤ 0.01; *β* = 0.24, p≤ 0.05** Model included only childhood Pb **Model *F* =5.75, p≤0.05**; R^2 = 0.06 Sway (static) Sagittal (n=97): ***r* = 0.22, p≤ 0.05; *β* = 0.22, p≤ 0.05** Model included only childhood Pb **Model *F* =4.90, p≤0.05**; R^2 = 0.05 Sway (balance) Tandem (sagittal sway) (n=88): ***r* = 0.19, p≤ 0.05; *β* = -0.18 ; p≤ 0.10** Model included weight and maternal education **Model *F* =3.77, p≤ 0.05;** R^2 = 0.12 Sway (balance) Tandem (transversal sway) (n=87): ***r* = 0.22, p≤ 0.05; β = 0.26, p≤ 0.05**	Concurrent blood Pb was significantly associated with changes in reaction time, sway oscillations, alternating arm movements and action tremor, but not gross motor development or neurological function#623.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				functions examined with 10 motor tasks Also measured PCB congeners, aldrin, β-HCH, DDE, DDT, Mirex, Hexachlorobenzene, Chlordane, *Cis*-Nonachlor, *Trans*-Nonachlor, Oxychlordane, and Hg		Model included weight and child PCB153 **Model *F* =4.41, p≤ 0.01;** R^2 = 0.14 Alt. Movements, Coefficient of Variation (n=99): ***r* = 0.24, p≤ 0.01; β = 0.22, p≤ 0.05** Model included alcohol during pregnancy **Model *F* =4.99, p≤ 0.01;** R^2 = 0.09 Alt. Movements, Coherence Between Hands (n=105): ***r* = -0.29, p≤ 0.001; β = -0.29, p≤ 0.01** Model included only childhood Pb **Model *F* =9.65, p≤0.01,** R^2 = 0.09 Alt. Movements, Synkinesis (n=104): ***r* = 0.24, p≤ 0.01; β = 0.23, p≤ 0.05** Model included maternal age and head circumference **Model *F* =4.80, p≤0.01,** R^2 = 0.13 Pointing Movements, Tremor (n=99): ***r* = 0.32, p≤ 0.001; β = 0.24 ; p≤ 0.05** Model included childhood Hg **Model *F* =7.61, p≤0.001,** R^2 = 0.14 Gross motor development and neurological examination were unaffected by prenatal and postnatal Pb exposure (data not shown)	
Prospective Dietrich (1987) Cincinnati, OH, USA *Population may overlap with Dietrich (1990) and others*	266 mothers and 96 children ages 3 to 6 months residing in pre-designated Pb-hazardous areas of Cincinnati Lead Study (CLS) Year=1979-1984 Male= 50.2%	3 and 6 months	Prenatal (maternal): 8.0(3.7) Cord: 6.4(4.5) Maternal exposure measured (1st trimester-50%, 2nd trimester-49%, 3rd trimester-1%); cord measured at birth (cord)	Behavioral development as assessed by the Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores of the Bayley Scales of Infant Development.	Multiple regression Birth weight, gestation, maternal age, child race, child sex, and socioeconomic status	Parameter estimates for fetal Pb exposure variables on MDI and PDI: β (SE) <u>Maternal Prenatal</u> **MDI at 3 months: -0.34 (0.17); p=0.05** **MDI at 6 months - 0.76 (0.34); p=0.02** PDI: No significant effects of prenatal Pb exposure. <u>Cord</u> **MDI at 3 months: -0.60 (0.26); p=0.02** MDI at 6 months: -0.66 (0.37); p = 0.08 PDI: No significant effects of cord Pb exposure	Maternal prenatal blood Pb was significantly associated with deficits in MDI at 3 and 6 months. Cord blood Pb was significantly associated with deficits in MDI at 3 months; Neither was associated with PDI
Prospective Dietrich (1990) Cincinnati, OH, USA	237 2-year old subjects from the Cincinnati Lead Study Cohort; Year=births	24 months	Prenatal (maternal): 8.0 (3.7) 24-month blood Pb: 17.45 (9.16)	Behavioral development as assessed by the Bayley Mental Development Index	Multiple regression analyses Birth weight, gestational age,	<u>Association between blood Pb level and performance on the Bayley MDI at 24 months of age</u>: β(SE) **Maternal prenatal Pb: 0.5058 (0.2188); p=0.0217** 24 months blood Pb: 0.1270 (0.0877); p=0.1490	Prenatal blood Pb levels were significantly associated with MDI scores at

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Population may overlap with Dietrich (1987) and others	between 1979-1984 % male not stated			(MDI).	Obstetrical Complications Scale, Postnatal Complications Scale, child sex, child race, composite index of tobacco and alcohol consumption, maternal age, socioeconomic status, and parity		24-months. Blood Pb at 24 months was not significantly associated with MDI scores.
Prospective Dietrich (1991) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	258 children from the Cincinnati Lead Study (CLS) cohort at age 4; Year=births between 1979-1984 Male= 50.8%;	4 years	Prenatal (maternal blood Pb measured at first prenatal visit): 75% of women= ≤10 Neonatal (10 days old): 75% of newborns=≤7 Postnatal: Mean lifetime blood Pb (quartiles): 1st: 7.9 2nd: 11.4 3rd: 15.2 4th: 23.7	Kaufman Assessment Battery for Children (K-ABC), subscales: Mental Processing Composite standard score (MPC); Sequential Processing standard score (SEQ); Simultaneous Processing standard score (SIM); Non-verbal standard score (NONVB); Achievement standard score (ACHIV)	Backward and forward stepwise multiple regression; bivariate regression Birth weight, maternal cigarette use during pregnancy, maternal marijuana use during pregnancy, child race, and preschool attendance	<u>Regression coefficients for blood Pb indices and K-ABC mental processing subscales and achievement</u>: β <u>MPC</u> Prenatal: 0.11; p=ns **Neonatal*:-0.63; p≤0.01** Postnatal:-0.07; p=ns <u>SEQ</u> Prenatal:0.20; p=ns **Neonatal*:-0.68; p≤0.01** Postnatal: 0.00; p=ns <u>SIM</u> Prenatal: 0.01; p=ns **Neonatal*:-0.50; p≤0.05** Postnatal: -0.12; p=ns <u>NONVB</u> Prenatal:-0.08; p=ns **Neonatal*: -0.63; p≤0.01** Postnatal: -0.0; p=ns <u>ACHIV</u> Prenatal: 0.04; p=ns **Neonatal*: -0.28; p≤0.05** Postnatal:0.07; p=ns *neonatal level by social class interaction model	Blood Pb at 10 days old was significantly associated with cognitive function with a social class interaction.
Prospective Dietrich (1992) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	259 subjects from the Cincinnati Lead Study Cohort; Year=births between 1979-1984 % male not stated	5 years	Maternal prenatal: 8.2 (3.8) Newborn (10 days): 4.8 (3.3) Mean 1st year: 10.6 (5.1) Mean 2nd year: 17.2 (8.4) Mean 3rd year: 16.3 (7.8) Mean 4th year: 14.1 (7.3)	Neurobehavioral assessment: a Screening Test for Auditory Processing Disorders(SCAN) at 57 months including the Filtered Word Subtest (FWS) and the Auditory Figure-Ground Subtest (AFGS) [Left (L), Right (R), and Total(T)] the	Multiple regression SCAN test regression adjustments included hearing screen, social class, HOME scores, birth weight, gestational age, obstetrical complications scale score, and alcohol consumption	<u>Adjusted regression coefficients for blood Pb indices and SCAN subset scores at 57 months</u>: Prenatal (maternal first trimester) blood Pb : FWS(T): -0.12; FWS(L): -0.11; FWS(R): -0.01; AFGS(T):-0.03; AFGS(L):-0.03; AFGS(R): -0.01; Newborn (10 days) blood Pb: FWS(T): -0.26 p≤0.10**; FWS(L): -0.20 p≤0.01;** FWS(T): -0.13 p≤0.10; AFGS(T): -0.17; AFGS(L) -0.13 p≤0.10; AFGS(R): 0.02 Mean 1st year blood Pb : FWS(T): -0.04; FWS(L): -0.00; FWS(R): -0.06; AFGS(T):-0.08; AFGS(L):-0.05; AFGS(R): -0.03;	Prenatal, neonatal, and postnatal blood Pb was significantly associated with poorer central auditory processing abilities at age 57 months; postnatal blood

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
			Mean 5th year: 11.9 (6.4) Blood Pb measured quarterly to age 5	Kaufman Assessment Battery for Children (K-ABC) at 60 months including a mental processing score (MPC), a simultaneous processing standard score (SIM), a sequential processing standard score (SEQ), a Non-verbal standard score (NONVB), and an achievement standard score (ACHIV)	K-ABC test regression adjustments included head circumference at birth, length at birth, cigarette consumption during pregnancy, social class, preschool attendance, maternal intelligence, HOME scores, and maternal age	Mean 2nd year blood Pb : FWS(T): -0.04; FWS(L): 0.00; FWS(R): -0.06 p≤0.10; AFGS(T):-0.01; AFGS(L):-0.01; AFGS(R): 0.01; Mean 3rd year blood Pb : FWS(T): -0.06; FWS(L): -0.01; **FWS(R): -0.07 p≤0.05;** AFGS(T):-0.01; AFGS(L):-0.02; AFGS(R): 0.02; Mean 4th year blood Pb : FWS(T): -0.07; FWS(L): -0.03; FWS(R): -0.05 p≤0.10; AFGS(T):-0.03; AFGS(L):-0.02; AFGS(R): 0.00; Mean 5th year blood Pb : FWS(T): -0.11 p≤0.10; FWS(L): -0.06 p≤0.10; **FWS(R): -0.08 p≤0.05;** AFGS(T):-0.06; AFGS(L):-0.05; AFGS(R): -0.00; Postnatal (mean lifetime) blood Pb: FWS(T): -0.07; FWS(L): -0.02; **FWS(T): -0.07; p≤0.05** AFGS(T): -0.04; AFGS(L): -0.03; AFGS(R): 0.01; <u>Adjusted regression coefficients for blood Pb indices and 5-year K-ABC scales at 60 months</u>: Prenatal (maternal first trimester) blood Pb : MPC: 0.22; SIM: 0.20; SEQ: 0.15; NONVB: 0.10; ACHIV: 0.10; Newborn (10 days) blood Pb: MPC: -0.10; SIM: -0.17; SEQ: -0.08; NONVB: -0.13; ACHIV: 0.01; Mean 1st year blood Pb : MPC: 0.07; SIM: 0.04; SEQ: 0.12; NONVB: 0.04; ACHIV: 0.12; Mean 2nd year blood Pb : MPC: 0.02; SIM: -0.03; SEQ: 0.04; NONVB: 0.02; ACHIV: 0.04; Mean 3rd year blood Pb : MPC: -0.06; SIM: -0.12; SEQ: -0.00; NONVB: -0.07; ACHIV: -0.03; Mean 4th year blood Pb : MPC: -0.12; **SIM: -0.20 p≤0.05**; SEQ: -0.05; NONVB: -0.15 p≤0.10; ACHIV: -0.05; Mean 5th year blood Pb : MPC: -0.13; SIM: -0.20 p≤0.10; SEQ: -0.07; NONVB: -0.15; ACHIV: -0.11; Postnatal (mean lifetime) blood Pb: MPC: -0.06; SIM: -0.13;SEQ: 0.00; NONVB: -0.08; ACHIV: -0.01;	Pb was significantly associated with poorer performance on cognitive development tests at age 60 months; however adjustment for HOME score and maternal IQ weakened the associations and few remained statistically significant.
Prospective Dietrich (1993b) Cincinnati, OH,	253 children follow-up in the Cincinnati Lead Study;	Followed up at 78 (2) months (=6.5 years)	Prenatal (maternal first trimester): 8.3 (3.7)	Full Scale IQ, Performance IQ, and Verbal IQ as assessed	Multiple linear regression with backward and forward	<u>Adjusted regression coefficients for blood Pb and WISC-R scores</u>: FSIQ; PIQ; VIQ *β* (SE) Prenatal: 0.15 (0.21); 0.06 (0.23); 0.16 (0.21);	Postnatal and average lifetime blood

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
USA *Population may overlap with Dietrich (1987) and others*	Year=births between 1979-1984 % male not stated		Newborn (10 days): 5.0 (3.4) Mean 1st year: 10.6 (5.1) Mean 2nd year: 17.1 (8.4) Mean 3rd year: 16.3 (7.7) Mean 4th year: 14.0 (7.2) Mean 5th year: 11.8 (6.3) Blood Pb measured quarterly to age 5	by the Wechsler Intelligence Scale for Children-Revised (WISC-R) full scale IQ (FSIQ), performance IQ (PIQ) and verbal IQ (VIQ)	elimination procedures HOME score, maternal IQ, birth weight, birth length, child sex, and cigarette consumption during pregnancy	Newborn: -0.03 (0.20); -0.22 (0.22); 0.11 (0.21); 1st year: 0.01 (0.14); -0.16 (0.15); 0.12 (0.14); 2nd year:-0.02 (0.08); -0.10 (0.09); 0.02 (0.08); **3rd year:** -0.13 (0.09); **-0.22 (0.10) p<0.05**; -0.04 (0.09) **4th year:** -0.015 (0.10); **-0.27 (0.11) p<0.05**; -0.02 (0.10); **5th year: -0.23 (0.11) p<0.05; -0.38 (0.12) p<0.05**; -0.07 (0.11); **6th year:-0.33 (0.14) p<0.05; -0.52 (0.15) p<0.001**; -0.12 (0.14); **Mean lifetime:** -0.13 (0.11); **-0.26 (0.12) p<0.05**; -0.01 (0.11); Authors state that average lifetime blood Pb > 20µg/dL was associated with deficits in PIQ on the order of approximately 7 points when compared to children ≤ 10µg/dL.	Pb was significantly with performance and full scale IQ at 6.5 years after adjustments including HOME score and maternal IQ.
Prospective Dietrich (1993a) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	245 6-year children enrolled in the Cincinnati Lead Study; Year=births between 1979-1984 Male=50.2%;	6 years	Maternal prenatal blood Pb: 8.4 (3.8) Neonatal (10 day) blood Pb: 4.8 (3.1) 6th year blood Pb: 10.1 (5.6)	Comprehensive and standardized assessment of gross- and fine-motor functioning measured by the Bruinsinks-Oseretsky Test of Motor Proficiency (BOTMP); there are eight subtests: running speed and agility, balance, bilateral coordination, strength, upper-limb coordination, response speed, visual-motor control, and upper=limb speed and dexterity	Forward and backward stepwise multiple regression HOME subscales, maternal IQ, social class, and child sex and race	Regression coefficients for blood Pb indices and BOTMP subscales: <u>Prenatal (maternal first trimester) blood Pb :</u> Bilateral coordination: -0.04 (0.08); ns Visual-motor control: 0.06 (0.08); ns Upper-limb speed and dexterity: -0.20 (0.12); ns Fine motor composite: -0.14 (0.21); ns <u>Newborn (10 day) blood Pb:</u> Bilateral coordination: -0.15 (0.09); ≤0.10 Visual-motor control: -0.10 (0.10); ns **Upper-limb speed and dexterity: -0.45 (0.14); p≤0.01** **Fine motor composite: -0.49 (0.24); p≤0.05** <u>Postnatal (mean lifetime) blood Pb:</u> **Bilateral coordination: -0.11 (0.04); p≤0.01** Visual-motor control: -0.05 (0.05); ns **Upper-limb speed and dexterity: -0.19 (0.07); p≤0.01** **Fine motor composite: -0.28 (0.12); p≤0.05** <u>Current blood Pb:</u> **Bilateral coordination: -0.18 (0.04); p≤0.01** **Visual-motor control: -0.12 (0.05); p≤0.05** **Upper-limb speed and dexterity: -0.31 (0.07); p≤0.01** **Fine motor composite: -0.46 (0.13); p≤0.01**	Blood Pb at 10 days, age 6 years, and mean lifetime blood Pb was significantly associated with several measures of gross and fine-motor functions, but maternal first trimester blood Pb was not.
Prospective Dietrich (2001) Cincinnati, OH, USA *Population may overlap with*	195 urban, inner-city adolescents from the Cincinnati Lead Study (CLS); Years=1997-1999; Male=53%	15.6 (0.8) 15-17 years	Maternal prenatal= 8.9 (3.9) (measured in 1st trimester) [Mean levels by category of average exposure presented	Self-Report of Delinquent Behavior and the Parental Report of Predelinquent and Delinquent Behavior (PRDB) in	Backward elimination and forward inclusion step-wise multiple regression Adjusted for birth weight, mean HOME	<u>Association of blood Pb and Self-Report of Delinquent Behavior at age 15 to 17</u>: β (SE) **Maternal prenatal Pb: β = 0.192 (0.76), p=0.002** **78 months Pb: β = 0.193 (0.061), p=0.002** **Avg Childhood Pb: β = 0.101(0.47), p=0.036** <u>Association of blood Pb and Parental Report of</u>	Maternal prenatal, 78 month, and average childhood blood Pb were significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Dietrich (1987) and others			as a figure (under 10µg/dL at birth, peaking between 18 and 21 month, then decreasing.] Adolescents:2.8 (1.3) Blood Pb measured prenatally (maternal), neonatally (10 days), quarterly to age 5, then at 5.5, 6, and 6.5 years and as adolescents.	adolescence; marijuana use also measured	score, parental IQ and current SES	Predelinquent and Delinquent Behavior at 15-17: β (SE) **Maternal prenatal PbB: β (SE)= 0.194 (0.89), p=0.032** 78 months PbB: β (SE)= 0.131 (0.72), p=0.70 Avg Childhood PbB: β (SE)= 0.090 (0.056), p=0.109 Subjects in the highest prenatal Pb category engaged in 2.3 more delinquent acts in the previous 12 months than those in the lowest category. Subjects in the medium and highest average childhood Pb category engaged in approximately 1.5 more delinquent acts than those in the lower category. Subjects in the highest 78 month Pb category engaged in 4.5 more delinquent acts than those in the lowest category Alcohol and marijuana use were independently associated with delinquent behavior as well. Marijuana was correlated with average childhood Pb: *r* = 0.27, ***P*≤0.05**	associated with an increase in self-reported delinquent behavior at age 15-17; maternal prenatal blood Pb was associated with parental reports of delinquent behavior at 15 to 17.

Prospective Emory (2003) Atlanta, GA, USA	79 urban low-socioeconomic status African-American infants – participants of an ongoing study of Pb exposure;
	Year=2000
	% male not stated
		7 months at assessment	Mean maternal blood Pb:
			0.72 (0.86) µg/dL
			Range 0.05-3.3
			
			Maternal exposure measured around 6-7 months gestation and at delivery
				Cognition in the 7-month-old infants was measured by novelty scores from the Fagan test for Infant Intelligence (FTII)	Chi squared.
					
					covariates not reported
						Mean (SD) maternal blood Pb for FTII novelty score catagories:
						Low Risk (>54.5, n=58): 0.65 (0.80) µg/dL
						Medium Risk (53.1-54.5, n=14): 0.89 (0.88) µg/dL
						High Risk (<53.1, n=7): 1.01 (1.26) µg/dL
						Mean maternal blood Pb level (µg/dL) by FTII percentiles: mean (SD)
						5th percentile: 1.18 (0.74)
						15th percentile: 0.94 (0.26)
						85th percentile: 0.44 (0.15)
						95th percentile: 0.28 (0.34)
						Observed (Expect.) number of subjects by 5th (Low) and 95th (High) percentiles of FTII and maternal blood Pb:
						Low FTII: Low Pb = 0 (2.5); High Pb = 5 (2.5);
						High FTII: Low Pb = 5 (2.5); High Pb = 0 (2.5);
						Chi-squared= 10.00; df = 1; p<0.004
						Observed number of subjects by 15th (low) and 85th (high) percentiles of FTII and maternal blood Pb:
						low FTII: low Pb = 7 (9.5); high Pb = 5 (2.5);
						high FTII: low Pb = 12 (9.5); high Pb = 0 (2.5);
						Chi-squared= 12.33; df = 1; p<0.001
							Maternal prenatal blood Pb levels were significantly associated with lower infant intelligence scores.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Ernhart (1986) Cleveland, OH, USA *Population may overlap with Ernhart (1987) and others*	359 infants whose mothers were recruited on their first antenatal visit to clinics that serve the indigent population of Cleveland, OH; 132 mother-infant pairs for whom both maternal and cord blood Pb data was available Year not stated % male not stated	At birth	Cord (N=162) 5.84 (2.02) Maternal (N=185) 6.48 (1.88)	Apgar assessments; Ballard Assessment of Gestational Age; The Brazelton Neonatal Behavioral Assessment Scale (NBAS); the Graham/Rosenblith Behavioral Examination of the Neonate; and examination for Fetal Alcohol Syndrome and general anomalies	Multiple regression analyses; paired maternal and cord analysis Maternal drinking, maternal smoking in pregnancy	Increments in variance of size, Apgar, and Anomalies Tallies, Pb effect variance: <u>Maternal</u> Head circumference= 0.001; ns Apgar, 1 min= 0.009; ns Apgar, 5 min=0.001; ns Fetal Alcohol Syndrome anomalies=0.005; ns General anomalies= 0.006; ns <u>Cord</u> Head circumference= 0.001; ns Apgar, 1 min= 0.001; ns Apgar, 5 min=0.00; ns Fetal Alcohol Syndrome anomalies=0.005; ns General anomalies= 0.00; ns Increment in variance of neurobehavioral tests, Pb effect variance: <u>Maternal</u> Brazelton Test: Habituation= 0.001; ns Orientation= 0.00; ns Motor performance= 0.002; ns Range of state=0.010; ns Regulation of state=0.001; ns Autonomic regulation=0.001; ns Abnormal reflexes=0.002; ns Graham/Rosenblith Test: General maturation= 0.001; ns Soft signs score= 0.004; ns **Muscle Tonus= 0.024; p=0.035** <u>Cord</u> Brazelton Test: Habituation= 0.00; ns Orientation= 0.004; ns Motor performance= 0.001; ns Range of state=0.00; ns Regulation of state=0.001; ns Autonomic regulation=0.003; ns **Abnormal reflexes=0.033; p=0.023** Graham/Rosenblith Test: General maturation= 0.001; ns **Soft signs score= 0.038; p=0.016** Muscle Tonus= 0.001; ns Increments in variance for 132 paired maternal and	Maternal blood Pb was significantly related to the Muscle Tonus Scale and cord blood Pb was significantly related to the Abnormal Reflexes Scale and the Neurological Soft Sign Scale. In paired maternal and cord blood Pb analysis, the significant association of cord blood Pb and Soft Sign Scale remained.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						cord blood Pb exposure indices <u>Maternal</u> Brazelton Abnormal reflexes=0.001; p=0.717 Graham/Rosenblith Neuro, soft signs= 0.007; p=0.354 Muscle tonus=0.016; p=0.153 <u>Cord</u> Brazelton Abnormal reflexes=0.006; p=0.373 Graham/Rosenblith **Neuro, soft signs= 0.056; p=0.008** Muscle tonus=0.015; p=0.162	
Prospective Ernhart (1987) Cleveland, OH, USA *Population may overlap with Ernhart (1986) and others*	119-145 children whose mothers were recruited on their first antenatal visit to clinics that serve the indigent population of Cleveland, OH; Year not stated Male=51%;	6 months ; 1, 2, and 3 years	Maternal (at delivery): 6.5 (1.8) Cord: 5.99(2.11) Maternal exposure measured at delivery; Exposure measured at birth (cord)	Bayley Mental Development Index (MDI) and Psychomotor Development Index (PDI), and modified Kent Infant Development (KID) scale at 6 months; Bayley MDI at 1 year and 2 years; Stanford-Binet Intelligence scale at 3 years	Multiple regression analyses Age, sex, race, birth weight, birth order, gestational exposure to other toxic substances, maternal intelligence, and several indicators of the quality of the caretaking environment, gestational exposure to alcohol and other toxic substances	<u>Maternal and cord blood Pb with developmental outcomes by incremental regression model</u> (variance): Maternal **6 month MDI: 0.0302; p<0.05** **6 month PDI: 0.0295; p<0.05** **6 month KID: 0.0779; p=0.002** 1 year MDI: 0.0002; p=ns 2 year MDI: 0.0020; p=ns 3 year S-B IQ: 0.0059; p=ns Cord 6 month MDI: 0.0046; p=ns 6 month PDI: 0.0006; p=ns 6 month KID: 0.0107; p=ns 1 year MDI: 0.0146; p=ns 2 year MDI: 0.0003; p=ns 3 year S-B IQ: 0.0125; p=ns Correlation between maternal and cord blood Pb= 0.79	Maternal blood Pb at delivery was significantly associated with MDI,PDI, and KID at six months but not at 1, 2, or 3 years, while cord blood Pb was not associated at any age.
Prospective Ernhart (1988) Cleveland, OH, USA *Population may overlap with Ernhart (1986) and others*	131-167 children whose mothers were recruited on their first antenatal visit to clinics that serve the indigent population of Year not stated % male not stated	6 months, 2 years, and 3 years	6 months: 10.05 (3.28) 2 years: 16.74 (6.50) 3 years: 16.95 (6.49)	Bayley Mental Development Index (MDI) at 6 months, 1 year, and 2 years and Psychomotor Development Index (PDI) at 6 months; Stanford-Binet Intelligence scale at 3 years	Incremental regression model Age at testing, race, sex, birth order, parent education, and 2 maternal tests: the intelligence measure PPVT-R, and Authoritarian Family Ideology (AFI); HOME included at ages 1, 2, and 3 years	Relationship of prior and current blood Pb levels with preschool Bayley MDI, PDI and Stanford-Binet measures of development status by incremental regression model (variance): <u>6 month Blood Pb</u> *6 month MDI:0.01; p=0.31 *6 month PDI:0.01; p=0.32 1 year MDI: 0.01; p=0.25 2 year MDI: 0.00; p=0.95 3 year S-B-IQ: 0.00; p=0.49 <u>2 years Blood Pb</u> 2 year MDI: 0.00; p=0.95 3 year S-B IQ:0.01; p=0.29 <u>3 years Blood Pb</u>	Blood Pb at 0.5, 2, and 3 years was not associated with and concurrent or subsequent development index or IQ scale.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						3 year S-B-IQ: 0.00; p=0.98 *does not include HOME in statistical adjustments	
Prospective Ernhart (1989) Cleveland, OH, USA Population may *overlap with Ernhart (1986) and others*	118-135 children whose mothers were recruited on their first antenatal visit to clinics that serve the indigent population of Cleveland, OH; Year not stated Male=51%;	58.3 (0.4) months	Maternal at delivery: 6.5(1.84) Cord: 5.89(2.10)	Cognitive development as assessed by the Wechsler Preschool and Primary Scale of Intelligence (WPPSI)	Linear regression Sex, race, birth order, birth weight, gestational age at birth, parental education, maternal scores (PPVT-R, AFI, AA/day, Cigs/day, Marijuana, other illicit drugs), HOME Score, Medical Problems, Psychosocial problems	Relationship of cord blood Pb level with WPPSI Scores by incremental regression model: Covariate variance (variance): <u>Maternal (N=135)</u> Full Scale IQ: 0.3746 (0.0008) Verbal IQ: 0.3192 (0.0019) Performance IQ: 0.3603 (0.0026) <u>Cord (N=118)</u> Full Scale IQ: 0.4455 (0.0008) Verbal IQ: 0.3615 (0.0019) Performance IQ: 0.4769 (0.0034)	Cord blood Pb and maternal blood Pb were not significantly associated with full scale or subscale IQ scores.
Prospective Ernhart (1990) Cleveland, OH, USA *Population may overlap with Ernhart (1986) and others*	165 children whose mothers were recruited on their first antenatal visit to clinics that serve the indigent population of Cleveland, OH; Year not stated Male=52%;	4.8 years	<u>Maternal at delivery:</u> Arthim.6.56 (1.81) Geom. 6.3 (1.33) <u>Cord:</u> Arthim. 6.03(2.12) Geom. 5.7 (1.41) <u>6 months:</u> Arthim. 10.05 (3.36) Geom.9.57 (1.36) <u>2 year:</u> Arthim.16.74 (6.50) Geom.15.64 (1.44) <u>3 years:</u> Arthim. 16.68 (5.93) Geom. 15.72 (1.41)	Language and Speech Development using the Sequenced Inventory of Communication Development Expressive and Receptive scores at ages 1, 2, and 3 and Speech Production at age 2 measuring Mean Length of Utterances, Intelligibility, and Spontaneity. Other test batteries included the Bayley MDI Scale at 6 months, 1, and 2 years; Stanford-Binet at 3 years; and the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) at 4 years, 10 months.	Multivariate regression analyses PPVT-R (maternal IQ estimate), race, sex, maternal authoritarianism, parent education, number of older siblings, maternal Michigan Alcoholism Screening Test, maternal average alcohol ounces per day in-pregnancy, cigarettes during pregnancy, prenatal marijuana use, prenatal street drug use, age of child at testing, HOME score, medical problems, and psychosocial stressors	<u>Correlations between language measures and concurrent or prior Pb measures</u>: Pearson; Adj. Partial 1 year Expressive: Maternal (n=145): -0.13; Adj -0.06; Cord (n=127): -0.18 p<0.05; Adj -0.05; 6 month (n=131): -0.08; Adj -0.04; 1 year Receptive: Maternal (n=145): -0.07; Adj +0.03; Cord (n=127): -0.16; Adj -0.06; 6 month (n=131): +0.08; Adj +0.15; 2 year Expressive: Maternal (n=142): -0.12; Adj +0.03 Cord (n=125): -0.07; Adj +0.04; 6 month (n=126): -0.11; Adj -0.12; 2 year (n=165): **-0.16 p<0.05;** Adj -0.03; 2 year Receptive: Maternal (n=142): -0.13; Adj +0.01; Cord (n=125): -0.09; Adj +0.1; 6 month (n=126): -0.04; Adj -0.12; 2 year (n=165): **-0.20 p<0.05;** Adj -0.01; 3 year Expressive: Maternal (n=138): -0.13; Adj +0.07; Cord (n=120): -0.08; Adj -0.06; 6 month (n=126): -0.05; Adj -0.12; 2 year (n=153): **-0.18 p<0.05;** Adj. -0.09; 3 year (n=165): **-0.21 p<0.01;** Adj -0.04; 3 year Receptive: Maternal (n=138): -0.13; Adj +0.04; Cord (n=120): -0.12; Adj -0.09; 6 month (n=126): -0.10; Adj -0.15;	Cord blood Pb was correlated with mean length of utterances at age 2, but all other associations of cognitive function were not associated with blood Pb from any age after adjustment for relative covariates. Authors conclude that this is likely a chance significant finding.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						2 year (n=153): **-0.19 p<0.05;** Adj -0.04; 3 year (n=165): **-0.17 p<0.05;** Adj +0.08; Mean Length of Utterances age 2: Maternal (n=140): -0.11; Adj -0.03; **Cord (n=124): -0.24 p<0.01; Adj -0.21 p<0.05** 6 month (n=124): -0.05; Adj -0.10; 2 year (n=161): -0.18 p<0.05; Adj -0.08; Intelligibility age 2: Maternal (n=140): -0.06; Adj +0.06; Cord (n=124): -0.14; Adj -0.08; 6 month (n=124): -0.09; Adj -0.17; 2 year (n=161): -0.04; Adj +0.04; Spontaneity age 2: Maternal (n=140): +0.05; Adj +0.13; Cord (n=124): -0.03; Adj +0.02; 6 month (n=124): +0.03; Adj +0.02; 2 year (n=161): +0.04; Adj +0.08; Multivariate analysis of 4 sets of language measures and concurrent or prior blood Pb measures with control of cofactors: None of the p values were statistically significant (all p>0.1)	
Prospective Factor-Litvak (1999) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	577 children in Kosovo, Yugoslavia followed from birth to age 10-12 years at 6-month intervals Year=born 1985-1986 % male not stated	7 years	Cumulative (4-7 years) : K. Mitrovica 30µg/dL Pristinia 6.3 µg/dL in	Bayley Scales of Infant Development to assess cognitive function in children up to 2 years; Mental Development Index (MDI) at ages 6, 12, 18, and 24 months; McCarthy Scales of Children's Abilities at age 4 years produced the the General Cognitive Index (GCI) which measures Perceptual Performance, Verbal, Quantitative, Memory, and Motor scales); Wechsler Intelligence Scale for Children-III (WISC III) at age 7 years (measures Total IQ,	Log linear regression model HOME score, ethnic group, maternal age, birth weight, maternal Raven's score, maternal education, birth order, sibship size, sex	Regression of measures of cognitive development and cumulative blood Pb: Bayley Scales of Infant Development (2 yrs of age) **MDI: β(95% CI)= -5.3 (-10.1, -0.5)** McCarthy Scales of Children's Abilities (4 yrs of age) **GCI: β(95% CI)=-9.4 (-14.2, -4.6)** **Perceptual Performance: β(95% CI)=-7.1 (-10.2, -3.9)** **Verbal: β(95% CI)= -2.7 (-5.4, -0.1)** **Quantitative: β(95% CI)= -5.9 (-9.6, -2.3)** **Memory: β(95% CI)= -3.2 (-5.8, -0.5)** **Motor: β(95% CI)= -4.3 (-8.3, -0.3)** WISC III (7 years of age) **Full Scale IQ: β(95% CI)= -9.0 (-12.4, -5.5)** **Performance IQ: β(95% CI)= -9.4 (-13.3, -5.6)** **Verbal IQ: β(95% CI)= -7.1 (-10.5, -3.7)**	Cumulative blood Pb is associated with poorer intellectual function at 2, 4, and 7 years.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				Verbal IQ, and Performance IQ)			
Cross Sectional Fergusson (1988b) New Zealand *Population may overlap with Fergusson (1993) and others*	888 children from the Christchurch Child Development Study (later as the Christchurch Health and Development Study) birth cohort (1977); examined at birth, 4 months, and then annually Year=1985-86 % male not stated	mean not reported 8-9 years	Dentine Pb mean not reported 6.2 (3.70) µg/g; measured at ages 6-8 years from Fergusson (1993)	Behavior measured by Rutter and Conners behavior ratings questionnaires	Bivariate correlations Maternal education, birth placement, child's gender, standard of living, avoidance of punishment, change of parents, changes of school, old weatherboard houses, traffic density, age of tooth, tooth position, sample selection hazard	Correlations between true dentine Pb values and inattentive/restless behavior **8 years: r=0.08; p<0.01** **9 years: r=0.08; p<0.01**	Dentine Pb is significantly correlated with inattention/restlessness at ages 8 and 9 years.
Prospective Fergusson (1993) New Zealand *Population may overlap with (Fergusson et al. 1988b) and others*	690-891 children from the Christchurch Health and Development Study birth cohort (1977); examined at birth, 4 months, and then annually. Year=1989-1990 % male not stated	mean not reported 12-13 years	Tooth (dentine) Pb: 6.2 (3.70) µg/g Measured at ages 6-8 years	Behavior, cognition, and educational outcomes at age 12-13 were measured by measures of word recognition using the Burt Word Reading Test, Reading comprehension by the Progressive Achievement Test (PAT), Measures of Scholastic Abilities (TOSCA), Teachers ratings of school performance, and Rutter and Conners f inattention/restlessness by parent teacher questionnaires.	Multiple regression Maternal education, paternal education, family size, gender, socio-economic status, ethnicity, number of school attended, maternal emotional responsiveness, avoidance of punishment, number of years residence in weatherboard housing	<u>Regression of mean test scores at 12-13 years by dentine Pb levels</u> (6-8 years; dose-response): <u>Standardized tests</u> **Burt (12 years): β=-0.07; p<0.05** Burt (13 years): β=-0.05; p=NS **PAT (12 years): β=-0.06; p<0.10** **TOSCA (13 years): -0.07; p<0.05** <u>Teachers ratings</u> Reading **12 years: β=-0.10; p<0.005** **13 years: β=-0.07; p<0.05** Written expression **12 years: β=-0.11; p<0.001** **13 years: β=-0.08; p<0.01** Mathematics **12 years: β=-0.06; p<0.05** **13 years: β=-0.16; p<0.001** Inattention/restlessness **12 years: β=0.11; p<0.001** **13 years: β=0.06; p<0.05**	Tooth Pb levels taken at 6-8 years had a statistically significant dose-response association with standardized tests of achievement and cognition, teachers' ratings and inattention/restlessness at age 12-13
Prospective Fergusson (1997) New Zealand *Population may overlap with (Fergusson et al. 1988b) and others*	1265 children from the Christchurch Health and Development Study birth cohort (1977); examined at birth, 4 months, annually until age 16 years, and at 18 years Year=1983-1995	6-8; 16-18	Dentine Pb levels at 6-8 years (µg g^{-1}) mean not reported 0-2: N= 91 3-5: N=418 6-8: N=241 9-11: N=87 12+: N=44	Cognitive and Educational Outcomes at age 18 assessed by measures of word recognition using the Burt Word Reading Test, number of years of secondary school education,	Multiple linear Burt Reading Test, number of School Certificate subjects passed; Logistic regression for low reading ability, failure to complete 3 years in high school, leaving school without formal educational	Educational outcomes at 16-18 years by dentine Pb level (µg g^{-1}) at 6-8 years: <u>Mean Burt Word Reading Test score (18 years):</u> 0-2 µg g^{-1}: 99.05 3-5 µg g^{-1}: 98.33 6-8 µg g^{-1}: 97.41 9-11 µg g^{-1}: 96.43 12+ µg g^{-1}: 94.08 **p<0.002** <u>% Scoring below 12-year-old average on Burt Test at 18</u>	Dentine Pb at age 6-8 years was significantly associated with poorer cognitive test scores and academic achievement at

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	% male not stated			mean number of School Certificate passes, and leaving school without formal qualifications	qualifications) Gender, maternal age, maternal education, socioeconomic status, standard of living, duration of breastfeeding, birth order, parental conflict, maternal punitiveness, class level, years lived near busy roads	years: 0-2 µg g^{-1}: 5.3 3-5 µg g^{-1}: 6.3 6-8 µg g^{-1}: 7.8 9-11 µg g^{-1}: 9.7 12+ µg g^{-1}: 16.5 **p<0.001** % Failing to complete 3 years of secondary school 0-2 µg g^{-1}: 6.1 3-5 µg g^{-1}: 6.8 6-8 µg g^{-1}: 7.8 9-11 µg g^{-1}: 9.1 12+ µg g^{-1}: 13.1 **p<0.02** % Leaving school with no qualifications 0-2 µg g^{-1}: 15.6 3-5 µg g^{-1}: 16.7 6-8 µg g^{-1}: 18.1 9-11 µg g^{-1}: 19.7 12+ µg g^{-1}: 24.1 **p<0.05** Mean number of School Certificate passes (C grade or better) 0-2 µg g^{-1}: 3.52 3-5 µg g^{-1}: 3.45 6-8 µg g^{-1}: 3.37 9-11 µg g^{-1}: 3.27 12+ µg g^{-1}: 3.06 **p<0.05**	age 18.
Prospective Fergusson (2008) New Zealand *Population may overlap with (Fergusson et al. 1988b) and others*	1265 children from the Christchurch Health and Development Study birth cohort (1977); examined at birth, 4 months, and then annually or bi annually Year=1991-1998 Male= 51 %	21 years	[mean levels not stated] Dentine Pb levels 0 – 2 µg/g (n=86) 3 – 5 µg/g (n=409) 6 – 8 µg/g (n=231); 9 – 11 µg/g (n=83); 12+ µg/g (n=44) Exposure measured in deciduous teeth collected at age 6-8	History of criminal behavior was based on police records and self-reported offenses.	Negative binomial regression models; pseudo-R^2 statistics Officially reported crime: family socioeconomic status at birth, ethnicity, parental criminal offending, parental alcoholism; intervening factors: leaving school without qualifications, GPA, ages 11-13 Self-reported crime:	Association between dentine Pb levels and officially reported crime (violent/prop. convictions ages 14-21): **B = 0.49 (0.17); p=0.005** Association between dentine Pb levels and self-reported crime: **B = 0.20 (0.10); p=0.047** Association between dentine Pb levels and officially reported crime (violent/prop. convictions ages 14-21) after adjustment for educational factors: **B = 0.41 (0.18); p=0.02** Association between dentine Pb levels and self-reported crime ages 14-21 after adjustment for educational factors: B = 0.07 (0.11); p=0.52	Dentine Pb levels at ages 6-8 were significantly associated with officially reported and self-reported crime from ages 14-21; association with Pb and self-reported crime was not significant after adjustment for

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
					maternal education level, child ethnicity, family conflict, maternal smoking during pregnancy, exposure to childhood physical abuse, parental alcohol problems, parental criminal offending; intervening factors: leaving school without qualification, grade point average at ages 11 – 13 years.	Authors state associations were largely explained by linkages between Pb exposure and educational underachievement.	educational factors.
Cross-sectional Fishbein (2008) Baltimore, MD USA	26 female injection heroin users, at least 18 years old, hepatitis C positive, premenopausal, not pregnant and living in Baltimore Year not stated Male= 0%	42.5 (5.1) years	Tibia Pb: 14.5 µg/g Current Tibia Pb measurement	Cognitive ability measured by The Cambridge Decision Making Task, The Logan Stop-Change Task, and The Stroop Color Word Interference Task.	Univariate distributions; small scale regression analyses; simple correlation analyses; linear regression models.	Tibia Pb concentrations and cognitive data: Cognitive flexibility: p=NS **Risky decisions: p<0.05** Impulsivity: p=NS Interaction effects of tibia Pb and cognitive functioning on frequency of heroin use: **Tibia Pb by cognitive flexibility** **β = -0.80; p=0.007** **Tibia Pb by risky decisions** **β = 0.75; p=0.007** Tibia Pb by impulsivity β=0.06; p=0.75	Tibia Pb concentrations were significantly associated with risky decision making; interactions of tibia Pb with cognitive inflexibility and risky decision making were significantly related to frequency of heroin use
Prospective Froehlich (2007) Rochester, NY USA *Population may overlap with Canfield (2003b) and others*	176 children in Rochester, NY; Year not stated Male = 51%	Enrolled during infancy; assessed at age 5	At 60 months: 6.1 (4.9) µg/dL	Executive function at 66 months from the Cambridge Neuropsychological Testing Automated Battery: spatial working memory (SWM), rule learning and reversal (RLR), spatial span (SS), and planning (P) *Also genotyped DRD4*	Pearson correlation coefficient; Multivariable linear regression Adjusted for income (SWR); neonatal intensive care unit and sex (RLR); HOME score, maternal IQ, and race (SS Span Length); mom's age at delivery, maternal education,	66 month executive function and 60 month blood Pb: *r*, adj*β* (SE) for all subjects without *DRD4* interaction SWM Total Errors: **0.19*,** 0.51 (0.34) SWM Between-Search Errors: **0.19*,** 0.47 (0.32) **RLR Stages Completed: -0.18*, -0.06 (0.03)**** **RLR Total Trials-Adjusted: 0.18*, 2.56 (1.25)**** **SS Span Length: -0.28*, -0.02 (0.1)**** SS Total Errors: 0.07, 0.04 (0.04) P Problems Solved in Min. Moves: **-0.23*,** -0.06 (0.04) **P Mean Moves-3 Move Problem: 0.24*, 0.08 (0.03)**** **p ≤ 0.01 *p ≤ 0.05	Blood Pb was significantly associated with several measures of impaired executive function at age 5. The effects of *DRD4-7* genotype and Pb on executive function were

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				exon III locus	marital status, and span length (SS Total Errors); maternal IQ and transferrin saturation (P Problems Solved in Min. Moves); and in utero tobacco exposure (P Mean Moves-3 Move Problem)	Boys showed more Pb-related impairment than girls (Pb-sex interaction: P Mean Moves p = 0.0008, P Problems Solved p = 0.049) *DRD4*-7 was associated with poorer spatial working memory and more impaired by increasing Pb for RLR.	independent and Pb effects were modified by DRD4 genotype and gender.
Cross-sectional Froehlich (2009) USA *Population may overlap with Braun (2006)*	2588 children from NHANES 2001-2004 Year=2001-2004 % male not stated	[mean age not stated] Range: 8 – 15 years old.	[blood Pb levels for the entire population were not stated] Current blood Pb level measures	ADHD (diagnosed using the National Institute of Mental Health Diagnostic Interview Schedule for Children; a caregiver's report of a previous ADHD diagnosis was also accepted), and prenatal tobacco A secondary outcome variable was created for children who had been treated with ADHD medication in the past year.	Logistic regression analyses; regression diagnostic analyses. Child gender, household income/poverty line ratio, race/ethnicity, mother's age at child's birth, birth weight, NICU admission, postnatal secondhand tobacco smoke exposure, preschool attendance.	AdjOR for ADHD by blood Pb tertile: 1st tertile (0.2-0.8 µg/dL) = 1.0 (reference) 2nd tertile (0.9-1.3 µg/dL) = 1.7 (0.97, 2.9)(*p*=0.06) **3rd tertile (> 1.3 µg/dL) = 2.3 (1.5, 3.8) (p=0.001)** AdjOR for ADHD by prenatal tobacco (Yes/no): No 1.0 (reference) **Yes = 2.4 (1.5, 3.7) (p=0.001)** AdjOR for ADHD by prenatal tobacco and 3rd tertile blood Pb **(> 1.3 µg/dL)**: **8.1(3.5, 18.7) (p=0.001 tobacco-Pb interaction term)**	Blood Pb levels were positively and significantly associated with ADHD in children aged 8 to 15 with significant interaction with prenatal tobacco exposure
Cross-sectional Fulton (1987) Edinburgh, Scotland *Population may overlap with (Thomson et al. 1989)*	501 children recruited from 18 primary schools in classes 3 and 4 in education authority primary schools in central Edinburgh. Year not stated, began in 1982 Male = 52%	6-9 years	Geometric mean: 10.4	British Ability Scales; behavior ratings by parents and teachers including tests to measure cognitive abilities (sampling, visuospatial, perceptual, short-term memory, and language functions) and educational attainment (number concepts and computational ability, and word reading)	Multiple regression analysis Child: age, sex, handedness, standardized height, birth problems score, length of gestation, birthweight, medical history score, days absent from school; Parents: mother's social class, father's social class, mother's qualifications, father's qualifications, father or single mother)	<u>Log blood Pb coefficients for ability and attainment tests</u>: β (SE) **BAS combined score: -3.79 (1.37); p=0.003** **Numbers score:-1.47 (0.83); p=0.039** **Reading score: -3.16 (1.05); p=0.001**	Concurrent blood Pb was significantly associated with lower British Ability Scales combined score, number skills, and word reading at age 6-9 years.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				All raw scores were transformed to give BAS combed scores.	unemployed, mother (or single father) at work, parents' health score, parents' mental health score, smoking, parent's vocabulary, parent's matrices test; Family: family size, birth order, family structure score, parent/child communication, parental involvement with school, child's interest parental participating with child; School: recent change of school, class year, time of day of tests; Household: people per room, car/telephone ownership, consumer goods ownership; Other: school, Pb		
Cross-sectional Gao (2008) China	188 people from 4 rural provinces in a larger cohort of people over 65; Year 2003-2005 Male = 50%	69.2 (4.1) (statistically significantly younger than the cohort without trace elements measured)	3.91 (6.27) µg/dL Range 0.30-39.34 (n=187, one excluded with 125.2µg/dL) *Table lists units as µg/L, but µg/dL is more consistent with measured values)	Cognitive assessment with the Community Screening Instrument for Dementia (CSID), the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning and Recall Tests, and the Indiana University Story Recall, Animal Fluency, and Token tests *Also measured Al, Ca, Cd, Cu, Fe, and Zn and genotyped APOE*	Analysis of Covariance Models (ANCOVA) of the composite z Score Adjusted for age, gender, education, BMI, and *APOE ε4* status	ANCOVA for composite z Score and blood Pb: Estimate: -0.009 (SE 0.008), $p = 0.2496$ Other elements were significantly associated (Ca $p < 0.0001$, Cd $p = 0.0044$, Cu $p = 0.0121$).	Concurrent blood Pb was not significantly associated with a composite cognitive function score in adults.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Glass (2009) Baltimore, MD, USA *Population may overlap with Shih (2006) and others*	1,001 older adults in the Baltimore Memory Study; Year=2001-2005 Male = 34.1%	59.4 (6.0) Range: 50-70	Mean tibia Pb at baseline (2001-2003): 18.8 (11.1) µg/g	Cognitive assessment by 20 tests grouped into 7 cognitive domains: language (Boston Naming, letter fluency, and category fluency), processing speed (simple reaction time), eye-hand coordination (Purdue pegboard, Stroop C form minus A form, and trail-making test A), verbal memory and learning (Rey auditory verbal learning test), visual memory (Rey complex figure recall and symbol digit), and visuoconstruction (Rey complex figure copy). All standardized so a negative coefficient indicates worse performance. *Neighborhood psychosocial hazards (NPH) also measured*	Multilevel hierarchical mixed-effects regression models Adjusted for age, sex, race/ethnicity, education, testing technician, and time of day	Adjusted association of tibia Pb, NPH, and their interaction with cognitive function: β (95%CI) Language (n=998) Tibia main effect: 0.004 (-0.002, 0.011) NPH middle vs low: 0.002 (-0.178, 0.181) NPH high vs. low: 0.105 (-0.086, 0.296) Tibia x Middle NPH: 0.001 (-0.008, 0.009) Tibia x High NPH: -0.009 (-0.017, -0.0001), $P < 0.1$ **X^2 test for Interaction (2 df): 6.5, $P = 0.039$** Processing Speed (n=999) Tibia main effect: 0.007 (-0.001, 0.015) NPH middle vs low: 0.141 (-0.084, 0.366) NPH high vs. low:0.038 (-0.200, 0.276) Tibia x Middle NPH: -0.012 (-0.022, -0.001), $P < 0.1$ Tibia x High NPH: -0.011 (-0.022, -0.0001), $P < 0.1$ X^2 test for Interaction (2 df): 5.4, $P = 0.067$ Eye-Hand Coordination (n=997) Tibia main effect: 0.002 (-0.004, 0.01) NPH middle vs low: 0.016 (-0.163, 0.20) NPH high vs. low: -0.047 (-0.237, 0.14) Tibia x Middle NPH: -0.004 (-0.012, 0.005) Tibia x High NPH: -0.006 (-0.015, 0.002) X^2 test for Interaction (2 df): 2.0, $P = 0.368$ Executive Functioning (n=996) Tibia main effect: 0.004 (-0.003, 0.01) NPH middle vs low: -0.038 (-0.205, 0.13) NPH high vs. low: 0.058 (-0.118, 0.232) Tibia x Middle NPH: -0.002 (-0.010, 0.006) **Tibia x High NPH: -0.010 (-0.018, -0.002), $P < 0.05$** **X^2 test for Interaction (2 df): 7.4, $P = 0.025$** Verbal Learning and Memory (n=997) Tibia main effect: 0.001 (-0.006, 0.01) NPH middle vs low: 0.164 (-0.055, 0.38) NPH high vs. low: 0.118 (-0.115, 0.35) Tibia x Middle NPH: -0.007 (-0.017, 0.004) Tibia x High NPH: -0.006 (-0.016, 0.005) X^2 test for Interaction (2 df): 1.8, $P = 0.407$ Visual Memory (n=997) Tibia main effect: 0.001 (-0.007, 0.01) NPH middle vs low: 0.016 (-0.210, 0.24) NPH high vs. low: 0.061 (-0.180, 0.30) Tibia x Middle NPH: 0.001 (-0.010, 0.011) Tibia x High NPH: -0.007 (-0.018, 0.004) X^2 test for Interaction (2 df): 2.9, $P = 0.235$ Visuoconstruction (n=1,000)	Tibia Pb and high neighborhood psychosocial hazards were significantly associated with impaired executive functioning, with a significant interaction for executive functioning and language scores.

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						Tibia main effect: 0.000 (-0.009, 0.01) NPH middle vs low: 0.149 (-0.089, 0.39) NPH high vs. low: 0.014 (-0.238, 0.27) Tibia x Middle NPH: -0.003 (-0.014, 0.008) Tibia x High NPH: -0.006 (-0.017, 0.005) X^2 test for Interaction (2 df): 1.0, *P* = 0.607	
Cross-sectional Golub (2009) USA	4159 adults (aged 20 and over) from NHANES 2005-6 Year = 2005-2006 Male=48%	46.50 years	1.75 µg/dL	Depression evaluated using the CDC's Patient Health Questionnaire (PHQ-9)	Relative risks were calculated using Poisson regression; odds ratios were calculated with ordinal logistic regression Age, sex, education level, ethnicity, and poverty income ratio.	Blood Pb in relation to depression prevalence (Poisson regression): Continuous Pb, RR = 1.01 (0.96, 1.07) Categorical Pb 0 – 0.88 µg/dL, RR = 1.00 (reference) 0.89 – 1.40 µg/dL, RR = 1.16 (0.99, 1.36) **1.41 – 2.17 µg/dL, RR = 1.20 (1.07, 1.36)** 2.18 – 26.4 µg/dL, RR = 1.16 (0.87, 1.54) Blood Pb in relation to depression prevalence (ordinal logistic regression): Continuous Pb, RR = 1.01 (0.94, 1.09) Categorical Pb 0 – 0.88 µg/dL, RR = 1.00 (reference) 0.89 – 1.40 µg/dL, RR = 1.22 (0.98, 1.51) **1.41 – 2.17 µg/dL, RR = 1.25 (1.07, 1.47)** 2.18 – 26.4 µg/dL, RR = 1.18 (0.83, 1.68)	Blood Pb levels were significantly associated with a higher risk of patient reported depression.
Prospective Gomaa (2002) Mexico City, Mexico *Population may overlap with Hu (2006) and others*	197 mother-infant pairs from the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) sequential birth cohort recruited from 3 low to moderate income hospitals; Year: 1994–1995 Male=54%	24 months	Infant blood Pb: Cord =6.7 (3.4) 12 mo.=7.2(2.8) 24 mo.=8.4(4.6) Maternal (1 month after delivery) Tibia bone: =11.5 (11.0)µg/g Trabecular bone: = 17.9 (5.2)µg/g	Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores as assessed using the Bayley Scales of Infant Development II (BSID-II; Spanish version)	Bivariate analysis and multiple linear regression using forward, backward, and stepwise methods Maternal age, IQ, and education; paternal education; marital status; breastfeeding duration; infant gender; and infant illness	Linear regression of MDI to cord blood Pb or maternal bone Pb β(SE): **Cord blood Pb β= -4.94(2.07); p=0.0179** **Maternal patellar Pb β=-0.16(0.07); p=0.03** 2nd quartile patellar Pb β=-5.25(2.81); p=0.06 **3rd quartile patellar Pb β=-7.66(2.85); p=0.01** **4th quartile patellar Pb β=-7.20(2.88); p=0.01** Maternal tibia Pb β=-0.10(0.10); p=0.30 Cord and patellar combined model Cord blood Pb β= -4.21(2.09); p=0.05 Maternal patellar Pb β=-0.13(0.07); p=0.07 2nd quartile patellar Pb β=-5.05(2.78); p=0.07 **3rd quartile patellar Pb β=-7.32(2.83); p=0.01** **4th quartile patellar Pb β=-6.33(2.88); p=0.03**	Cord blood Pb and maternal patella Pb one month after delivery were significantly associated with the decreased MDI scores but maternal tibia Pb was not.
Prospective Gump (2008) Oswego, NY, USA *Population may overlap with Gump (2009)*	154 children enrolled in the Oswego Children's Study; Year not stated Male=46% (of original 169 participants)	9.5 (0.04)	Range Cord: <1.0 - 6.3 Postnatal (mean age 2.6):1.5-13.1 Quartiles Cord: ≤1.0, 1.1-1.4, 1.5-2.0, 2.1-4.4 Postnatal (mean age	Adrenocortical responses to an acute stressor measured using assays of salivary cortisol before and after standard cold pressor task	Regression (Pb as continuous variable); Test of linear contrast across Pb quartiles Demographics, health/nutrition, infant/birth	Test of linear contrast across quartiles: Initial salivary cortisol: Pre and postnatal Pb exposure p>0.05 Cortisol response to acute stress at 9.5 year of age: **Prenatal Pb –** **cortisol responses p<0.001** **p<0.0001 after adjustment for postnatal Pb** **Postnatal Pb –**	Cord and early childhood blood Pb was significantly associated with increased cortisol response to

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
			2.6):1.5-2.8, 2.9-4.1, 4.2-5.4, 5.5-13.1		characteristics/substance use	**cortisol responses p<0.005** **p<0.05 after adjustment for prenatal Pb** <u>Regression of cortisol reactivity and blood Pb:</u> Prenatal: **21 min (p<0.005); 40 min (p<0.01); 60 min (p<0.05)** Postnatal Pb: **21 min (p<0.05);** 40 min (p<0.10); **60 min (p<0.05)**	acute stress at age 9.5 years.
Prospective Gump (2009) Oswego, NY, USA *Population may overlap with Gump (2008)*	108 children from the Oswego Children's Study; Year not stated % male not stated	9.5	Early childhood (mean age 2.3 years): Range = 1.5 to 13.10 µg/dL	Adrenocortical responses to an acute stressor measured using assays of salivary cortisol before and after standard cold pressor task, mirror tracing task and reaction time	A series of regression analyses Adjustments differ by time point including mother's age, father's age, HOME score, birth weight, head circumference, maternal coffee consumption and other factors	Association between Socioeconomic Status (SES) and cortisol following acute stress, then controlling for blood Pb, and sobel test: Cortisol (full model) **SES→cortisol 4.04; p<0.05** SES(+Pb)→ 1.51; p>0.05**; Sobel test z=2.04; p<0.05** Change at 21 min **SES→cortisol 4.46; p<0.05** SES(+Pb)→ 1.44; p>0.05; Sobel test z=1.64; p<0.1 Change at 40 min SES→cortisol 2.89; p<0.1 SES(+Pb)→ 1.08; p>0.05; Sobel test z=1.50; p>0.05 Change at 60 min SES→cortisol 2.37; p>0.05 **SES(+Pb)→ 0.76; p>0.05; Sobel test z=1.90; p<0.05** Authors state blood Pb was a significant mediator of SES effect on cortisol response to acute stress in full model and at 60 minutes.	Childhood blood Pb was a significant mediator of the association between socioeconomic status and heightened adrenocortical responses to acute stressors at age 9.5 years.
Cross-sectional Groenewold (2007) Louisville, KY, USA	2011 children enrolled in the 3rd grade from Jefferson County Public Schools, Louisville Metro Health Department Year=2003 Male= 47.8%	3rd grade (usually age 8-9)	Mean peak blood Pb: 7.17 (5.01)	Comprehensive Test of Basic Skills (CTBS) portion of the Commonwealth Accountability Testing System	Multiple regression Sex, race, missing race effect, school attendance, individual and area-based SES	Regression of decrements in CTBS scores per 1 µg/dL increase in blood Pb level: β(95% CI) **Total Battery: -0.430 (-0.599, -0.261); p<0.001** **Reading: -0.426 (-0.600, -0.253); p<0.001** **Math: -0.324 (-0.497, -0.151); p<0.001** **Language: -0.435 (-0.600, -0.270); p=0.037**	Blood Pb levels are significantly associated with decreased CTBS scores in the third grade (usually age 8-9).
Cross-sectional Ha (2009) Korea	1778 children in the Children's Health and Environment Research study (CHEER) in South Korea; Year=recruited in 2005 Male=52%	7.1(0.8)	Geometric mean =1.8(1.71) Measured when outcome assessed	ADHD evaluated using abbreviated Conners' scale for ADHD screening (Korean version), blood Hg	Logistic regression Age, gender, household income, parental history of neuropsychiatric disease, and residential area	Multivariate regression of blood Pb and Conners' ADHD score for each 1µg/dL blood Pb: **β= 0.50, p < 0.0001** ADHD symptoms in children with blood Pb: OR (95% CI) <1.0 µg/dL -reference 1-<1.5µg/dL Adj.OR= 1.28 (0.57, 2.86) <2.5 µg/dL Adj.OR= 1.32 (0.63, 2.74) <3.5 µg/dL Adj.OR= 1.65 (0.77, 3.56) >3.5 µg/dL Adj.OR= 1.98 (0.76, 5.13); p- trend =0.07 Blood mercury was not associated with ADHD.	Blood Pb was significantly associated with ADHD screening score, but not specific ADHD symptoms in elementary school children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Hornung (2009) Cincinnati, OH and Rochester NY, USA *Population may overlap with Canfield (2003b) and others*	221 children enrolled in the Cincinnati Pb Study during 1979-1984 and 176 children enrolled in the Rochester Longitudinal Study Year= 1994-1995 Male=51%	6 years	Geometric mean (5^{th} – 95^{th} percentile) Lifetime: 8.5 (3.0-22.1) Peak: 13.6 (4.6-34.4) Early Childhood: 8.9 (3.0-23.8) Concurrent: 6.0 (1.9-17.9) Measured yearly from 1-6 years of age	Cognitive development evaluated using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI) and the Wechsler Intelligence Scale for Children revised (WISC-R)	Multiple regression models Site, average childhood blood Pb, HOME score, birth weight, maternal IQ, maternal education level.	Log-linear relationship between IQ at age 6 and blood Pb level at various ages β (SE): 1 year, β = -0.08 (1.02); *p*=0.934 2 years, β = -0.46 (1.08); *p*=0.670 **3 years, β = -2.61 (1.05); *p*=0.013** **4 years, β = -2.85 (1.07); *p*=0.008** **5 years, β = -4.39 (0.95); *p*<0.001** **6 years, β = -3.49 (1.03); *p*<0.001** Final model for blood Pb and log-linear relationship with age 6 IQ: **6 to 2 year Ratio β = -7.00 (1.54); p<0.001** **Avg. childhood blood Pb β = -3.19 (1.23); *p*=0.010**	Average childhood blood Pb and blood Pb at ages 3, 4, 5, and 6 were significantly associated with lower IQ at age 6.
Case-control Hsieh (2009) Taiwan	22 workers in a Pb paint factory and 18 factory workers that did not use Pb; Year not stated Male = 72-77%	Referents = 46.0 (10.14) years Pb exposed = 45.7 (11.72) years	Blood Referents=3.4(1.1) Pb=16.99 (10.38) Tibia (µg/g) Referent=18.5 (22.4) Pb=61.55 (30.21) Patella (µg/g) Referent=7.14 (9.81) Pb=66.29 (19.48)	Magnetic resonance spectroscopy (MRS) imaging data, brain N-acetyl aspartate (NAA), choline (Cho), and total creatinine (tCr)	*t*-tests, chi-square and Fisher exact tests; multiple linear regressions using standardized regression coefficients. Sex, age, smoking status, alcohol use, work duration, BMI, and betel nut chewing.	Regression coefficients of human brain Cho:tCr ratios with Pb: Frontal lobe gray matter **Blood, β = -0.014 (0.005) (*p*<0.05)** **Patella, β = -0.004 (0.001) (*p*<0.05)** **Tibia, β = -0.004 (0.001) (*p*<0.05)** Occipital lobe gray matter **Blood, β = -0.016 (0.005) (*p*<0.05)** **Patella, β = -0.004 (0.001) (*p*<0.05)** **Tibia, β = -0.004 (0.001) (*p*<0.05)** Occipital lobe subcortical white matter **Blood, β = -0.018 (0.007) (*p*<0.05)** **Patella, β = -0.006 (0.002) (*p*<0.05)** **Tibia, β = -0.004 (0.002) (*p*<0.05)** Occipital lobe white matter **Blood, β = -0.018 (0.007) (*p*<0.05)** **Patella, β = -0.006 (0.002) (*p*<0.05)** **Tibia, β = -0.004 (0.002) (*p*<0.05)** Regression coefficients of human brain NAA:tCr ratios with Pb: Frontal lobe gray matter **Blood, β = -0.023 (0.005) (*p*<0.05)** **Patella, β = -0.004 (0.001) (*p*<0.05)** **Tibia, β = -0.003 (0.001) (*p*<0.05)** Frontal lobe subcortical white matter **Blood, β = -0.011 (0.005) (*p*<0.05)** **Patella, β = -0.003 (0.001) (*p*<0.05)** Tibia, β = -0.004 (0.001) Frontal lobe white matter **Blood, β = -0.015 (0.006) (*p*<0.05)** **Patella, β = -0.004 (0.002) (*p*<0.05)** Tibia, β = -0.001 (0.002) Occipital lobe white matter	Blood and bone Pb levels were significantly associated with altered brain metabolism (decreased NAA:tCr and Cho:tCr ratios) in adults.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Blood, β = -0.018 (0.007) (*p*<0.05) **Patella, β = -0.006 (0.002) (*p*<0.05)** **Tibia, β = -0.005 (0.002) (*p*<0.05)**	
Prospective Hu (2006) Mexico City, Mexico *Population may overlap with Gomaa (2002) and others*	146 infant-mother pairs from the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) sequential birth cohort recruited from 3 low to moderate income hospitals; Year=1997-1999 Male children=76%	24 months Maternal age: 27.1 (5.3)	Whole Blood Pb: 1st tri.= 7.1(5.1) 2nd tri. = 6.1 (3.2) 3rd tri. = 6.9 (4.2) Delivery = 7.3 (4.3) Plasma Pb **(µg/L)**: 1st tri.= 0.16 (0.14) 2nd tri. = 0.14 (0.11) 3rd tri. = 0.16 (0.24) Child blood Pb: Cord = 6.2 (3.9) 12 mon = 5.22 (3.41) 24 mon = 4.79 (3.71)	Bayley Scales of Infant Development Mental Development Index (MDI) at 24 months	Multivariate linear regression Adjusted for infant's concurrent blood Pb (24 months of age), sex, maternal age, current weight, height-for-age Z-score, and maternal IQ	Adjusted single-trimester regression for MDI at 24 months and logPb exposure: β (95% CI); *p*-value Blood Pb in Pregnancy: **1st trimester: -4.13 (-8.10, -0.17); p=0.04** **2nd trimester: -4.08 (-8.29, 0.12); p=0.06** 3rd trimester: -2.42 (06.38, 1.54); p=0.23 Average: -3.52 (-7.66, 0.63); p=0.10 Plasma Pb in Pregnancy: **1st trimester: -3.77 (-7.12, -0.42); p=0.03** 2nd trimester: -2.48 (-5.74, 0.77); p=0.13 3rd trimester: -0.32 (-3.38, 2.74); p=0.83 Average: -3.11 (-6.53, 0.31); p=0.07 Child blood Pb: Cord: -0.35 (-4.7, 4.03) 12 month: -2.38 (-6.24, 1.49); p= 0.23 24 month: -1.00 (-3.93, 1.94); p=0.50 Multivariate model of MDI at 24 months and maternal Pb during pregnancy: *β*; *p*-value Plasma model (R^2 = 0.22) **1st trimester: *β* = -3.54; p = 0.03** 2nd trimester: *β* = 0.80; p = 0.65 3rd trimester: *β* = 1.18; p = 0.44 24 month blood Pb: *β* = -0.01; p = 0.62 Blood model (R^2 = 0.21) 1st trimester: *β* = -2.40; p = 0.19 2nd trimester: *β* = -1.29; p = 0.56 3rd trimester: *β* = 1.42; p = 0.46 24 month blood Pb: *β* = -0.01; p =0.80	Maternal blood Pb in 1st trimester was significantly associated with lower MDI scores in their children at age 24 months.
Cross-sectional Hubbs-Tait (2007) OK, USA *Population may overlap with Hubbs-Tait (2009)*	42 children 3-5 years old, attending rural Head Start centers in northern Oklahoma. Year= 2006; % male not stated	4.92 (0.59)	1.86 (1.24, 2.90)	Teachers rated children's behavior on the California Preschool Social Competency Scale, Howes' Sociability subscale, and the Preschool Behavior Questionnaire; McCarthy Scales of Children's Abilities	Hierarchical regression analyses	McCarthy Scales of Children's Ability Verbal Score β=-0.14 ; p=0.33 McCarthy Scales of Children's Ability Perceptual Score β=-0.13; p=0.41 California Preschool Social Competency (girls) **β= -0.60; p=0.02** Sociable (girls) **β=-0.67; p=0.01** Preschool Behavior Questionnaire Anxious (boys) β= 0.17; p=0.46	Concurrent blood Pb was significantly associated with lower teacher ratings of girls' sociability and classroom social competence at age 3-5 years.
Cross-sectional Hubbs-Tait (2009)	112 children 3-5 years old, attending	4.15 (0.55)	2.10 (1.16)	Cognition was evaluated by	Correlation, ANOVA, hierarchical regression	Correlation of blood Pb and cognition scores PPVT-III r^2=-0.004	Concurrent blood Pb in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
OK, USA *Population may overlap with Hubbs-Tait (2007)*	rural Head Start centers in northern Oklahoma. Year= 2006 Male=52%			Peabody Picture Vocabulary Test–III (PPVT–III) and McCarthy Scales of Children's Abilities (MSCA) test; *Also tested blood Zn and Fe (transferrin receptors)*	child age, parent education, and monthly household income.	MSCA-verbal r^2=0.012 **MSCA-perceptual r^2=-0.241; p<0.01** Hierarchical regression for MSCA-perceptual and blood Pb with home environment-books and library visits (MSCA-verbal and PPVT-III models did not include significant Pb component): **Blood Pb r^2 = 0.36; β=-0.189 (SE=0.75); p<0.05** ANOVA for MSCA-perceptual and blood Pb: <5µg/dL MSCA-P = 45.19 **>5µg/dL MSCA-P = 33.67; p=0.031 to Pb<5** <2.5µg/dL MSCA-P = 46.20 **>2.5µg/dL MSCA-P = 42.29; p=0.048 to Pb<2.5** Authors state MSCA-Verbal and PPVT-III scores were related to iron status and permissive parenting exacerbated negative effects of higher Pb or lower iron	children was significantly associated with lower perceptual cognition scores.
Cross-sectional Hwang (2009) Taiwan	412 steel plant workers in Taiwan (n=17 office workers and n=395 manufacturing workers); Year not stated Male=99.7%	36(6.5)	5.9 (3.4)	Hearing thresholds; *Blood Mn, Cu, Zn, As, Cd also measured*	Logistic regression Age, noise level No effect of gender, cigarette smoking, use of ear protection	<u>Effect of blood Pb on the odds ratio for hearing loss</u> [frequency-OR (95%CI)]: Blood Pb levels ≤4 µg/dL - reference Blood Pb levels 4-7 µg/dL 500-2000 Hz –NA p>0.05 3000 Hz Adj.OR=0.75 (0.17,3.29); p>0.05 4000 Hz Adj.OR=3.54 (1.40, 8.97); p>0.05 6000 Hz Adj.OR=2.11 (0.94, 4.77); p>0.05 8000 Hz Adj.OR=3.0 (0.78, 11.5); p>0.05 Blood Pb levels ≥7 µg/dL 500-2000 Hz –NA p>0.05 **3000 Hz Adj.OR=4.49 (1.28,15.8) p<0.005** **4000 Hz Adj.OR=6.26 (2.35,16.6) p<0.005** **6000 Hz Adj.OR=3.06 (1.27,7.39) p<0.05** **8000 Hz Adj.OR=6.16 (1.59,23.9) p<0.05**	Concurrent blood was significantly associated with hearing loss at sound frequencies of 3000-8000 Hz in steel plant workers.
Prospective Jedrychowski (2008) Krakow, Poland *Population may overlap with Jedrychowski (2009a)*	452 Krakow inner city children born to women attending prenatal clinic in 1st or 2nd trimester; Year=2001-2003 % male not stated	6 months = 26.7(1.6) wks	Cord Pb= 1.42 (0.71)	Cognitive development evaluated using Fagan Test of Infant Intelligence (FTII) assessed visual recognition memory (VRM) by scaled "novelty score": FTII-1=low risk; FTII-2= suspected risk; FTII-3 =high risk	Linear regression; logistic regression; Spearman rank correlation Gestational age, gender of the child, and maternal education	<u>Mean Pb cord blood level by FTII score:</u> Low risk (FTII 1) Pb= 1.38, 95% CI: 1.31-1.45 Suspected risk (FTII 2) Pb= 1.46, 95% CI: 1.26-1.67 High risk (FTII 3) Pb= 1.61, 95% CI: 1.35-1.87 Spearman correlation coefficient for Fagan VRM score and cord blood Pb = **-0.16, p=0.007** <u>FTII higher risk score by cord blood Pb:</u> **Blood Pb (group 3 vs 1and2;continuous by µg/dL):** **Adj. OR (95% CI)= 1.47 (1.07-2.01)** **Blood Pb by 75th percentile (≤1.67 vs >1.67 µg/dL):** **Adj. OR (95% CI)= 2.33 (1.32-4.11)**	Cord blood Pb was significantly associated with lower Fagan visual recognition memory scores and increased scoring in the high-risk group of develop-ment delay in 6-month olds.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Jedrychowski (2009a) Krakow, Poland *Population may overlap with Jedrychowski (2008)*	457 Krakow inner city children born to women attending prenatal clinic in 1st or 2nd trimester; Year=2001-2004 Male =51%	Mother's age: 27.50 (3.52)	Cord: 1.38 (0.59) Girls: 1.41 (0.62) Boys: 1.35 (0.55)	Gender-specific cognitive deficits in first 3 years of life measured by the Bayley Mental Development Index (MDI)	Linear multivariate regression;Generalized Estimating Equations (GEE) longitudinal panel model; Chi-square; analysis of variance Age, gender of child, maternal education, parity, breastfeeding, prenatal and postnatal environmental tobacco smoke	Cord blood Pb level (in quartiles) and MDI scores at 36 months: β (95%CI): Total: 1st: ≤0.99: reference **2nd: 1.00-1.21: -3.494 (-6.214, -0.775); p=0.012** **3rd: 1.22-1.67: -4.459 (-7.223, -1.694); p=0.002** **4th: >1.67: -3.163 (-5.914, -0.412); p=0.024** Boys: 1st: reference **2nd: -5.451 (-9.064, -1.839); p=0.003** **3rd:-8.373 (-12.006, -4.741); p=0.000** **4th: -6.158 (-9.946, -2.370); p=0.002** Girls: 1st: reference 2nd: -1.810 (-5.905, 2.287); p=0.384 3rd: -0.040 (-4.284, 4.203); p=0.985 4th:-0.738 (-4.796, 3.319); p=0.720 Cognitive development of children over follow-up in the GEE models β (95%CI): 1st: reference 2nd: -1.81 (-3.98, 0.35); p=0.100 **3rd: -2.88 (-5.04, -0.71); p=0.009** **4th: -3.00 (-5.22, -0.70); p=0.010** Spearman correlation coefficient at 36 months between cord blood Pb exposure and cognitive function: **Boys: r=-0.239; p=0.0007** Girls: r= -0.058; p=0.432	Cord blood Pb was significantly associated with impaired cognitive function in boys, but not girls.
Prospective Jedrychowski (2009b) Krakow, Poland *Population may overlap with Jedrychowski (2008)*	444 Krakow inner city children born to women attending prenatal clinic in 1st or 2nd trimester; Year= 2001-2004 Male=50.7%	Assessed at 12, 24, 36 months of age	Geometric mean Cord male = 1.30 Cord female =1.28 Cord both = 1.23 Range 0.44-6.9	Mental development assessed using the Bailey Mental Developmental Index (MDI) 2nd edition (BSID-II)	Chi-square, ANOVA, multiple linear regression; generalized estimating equations (GEE) maternal education, parity, gender of child and prenatal ETS exposure	<u>Multiple linear regression for cord blood Pb below <5µg/dL and MDI at various</u> ages: β (95%CI) 12 mo β=-5.42(–11.19, 0.35) p=0.066 **24 mo β=-7.65(–14.68,-0.62)p=0.033** **36 mo β=-6.72(–12.5, -0.89)p=0.024** GEE model of MDI of children from 12-36 months with cord blood Pb <5µg/dL β (95%CI) by log Pb: **β=-6.62 (–1.52, -1.72); p=0.008**	Cord blood Pb was significantly associated with reduced cognitive development (by MDI) at 24 and 36 months.
Prospective Jusko (2008) Rochester, NY, USA *Population may overlap with Canfield (2003b)*	194 children in Rochester, NY; Year = 1994-1995 Male=50%	6	7.2(4.1) avg. 11.4(7.3) peak 5(3.3) 6 yr Exposure assessed at 6, 12, 18 months and 2, 3, 4, 5, and 6 years; Intelligence assessed at 6 years	Intelligence evaluated using Wechsler preschool and primary scale of intelligence-revised (WPPSI-R)	Linear regression Income, sex, mother's education, race, prenatal smoking, birth weight, transferrin saturation, mother's IQ, HOME-SF score	Regression of Blood Pb with WPPSI-R score at age 6: <u>Lifetime average blood Pb</u>: **Full-scale IQ (p-trend =0.006)** **Performance IQ (p-trend =0.002)** Verbal IQ (p-trend =0.11 <u>Concurrent blood Pb (6 years of age):</u> **Full-scale IQ (p-trend =0.03)** **Performance IQ (p-trend =0.004)**	Blood Pb concentrations (concurrent, <24 months, peak, and lifetime average) were significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
and others			of age		Generalized additive model non-linear model for peak blood Pb	Verbal IQ (p-trend =0.28 Infancy blood Pb (6-24 months of age): Full-scale IQ (p-trend =0.05) **Performance IQ (p-trend =0.02)** Verbal IQ (p-trend =0.34) Peak blood Pb: **Full-scale IQ (p-trend =0.03)** **Performance IQ (p-trend =0.02)** Verbal IQ (p-trend =0.19) Children with lifetime average and infancy blood Pb ≥5µg/dL full-scale IQ (4.9 points, p=0.03, 5.2 points, p=0.02 respectively) and performance IQ (4.9 points, p=0.03; 5.4 points, p=0.01 respectively) not verbal IQ (p=0.09, p=0.11 respectively) compared with children with lifetime average blood Pb <5µg/dL. An inverse association (*p* = 0.003) between peak blood Pb levels and full-scale IQ down was supported with nonlinear modeling down to 2.1 µg/dL, the lowest observed peak blood Pb concentration in the study.	associated with decreased full-scale and performance IQ, but not verbal IQ, at age 6.
Case-control Kamel (2002) New England, USA *Population may overlap with Kamel (2003) and others*	109 ALS cases from two major referral centers in Boston, MA and 256 population-based controls (only 41 with Pb measures) identified by random-digit dialing frequency matched by age, sex, and region of residence. Year= 1993-1996 Male= 61%	Range 30-80 Age 30-55 (n=38 cases, 85 controls) Age 56-65 (n=37 cases, 73 controls) Age 66-80 (n=34 cases, 98 controls)	Blood Pb: Median (range) 4.0 (0.5, 14.0) Patella Pb (µg/g): Median (range) 15.0 (0.0, 107) Tibia Pb (µg/g) Median (range) 13.0 (-6.0, 61) Occupational Pb exposure also assessed by self-report (yes/no), and number of days of exposure	Amyotrophic lateral sclerosis (ALS): cases were defined as having received an initial diagnosis by a board-certified neurologist of ALS within the 2 years before enrollment.	Logistic regression Models adjusted for age, square root of age, sex, region, education, and inactivity	Association of self-reported occupational exposure to Pb with ALS: AdjOR (95% CI) Occupational exposure: Not exposed, ref. **Exposed vs: 1.9 (1.1, 3.3)** Lifetime days of Pb exposure: 0 days, ref. 1-399 days: 1.6 (0.6, 3.9) 40-1999 days: 1.9 (0.8, 4.3) **2000+ days: 2.3 (1.1, 4.9)** **Trend: p=0.02** Association of categorical blood and bone Pb with ALS: AdjOR (95% CI) Blood Pb: <1-2 µg/dL, ref. **3-4 µg/dL: 14.3 (3.0-69.3)** **5-14 µg/dL: 24.5 (4.3-139.3)** Patella Pb: -4-9 µg/g, ref. 10-20 µg/g: 2.1 (0.6-7.4) 21-107 µg/g g: 2.8 (0.6-12.4) Tibia Pb: -7-7 µg/g, ref. 8-14 µg/g: 1.6 (0.5-5.6) 15-61 µg/g:1.3 (0.4-4.9) Association of blood and bone Pb as a continuous variable with ALS: AdjOR (95% CI) **Blood Pb: 1.9 (1.4-2.6)** Patella Pb: 3.6 (0.6-20.6) Tibia Pb: 2.3 (0.4-14.5)	Concurrent blood Pb was significantly associated with ALS, while bone Pb associations were not statistically significant. Self-reported occupational exposure to Pb and days of exposure were also significantly associated with ALS.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Case-control Kamel (2003) New England, USA *Population may overlap with Kamel (2002) and others*	103 ALS cases were recruited from two major referral centers in Boston, MA and 38 controls were identified by random-digit dialing frequency matched by age, sex, and region of residence. Year=1993-1996; Male: 61%	mean not reported range 30-80 years	Blood Pb - genotype: *ALAD K59N 1-1*: 3.0 *ALAD K59N 2*: 2.8 *ALAD IVS2 mm*: 2.9 *ALAD IVS2 M*: 2.9 *VDR bb*: 2.9 *VDR B*: 3.0 Patella Pb (µg/g) *ALAD K59N 1-1*: 14.0 *ALAD K59N 2*: 7.3 *ALAD IVS2 mm*: 13.0 *ALAD IVS2 M*: 8.6 *VDR bb*: 12.0 *VDR B*: 12.0 Tibia Pb (µg/g) *ALAD K59N 1-1*: 14.0 *ALAD K59N 2*: 8.6 *ALAD IVS2 mm*: 14.0 *ALAD IVS2 M:* 8.3 *VDR bb:* 13.0 *VDR B:* 13.0	Amyotrophic lateral sclerosis (ALS): cases were defined as having received an initial diagnosis by a board-certified neurologist of ALS within the 2 years before enrollment. Polymorphisms were examined in *ALAD* and *VDR*	Multiple logistic regression Models adjusted for age, square root of age, sex, region, education, and inactivity	Associations of ALS with Pb and genotype: AdjOR (95% CI) **Blood Pb only: 1.9 (1.4-2.6)** **Blood Pb and *ALAD 2*: 2.0 (1.4-2.8)** **Blood Pb and *ALAD I2-2*:1.8 (1.3-2.6)** **Blood Pb and *VDR*: 1.9 (1.4-2.7)** Occupational exposure only: 2.2 (0.68-7.3) Blood and bone Pb only estimates are the same as in (Kamel *et al.* 2002) Patella, Tibia Pb, and occupational exposure to Pb models were not significantly changed with the addition of genotypes to the model None of the genetic polymorphisms were independently associated with ALS alone or in the models with Pb.	The association between concurrent blood Pb was not significantly modified by *ALAD* or *VDR* genotypes, nor were non-significant associations with bone Pb or occupational exposure to Pb.
Case-control Kamel (2005) New England, USA *Population may overlap with Kamel (2002) and others*	103 ALS cases were recruited from two major referral centers in Boston, MA and 38 controls were identified by random-digit dialing frequency matched by age, sex, and region of residence. Year= 1993-1996; % male not stated	mean not reported range 30-80 years	Blood (µg/dL): Case = 5.2 (0.4) Control = 3.4 (0.4) Patella (µg/g): Case = 20.5 (2.1) Control = 16.7 (2.0) Tibia (µg/g): Case = 14.9 (1.6) Control = 11.1 (1.6)	Amyotrophic lateral sclerosis (ALS): cases were defined as having received an initial diagnosis by a board-certified neurologist of ALS within the 2 years before enrollment. Polymorphisms were examined in *ALAD.*	Logistic regression Models adjusted for age, sex, region, education, and inactivity	Complete occupational history of possible Pb exposures generated results virtually identical to the self-reported data in (Kamel *et al.* 2002). Residential and recreational/hobby Pb exposures were not associated with ALS (data not shown). Blood and bone Pb only estimates are the same as in (Kamel *et al.* 2002) *ALAD* polymorphism was not significantly associated with ALS (same results as in (Kamel *et al.* 2003))	Residential and recreational Pb exposures were not associated with ALS. Significant associations of blood Pb and self-reported occupational Pb exposure with ALS were previously reported.
Prospective Kamel (2008) New England, USA *Population may overlap with Kamel (2002) and others*	110 ALS identified through death certificates Year= 1993-1996; Followed for death through 2003 Male= 61%	Median= 60 years Range= 30-79	Median (95% CI): 4.0 (0.5, 14.0)	Amyotrophic lateral sclerosis (ALS) survival: National Death Index Plus and the Social Security Administration Death Index through Dec. 31, 2003.	Cox proportional hazard analysis	Relationship of survival of ALS cases to Pb exposure: AdjHR (95% CI) **Blood Pb** **Diagnosis to death: 0.9 (0.8, 1.0)** **Symptoms to death: 0.9 (0.8, 1.0)** Patella Pb **Diagnosis to death: 0.5 (0.2, 1.0))** Symptoms to death: 0.6 (0.3, 1.2) Tibia Pb	Shorter survival from diagnosis to death had an inverse non-statistically significant association with blood Pb, patella Pb, tibia

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Diagnosis to death: 0.3 (0.1, 0.7) Symptoms to death: 0.3 (0.2, 0.7) Occupational Pb exposure Diagnosis to death: No (referent) Yes: 0.7 (0.5, 1.2) Symptoms to death: No (referent) No: referent Yes: 0.7 (0.4, 1.2)	Pb, and occupational Pb exposure.
Cross-sectional Kim(2009) Korea *Population may overlap with Kim (2010)*	261 children from four areas in Korea (Seoul, Ulsan, Seongnam, and Yeoncheon); Year=2007; % male not stated	9.7 (0.6)	1.73(0.8)	Cognitive function assessed using the abbreviated Korean Educational Development Institute-Wechsler Intelligence Scales (KEDI-WISC), blood Mn	Chi-square, student's t-test, ANOVA, linear and multiple linear regression The age, sex, maternal and paternal education, yearly family income, maternal smoking during pregnancy, birth weight, mother's age at birth, and indirect smoking	Linear regression analysis of blood Pb and IQ: **Full-scale IQ β =-0.174, p = 0.005** **Verbal IQ β = -0.187, p = 0.003** Performance IQ β = --0.104; p = 0.106 Additive interaction of blood Pb and Mn on IQ: Full-scale IQ **Blood Pb β =-0.17; p <0.001** **Blood Mn β =-0.12; p < 0.05** Verbal IQ **Blood Pb β =-0.19; p <0.001** **Blood Mn β =-0.12; p < 0.05** Performance IQ β = --0.104; p = 0.106 Blood Pb β =-0.10; p >0.05 Blood Mn β =-0.08; p > 0.05 Blood Mn was also associated with reduced Full-scale, and verbal IQ measures. Negative effect of Pb on IQ was not observed in children with blood Mn<1.4µg/dL; authors suggest additive interaction and effect modification by blood Pb and Mn.	Concurrent blood Pb was significantly associated with reduced cognitive function at age 9.
Cross-sectional Kim (2010) Korea *Population may overlap with Kim (2009)*	275 third and fourth grade children from one school in each town: Seoul, Seongnam, Ulsan, and Yeoncheon; Year = 2007 Male = 53.1%	9.7 (0.6) years Range: 8-10	All (Geom. mean): 1.5 (SD 1.6) µg/dL Median: 1.6 Range:0.4-4.9 4^{th} quartile > 2.18 Girls (Geom. mean): 1.4 (SD 1.53) µg/dL Range:0.44-3.19 Boys (Geom. mean): 1.7 (SD 1.58) µg/dL Range:0.42-4.91	Inattention-hyperactivity and Neurocognitive profiles: Teachers completed the Attention-Deficit Hyperactivity Disorder Rating Scale IV, Parents completed the Korean version of the Learning Disability Evaluation Scale, and children performed neurocognitive tests: the Continuous Performance Test (CPT), the Children's	Linear regression analysis for log blood Pb Logistic regression analysis for high (>2.18µg/dL) and low (<2.18) Pb levels and *t*-test of difference Adjusted for sex, SES, parental education, secondhand smoke, and smoking during pregnancy	Regression within blood Pb catagories high Pb (≥2.18); low Pb (<2.18): $_{adj}B$ (95% CI) ADHD rating scale Inattention: 1.8 (-1.3, 4.9); **-2.45 (-4.3, -0.6) *p* < 0.01** Hyperactivity: 0.7 (-2.1, 3.5); -1.10 (-2.6, 0.4) Total score: 2.5 (-3.0, 8.0);**-3.54 (-6.7, -0.4) *p* < 0.05** Learning Disability Evaluation Test Listening: -1.0 (-2.4, 0.3); 0.56 (-0.1, 1.3) Thinking: -0.8 (-1.9, 0.4);**0.62 (-0.01, 1.2) *p* < 0.05** Talking: -1.0 (-2.4, 0.3); **0.89 (0.2, 1.6) *p* < 0.01** **Reading: -1.6 (-3.0, -0.2) *p*<0.05; 0.9 (0.1, 1.7) *p*<0.05** Writing: -1.2 (-2.6, 0.2); **0.98 (0.2, 1.7) *p* < 0.01** Spelling: -1.4 (-2.9, 0.1); **0.89 (0.1, 1.7) *p* < 0.05** **Calcul.: -1.6 (-2.9, -0.2) *p*<0.05; 0.82 (0.1, 1.6) *p*<0.05** Visual Continuous Performance Test **Omission errors: 15.5 (1.1, 29.8) *p* < 0.05; -8.38 (-16.2, -0.6) *p* < 0.05** Commiss. errors: -3.5 (-20.2, 13.3); -2.99 (-10.6, 4.6)	Concurrent blood Pb was significantly associated with inattentive and hyperactivity symptoms and learning difficulties in 8-10 year old children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				Color Trails Test, and the Stroop Color and Word Test.		Reaction time: 4.0 (-4.8, 12.8); -1.11 (-4.9, 2.6) React time var.: 1.6 (-19.8, 23.0); -5.08 (-14.7, 4.5) Children's Color Trail Test CCTT-1 total time: 4.4 (-7.6, 16.4); not reported CCTT-2 total time: -1.1 (-7.8, 5.6); not reported Difference interference: 0.2 (-5.9, 6.4); 1.78 (-1.4, 4.9) Stroop Word and Color Test Word reading: -2.9 (-8.8, 3.0); not reported Color naming: -5.2 (-11.8, 1.4); not reported Color–word: -7.2 (-14.2, -0.3) $p < 0.05$; not reported Interference: -1.2 (-9.0, 6.5); -1.03 (-4.4, 2.2)	
Cross-sectional Kordas (2004) Torreón, Mexico *Population may overlap with Kordas (2006) and others*	724 children attending first grade at one of 9 public school and living near a metal foundry in Mexico; Year=2001 Male=54%	Range = 6.2 to 8.5 years	11.5 (6.1) µg/dL	Cognitive outcomes were measured using 14 tasks designed to assess specific and global aspects of cognition: Cognitive Abilities Test (CAT), the Wechsler Intelligence Scale for Children-Revised Mexican Version (WISC-RM) Coding, Digit Retention and Arithmetic; Number and Letter Sequencing, a computer-based Test of Cognitive Abilities, Math Achievement Test, a Test of Visual-Spatial Abilities and the Peabody Picture Vocabulary Test (PPVT)	Multiple regression models; regression coefficients Gender, age, socioeconomic status, school, Hb, ZPP, and Ferritin	Multiple regression models of concurrent blood Pb and PPVT performance in the first-grade: **β=-0.371; p=0.005**	Blood Pb was significantly associated with the lower PPVT scores in children 6-8 years old.
Cross-sectional Kordas (2006) Torreón, Mexico *Population may overlap with Kordas (2004) and*	532 children attending first grade at one of 9 public school and living near a metal foundry in Mexico; Year= 2001	Range = 6.2 to 8.5 years	All: 11.4 (6.1) Girls: 11.1 (5.8) Boys: 11.7 (6.4)	Cognitive function on 14 tasks that assess specific and global aspects of cognition: Math achievement test, Peabody picture vocabulary test,	Spline (segmented), and logistic regression models in stratums of Pb exposure. Child's age, gender, hemoglobin, family	<u>Adjusted change in cognitive performance for every 1 µg/dL increase in blood Pb (below the cutpoint):</u> Linear regressions: β (95% CI) Math (10µg/dL): -0.42 (-9.2, 0.08) PPVT (12µg/dL): -0.71 (-1.43, 0.02), p<0.01 Distractibility (freedom) (12µg/dL): -0.40 (-1.17, 0.37) Sequencing (10µg/dL): -0.20 (-0.50, 0.10)	Concurrent blood Pb level (below 12µg/dL) was associated with poorer cognitive

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
others	Male=54%			freedom from distractibility factor, sequencing, Sternberg memory, figure matching and design, visual search, cognitive abilities test (CAT): stimulus discrimination, and visual memory span	possessions, forgetting homework, house ownership, crowding, maternal education, birth order, family structure, arsenic exposure, tester, and school	Sternberg (10µg/dL): -0.16 (-0.37, 0.05) Figure matching (10µg/dL): -0.20 (-0.47, 0.06) **Figure Design (12µg/dL): -0.31 (-0.62, -0.01), p<0.05** Visual search correct (10µg/dL): -0.01 (-0.52, 0.51) CAT mean decision time (10µg/dL): 0.05 (-0.07, 0.17) Logistic regressions: OR (95% CI) Visual search err. (10µg/dL): 1.09 (0.92, 1.28), p<0.1 Stimulus discrim. correct (8µg/dL): 0.85 (0.63, 1.13) Visual mem. span correct (10µg/dL): 0.90 (0.74, 1.10) CAT number of errors (14µg/dL): 1.06 (0.96, 1.17)	performance on a figure design task to assess cognition. Regression slopes were steeper at lower blood Pb levels.
Cross-sectional Kordas (2007) Torreón, Mexico *Population may overlap with Kordas (2004) and others*	550 children attending first grade at one of 9 public school and living near a metal foundry in Mexico; Year=2001 Male= 54%	6.9 (0.4) years	11.5 (6.1)	Micronutrient status, sleep, classroom behavior, and activity	Regression analysis Behavior outcome: age, sex, economic, status, home ownership, crowding, maternal education, family structure, and parent's involvement in schooling Sleep: heightened anxiety, bedroom sharing, and who decided on child's sleep and wake-up time, age, sex, and crowding in the home	AdjOR (95% CI)/ β(95% CI) between blood Pb, physical activity and sleep (blood Pb <10µg/dL vs ≥10µg/dL) <u>Sleep characteristic</u> Bedtime (min): β (95% CI)=-5.0 (-12.0, 1.9) **Wake up time: β (95% CI)=9.6 (5.7, 13.5); p<0.01** Sleep latency: OR (95% CI)= 1.2 (0.8, 1.8) **Daily sleep: OR (95% CI)= 2.6 (1.0, 6.5); p<0.05** Wakes at night: OR (95% CI)=1.0 (0.7, 1.5) Poor sleeper: OR (95% CI)=0.9 (0.6, 1.4) Low morning energy: OR (95% CI)=1.2 (0.8, 1.7) Wants to sleep more: OR (95% CI)= 1.3 (0.9, 1.9) Fussy: OR (95% CI)=1.4 (0.9, 2.2) Tired before 4PM: OR (95% CI)=0.7 (0.4, 1.2) Nap >3 d/wk: OR (95% CI)=0.8 (0.5, 1.4) Nap ≥ 1h/d: OR (95% CI)=1.0 (0.7, 1.4) <u>Observed Behavior</u> On task: β (95% CI)=0.6 (-3.2, 4.5) Off-task active: β (95% CI)= -1.9 (-4.9, 1.0) Off-task passive: β (95% CI)= 1.3 (-1.2, 3.8) <u>Activity at recess:</u> β (95% CI)=-3.6 (-8.6, 1.3)	Blood Pb was significantly associated with later waking time and shorter duration of sleep.
Cross-sectional Krieg (2009) USA *Population may overlap with Lanphear (2000) and others*	2,611 to 2,823 people by endpoint from NHANES III; Year = 1991-1994 % male not stated	20-59 years	2.88(SE 0.13) Measured when outcome assessed	Neurobehavioral test performance (simple reaction time, symbol-digit substitution, and serial digit learning), serum folate, homocysteine, vitamin B12	Linear Regression Age, sex, education, family income, race-ethnicity, computer or video game familiarity, alcohol use within the last 3 h, and test language	Regression of log blood Pb and test performance: slope (SE), p-value simple reaction time (mean ms)= -0.38(6.23); p=0.95 symbol-digit substitution mean total latency (s) =0.11(0.46); p=0.82 number of errors =-0.33(0.23); p=0.16 serial digit learning performance trials to criterion =-0.22(0.25);p=0.39 total score = -0.52(0.48);p=0.29 Log serum homocysteine and log blood Pb (p=0.0015) Authors state simple reaction time, symbol-digit substitution and serial digit learning performance was not related to serum folate or serum vitamin B12.	Blood Pb level was not significantly associated with neuro-behavioral test performance in adults.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional Krieg (2005) USA *Population may overlap with Krieg (2009) and others*	4,937 adults aged 20-59 years from NHANES III. Year=1991-1994; Male = 46%	20-59 years	NHANES III: Geom. mean 2.51 Arith. mean 3.30 Range: 0.7-41.8	Neurobehavioral tests: Simple reaction time, Symbol-digit substitution, and Serial digit learning Also performed meta-analysis of 26 occupational studies (all with exposed blood Pb >15µg/dL)	Regression analysis Sex, age, education, family income, race-ethnicity, computer or video game familiarity, alcohol use, test language, and survey phase	Relationship between test performance and log10 blood Pb from NHANES III: Adjusted Slope (SE); *p* Simple reaction time Mean reaction time(ms): 4.65 (3.95); *p*=0.2440 Symbol-digit substitution: Mean total latency(s): 0.40 (0.36); *p*=0.2745 Number of errors: -0.04 (0.16); *p*=0.8172 Serial digit learning Trials to criterion: -0.18(0.16); *p*=0.2567 Total score: -0.45 (0.38); *p*=0.2361	Concurrent blood Pb was not significantly associated with performance on the three neurobehavioral tests
Cross-sectional Krieg (2009) USA *Population may overlap with Lanphear (2000) and others*	Subjects were selected from NHANES III. There were 842 Children (age 12-16 years), 2093 adults (age 20-59 years), and 1799 older adults age ≥60 years Year=1991-1994 % male not stated	12-16, 20-59, and 60+	Mean (SE) blood Pb concentration by age group: 12-16 years: 1.95 (0.16) 20-59 years: 2.85 (0.16) 60 + years: 4.02 (0.06)	Cognitive function was measured by the Wechsler Intelligence Scale for Children-Revised (WISC-R) and the Wide Range Achievement Test-Revised (WRAT-R); genotypes *ALAD* rs1800435: CC/CG vs GG for each age-group. Serum homocysteine also measured in adults.	Regression analyses Children: sex, education of family reference person, family income, race-ethnicity, and test language Adults: sex, age, education, family income, race-ethnicity, computer or video game familiarity, alcohol use in the last 3 hours, and test language Older adults: sex, age, education, family income, race-ethnicity, and test language	Adjusted mean Blood Pb was higher in GG than CC/CG, with only in **children age 12-16 reaching statistical significance: 2.02, 1.28 (p=0.0175)** Regression analysis between measures of cognitive function and log blood Pb: Slope (SE), *p* 12-16 year olds: WISC-R Block design scaled score: **All: -1.50 (0.58); *p*=0.0165** *ALAD* CC/CG: -2.65 (1.64); *p*=0.1206 ***ALAD* GG: -1.31 (0.63); *p*=0.049** Interaction: F = 0.54, *p* = 0.4707 WISC-R Digit span scaled score: **All: -1.86 (0.53); p=0.0018** *ALAD* CC/CG: -3.14 (2.29); *p*=0.1835 ***ALAD* GG: -1.67 (0.49); *p*=0.0022** Interaction: F = 0.44; *p* = 0.5136 WRAT-R Reading standardized score: **All: -12.77 (2.18); p=0.0005** *ALAD* CC/CG: -19.29 (11.95); *p*=0.1201 ***ALAD* GG: -11.80 (3.06); *p*=0.0008** Interaction: F = 0.41; *p* = 0.5275 WRAT-R Math standardized score: **All: -11.08 (4.55); p=0.0231** *ALAD* CC/CG: -16.37 (17.88); *p*=0.3695 ***ALAD* GG: -9.86 (4.76); *p*=0.0498** Interaction: F = 0.13; *p* = 0.7169 Ages 20-59 years: Simple reaction time, Mean reaction time: All: -6.33(7.10); p=0.3820 ***ALAD* CC/CG: -38.24 (17.87); *p*=0.0432** *ALAD* GG: -2.06 (7.61); *p*=0.7892 **Interaction: F = 4.28; *p* = 0.0499** Symbol-digit substitution, Mean total latency(s) :	Previously reported significant associations of concurrent blood Pb with decreases in WISC-R and WRAT-R cognitive measures in children 12-16 were not modified by *ALAD* genotype. No significant differences were found between blood Pb and cognitive function in adults - except in 20 - 59 year olds' mean reaction time decreased as blood Pb increased in the *ALAD* rs1800435 CC/CG group (an improvement in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						All: 0.93 (0.55); *p*=0.1054 *ALAD* CC/CG: 2.71 (1.46); *p*=0.0756 *ALAD* GG: 0.68 (0.56); *p*=0.2377 Interaction: F = 1.89; *p* = 0.1825 Symbol-digit substitution, Number of errors: All: 0.00 (0.19); *p*=0.9815 *ALAD* CC/CG: 0.58 (0.32); *p*=0.0822 *ALAD* GG: -0.19 (0.22); *p*=0.3862 Interaction: F = 3.59; *p* = 0.0707 Serial digit learning, Trials to criterion: All: -0.02(0.29); *p*=0.9556 *ALAD* CC/CG: -0.77 (0.72); *p*=0.2927 *ALAD* GG: 0.06 (0.28); *p*=0.8339 Interaction: F = 1.29; *p* = 0.2679 Serial digit learning, Total score: All: -0.03(0.67); *p*=0.9622 *ALAD* CC/CG: -1.11 (1.38); *p*=0.4302 *ALAD* GG: 0.05 (0.66); *p*=0.9406 Interaction: F = 0.78; *p* = 0.3863 60+ years: Word recall (number correct) : All: -0.06(0.06); *p*=0.2941 *ALAD* CC/CG: 0.02 (0.17); *p*=0.9063 *ALAD* GG: -0.06 (0.08); *p*=0.4403 Interaction: F = 0.15; *p* = 0.6991 Story recall (number correct) : All: -0.05(0.15); *p*=0.7345 *ALAD* CC/CG: -0.88 (0.55); *p*=0.1242 *ALAD* GG: 0.16 (0.17); *p*=0.3531 Interaction: F = 3.15; *p* = 0.0890	performance).
Cross-sectional Krieg (2010) USA *Population may overlap with Lanphear (2000) and others*	Children aged 12 to 16 (n=842), adults aged 20-59 (n=2093), and adults over 60 years old (n=1799) from NHANES III; Year= 1991-1994 % male not stated	Subjects selected from age ranges and no mean age is reported within these groups	<u>Age 12-16:</u> 1.95 (SE 0.16) Range 0.7-39.8 <u>Age 20-59:</u> 2.85 (SE0.16) Range 0.7-28.1 <u>Over 60:</u> 4.02 (SE 0.08) Range 0.7-52.9 Blood Pb did not change by *VDR* genotype	Cognitive tests including components of WISC-R and WRAT-R (children), neurobehavioral test components from NES2 (adults 20-59), and word and story recall (adults over 60) *Also studied interaction of test-Pb association with VDR*	Log linear regression model All adjusted for sex, education (of caregiver in children), family income, race-ethnicity, and test language Adults aged 20-59 also adjusted for age, computer/video game familiarity, and alcohol use in last 3 hours	<u>Age 12-16 slope (95%CI) for test and log Blood Pb:</u> **Block design (WISC-R): -1.50 (-2.69, -0.30), p=0.0165** **Digit span (WISC-R): -1.86 (-2.96, -0.77), p=0.0018*** **Reading (WRAT-R): -12.77 (-19.35, -6.20), p=0.0005** **Math (WRAT-R): -11.08 (-20.49, -1.67), p=0.0231*** <u>Age 20-59 slope (95%CI) for test and log Blood Pb:</u> Reaction time: -6.33 (-21.03, 8.63), p=0.3820 Symbol-digit latency: 0.93 (-0.21, 2.07), p=0.1054 Symbol-digit errors: 0.00 (-0.38, 0.39), p=0.9815* Serial digit trials: -0.02 (-0.62, 0.59), p=0.9556 Serial digit total: -0.03 (-1.41, 1.35), p=0.9622 <u>Over 60 slope (95%CI) for test and log Blood Pb:</u> Word recall: -0.06 (-0.19, 0.06), p=0.2941 Story recall: 0.05 (-0.26, 0.37), p=0.7345	Some *VDR* genotypes modified the relationship between blood Pb and several cognitive tests including WISC-R digit span, others did not significantly alter previously reported associations of blood Pb with

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				genotypes and blood Pb association with serum homocysteine	Adults over age 60 also adjusted for age	*Results showed significant interaction with VDR genotype *[Cognitive function and Pb findings are consistent with previous reports in these subjects by Lanphear (2000) and Kreig (2009)]*	impaired cognitive function in children but not adults.
Cross-sectional Lanphear (2000) USA *Population may overlap with Krieg (2009) and others*	4,853 children from NHANES III Year=1988-1993 % male not stated	Range: 6 – 16 years	Geometric mean: 1.9 µg/dL Exposure measured when outcome assessed	Intelligence measured by the Arithmetic and Reading subtests of the Wide Range Achievement Test (WRAT-R) and the Block Design and Digit Span subtests of the Wechsler Intelligence Scale for Children (WISC-R).	Multivariate analysis; multiple linear regression analyses. Gender, race/ethnicity, poverty, region of the country, parent or caregiver's marital status, serum ferritin level, serum cotinine level, *in utero* and post natal exposure to tobacco, birthweight, admission to a NICU.	<u>Adjusted regression of cognitive/academic test scores and blood Pb < 10µg/dL</u>: Arithmetic **coefficient (SE) = -0.70 (0.17); p< 0.001** Reading **coefficient (SE) = -0.99 (0.19); p< 0.001** Block Design **coefficient (SE) = -0.10 (0.04); p= 0.009** Digit Span **coefficient (SE) = -0.05 (0.02); p= 0.04** <u>Adjusted regression of cognitive/academic test scores and blood Pb <5µg/dL</u>: Arithmetic **coefficient (SE) = -1.06 (0.48); p= 0.03** Reading **coefficient (SE) = -1.66 (0.36); p< 0.001** Block Design coefficient (SE) = -0.05 (0.07); p= 0.45 Digit Span coefficient (SE) = -0.09 (0.07); p= 0.20	Blood Pb below 10µg/dL was significantly associated with deficits in cognition and academic skills in children, while those below 5µg/dL were only significantly associated with deficits in arithmetic and reading.
Pooled analysis Lanphear (2005)	Pooled analysis of 7 prospective studies of blood Pb and IQ in children initiated before 1995 (n=1,333): Boston (Bellinger (1992)), Cincinnati (Dietrich (1993b)), Cleveland (Ernhart (1989)), Mexico City (Schnaas, (2000)), Port Pirie Australia (Baghurst (1992)), Rochester (Canfield (2003a)), and Yugoslavia (Wasserman (1997)).	Birth through 10 years of age. [ages for individual studies not stated]	<u>Median (5^{th} – 95^{th}):</u> Concurrent 9.7 (2.5 – 33.2) Peak 18.0 (6.2 – 47.0) Early childhood 12.7 (4.0 – 34.5) Lifetime average 12.4 (4.1 – 34.8)	IQ score as measured by Wechsler Intelligence Scales for Children, Wechsler Preschool and Primary Scales of Intelligence.	Multiple regression analysis; univariate regression analysis Child's sex, birth order, birth\ weight, maternal education, maternal age, marital status, prenatal alcohol exposure, HOME Inventory score.	<u>Mean adjusted changes in full-scale IQ score associated with an increase in blood Pb concentration (log scale), from the 5^{th} to 95^{th} percentile* of the concurrent blood Pb level at the time of IQ testing</u>: **Early childhood β(95% CI)=-2.04 (-3.27, -0.81)** **Peak β(95% CI)=-2.85 (-4.10, -1.60)** **Lifetime average β(95% CI)=-3.04 (-4.33, -1.75)** **Concurrent β(95% CI)=-2.70 (-3.74, -1.66)** *5^{th} and 95^{th} percentiles listed with these results differed from those in another table included in the Blood Pb column.	Early childhood, peak, lifetime average and concurrent blood Pb was significantly associated lower IQ score in a pooled analysis of 7 prospective cohort studies.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Leviton (1993) Boston, MA, USA *Population may overlap with Bellinger (1994b)*	1923 children born at the Lying-In Division of the Boston Hospital for Women; Year= 1979-1980 Male=50%	8 years	Cord blood Pb 6.8 µg/dL Tooth (dentin) Pb 2.8 µg/g	Boston Teachers Questionnaire (BTQ) to assess academic performance and behavior.	Multivariate analysis Single-parent family, gestational age <37 weeks, mother not a college graduate, self-identification as black, only one child in family, and day care during first 3 years	Risk Ratios (95% CI) for cognitive performance at age 8 with cord blood Pb levels (≥10µg/dL vs <10µg/dL): Girls **Tasks : 2.1 (1.0, 4.4)** **(dependent, impersistent, inflexible and inappropriate approach)** Behavior, hyperactivity, reading, arithmetic, directions, and daydreaming not significant Boys **Arithmetic: 1.6 (1.0, 2.8)** **Directions: 2.7 (1.4, 5.2)** **Tasks: 2.3 (1.2, 4.5)** Behavior, hyperactivity, reading, and daydreaming NS Risk Ratios (95% CI) for cognitive performance at age 8 with dentin Pb content (≥5µg/g vs <5µg/g) Girls **Reading: 2.1 (1.1, 4.2)** **Daydreaming: 2.0 (1.1, 3.5)** **Tasks: 2.3 (1.1, 5.0)** Behavior, hyperactivity, arithmetic, and directions NS Boys: None were statistically significant	Cord blood Pb over 10µg/dL was statistically significantly associated with task difficulty in girls, and arithmetic, directions, and task difficulty in boys. Dentin Pb was statistically significantly associated with reading, task difficulties and daydreaming in girls, but not in boys.
Case-control (Louis *et al.* 2003) New York, NY, USA *Population may overlap with (Louis et al. 2005) and (Louis et al. 2011)*	100 Essential tremor (ET) patients from the Neurological Institute of New York, Columbia-Presbyterian Medical Center (CPMC) and 143 controls from random-digit dialing frequency matched on age, sex, and ethnicity. Year= 2000-2004 (from (Louis *et al.* 2011)); Male: Cases: 46% Controls: 21%	68 years Cases: 70.7 (9.9) yrs Controls: 66.2 (9.7) yrs	2.89 Cases: 3.3 (2.4) Controls: 2.6 (1.6)	Essential Tremor (ET) diagnosis examination of cases and controls by the treating neurologist at the Neurological Institute of New York, Columbia-Presbyterian Medical Center	Mann-Whitney non-parametric test Spearman's correlation with total tremor score Logistic regression Age, sex, ethnicity, years of education, number of rooms in home, number of cigarette pack-years, and current reported consumption of vitamin C, calcium, and iron	Blood Pb in cases and controls: median **Cases=2.7, Controls=2.3; z = 2.08, p = 0.038** Correlation between total tremor score and blood Pb: **All subjects: r = 0.14, p = 0.03** ET cases: r = 0.07, p = 0.48 Association of unit increase in blood Pb and ET diagnosis: AdjOR (95%CI) Control: reference **Cases: 1.19 (1.03, 1.37); p=0.02**	Concurrent blood Pb was significantly associated with essential tremor.
Case-control (Louis *et al.* 2005) New York, NY,	63 Essential tremor (ET) patients from the Neurological	Cases: 67.4 (16.6) yrs Controls	2.88 Cases: 3.5 (2.2)	ET diagnosis from the treating neurologist at the Neurological	X^2 and Fisher's exact test Logistic regression, Pearson's correlation	Blood Pb in cases and controls: mean **Cases=3.5, Controls=2.6; p = 0.007**	Concurrent blood Pb was significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
USA *Population may overlap with (Louis et al. 2003) and (Louis et al. 2011)*	Institute of New York, Columbia-Presbyterian Medical Center (CPMC) and 101 controls from random-digit dialing frequency matched on age, sex, and ethnicity. Year= 2000-2004 (from (Louis *et al.* 2011)); Male: Cases: 57.1% Controls: 43.6%	64.9 (11.1) yrs	Controls: 2.5 (1.5) Mean log blood Pb concentration by *ALAD* allele and diagnosis: *ALAD* 1/1 (N=129) Cases: 2.63 (1.82) Controls: 2.29 (1.78) *ALAD* 1/2 or 2/2 (N=35) Cases: 3.8 (1.78) Controls: 2.0 (1.78)	Institute of New York, Columbia-Presbyterian Medical Center	Analysis adjustments included age, family history of ET, and sex	*ALAD* genotype and ET: n (%); OR (case vs. control) 1/1: 45 cases (71.4%), 84 controls (83.2%) 1/2 or 2/2: 18 cases (28.6%), 17 controls (16.8%) OR = 1.98 (95% CI 0.93-4.21), *P* = 0.077 Logistic model of ET including *ALAD* 2 allele, log blood Pb concentration, and an *ALAD*xblood Pb interaction: **Interaction: AdjOR = 7.81 (1.08-4789.68), *P* = 0.046** Stratified by genotypes: OR (95% CI), *P* *ALAD* 1/1: 2.69 (0.61-11.82), *P* = 0.19 ***ALAD* 1/2 or 2/2: 80.29 (3.08-2,096.36), *P* = 0.008** Proportion of subjects with *ALAD* 2 allele by blood Pb tertile: n/total (%) cases; controls Lowest (≤2µg/dL): 2/14 (14.3%); 9/41 (22.5%) Middle (2.04-3.236µg/dL): 2/22 (9.1%); 3/32 (9.4%) Highest (≥3.3µg/dL): 14/27 (51.9%); 5/28 (17.9%)* ***Fisher's exact test, *P* = 0.009** Logistic model of ET including *ALAD* 2 allele, log blood Pb tertile, and an *ALAD*xblood Pb tertile interaction: **Interaction: OR = 2.92 (95% CI 1.05-8.12), *P* = 0.04** Stratified by genotypes: OR (95% CI), *P* *ALAD* 1/1: 1.23 (0.78-1.96), *P* = 0.37 ***ALAD* 1/2 or 2/2: 3.60 (1.45-8.97), *P* = 0.006** Correlation of log blood Pb with total tremor score: Pearson's *r*, *P*-value **Cases 0.27, *P*=0.03**; Controls -0.01, *P*=0.91 **Adjusted for age and ET meds, Case 0.28, *P*=0.03** 1/1: Cases 0.20, *P*=0.20; Controls not reported 1/2 or 2/2: Cases 0.43, *P*=0.07; Controls 0.03, *P*=0.76 **Adjusted for age and ET meds, Case 0.66, *P*=0.005**	associated with essential tremor, particularly in subjects carrying the *ALAD* 2 allele.
Case-control (Louis *et al.* 2011) New York, NY, USA *Population may overlap with (Louis et al. 2003) and (Louis et al. 2005)*	106 Essential tremor (ET) patients from the Neurological Institute of New York, Columbia-Presbyterian Medical Center (CPMC) and 151 controls from random-digit dialing frequency	All: 65.8 (13.8) yrs Cases: 68.2 (15.2) yrs Controls: 64.1 (12.5) yrs	Blood Pb All: 2.9 (1.8) Cases: 3.1 (2.1) Controls: 2.7 (1.6) Blood harmane: mean (SD) (g^{-10}/ml) All: 0.17 (0.74) Cases: 0.20 (0.77) Controls: 0.15 (0.72) Blood Pb and	Total tremor score: clinical measure of tremor severity; ranges from 0-36. ET diagnosis from the treating neurologist at the Neurological Institute of New York, Columbia-Presbyterian Medical Center. Blood harmane (1-methyl-	Spearman's correlations and Kruskal-Wallis non-parametric tests; Multivariate linear regression; Age, gender, white race and cigarette pack-years	Spearman's Correlations: **Blood Pb and total tremor score: p=0.045** **Blood harmane and total tremor score: p=0.007** Total tremor score by toxicant group: mean (SD) Group 1: ↓harmane and ↓ Pb: 8.4 (8.2) Group 2: ↑harmane and ↓ Pb: 10.8 (10.0) Group 3: ↓ harmane and ↑ Pb: 10.1 (9.6) Group 4: ↑ harmane and ↑ Pb: 13.7 (10.4) **Kruskal-Wallis, p-0.028** Group 1: ↓harmane and ↓ Pb: 8.4 (8.2) Group2 + Group 3: 10.5 (9.8) Group 4: ↑ harmane and ↑ Pb: 13.7 (10.4)	Blood Pb and blood harmane were significantly associated with total tremor score in combination – suggesting an additive effect.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	matched on age, sex, and ethnicity. Year= 2000-2004 Male:43.2%		harmane were not correlated (r = 0.008, p = 0.90)	9H-pyrido[3,4-β]indole) was also measured.		**Kruskal-Wallis, p=0.01** Linear regression for log-tremor score and toxicant group: β, p **Unadjusted: β=0.116, p = 0.006** **Adj. age: β=0.098, p = 0.02** **Fully adjusted: β=0.087, p = 0.04** Restricted to ET cases (n=106) Total tremor score by toxicant group: mean (SD) Group 1: ↓harmane and ↓ Pb: 17.3 (5.5) Group2 + Group 3: 20.1 (8.1) Group 4: ↑ harmane and ↑ Pb: 22.3 (7.1) Kruskal-Wallis, p=0.08 Restricted to ET cases (n=106) Linear regression for log-tremor score and toxicant group: β, p **Unadjusted: β=0.06, p = 0.01** **Fully adjusted: β=0.06, p = 0.018** Restricted to controls (n=151) Total tremor score by toxicant group: mean (SD) Group 1: ↓harmane and ↓ Pb: 3.5 (2.3) Group2 + Group 3: 3.9 (2.9) Group 4: ↑ harmane and ↑ Pb: 4.8 (3.1) Kruskal-Wallis, p=0.24 Restricted to controls (n=151) Linear regression for log-tremor score and toxicant group: β, p Unadjusted: β=0.06, p = 0.16 Fully adjusted: β=0.05, p = 0.26	
Meta-analysis Marcus (2010)	Meta-analysis of 18 studies of Pb and conduct problems in children and adolescents (n=8561): 11 blood Pb (Braun (2008), Burns (1999), Chen (2007), Chiodo (2004) and (2007), Dietrich (2001), Nigg (2008), Sciarillo (1992), Thomson (1989), Wasserman (2001),and Yule (1984)), 2 tooth Pb (Bellinger (1994b) and Needleman	Blood Pb: Braun08: 12.0 Burns99: 12.0 Chen07: 7.0 Chiodo04: 7.8 Chiodo07: 6.9 Dietrich01: 15.6 Nigg08: 13.3 Sciarillo92: 3.8 Thoms.89: 9.5 Wasser.01: 4.5 Yule84: 8.5 Tooth Pb: Bellinger94: 7.0 Needle.90: 18.4 Hair Pb: Marlowe82: 9.7	Blood Pb: Burns , 1999: Females = 14.3 Males = 13.9 Chen, 2007: 26.0 Chiodo, 2004: 5.4 Chiodo, 2007: 5.0 Dietrich, 2001: 1.2 Nigg:, 2008: 1.0 Sciarillo, 1992: 18.0 Thomson, 1989: 10.4 Wasserman, '01: 9.6 Yule, 1984: 13.5	Conduct Problem measures varied by study, including BASC-PRS, BASC-TRS, CBCL, CBCL-Ex, CR, CRS, CRS-CP, MHDS-CD, NYS, PRDB, RS, SDB, SRA, TRF-DB, TRF-Ex, WPIC-Ag, WPIC-P, and WPIC-T.	Pearson's product-moment correlation coefficients corrected for bias using a Fisher's Zr transformation converted back to r Effect sizes weighted by samples size with the inverse variance weight (sample size - 3) Maximum likelihood random effects model and a Q test of homogeneity Adjustments varied by study and included sex,	Correlation coefficient of Pb and conduct problems (Adjusted effect): r Blood Pb: Braun, 2008: 0.07 Burns , 1999: Females 0.35 Males 0.27 Chen, 2007: 0.18 Chiodo, 2004: 0.14 (0.12) Chiodo, 2007: 0.10 (0.09) Dietrich, 2001: 0.10 Nigg:, 2008: 0.18 Sciarillo, 1992: 0.17 Thomson, 1989: 0.07 Wasserman, 2001: (0.32) Yule, 1984: 0.16 Tooth Pb: Bellinger, 1994: 0.12 (0.09)	Blood, bone, and tooth Pb were significantly associated with increased in conduct problems in a meta-analysis of 15 studies. Three studies that measured hair Pb had larger effect sizes and were not included in the final meta-analysis.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	(1990)), 3 hair Pb (Marlowe (1982), (1985), and (1993)), and 2 bone Pb (Needleman (2002) and (1996))	Marlowe85: 8.4 Marlowe93: 3.5 Bone Pb: Needle.96: 12.0 Needle.02: 15.7			race/ ethnicity, maternal marital status, sibship size, birth order socioeconomic status, social class, parental education, parental IQ, alcohol use during pregnancy, prepregnancy, weight, cesarean section, birth weight, colic, prenatal care, maternal smoking, current medication use by child, home environment, caretaker education, current caretaker marijuana use, and disruption in caregiving	Needleman, 1990: 0.16 Hair Pb: Marlowe, 1982: 0.41 Marlowe, 1985: 0.44 Marlowe, 1993: (0.48) Bone Pb: Needleman, 1996: 0.12 Needleman, 2002: 0.14 **All studies: *r* = 0.19 (95% CI 0.14, 0.23), *p* < 0.001** (Q test p < 0.001 indicating heterogeneity) **Excluding Hair: *r* = 0.15 (95% CI 0.11, 0.18), *p* < 0.001** (Q test p =0.31 improving homogeneity)	
Prospective McMichael (1994) Port Pirie, Australia *Population may overlap with Wigg (1988) and others*	262 children living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; re-evaluated at age 8. Year = 1979-1982 (at baseline). Male = 43.3%	Average age when teeth were shed: 6.8 (0.7) years	Cord blood Pb: 8.9 (0.3) µg/dL Tooth Pb (geometric mean, whole deciduous incisor): 8.6 (1.9) µg/g	Intellectual status at age 7: Wechsler Intelligence Scale for Children (WISC-R)	One-tailed variance ratio and Student's t tests (clear directional hypothesis) and 90% CIs Multiple regression model with final covariates: sex, birth weight, birth order, feeding style (breast, bottle, or mixed feeding), duration of breast feeding, parental smoking, mother's age at birth, period of residence in Port Pirie, SES, HOME score, mother's IQ, father's education, parents living together, and age the tooth was shed	Adjusted effect from an increase in tooth Pb from 3 to 22 µg/g: Estimate and 90% CI, one-tailed test *p* value Information: 0.6 (-0.6, 1.8), **p < 0.001** Similarities: 1.0 (-0.2, 2.3), **p < 0.001** Arithmetic: 1.1 (-0.1, 2.4), **p < 0.001** Vocabulary: 0.2 (0.8, 1.1), **p < 0.01** Comprehension: 0.4 (-0.7, 1.4), **p < 0.01** Picture Completion: 0.1 (-0.9, 1.0), *p* = 0.09 Picture Arrangement: 0.0 (-1.2, 1.3), *p* = 0.02 **Block Design: 2.5 (1.2, 3.8) p < 0.01** Object Assembly: 0.5 (-0.4, 1.4), *p* = 0.06 Coding: 0.1 (-1.1, 1.3), *p* = 0.49 Verbal IQ: 4.2 (-0.8, 9.1), **p = 0.01** Performance IQ: 4.5 (-0.8, 9.8), **p < 0.01** **Full-scale IQ: 5.1 (0.2, 10.0), p < 0.01** Partial regression coefficient per log unit tooth Pb: **Block Design: -1.25 points (90% CI -0.61, -1.89)** **Full-scale IQ: -2.55 points (90% CI -0.13, -4.9)**	Tooth Pb was significantly associated with decreased performance on full-scale IQ and block design test at age 7.
Cross-sectional Min (2007) Seoul, Korea	61 children aged 7-16 years; recruited during family health examination in	Mean not stated 7 to 16 years	Overall: 2.89 7-10 yrs (n=21): 2.73 (0.92)	Neurobehavioral function as measured by the Swedish	Linear regression Models included age, gender, and mother's	Multiple linear regression of neurobehavioral test and blood Pb: Pb Estimate (SE), *P*-value; R^2 **Simple reaction time: 16.80 (8.45), *P* =0.05; R^2=0.68** Digit span : -0.51 (0.29), *P* =0.08; R^2=0.46	Concurrent blood Pb was significantly associated with

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	Seoul, Korea. Year not stated Male = 54%		11-13 yrs: (n=24): 3.04 (0.75) 14-16 yrs (n=24): 2.74 (0.71)	performance evaluation system-Korean adaptation. Included: simple reaction time, symbol digit (measure of perceptual speed), digit span (short term memory capacity); finger tapping speed for dominant and non-dominant hands (maximum rate of repetitive movement).	neurobehavioral test performance.	Symbol digit: 147.72 (118.80),*P* =0.22; R^2=0.71 Finger tapping speed (dominant): -0.35 (1.43),*P* =0.81; R^2=0.55 Finger tapping speed (non-dominant): 0.44 (1.74), *P*=0.79; R^2=0.43	longer simple reaction time – an indicator of attention – in school age children.
Prospective Min (2009) Cleveland, OH	278 inner-city children from cohort study of prenatal cocaine; recruited at birth Year = 1994-1996 Male=48%	4,9, and 11	At age 4: 7(4.1)	Intelligence assessed using the abbreviated Wechsler Preschool and Primary Scales of Intelligence-Revised (WPPSI-R) at 4 years and the entire Wechsler Intelligence Scales for Children-Fourth Edition (WISC-IV) at 9 and 11 years of age	Multiple regression analysis Adjustments differ by endpoint including HOME score, current caregiver's PPVT-R at 4 years, sex, parity, maternal marital status, and head circumference at birth, race, log of prenatal cocaine and alcohol average	<u>Regression of blood Pb at 4 (<5µg/dL vs ≥5µg/dL) and cognition:</u> adjusted mean decline at higher blood level <u>Tested at 4 years of age</u> Full Scale IQ 2.19 (p=0.23) **Performance 5.01(p=0.01)** <u>Tested at 9 years of age</u> Full Scale IQ 2.83 (p=0.11) Verbal comprehension 1.72 (p=0.32) **Perceptual reasoning 4.73 (p=0.01)** WJTA Math 3.02(p=0.06) **MJTA Reading 6.05 (p=0.003)** <u>Tested at11 years of age</u> Full Scale IQ 2.13(p=0.23) Verbal comprehension 1.8 (p=0.26) Perceptual reasoning 2.61 (p=0.16) Working memory 1.82 (p=0.41) WJTA Math 1.63 (p=0.37) **MJTA Reading 3.86 (p=0.04)** <u>Regression of blood Pb at 4 and cognition in all children:</u> coefficient (SE) <u>Tested at 4 years of age</u> **Full Scale IQ -0.50(0.20) (p≤0.05)** Verbal -0.20(0.190) **Performance -0.74(0.22)(p≤0.001)** <u>Tested at 9 years of age</u> **Full Scale IQ -0.41(0.19) (p≤0.05)** Verbal comprehension -.35(0.18) (p≤0.10) **Perceptual reasoning -0.45(0.21) (p≤0.05)**	Blood Pb at age 4 was significantly associated with decreased full scale IQ at age 4, 9 and 11; performance IQ at 4; perceptual reasoning and reading scores at age 9 and 11; and verbal comprehension and math scores at age 11.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Working memory -0.31(0.21) Processing speed –0.25(0.19) WJTA Math -0.33(0.18) (p≤0.10) **MJTA Reading –0.58(0.23) (p≤0.05)** Tested at11 years of age **Full Scale IQ -0.54(0.19) (p≤0.01)** **Verbal comprehension -.51(0.17) (p≤0.01)** **Perceptual reasoning -0.61(0.20) (p≤0.01)** Working memory -0.43(.24) (p≤0.10) Processing speed –0.24(0.20) **WJTA Math -0.45(0.20) (p≤0.05)** **MJTA Reading –0.60(0.21) (p≤0.01)**	
Cross-sectional (Minder *et al.* 1994) Netherlands	43 boys who attended special education schools in the Netherlands. Year not stated Male=100%	8 - 12 years	Hair Pb 1.26 ppm (1.09) **Lack of blood Pb measure limits the utility*	Attention measured by varied psychological tests including Eye-Hand Coordination, Simple Reaction Time, and Choice Reaction Time from the Neurobehavioral Evaluation System; Mazes, Digit Span, and Coding from the Wechsler Intelligence Scale for Children-Revised (WISC-R); Underlining Test (shortened version), Stroop Test, Trail Making Test A and B, Beery Test, and Dichotic Listening Test.	Correlation and multiple regression analysis Adjusted for age, SES, IQ, and pica	Correlation of hair Pb with test performance time: *r*, *p* **Simple Reaction Time: *r*=0.37, *p*=0.008** **Trail Making Test A: *r*=0.29, *p*=0.032** **Trail Making Test B: *r*=0.40, *p*=0.004** other tests p>0.05 Proportion of test score variance explained by Pb: **Simple Reaction Time:, 8.3, *p*=0.046** Trail Making Test A: 5.0, *p*=0.155 **Trail Making Test B: 11.7, *p*=0.022** **Trail Making Test B, reaction time correct.:9.9, *p*=0.037**	Hair Pb was significantly associated with slower reaction time and less flexibility in changing attention focus in children with learning problems.
Cross-sectional (Minder *et al.* 1998) Netherlands	313 boys who attended special education schools in the Netherlands. Year not stated Male=100%	9-12 years	4.4 (2.2) Range: 0.8-16.0	Cognition was assessed by extensive theory-based testing: the Simple Reaction Time task, Block Task compatible and incompatible, Digit Span forward and backward, Digit Span	Student's t-test, log transformed Socioeconomic status, thumb sucking and/or nail biting, and season	There were no significant correlations between blood PB and cognitive test results (data not shown). Blood Pb levels did not effect the final model when included as an independent variable or when forced to load on reaction time(n=267).	Blood Pb was not significantly correlated with any cognitive test in children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				sequence, Letter Span, Counting Span forward and backward, Trail Making Test A and B, Trail Making Test revised, Sternberg task, Brus reading Speed task, Raven task, and Bourdon-Vos task			
Retrospective cohort Miranda (2007) NC, USA *Population may overlap with Miranda (2009)*	8,603 4th grade children tested for reading and 8,627 tested for math at the North Carolina Education Research Data Center without a limited English proficiency and who were either black or white Year: 2000 – 2004 % male not stated	4th grade [age not reported, 4th grade is usually 9 – 10 years old]	5.19 µg/dL Pb screening data from the Childhood Lead Poisoning Prevent. Program in 1995-1998 (<5 years of age)	Educational achievement in 4th grade was measured by performance on state-required End of Grade (EOG) test results	Multivariate regression analysis Sex, race, school system, whether the school is a charter school, participation in the free or reduced-price lunch program, parental education, daily computer use, age at which blood Pb screen occurred.	Multivariate Regression model, 4th grade Reading EOG: **2 µg/dL Coefficient = -0.70; p=0.05** **4 µg/dL Coefficient = -1.77; p<0.0001** **6 µg/dL Coefficient = -2.33; p<0.0001** **8 µg/dL Coefficient = -2.66; p<0.0001** **≥10 µg/dL Coefficient = -2.92; p<0.0001** Multivariate Regression model, 4th grade Mathematics EOG: **2 µg/dL Coefficient = -0.71; p=0.03** **4 µg/dL Coefficient = -1.53; p<0.0001** **6 µg/dL Coefficient = -2.13; p<0.0001** **8 µg/dL Coefficient = -2.35; p<0.0001** **≥10 µg/dL Coefficient = -2.07; p<0.0001**	Blood Pb levels in early childhood (<5 years) are significantly associated with lower educational achievement in 4th grade (9-10 years) as measured by performance on end-of-grade testing.
Retrospective cohort Miranda (2009) NC, USA *Population may overlap with Miranda (2007)*	57,678 children from the North Carolina Childhood Lead Poisoning Prevention Program blood Pb surveillance registry linked to the North Carolina Education Research Data Center for all 100 counties in NC; self-reported as black or white without limited English proficiency; Year: 1995-1999 (Pb) and 2001-2005	Age range: 9-36 months when blood Pb measured Testing done in 4th grade [age not reported, 4th grade is usually 9 to 10 years old]	Mean: 4.8µg/dL Median: 4µg/dL Range: 1-16 Pb screening data from the Childhood Lead Poisoning Prevent. Program in 1995-1998	4th-grade reading scores from End of Grade (EOG) testing	Multivariate linear regression with EOG as the response variable and blood Pb level modeled using dummy variables for each blood Pb level Predictor variables: race, sex, parental education, free/reduced lunch program, and charter school (indicator of lower SES in NC)	Multivariate Regression of 4th-grade reading EOG score (ref: white, female, screened 9-18 months, Wake County Schools, no free/reduced lunch, parents HS graduates, blood Pb=1µg/dL) coeff. (95%CI), *p>t* **Pb=2µg/dl (dummy var.): -0.30 (-0.58, -0.01), 0.04** **Pb=3µg/dl (dummy var.): -0.46 (-0.73, -0.19), 0.00** **Pb=4µg/dl (dummy var.): -0.52 (-0.79, -0.24),0.00** **Pb=5µg/dl (dummy var.): -0.80 (-1.08, -0.51), 0.00** **Pb=6µg/dl (dummy var.): -0.99 (-1.29, -0.68), 0.00** **Pb=7µg/dl (dummy var.): -1.07 (-1.40, -0.74), 0.00** **Pb=8µg/dl (dummy var.): -1.35 (-1.73, -0.97), 0.00** **Pb=9µg/dl (dummy var.): -1.20 (-1.64,-0.75), 0.00** **Pb=10+µg/dl (dummy var.): -1.75 (-2.09, -1.41), 0.00** Screened 18-27 months: 0.36 (-0.10, 0.17), 0.61 **Screened 27-36 months: -0.61 (-0.78, -0.43), 0.00** **Black (1=black, 0=white): -3.55 (-3.71, -3.40), 0.00** **Male (1=Male, 0=female): -1.50 (-1.62, -1.38), 0.00** **Free/Reduced Lunch: -2.09 (-2.24, -1.94), 0.00**	Blood Pb levels in early childhood (<5 years) contribute to lower scores on reading tests at the end of the 4th-grade in a dose-dependent manner. Parental education and low SES are stronger predictors of test scores, but

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	(testing) % male not stated					**Parents with some HS: -2.78 (-3.01, -2.55), 0.00** **Parents with some post-HS: 2.00 (1.84, 2.15), 0.00** **Parents completed college: 4.94 (4.75, 5.12), 0.00** **Parents completed grad. school: 7.12 (6.77, 7.47), 0.00** **Charter schools: -2.58 (-3.06, -2.10), 0.00**	Pb shows an independent effect.
Cross-sectional Muldoon (1996) PA and MD, USA	530 elderly women from the Study of Osteoporotic Fractures (SOF), two clinics. Rural dwellers came from Monongahela Valley (PA) and urban dwellers came from the Baltimore clinic (MD); Year=1990-1991 Male=0%;	mean=70.5; no SD reported	Geometric mean: 4.8 (1.6)	Cognitive function assessed by neuropsychological tests of memory, language, visuospatial ability, and general intellectual status measured with Mini-Mental Status Examination, part B of the Trailmaking Test, the Digit Symbol substitution test from the Wechsler Adult Intelligence Scale-revised (WAIS-R), and an Incidental Memory test	Logistic regression analyses; analysis of variance; analysis of covariance <u>For Trailmaking, Digit Symbol, and Incidental Memory tests:</u> Age, education, and tobacco and alcohol consumption <u>For Reaction Time tests totals:</u> Age, tobacco and alcohol consumption, and history of diabetes and/or arthritis	Association of blood Pb levels(low ≤3µg/dL, medium 4-7µg/dL, and high >8µg/dL), and performance on neuropsychological test scores: Adj. OR (95% CI) Rural Monongahela Clinic: <u>Trailmaking</u> Low blood Pb: reference **Medium blood Pb: 2.05 (1.05,4.02)** **High blood Pb: 2.60 (1.04, 6.49)** Digit Symbol Substitution Low blood Pb: reference **Medium blood Pb: 2.03 (1.06, 3.88)** **High blood Pb: 3.73 (1.57, 8.84)** <u>Incidental Memory</u> Low blood Pb: reference Medium blood Pb: 1.37 (0.77, 2.41) High blood Pb: 1.89 (0.83, 3.41) <u>Reaction Time tests totals</u> Low blood Pb: reference Medium blood Pb: 1.37 (0.71, 2.65) High blood Pb: 1.16 (0.45, 3.01) Urban Baltimore Clinic <u>Trailmaking</u> Low blood Pb: reference Medium blood Pb: 0.97 (0.40, 2.40) High blood Pb: 0.79 (0.20, 3.04) <u>Digit Symbol Substitution</u> Low blood Pb: reference Medium blood Pb: 0.61 (0.25, 1.50) High blood Pb: 0.64 (0.16, 2.47) <u>Incidental Memory</u> Low blood Pb: reference Medium blood Pb: 0.50 (0.22, 1.16) High blood Pb: 0.99 (0.28, 3.49) <u>Reaction Time tests totals</u> Low blood Pb: reference Medium blood Pb: 0.61 (0.23, 1.58) High blood Pb: 1.07 (0.30, 3.84)	Blood Pb in elderly women was significantly associated with poorer cognitive performance on the Trailmaking and Digit Symbol Substitution tests in the rural population, but not in the urban population.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional Needleman (1979) MA, US *Population may overlap with (Needleman et al. 1990)*	58 children with high dentine levels and 100 children with low dentine Pb levels. Year=1975-1979 % male not stated	First and second grade	Dentine Pb levels: High: >24 ppm Low: <6 ppm	Wechsler Intelligence Scale for Children (Revised) (WISC-R);	Student t-test; analysis of covariance Mother's age at subject's birth, mother's educational level, father's socioeconomic status, number of pregnancies, and parental IQ	High vs. low dentine Pb and cognitive performance: **Full-scale IQ: p-value=0.03** Verbal IQ: p-value=0.06 Performance IQ: p-value=0.13 **Seashore Rhythm Test: p-value=0.002** Token Test: p-value=0.09 **Sentence-Repetition Test: p-value=0.04**	Children with high dentin Pb levels scored significantly lower on the Full Scale IQ, the Seashore Rhythm Test, and the Sentence-Repetition Test.
Prospective (Needleman *et al.* 1990) MA, US *Population may overlap with (Needleman et al. 1979)*	132 adolescents who had been studied as primary school-children in 1975-1978 were reexamined in 1988. Year= 1988 Male=55.3%	18.4 years	Tooth (dentin) Pb Median=8.2 ppm Range: <5.9 to >22.2 ppm	Neurobehavioral deficits and academic achievement in high school and shortly following graduation where measured by a battery of tests from the Neurobehavioral Evaluation System.	Multiple regression analysis Mother's age at time of subject's birth, mother's educational level, mother's IQ, family size, socioeconomic status, sex, age at time of testing, birth order, alcohol use, and whether the subject and the mother left the hospital at the same time	Dentine Pb levels >20ppm vs <10 ppm AdjOR (95% CI) **Diminished academic success: 7.4 (1.4, 40.8)** **Reading disability: 5.8 (1.7, 19.7)** Multiple regression analysis of academic achievement deficits. Dentin Pb levels >20 ppm vs. <10ppm **Highest grade achieved: β(SE)=-0.027(0.01); p=0.013** **Reading grade equivalent: β(SE)=-0.072(0.02);p=0.001** **Class standing: β(SE)=-0.006(0.003); P=0.048** **Absenteeism: β(SE)=4.73 (1.8); p=0.01** **Grammatical reasoning: 0.178(0.068); p=0.011** **Vocabulary: -0.122(0.033); p=0.001** **Minor antisocial behavior: -0.739(0.035); p=0.038**	Dentin Pb was significantly associated with academic achievement deficits and self-reports of delinquent activity in young adulthood.
Meta-analysis Needleman (1990)	Meta-analysis of 12 studies of Pb and childhood IQ: 7 with blood Pb (Yule (1981), Lansdown (1986), Ernhart (1985), Schroeder (1985), Hawk (1986), Fulton (1987), and Hatzakis (1987)) and 5 with tooth Pb (Winneke (1983), Needleman (1985), Fergusson (1988a), Pocock (1987), and Hansen (1989)).	Ranged from preschool to age 12 years	<u>Blood Pb (µg/dL)</u> Yule, 1981: 13 Lansdown, 1986: 13 Ernhart, 1985: >30 Schroeder, 1985: 30 Hawk, 1986: 21 Fulton, 1987: 11.5 Hatzakis, 1987: 23 <u>Tooth Pb (ppm)</u> Winneke, 1983: 6.2 Needleman, '85: 12.7 Fergusson, 1988: 6.2 Pocock, 1987: 5.1 Hansen, 1987: 10.7	Children's IQ	Multiple regression analysis Within group P values compared for homogeneity using the Rosenthal technique. Joint p-values and averaged effect sizes calculated using two different methods (Fisher and Mosteller). Correlations were converted to z-scores and weighted averages	Final adjusted model for Pb in each study: *r* (SE), *P* <u>Blood Pb</u> **Yule, 1981 (n=129): -8.08 (4.63), *P* = 0.04** Lansdown, 1986 (n=86): 2.15 (4.48), *P* = 0.68 Ernhart, 1985 (n=80): NA, estimated from data ***P* = 0.04** **Schroeder, 1985 (n=104): -0.199 (0.07), *P* = 0.003** **Hawk, 1986 (n=75): -0.255 (0.15), *P* = 0.05** **Fulton, 1987 (n=501): -3.70 (1.31), *P* = 0.003** **Hatzakis, 1987 (n=509): -0.266 (0.07), *P* = 0.001** **ALL: z=-5.46, *P* < 0.001; weighted *r* = -0.152 (-0.2, -0.1)** <u>Tooth Pb</u> Winneke, 1983 (n=115): -0.125 (4.66), *P* = 0.49 **Needleman, 1985 (n=218): -0.21 (0.07), P = 0.001** Fergusson, 1988 (n=724): -1.46 (1.25), *P* =0.12 Pocock, 1987 (n=388): -0.77 (0.63), *P* = 0.11 **Hansen, 1989 (n=156): -4.27 (1.91), *P* = 0.01** **ALL: z=-2.65, *P* = 0.004; weighted *r* = -0.08 (-0.13, -0.03)**	Blood and tooth Pb were significantly associated with decreases in children's IQ in a meta-analysis of 12 studies.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
					were sued to construct estimates and 95% CIs.	Sensitivity analysis showed that no single study was responsible for the significance of the final findings. The authors concluded that the hypothesis that Pb lowers children's IQ at relatively low dose is strongly supported.	
Retrospective Needleman (1996) Pittsburgh, PA, USA	212 boys from a cohort of students enrolled in the Pittsburgh Youth Study (PYS), boys in the low-Pb group were matched to boys in the high-Pb group; Year not stated Male=100%	12.4 (0.72)	Bone Pb (µg/g) measured at 12 years of age: mean not reported	Child Behavior Checklist (CBCL): teachers' and parents' reports given at ages 7 and 11; subjects' self-reported anti-social behavior scale (SRA) given at subjects mean age of 7.4 years, the Self-reported Delinquency scale (SRD) at subjects mean age of 10.9 years	Analysis of covariates (ANCOVA) Mother's intelligence quotient (Raven's score), mother's highest grade achieved, mother's age at child birth, both parents present in the home, child's age, caregiver's job code, number of siblings, race, and child's health status	Association between bone Pb at age 12 and CBCL Scores OR (95% CI): <u>Attention:</u> **Parent: 19.35 (8.9, 41.6)** Teacher: 1.71 (0.57, 5.1) <u>Delinquency</u> Parent: 1.89 (0.83, 4.3) Teacher: 2.16 (0.96, 4.6) <u>Aggression:</u> Parent: 1.49 (0.45, 4.9) **Teacher: 2.18 (1.03, 4.6)** At 11 years of age, parents reported significant Pb related association with the following CBCL clusters scores: somatic complaints and delinquent, aggressive, internalizing, and externalizing behavior. Teachers reported significant associations of Pb with somatic complaints, anxious/depressed behavior, social problems, attention problems, and delinquent, aggressive, internalizing, and externalizing behavior. CBCL scores were more likely to worsen between 7 and 11 years of age in high-Pb subjects vs. low-Pb subjects Low-Pb group: scored > 30th percentile on the self-reported anti-social scale High-Pb group: scored <70th percentile on the self-reported anti-social scale	Bone Pb at age 12 was significantly associated with increased attention and aggression at age 12, and several self-reported measures of antisocial (age 7.4) and delinquent behavior (age 10.9). The authors suggest that the effect follows a developmental course.
Case-control Needleman (2002) PA, USA	Cases: 194 youths adjudicated as delinquent by the Juvenile Court; Controls: 146 non-delinquent youths from the same high schools Year=1996 – 1998 % male not stated	Range: 12-18 years	Tibia bone Pb (ppm) Cases: 11.0 (32.7) Controls: 1.5 (32.1)	Delinquents (cases) were youths arrested and adjudicated by the Juvenile Court as delinquent	Logistic regression Race, parents' education and occupation, presence of two parental figures in the home, number of children in the home, neighborhood crime rate.	Odds ratio for delinquency by tibia bone Pb All subjects: **AdjOR (95% CI)=3.7 (1.3, 10.5)** Whites: **AdjOR (95% CI)=3.8 (1.1, 13.3)** African Americans: **AdjOR (95% CI)=2.2 (0.5, 10.0)**	Tibia bone Pb was significantly associated with delinquency (arrest and adjudication) in white and African-American youth (age 12-18).

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross sectional Nicolescu (2010) Romania	83 children 8 to 12 years old from Bucharest (n=37) and Pantelimon (n=46) without symptoms Year = 2006-2007 % male not stated	9.9 (SD not reported)	Bucharest: 3.2 Pantelimon:5.1 (SDs not reported) Median (1%, 99%) for both towns: 3.7 (1.1, 14.2)	Neurobehavioral measures of attention with 4 (of 7) attention tasks from the ADHD-tailored German KiTAP-battery and behavioral ratings from parents and teachers: ICD-10 (hyperactivity), DSM-IV (attention deficit), and the foreign assessment for attention deficit/hyperactivity disorders in Romanian *Blood Hg and Al also measured*	Multiple linear regression Adjusted for town, gender, age, computer experience, handedness, eye problems, number of siblings, parental education, maternal smoking during pregnancy, maternal alcohol during pregnancy, and family psychopathology	<u>KiTAP performance correlation with blood Pb</u> Response Time Alertness:0.14 **Errors, Alertness: 0.25, *p* < 0.05** Response Time Go-No-Go: 0.21 **False Alarm Rate Go-No-Go: 0.33, *p* < 0.01** Response Time Distractibility:-0.02 **False Alarm Rate Distractibility 0.23, *p* < 0.05** **Response Time Flexibility: 0.31, *p* < 0.01** **False Alarm Rate Flexibility: 0.45, *p* < 0.01** <u>ADHD correlation with blood Pb: Parents/Teachers</u> **Inattention: 0.32, p < 0.01/0.26, p < 0.05** Hyperactivity: **0.30, p < 0.01**/0.12 Impulsivity: **0.33, p < 0.01**/ 0.15 **ADHD-total: 0.33, p < 0.01/0.22, p < 0.05** <u>Adjusted Change in KiTAP False Alarm Rate with a doubling of blood Pb</u>: % change (95% CI), *p* value Alertness: 14 (-13, 58), *p* > 0.10 Go-No-Go: 28 (-0.05, 72), *p* = 0.09 **Distractibility: 35(-0.01, 84), *p* = 0.05** Flexibility: 28% (-10, 84), *p* > 0.10 There were no increases with Response Time <u>Adjusted Change in Parental ADHD with a doubling of blood Pb:</u> % change (95% CI), *p* value Inattention: 4, (-12, 23), *p* > 0.10 Hyperactivity: 17(-0.02, 41), *p* = 0.08 **Impulsivity: 23(-0.01, 52), *p* = 0.05** ADHD total: 11 (-0.06, 29, *p* > 0.10 <u>Adjusted Change in Teacher's ADHD with a doubling of blood Pb:</u> % change (95% CI), *p* value Inattention: 14 (-0.05, 36), *p* > 0.10 Hyperactivity: 14 (-0.07, 39), *p* > 0.10 Impulsivity: 21 (-0.04, 52), *p* = 0.09 ADHD total: 16 (-0.02, 37), *p* = 0.08 Restriction to children with blood Pb <10 µg/dl had only a marginal influence on outcome (data not shown). *Hg and Al were not associated*	Blood Pb levels were associated with ADHD-related behaviors in children from 8-12 years of age.
Case-control Nigg (2008) USA *Population may overlap with Nigg (2010)*	150 children participated (47 with ADHD Predominantly Inattentive type, 50 with ADHD-Combined type, and 53 control subjects)	14 years Range 8-17 years	<u>Child blood Pb</u> 1.03 (SE 0.04) µg/dL Range 0.40-3.47 <u>Maternal blood Pb</u> (at the time of assessment): mean not stated	Attention-deficit/hyperactivity disorder (ADHD) measured with the Child Behavior Checklist (CBCL), Conners Rating Scale-Revised (CRS),	Pearson Correlation Gender, family income, age	<u>Unadjusted blood Pb and ADHD diagnosis</u>: mean (SD) ADHD-PI: 0.95 (0.46) ADHD-C: 1.26 (0.67) Control: 0.89 (0.39) **p-value=<0.01** <u>Pearson Correlations of Blood Pb with Behavioral Measures</u>: Child Pb; Maternal Pb **Child Estimated FSIQ: C -0.18, p<0.05;** M 0.10;	Concurrent blood Pb levels were statistically significantly higher in ADHD-combined type

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	Year not stated % Male: Controls=60%, ADHD-PI=49% ADHD-C=80%		Range 0-5.3 Correlation with child blood Pb: r = 0.16, p = 0.053	and the ADHD Rating Scale; Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-E); Wechsler Intelligence Scales for Children-4th Edition (WISC-IV); Wechsler Individual Achievement Test-2nd Edition (WIAT-II); Cognitive control assessed by Stop task ADHD diagnosed independently by two licensed clinicians.		**DSM-IV Inattention: C 0.18, p<0.05;** M -0.10; Not significant after adj for income and gender **DSM-IV Hyperactivity: C 0.31, p<0.01;** M 0.03; **After adj for income and gender, p<0.05** **After adj for Inattention: *β* = 0.19, p=0.001** **DSM-IV ADHD: C 0.24, p<0.01;** M -0.10; DSM-IV Conduct Disorder: C 0.02; **M 0.21, p<0.05;** CRS Cognitive Problems: C 0.14; M -0.10; **CRS Hyperactivity: C 0.25, p<0.01;** M -0.10; **CRS Oppositional: C 0.18, p<0.05;** M -0.06; **CRS ADHD Index: C 0.17, p<0.05;** M -0.06; **CBCL Attention Problems: C 0.21, p<0.05;** M -0.09; The authors use path models to show blood Pb levels were linked with a lower IQ (p<0.05), but that IQ did not account for effects on hyperactivity. Instead, they state that hyperactivity mediated effects of Pb on IQ. This effect was independent of effects of Pb on IQ. The also show that cognitive control mediates the effect of blood Pb on ADHD hyperactive-impulsive symptoms with income, gender, and age covaried.	than in non-ADHD control children. Blood Pb was significantly correlated with hyperactivity-impulsivity after controlling for covariates. Blood Pb was also significantly associated with lower IQ scores, but IQ did not account for the effects on hyperactivity.
Case-control Nigg (2010) USA *Population may overlap with Nigg (2008)*	236 children participated (61 ADHD-Combined type, 47 ADHD Predominantly Inattentive type, 99 non-ADHD control, 29 unclassified borderline, situational or not otherwise specified cases). There were 78 sibling pairs (n=156 siblings) Year= % Male: Control-43%; NOS=48%; ADHD-PI=68%; ADHD-C=74%	6-17 years	Child unadj. Blood Pb: Control= 0.20 (0.30) NOS=0.78 (0.24) ADHD-PI=0.72 (0.35) ADHD-C=0.88 (0.44) All: 0.73 (0.04)	ADHD diagnosed by a semi-structured clinical interview (Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS-E) completed by parents; ADHD rating scale and Conners ADHD Rating Scale completed by parents and teachers; IQ measured by WISC-IV; academic achievement estimated by WIAT-2; behavior disorders measured by DSM-IV	Regression models Household income, maternal smoking, child age, child sex, child hemoglobin level; IQ	<u>Regression of child blood Pb with parent-reported ADHD symptoms</u>: standardized results, parameter (SE) <u>KSADS Lifetime</u> Inattention: 0.11(0.07); NS **Hyp-Imp: 0.18 (0.06); p<0.001** <u>Conners</u> **Cognitive: 0.20 (0.07); p<0.01** **Hyp-Imp: 0.25 (0.07); p<0.001** <u>Regression of child blood Pb with teacher behavior ratings</u>: standardized results, parameter estimates (SE) <u>ADHD Rating Scale</u> Inattention: 0.06 (0.06); NS Hyp-Imp: 0.09 (0.06) ; NS <u>Conners</u> **Cognitive: 0.15 (0.06); p<0.05** Hyp-Imp: 0.11 (0.06); NS	Concurrent blood Pb was significantly associated with parent and teacher reported Conners cognitive impairments and reports of hyperactive-impulsiveness by parents in children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Nordberg (2000) Stockholm, Sweden	762 participants of the Kungsholmen Project registered in 1987; Years (follow-up)= 1994-1996; Male=23%	87.3 (4.9) (all ≥75 years)	3.7 (2.3) Men = 4.6 Women = 3.5	Cognitive function measured on the Mini-Mental State Examination (MMSE)	Student's t-test; Chi-squared test; multiple regression	No relationship was found between Pb concentrations and MMSE [data not reported]	Pb blood levels were not significantly associated with cognitive function (by MMSE) in elderly people.
Prospective nested case-control Opler (2004, 2005) Oakland, CA, USA *Population may overlap with Opler (2008)*	44 cases (with schizophrenia) and 75 matched controls from a cohort of live births in the Prenatal Determinants of Schizophrenia (PDS) study; Years: enrolled 1959-1967 % male not stated	mean not reported 15 - 22 years	Dichotomized maternal blood Pb in the 2nd trimester (≥ 15 or <15, estimated from δ -ALA ≥9.05 ng/ml)	Schizophrenia (includes schizophrenia, schizoaffective disorder schizophrenia, schizotypal personality disorder, delusional disorder, and nonaffective psychoses not otherwise specified)	Logistic regression Maternal age	Odds ratios for schizophrenia associated with 15 µg/dL blood Pb (estimated from delta-ALA≥9.05) by conditional logistic regression: Adj. OR (95 %CI)= 2.43 (0.99, 5.96), p =0.051	Maternal blood Pb ≥15 µg/dL in the 2nd trimester was significantly associated with a greater odds ratio for schizophrenia at borderline significance (p=0.51) in 15-22 year old children.
Pooled prospective nested case-control Opler (2008) Oakland, CA; Providence, RI; and Boston, MA, USA *Population may overlap with Opler (2004, 2005)*	71 cases (with schizophrenia) and 129 matched controls (44 cases and 75 controls from the Prenatal Determinants of Schizophrenia (PDS) study and 27 cases and 54 controls from the New England cohort of the National Collaborative Perinatal Project (NE-NCPP);Year= 1959-1966 and 1969-1967; % male not stated	Not stated	Dichotomized to maternal blood Pb in 2nd trimester of ≥ 15 or <15 (estimated from δ -ALA)	Schizophrenia (includes schizophrenia, schizoaffective disorder schizophrenia, schizotypal personality disorder, delusional disorder, and nonaffective psychoses not otherwise specified)	Multilevel random-intercept logistic regression Maternal age and maternal education	Odds ratios for schizophrenia associated with 15 µg/dL blood Pb (estimated from delta-ALA≥9.05) in PDS and NE-NCPP: Conditional logistic regression: **Adj.OR (95% CI)= 2.17 (1.12-4.17), p-value=0.020** Random intercept logistic regression: **Adj.OR (95% CI)= 1.92 (1.05-3.52), p=0.035**	Maternal blood Pb ≥15 µg/dL in the 2nd trimester was significantly associated with a greater odds ratio for schizophrenia in 15-22 year old children.
Cross-sectional Osman (1999)	155 children from three towns in the	8.1 (2.1); Range: 4-14	Median: 7.2 Range: 1.9-28.1	Hearing was measured by	Multiple linear regression	Blood Pb and right and left hearing thresholds at different frequencies (covariates in model): *B* (95% CI)	Concurrent blood Pb was

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Poland	Katowice region - an industrial area in Poland, selected from the Katowice Lead Monitoring Programme cohort and the town of Bytom. Year not stated Males=52%		Children were selected based on blood Pb measured 1-3 years prior to current study (with a new blood Pb measure). 120 (42%) over 15µg/dL and 92 (33%) below 5µg/dL were invited to participate. 54% chose to participate.	audiologic tests (screening tympanometry) and BAEPs recording	Age, gender, 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	Right ear: **0.5 kHz (age): 0.054 (0.035, 0.074)** **1 kHz (age, Apgar): 0.044 (0.026, 0.062)** **2 kHz (age, Apgar): 0.048 (0.029, 0.066)** **4 kHz (Apgar): 0.060 (0.039, 0.081)** **6 kHz(Apgar): 0.068 (0.044, 0.092)** **9 kHz(Apgar): 0.072 (0.050, 0.094)** Left ear: **0.5 kHz (age): 0.051 (0.026, 0.075)** **1 kHz (Apgar, gentamycin): 0.032 (0.014, 0.050)** **2 kHz (Apgar): 0.036 (0.019, 0.053)** **4 kHz (Apgar): 0.039 (0.020, 0.059)** **6 kHz (Apgar, no ear pathol.): 0.026 (0.004, 0.049)** **8 kHz (Apgar): 0.047 (0.024, 0.070)** No significant associations between BAEPs latencies in the whole study group (data not shown, except below). After adjusting for age, the effect of Pb for latency of wave I: B=0.057 (0.016-0.098), *P* = 0.052	significantly associated with increased hearing thresholds in children at all frequencies tested.
Prospective and cross-sectional Otto (1985) NC, USA	49 children (48 from low-income black families considered to be at risk for Pb poisoning) evaluated and followed up for 5 years. Baseline Year = 1977-1978 Male=53%	6-12 years	Baseline mean: 28 range 6-59 Current (5 years after baseline) mean: 14 range: 6-30 Correlation of baseline and current blood Pb = 0.74	Sensory function tests: slow wave voltage measured during passive sensory conditioning, active sensory conditioning, electro-encephalograph/electro-oculograph, brainstem auditory evoked potential (BAEP), Pattern-reversal evoked potentials for neurological assessment of visual system.	Multivariate regression Age, SES, gender, maternal IQ, and HOME	<u>Regression of baseline blood Pb and slow wave voltage during passive conditioning:</u> Pb quadratic: *F* = 1.18 (3,41df), *P* = 0.33 Current blood Pb was not associated <u>Regression of current blood Pb and slow wave voltage during active conditioning</u>: **Multivariate: *F* = 2.85 (6,39df), *P* = 0.02** Univariate: Frontal Cortex (500-1000msec): *P* = 0.15 Central Cortex (500-1000msec): *P* = 0.37 Parietal Cortex (500-1000msec): *P* = 0.71 **Frontal Cortex (1000-1500msec): *P*=0.025, r^2=0.11** **Central Cortex (1000-1500msec): *P*=0.046, r^2=0.09** **Parietal Cortex (1000-1500msec): *P*=0.002*, r^2=0.20** (*SES and maternal IQ kept in model) Baseline blood Pb was only significant at Parietal Cortex, 1000-1500msec (data not shown) <u>Regression of baseline blood Pb and BAEP latencies:</u> Multivariate: *F* = 2.32 (3,41df), *P* = 0.09 Univariate: Wave I: *F* = 2.15 (3,51df), *P* = 0.15 **Wave III: *F* = 9.06 (1,41df), *P* = 0.004*** (*sex kept in model) **Wave V: *F* = 8.67 (1,41df), *P* = 0.005**** (**sex and HOME kept in model) IPL V-1: *F* = 1.29 (1,42df), *P* = 0.26* (*sex kept in model)	Concurrent blood Pb was significantly associated with increased slow wave negativity during active conditioning but not during passive conditioning. Prior blood Pb, but not current blood Pb, was significantly associated with brainstem auditory evoked potential - suggestive of subclinical pathology of the auditory pathway. Significant associations

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						IPL V-III: *F* = 0.14 (1,43df), *P* = 0.71 IPL III-I: *F* = 2.16 (1,44df), *P* = 0.15 Current blood Pb was not associated with BAEP latencies (data not shown) <u>Regression of baseline blood Pb and pattern-reversal visual evoked potential latencies and amplitude:</u> Multivariate: *F* = 1.87 (3,39df), *P* = 0.15 Univariate: N1 latency: *F* = 0.09 (1,41df), *P* = 0.77 P1 latency: *F* = 1.03 (1,41df), *P* = 0.32 **N2 latency: *F* = 5.65 (1,41df), *P* = 0.022** **N1P1 amplitude: *F* = 7.22 (1,40df), *P* = 0.01*** (*SES kept in model) Current blood Pb had similar results, except N2 latency was not associated (data not shown). The significant associations were not in the predicted direction.	between concurrent and prior blood Pb with visual evoked potentials were not in the predicted direction.
Cross-sectional Park (2010) Boston, MA, USA *Population may overlap with Payton (1998) and others*	448 men from the Normative Aging Study Year= 1993-1996; (initially enrolled in 1963) Male= 100%	At bone Pb measurement: 64.9 (7.3) At first audiometric test: 42.5 (8.4)	Tibia Pb (µg/g): 22.5 (14.2) Patella Pb (µg/g): 32.5 (20.4)	Age-related hearing loss measured by hearing threshold examination at frequencies (kHz) 0.25, 0.5, 1, 2, 3, 4, 6 and 8.	Linear model (cross-sectional) and linear mixed effects model (longitudinal) Full adjustment included age, race, education, BMI, pack-years of cigarettes, diabetes, hypertension, occupational noise, and noise notch	<u>Adjusted effects estimates in hearing threshold (dB HL) with one IQR increase in bone Pb</u>: Estimate (95% CI) Tibia Pb (n=448; IQR = 15µg/g) 0.25 kHz: 0.42 (-0.38, 1.21) 0.5 kHz: 0.07 (-0.68, 0.82) 1 kHz: 0.22 (-0.65, 1.10) 2 kHz: 1.10 (-0.43, 2.62) 3 kHz: 1.17 (-0.72, 3.06) **4 kHz: 2.18 (0.13, 4.23), *p* < 0.05** 6 kHz: 1.71 (-0.28, 3.71) 8 kHz: 1.75 (-0.35, 3.86) Pure Tone Average (PTA): 0.83 (-0.18, 1.83) Patella Pb (n=447; IQR = 21µg/g) 0.25 kHz: 0.56 (-0.21, 1.33) 0.5 kHz: 0.50 (-0.23, 1.23) 1 kHz: 0.80 (-0.05, 1.64) **2 kHz: 1.81 (0.34, 3.28), *p* < 0.05** **3 kHz: 2.32 (0.50, 4.15), *p* < 0.05** **4 kHz: 3.43 (1.46, 5.41), *p* < 0.001** **6 kHz: 2.54 (0.61, 4.47), *p* < 0.05** **8 kHz: 2.65 (0.61, 4.68), *p* < 0.05** **Pure Tone Average (PTA): 1.58 (0.62, 2.55), *p* < 0.01** <u>Adjusted odds ratios in air conduction PTA hearing loss for a one IQR increase in bone Pb</u>: AdjOR (95% CI) Tibia Pb: 1.19 (0.92, 1.53) **Patella Pb: 1.48 (1.14, 1.91)** <u>Longitudinal adjusted effects estimates from hearing thresholds with a 1 IQR increase in tibia Pb for a time x</u>	Patella Pb was significantly associated with poorer hearing thresholds and age-related hearing loss, while tibia Pb was not. In longitudinal analyses, tibia Pb was significantly associated with the rate change in hearing thresholds at 1, 2, and 8Hz.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						tibia interaction term: β (SE) 0.25 kHz: 0.026 (0.018) 0.5 kHz: 0.026 (0.018) **1 kHz: 0.038 (0.017), $p < 0.05$** **2 kHz: 0.082 (0.026), $p < 0.01$** 3 kHz: 0.045 (0.030) 4 kHz: 0.049 (0.026) 6 kHz: 0.058 (0.003) **8 kHz: 0.090 (0.035), $p < 0.05$** **Pure Tone Average (PTA): 0.050 (0.017), $p < 0.01$** Time alone was significantly associated with hearing loss at all frequencies (all $p < 0.001$) and tibia Pb alone was not associated at any frequency (all $p > 0.05$).	
Prospective Payton (1998) Boston, MA, USA *Population may overlap with Wright (2003) and others*	141 middle-aged to elderly men from the Normative Aging Study (NAS); Year= 1993-1994 (initially enrolled in 1963) Male=100%	66.8 (6.8)	Blood Pb: 5.5 (3.5) Patella Pb (µg/g): 31.7 (19.2) Tibia Pb (µg/g): 22.5 (12.2)	Cognitive tests: Neurobehavioral Evaluation System (NES2) measuring continuous performance, and pattern comparison, pattern memory; the Wechsler Adult Intelligence Scale-Revised (WAIS-R) measuring digit span and backward, vocabulary; the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) measuring word list memory, constructional praxis, Boston naming test, and verbal fluency	Backwards-elimination multivariate linear regression; Pearson correlation coefficients; smooth plots Age, education	Regression models of cognitive outcomes in relation to blood, tibia, and patella Pb β(SE): Continuous performance (sustained attention) (ms): Blood Pb: 0.256 (1.393); p=0.90 Tibia Pb: -0.381 (0.416); p=0.40 Patella Pb: -0.475 (0.258); p=0.07 Pattern Comparison (perceptual speed) (s): **Blood Pb: 0.074 (0.032); p=0.020** Tibia Pb: 0.011 (0.010); p=0.30 Patella Pb: 0.005 (0.006);p=0.50 Pattern comparison (perceptual speed) (total # correct): Blood Pb: 0.012 (0.032); p=0.70 Tibia Pb: 0.014 (0.010); p=0.20 Patella Pb: 0.004 (0.006); p=0.10 Pattern Memory (immediate visual memory) (s): Blood Pb: .062 (0.037); p=0.10 Tibia Pb: 0.021 (0.011); p=0.053 Patella Pb: 0.011 (0.007); p=0.10 Pattern Memory (immediate visual memory) (total # correct): Blood Pb: -0.054 (0.073); p=0.50 Tibia Pb: 0.022 (0.023); p=0.30 Patella Pb: 0.018 (0.014); p=0.20 Digital Span Backward (auditory working memory) (total#): Blood Pb: -0.036 (0.054); p=0.50 Tibia Pb: 0.015 (0.016); p=0.40 Patella Pb: 0.010 (0.010); p=0.30 Vocabulary (verbal ability) (total #): **Blood Pb: -0.841 (0.200); p=0.0001** Tibia Pb: -0.030 (0.067); p=0.70 Patella Pb: -0.041 (0.039); p=0.30	Blood Pb was significantly associated with slower pattern comparison speed, and a deficit in vocabulary, word list memory, spatial ability and verbal ability. Tibia Pb was significantly associated with a deficit in spatial ability.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (μg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Word List Memory (immediate verbal memory) (total #): **Blood Pb: -0.182 (0.086); p=0.036** Tibia Pb: -0.003 (0.028); p=0.90 Patella Pb: -0.008 (0.017); p=0.60 Constructional praxis (spatial ability) (total #): **Blood Pb: -0.105 (0.039); p=0.008** **Tibia Pb: -0.031 (0.012); p=0.010** Patella Pb: -0.015 (0.007); p=0.053 Boston Naming Test (verbal ability) (total #): **Blood Pb: -0.036 (0.016); p=0.028** Tibia Pb: 0.0002 (0.005); p=1.0 Patella Pb: -0.002 (0.003); p=0.50 Verbal Fluency Test (verbal ability) (total #): Blood Pb: -0.203 (0.120); p=0.09 Tibia Pb: -0.011 (0.039); p=0.80 Patella Pb: -0.005 (0.024); p=0.80	
Cross-sectional Peters (2010) Boston, MA, USA *Population may overlap with Payton (1998) and others*	811 men in the Normative Aging Study; Year=1993-1997; (initially enrolled in 1963) Male = 100%	67.9 (6.99)	Blood : 5.07(.76) Patella (μg/g) 29.8(18.7) Tibia (μg/g) 21.3(13.2) Measured when outcome assessed	Cognitive assessment (Mini-Mental State Examination-MMSE), stress (health and behavior questionnaire and Perceived Stress Scale-PSS)	Multivariable regression Age, education, computer experience, English as a first language, smoking, and alcohol intake	Multiple regression of modifying potential of high stress on relationship of log-Pb and MMSE scores β (95%CI): **Blood Pb β=-0.57 (–0.90,-0.24) (p < 0.05)** **p=0.02 for stress interaction** Patella Pb β=-0.19 (–0.44,0.06) (p>0.05) p=0.06 for stress interaction Tibia Pb β=-0.14 (–0.38,0.10) (p>0.05) p=0.29 for stress interaction. **High Pb (above median blood, patella, or tibia Pb) and or high PSS scores were associated with a 0.05–0.08 reduction on the MMSE for each year of age compared with those with low Pb levels and PSS scores (*p* < 0.05).**	Blood Pb was significantly associated with deceased cognition in older men with higher stress. Although bone Pb alone was not significantly associated with cognition, high stress and blood or bone Pb modify the association between age and cognition.
Prospective Pilsner (2010) Mexico City, Mexico *Population may overlap with Gomaa (2002) and others*	255 mother-child pairs from the Early Life Exposures in Mexico to Environmental Toxicants (ELEMENT) sequential birth cohort recruited	Mothers: 24.6 (5.1) years Children: Pb measured at birth and MDI at 24 months	Maternal bone Pb (1 month postpartum) Tibia: 10.5 (10.4)μg/g Patella: 14.7 (13.7)μg/g Cord blood: 6.7 (3.6)μg/dL	Bayley Mental Development Index at age 24 months (MDI-24) scores *Also studied MTHFR C677T (rs1801133) and A1298C (rs1801131)*	Multiple regression model Adjusted for maternal age, gestational age, maternal IQ, parity, low folate status, and marital status	Maternal MTHFR genotype was related to MDI-24 score, but there was no significant interaction with Pb exposure. *[Maternal bone and child cord blood Pb previously shown to be associated with MDI-24 in Gomaa (2002)]*	*MTHFR* genotype does not significantly modify a previously reported associations of maternal bone and child cord

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	from 3 low to moderate income hospitals; Year: 1994–1995 Male =			*genotype*			blood Pb with child neuro-development.
Meta-analysis; Pocock (1994)	Meta-analysis of 19 studies of Pb and children's IQ since 1979: 5 prospective (Baghurst (1992), Dietrich (1993b), Ernhart (1985), Cooney (1991), and Bellinger (1992)) and 9 cross-sectional blood Pb (Hatzakis (1987), Fulton (1987), Winneke (1990), Silva (1988), Lansdown (1986), Harvey (1988), Wang (1989), Yule (1981), and Winneke (1985)), and 7 cross-sectional tooth Pb (Fergusson (1988a), Smith (1983), McMichael (1994), Fulton (1989), Needleman (1979), Winneke (1983), and Bergomi (1989)).	Children age 5 or more	<u>Pros. Blood Pb (at 2)</u>: Baghurst, 1992: 21.2 Dietrich, 1993: 17.5 Ernhart, 1985: 16.7 Cooney, 1991: 14.2 Bellinger, 1992: 6.8 <u>Cross-Sect blood Pb</u>: Hatzakis, 1987: 23.7 Fulton, 1987: 11.5 Winneke, 1990: Bucharest: 18.9 Budapest: 18.2 Moden:11.0 Sofia:18.2 Dusseldorf, @6: 8.3 Dusseldorf, @8: 7.4 Silva, 1988: 11.1 Lansdown, '86: 12.9 Harvey, 1988: 12.3 Wang, 1989: 21.1 Yule, 1981: 13.5 Winneke, 1985: 8.2 <u>Cross-Sect tooth Pb (µg/g)</u>: Fergusson, 1988: ~6 Smith, 1983: 5.1 McMichael, '94: 8.6 Fulton, 1989: 9.3 Needleman, '79: 12.7 Winneke, '83: 6.2 Bergomi, 1989: 6.1	Children's IQ assessed by the Wechsler intelligence scale for children-revised (WISC-R), Wechsler preschool and primary scale of intelligence (WPPSI), the British ability scale	Multiple regression of full scale IQ on Pb (some original data obtained from study authors to allow comparison) The fixed effect method of Thompson and Pocock (1992) was employed.	Estimated change in IQ (SE) for an increase from 10 to 20 µg/dL blood Pb or 5 to 10µg/g tooth Pb: <u>Prospective, Blood</u>: Adjusted [Unadjusted] Baghurst, 1992: -3.3 (1.6) [-8.5 (1.5)] Dietrich, 1993: -1.3 (0.9) [-2.6 (1.5)] Ernhart, 1985: -1.1 (0.9) [-12.1 (1.5)] Cooney, 1991: 0.39 (2.0) Bellinger, 1992: -5.8 (2.1) [-7.1 (2.5)] <u>Cross-Sectional, Blood</u>: Adjusted [Unadjusted] Hatzakis, 1987: -2.7 (0.7) [-3.8 (0.8)] Fulton, 1987: -2.6 (1.0) [-3.8 (1.1)] <u>Cross-Sectional, Tooth</u>: Adjusted [Unadjusted] Smith, 1983: -0.65 (0.54) [-1.84 (0.6)] **<u>Meta-analysis:</u>** Mean (SE) change in IQ for a doubling of body burden of Pb: Prospective @ birth (n=1166): 0.18 (0.62) Prospective @ 2 yrs (n=1197): -1.85 (0.51) Prospective, mean (n=1260): -0.88 (0.58) Cross-sect. Blood (n=3499): -2.53 (0.41) *Cross-sect. Blood (n=3499): -1.74 (0.43) Cross-sect. Tooth (n=2095): -0.95 (0.25) *Wang, 1989 removed: *P* test for heterogeneity was significant when included. Overall conclusion was that a doubling of blood Pb levels from 10 to 20 µg/dL, or tooth Pb from 5 to 10 µg/g was associated with an avg estimated deficit in IQ of ~1-2 points. Authors caution interpretation of these results and Pb literature in general, citing questions about representativeness of the samples, residual confounding, selection bias, and reverse causality.	Blood and tooth Pb were associated with decreases in children's IQ in a meta-analysis, with prospective studies showing an association with age 2 Pb, but not Pb at birth and tooth Pb showing smaller, but consistent, reductions in IQ as well.
Cross-sectional Prpic-Majic (2000) Zagreb, Croatia	275 3rd and 4th grade students from 3 elementary	Calc. mean age: 9.84 years	Blood Pb at time of testing: 7.08 (1.788)	General cognitive development: Wechsler Intelligence	Multiple stepwise regression	Pb was not independently associated with any cognitive test, but if forced into the models: adjβ (95% CI) VIQ: -0.16 (-0.089, 0.057)	Blood and erythrocyte Pb were not

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	schools in urban areas with different traffic conditions in Zagreb, Croatia; Year not stated Male=52%		*Also measured Pb in erythrocytes, ALAD, EP, hemoglobin, and hematocrit*	Scale for children—Revised (WISC-R) including verbal, (VIQ), nonverbal (NIQ), and general intelligence quotient (IQ); Visual motor integration: Bender Gestalt Test Error Score; Attention and complex psychomotor reactions: Complex Reaction-meter Drenovac	Adjusted for age, parental education, and gender	NIQ: -0.031 (-0.121, 0.060) IQ: -0.025 (-0.099, 0.050) *Erythrocyte Pb was also not associated*	associated with intelligence quotients, visual motor integration, or attention and complex psychomotor reactions.
Cross-sectional (Rabinowitz *et al.* 1992) Taiwan	493 children in grades 1-3 of seven primary schools in Taiwan Year not stated % male not stated	mean not stated grades 1-3	Tooth (dentin) Pb 4.6 (3.5) µg/g	Teachers filled out the Boston Teachers Questionnaire (BTQ) to assess academic performance and behavior.	Logistic regression analysis	Incisor Pb levels (>5.6 ppm (Q4) vs. <2.9 ppm (Q1) with teacher reported academic performance and behavior. Girls: Behavior: X^2=4.9; p-value=0.20 Hyperactive: X^2=2.8; p=0.40 Reading: X^2=2.6; p=0.50 Math: X^2=1.8; p=0.60 Directions: X^2=0.50; p-value=0.90 Daydreaming: X^2=0.60; p-value=0.90 Tasks: X^2= 1.1; p-value=0.80 Boys: Behavior: X^2=5.2; p-value=0.16 **Hyperactive: X^2=6.2; p=0.10; X^2 for trend<0.01** Reading: X^2=5.7; p=0.13 Math: X^2=2.4; p=0.50 Directions: X^2=2.7; p-value=0.40 Daydreaming: X^2=0.80; p-value=0.90 **Tasks: X^2= 13.5; p-value=0.004; X^2 for trend<0.005**	Tooth Pb was significantly associated with learning problems (BTQ hyperactivity and tasks) in school aged boys.
Prospective Rajan (2007) Boston, MA, USA *Population may overlap with Payton (1998) and others*	744 participants from the Normative Aging Study (NAS) for whom bone and blood Pb measurements and psychological assessment data was available; Year= 1991 – 2002 (initially enrolled in	67 (7) years	Blood: 6.2 (4.1) µg/dL Tibia: 22.1 (13.8) µg/g Patella: 31.4 (19.6) µg/g Measured beginning in 1991 and	Psychiatric symptoms were assessed by the Brief Symptom Inventory, a self-administered 53-item questionnaire that assesses nine primary symptom dimensions in the last 30 days: anxiety,	Repeated-measures logistic regression models. Age at bone scan, alcohol consumption, education, time between Brief Symptom Inventory assessments, and cumulative smoking	adjOR (95% CI) for an interquartile increment in tibia Pb (14 µg/g) and psychiatric symptoms: Phobic anxiety = 1.13 (0.90, 1.41) **Somatization = 1.21 (1.01, 1.46)** Global severity index = 1.15 (0.96, 1.38) adjOR (95% CI) corresponding to an interquartile increment in patella Pb (20 µg/g): Phobic anxiety = 1.24 (0.99, 1.55) Somatization = 1.09 (0.90, 1.32) **Global severity index = 1.23 (1.02, 1.47)**	Cumulative bone Pb burden was associated with the increased risk of psychiatric symptoms, and significantly associated with somatization (tibia) and

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	1963) Male=100%		subsequently at 3-year intervals in a 6-year period	depression, hostility, interpersonal sensitivity, obsessive-compulsive, paranoid ideation, phobic anxiety, psychoticism, somatization			global severity index (patella)
Cross-sectional Rajan (2008) Boston, MA, USA *Population may overlap with Payton (1998) and others*	982 men from the Normative Aging Study, ; Year=1993-2001 (initially enrolled in 1963) Male=100%	≥49 years 49-61: n=151, 15.4% 62-71: n=474, 48.3% ≥72: n=357, 36.3% *ALAD 1-1:* 49-61 (n=133) 62-71 (n=398) ≥72 (n=287) *ALAD 1-2 & 2-2:* 49-61 (n=18) 62-71 (n=76) ≥72 (n=70)	Calc. means: Blood: 5.3µg/dL Tibia: 21.8µg/g Patella: 29.1µg/g *ALAD 1-1 (n=818)*: Blood: 5.4 (2.9) Tibia: 21.9 (13.8) Patella: 29.3 (19.1) *ALAD-2* carriers (1-2 and 2-2 genotypes, n=164): Blood: 4.8 (2.7) Tibia: 21.2 (11.6) Patella: 27.9 (17.3)	Cognitive test battery included: Consortium to Establish a Registry for Alzheimer's Disease (CERAD; visuospatial, executive function, language, and immediate and delayed verbal memory), the Neurobehavioral Evaluation System (NES; visuospatial, perceptual speed, and visual memory), and the Wechsler Adult Intelligence Scale (WAIS; working memory and general intelligence). All cognitive tests converted to z-scores with a positive score indicating better test performance. *ALAD exon 4 SNP (rs1800435) also genotyped*	Multiple linear regression models (with a smoothing parameter for Pb biomarker, if significantly different from a linear model a likelihood ratio test) Adjusted for main effect of Pb biomarker, *ALAD* genotype age at cognition test, education, alcohol consumption, cumulative smoking, and English as a first language	Adjusted difference in Test z Score Per IQR higher Pb concentration: ALAD 1-2/2-2 vs. ALAD 1–1: Pb*ALAD Parameter Estimate (95% CI) <u>Visuospatial</u> Constructional praxis Blood (n=959): -0.05 (-0.23, 0.13) **Tibia (n=728): -0.25 (-0.49, -0.02), p<0.05** Patella (n=728): 0.02 (-0.19, 0.23) Pattern Memory Blood (n=490): 0.19 (-0.05, 0.42) Tibia (n=397): 0.12 (-0.20, 0.44) Patella (n=395): 0.12 (-0.16, 0.39) Pattern Comparison Blood (n=907): -0.01 (-0.20, 0.18) Tibia (n=705): -0.04 (-0.28, 0.20) Patella (n=705): -0.09 (-0.31, 0.13) <u>Executive function/language/general intelligence</u> Verbal fluency Blood (n=916): -0.03 (-022, 0.16) Tibia (n=709): -0.11 (-0.34, 0.13) Patella (n=709): -0.025 (-0.24, 0.19) Boston naming test Blood (n=500): 0.04 (-0.20, 0.29) Tibia (n=403): -0.16 (-0.50, 0.18) Patella (n=401): -0.15 (-0.44, 0.13) Vocabulary Blood (n=501): -0.21 (-0.43, 0.01), p<0.1 Tibia (n=401): -0.27 (-0.60, 0.05) Patella (n=399): -0.15 (-0.42, 0.12) <u>Verbal memory/working memory</u> Word list memory Blood (n=913): 0.003 (-0.18, 0.19) Tibia (n=708): 0.08 (-0.15, 0.31) Patella (n=708): 0.14 (-0.07, 0.34) Word list delayed recall Blood (n=912): -0.05 (-0.23, 0.13) Tibia (n=707): 0.13 (-0.10, 0.36)	There was no clear pattern of *ALAD* modifying the relationship of Pb to cognition, the cognitive test with a significant *ALAD*-bone interaction were also significantly associated with cumulative Pb burden in a previous report on these same subjects (see Weisskopf et al. (2007b)).

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Patella (n=707): 0.09 (-0.12, 0.30) Digit span backward (total number) Blood (n=863): -0.17 (-0.36, 0.03) Tibia (n=678): -0.12 (-0.36, 0.12) Patella (n=677): -0.005 (-0.22, 0.22) Digit span backward (longest span) Blood (n=864): -0.14 (-0.33, 0.06) Tibia (n=679): -0.06 (-0.30, 0.18) Patella (n=678): 0.02 (-0.20, 0.24) Perceptual speed Continuous performance Blood (n=486): -0.18 (-0.42, 0.06) Tibia (n=392): -0.25 (-0.59, 0.08) Patella (n=390): -0.16 (-0.44, 0.12) Pattern memory Blood (n=490): -0.04 (-0.28, 0.19) Tibia (n=397): -0.08 (-0.41, 0.26) Patella (n=395): 0.06 (-0.22, 0.35) Pattern comparison Blood (n=907): 0.02 (-0.16, 0.20) Tibia (n=705): 0.04 (-0.19, 0.27) Patella (n=705): 0.21 (0.001, 0.41), p<0.1	
Cross-sectional Rhodes, (2003) Boston, MA, USA *Population may overlap with Payton (1998) and others*	526 men in the Normative Aging Study; Year= 1991-1995; (initially enrolled in 1963) Male = 100%	67.1 (7.20) years	Blood: 6.3 (4.16) µg/dL Tibia: 21.9 (13.5) µg/g Patella: 32.2 (19.8) µg/g Bone generally measured within 1 month of blood and BSI (excluded if >3 months)	Mood symptoms evaluated with Brief Symptom Inventory (BSI) included in the Health and Social Behavior Survey at the time of blood collection Measures include: anxiety ≥0.5 (n=77), depression ≥0.5 (n=85), phobic anxiety ≥0.2 (n=40), general severity index > 0.44 (GSI, n=71), positive symptom total >18 (PST, n=83), and combined BSI measure (≥0.5 anxiety, ≥0.5 depression, and ≥0.2	*T* tests were used to compare Pb levels with BSI measures Logistic regression models for each BSI outcome (â) Adjusting for age, age^2, alcohol intake, employment status, and education status Odds ratios estimated from β coefficients for an increase from the midpoints of the lowest to the highest quintile	Anxiety: mean ≥0.5, mean <0.5, p; â (SE), *P* Blood: 6.5, 6.2, NS; 0.0241 (0.0293), 0.41 Tibia:22.4, 21.8, NS; 0.0046 (0.0097), 0.64 Patella:35.6, 31.5, p<0.1; 0.0112 (0.0062), 0.07 Depression: mean ≥0.5, mean <0.5, p; â (SE), *P* Blood: 6.6, 6.2, NS; 0.0275 (0.0285), 0.33 Tibia: 23.4, 21.6, NS; 0.0067 (0.0090), 0.45 **Patella: 36.5, 31.3, p<0.05**; 0.0109 (0.0059), 0.07 Phobic Anxiety: mean ≥0.2, mean <0.2, p; â (SE), *P* Blood: 7.3, 6.2, NS; 0.0541 (0.0349), 0.12 **Tibia: 26.3, 21.5, p<0.05;** 0.0151 (0.0107), 0.16 **Patella: 40.3, 31.5, p<0.05; 0.0144 (0.0072), 0.05** GSI: mean >0.44, mean 0.44, p; â (SE), *P* Blood: 6.8, 6.2, NS; 0.0436 (0.0291), 0.13 Tibia: 23.5, 21.6, NS; 0.0036 (0.0098), 0.72 Patella: 36.3, 31.5, p<0.1; 0.0082 (0.0064), 0.20 PST: mean >18, mean 18, p; â (SE), *P* Blood: 6.4, 6.3, NS; 0.0161 (0.0293), 0.58 Tibia: 23.4, 21.6, NS; 0.0058 (0.0092), 0.53 Patella: 35.3, 31.5, p<0.15; 0.0071 (0.0061), 0.25 Combined BSI: mean >, mean <, p; â (SE), *P* **Blood: 8.8, 6.2, p<0.05; 0.1201 (0.0423), 0.005** **Tibia: 31.8, 21.5, p<0.05; 0.0271 (0.0127), 0.03**	Blood and tibia, and patella Pb were significantly associated with a combined mood measure (including elevated anxiety, depression, and phobic anxiety); patella Pb was significantly associated with depression; and tibia and patella Pb were significantly associated with phobic anxiety.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				phobic anxiety, n=20)		**Patella: 51.8, 31.4, p<0.05; 0.0286 (0.0091), 0.002** Odds Ratio and 95% CI for a low-high quintile increase: **Phobic Anxiety, Patella (45µg/g): 1.91 (1.01-3.61)** **Combined BSI, Blood (8.9µg/dL): 2.91 (1.39-6.09)** **Combined BSI, Tibia (27µg/g): 2.08 (1.06-4.07)** **Combined BSI, Patella (45µg/g): 3.62 (1.62-8.08)**	
Prospective Ris (2004) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	195 children from the Cincinnati Lead Study (CLS); Year=1997-1999 Male=54%	15.6 (0.8) Range: 15-17	Maternal prenatal = 8.9 (3.9) measured in 1st or early 2nd trimester Average Childhood (first five years) mean not reported 78 months (6.5 years) mean not reported	Neuropsychological measures: executive (Wisconsin Card Sorting Test-WCST; Rey-Osterrieth Complex Figure-ROCF), attention (Continuous Performance Test-CPT), memory (California Verbal Learning Test-CVLT-C), achievement (Wide Range Achievement Test-3rd Ed-SRAT-3); verbal (vocabular subtest), visuoconstruction (Block Design Subtest-BD), fine-motor (Grooved Pegboard Test-Gpegs; Finger Tapping Test-Tapping)	Stepwise multiple regression Adjustments differ by endpoint including maternal IQ, SES, and average HOME score, sex, and adolescent marijuana consumption,	Adjusted relationships between neuropsychological factors and blood Pb variables: Memory Prenatal Pb: β (SE)= -0.002 (0.02), p=0.89 Avg Childhood Pb: β (SE)= 0.003 (0.015), p=0.79 78 months Pb: β (SE)= 0.013 (0.17), p=0.43 Learning/IQ Prenatal Pb: β (SE)= -0.075 (0.54), p=0.17 Avg Childhood Pb: β (SE)= -0.034 (0.029), p=0.25 78 months Pb: β (SE)= -0.081 (0.043), p=0.06 Attention **Prenatal Pb: β (SE)= -0.156 (0.06), p=0.001** **Avg Childhood Pb: β (SE)= -0.133(0.04), p= 0.005** **78 months Pb: β (SE)= -0.119 (0.051), p= 0.02** **Authors state a significant blood Pb x sex interaction (p<0.003-0.0004) with significant associations for males only**. Visuoconstruction **Prenatal Pb: β (SE)= -0.157 (0.061), p= 0.011** Avg Childhood Pb: β (SE)=-0.028 (0.041), p=0.50 78 months Pb: β (SE)=0.014 (0.052), p=0.79 **Authors state a significant blood Pb x sex interaction (p<0.27-0.05) with significant associations for males only**. Fine-motor Prenatal Pb: β (SE)= -0.017 (0.02), p= 0.42 Avg Childhood Pb: β (SE)= -0.016 (0.013), p=0.21 **78 months Pb: β (SE)= -0.046 (0.016), p= 0.004**	Maternal prenatal blood Pb was significantly associated with decreased attention and visuo-construction scores; blood Pb at 78 months was associated with decreased attention and fine-motor scores; and average childhood blood Pb was significantly associated with decreased attention scores – all neuropsychological measures at age 15-17.
Prospective Rothenberg (1989) Mexico City, Mexico *Population may overlap with Rothenberg (1994)*	42 infants in the Mexico City Prospective Lead Study of women recruited at the National Institute of Perinatology and the General Hospital in Mexico	48 hours; 15 and 30 days	Maternal at 36 weeks: 15.0(6.4) Maternal at delivery: 15.5(5.7) Cord: 13.1(6.0)	Brazelton Neonatal Behavioral Assessment Scale (NBAS) administered in the hospital and at 15 and 30 days after birth; 7 NBAS cluster scales calculated from each NBAS	Bivariate correlations; forward multiple regression analyses; multiple regression analyses	Effect of Pb on NBAS scales in multiple regression models: Difference in maternal Pb (36 weeks and delivery) **Regulation of State (15 days):** **Partial r^2=0.068; p=0.049; coefficient=0.101** Regulation of State (30 days): Partial r^2=0.061 ; p= 0.055; coefficient = 0.091 Autonomic Regulation (30 days): Partial r^2= 0.048 ; p=0.073; coefficient=-0.022	Change in maternal blood Pb level between 36 weeks and delivery predicted NBAS regulation of state at 15

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
and others	City on or before their 36th week of pregnancy. Year not stated % male not stated			protocol sheet		 <u>Maternal at delivery and cord</u> Regulation of State (30 days): Partial r^2= 0.071 ; p=0.042; coefficient = -0.136 <u>Difference between Maternal at 36 weeks and cord Pb</u> **Autonomic Regulation (30 days):** **Partial r^2= 0.047; p=0.047; coefficient= -0.024**	days. Difference in maternal Pb at 36 weeks and cord Pb predicted NBAS autonomic regulation at 30 days
Prospective Rothenberg (1994) Mexico City, Mexico *Population may overlap with Rothenberg (1989) and others*	30 babies, the last born in the Mexico City Prospective Lead Study of women recruited from the National Institute of Perinatology and the General Hospital in Mexico City at a gestational age range of 36.5-41.9 weeks and no major congenital. anomalies; Year not stated % male not stated	Median: 9 days (range 2 - 39 days); 3 months	mean not reported Maternal blood Pb measured 12, 20, 28, 36 weeks, delivery; cord Pb measured at birth	Brainstem auditory evoked responses (BAER)	Pearson correlation	Pearson correlation for maternal blood Pb (at 12, 20, 28, or 36 weeks of pregnancy; delivery and cord blood Pb): <u>Latency of Wave I</u> **20 wks r=-0.42; p=0.03** <u>Latency of Peak II</u> **20 wks r=-0.39; p=0.04** **28 wks r=-0.51; p=0.005** **36 wks r=-0.52; p=0.007** **maternal at delivery r=-0.44; p=0.03** **cord Pb r=-0.44; p=0.02** <u>I-V interpeak interval</u> **12 wks r=0.46; p=0.03** <u>III-V interpeak interval</u> **12 wks r=0.51; p=0.02** **20 wks r=0.57; p=0.002** **28 wks r=0.45; p=0.01** **36 wks r=0.51; p=0.009** Other correlations were not statistically significant	Maternal blood Pb during pregnancy was significantly associated with decreased latency of waves I and peak II and increased interpeak I-V and III-V interval. Cord blood PB and maternal blood Pb at delivery was significantly associated with latency of peak II.
Prospective Rothenberg (2000) Mexico City, Mexico *Population may overlap with Rothenberg (1989) and others*	100 in the Mexico City Prospective Lead Study of women recruited at the National Institute of Perinatology and the General Hospital in Mexico City on or before their 36th week of pregnancy. Year not stated % male not stated	5.5 years Range: 5-6 years	Geometric means Maternal (20-wks) = 8.1(+8.1/-4.0) Infant Cord=8.7(+8.4/-4.3) 12 mo. not reported 18 mo.=10.8(+9.4/-5.2) 48 mo. not reported 60 mo.=8.0 (+6.2/-3.7) Abstract presents different mean for	Brainstem auditory evoked response (BAER), head circumference	Linear multiple regression; orthogonal polynomial multiple regression, t-test, ANOVA Head circumference, age at time of testing, and sex	Effect of 20-week maternal blood Pb on BAER interval (milliseconds) <u>Interval I-V</u> Linear multiple regression ln (Pb) β (95% CI): β= -0.044 (-0.097, 0.009); p=0.106 **Orthogonal polynomial multiple regression** **Linear component ln(Pb) β (95% CI):** **β= -0.045 (-0.082, -0.008), p=0.018** **Quadratic component ln(Pb) β (95% CI):** **β= 0.050 (0.016, 0.084), p=0.004** <u>Interval III-V</u> **Linear multiple regression ln(Pb) β (95% CI):** **β= -0.051 (-0.100, -0.002), p=0.044** **Orthogonal polynomial multiple regression**	Maternal blood Pb (20 week) and postnatal blood Pb (12 and 48 month) was significantly associated with changes in the BAER I-V and III-V inter-peak intervals.

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			maternal Pb (7.7; range 1–30.5)			**Linear component ln(Pb) β (95% CI):** **β= -0.048 (-0.083, -0.014), p=0.007** **Quadratic component ln(Pb) β (95% CI):** **β= 0.044 (0.013, 0.075), p=0.007** Effect of 12-mo. infant blood Pb on BAER interval (ms) Interval I-V Linear multiple regression ln (Pb) β (95% CI): **β= -0.063 (-0.123, -0.003); p=0.044** Interval III-V Linear multiple regression ln(Pb) β (95% CI): β= -0.031 (-0.089, 0.026), p=0.278 Effect of 48-mo. infant blood Pb on BAER interval (ms) Interval I-V Linear multiple regression ln (Pb) β (95% CI): **β= -0.084 (-0.161, -0.007); p=0.033** Interval III-V Linear multiple regression ln(Pb) β (95% CI): **β= -0.076 (-0.149, -0.003), p=0.040** Authors also report association between maternal and infant blood Pb level and head circumference at 72 mo.	
Prospective Rothenberg (2002) Mexico City, Mexico *Population may overlap with Rothenberg (1989) and others*	45 participants in the Mexico City Prospective Lead Study of women recruited at the National Institute of Perinatology and the General Hospital in Mexico City on or before their 36th week of pregnancy with normal visual acuity. Year not stated Male= 47%	109 (11.3) months =9.08 years Range: 84-124 months (age 7-10)	Maternal (12 weeks): tertile med. (range) T1 (ref) = 4.0 (2-5.5) T2 (low) = 8.5 (6-10) T3 (mod) = 14.0 (10.5-32.5) Child at testing: tertile median (range) T1 (ref) = 4.0 (2-4.5) T2 (low) = 6.0 (5-6.5) T3 (mod) = 7.5 (7-16) Pb measured at 12 weeks gestation and then every 8 weeks, maternal and cord blood at birth, and child every 6 months until ERG testing.	Children were assessed for retinal function by electroretinographic (ERG) testing: full-field scotopic flash ERGs were recorded over a 4-log-unit range (-1.37 to +1.85 log scotopic troland/second [scot td/sec]). Scotopic voltage (V)-log intensity (I) and implicit time (IT)-log I functions were generated. Serum Fe, Zn, and retinol also measured.	Repeated measures ANOVA; simple ANOVA with the Tukey honest significant difference method; Huynh-Feldt corrected degrees of freedom for F-tests. Pearson correlation coefficients	Repeated-measures ANOVA showed that only maternal 12 week showed a dose-response relationship with ERG measures. Increase in ERG with increasing 12 week maternal Pb **a-wave amplitude (+12 ms): $F_{2,36}$=4.104, p= 0.025** **a-wave amplitude (peak): $F_{2,36}$=5.75, p=0.007** **b-wave amplitude: $F_{2,36}$=5.75, p= 0.007** Pearson correlation coefficients of blood Pb and ERG testing: Maternal 12 weeks; Child @ testing (Coeff., *P*) a-Wave peak amplitude (scot td/sec) -0.36: M 0.103, *P*=0.532; C -0.042, *P*=0.783 **+0.37: M 0.459, *P*=0.003;** C 0.050, *P*=0.743 **+0.88: M 0.460, *P*=0.003**; C 0.056, *P*=0.713 **+1.35: M 0.364, *P*=0.023;** C 0.107, *P*=0.484 **+1.85: M 0.341, *P*=0.033;** C 0.210, *P*=0.167 b-Wave amplitude (scot td/sec) **-0.36: M 0.421, *P*=0.008;** C 0.118, *P*=0.440 **+0.37: M 0.439, *P*=0.005;** C 0.107, *P*=0.485 **+0.88: M 0.339, *P*=0.035;** C 0.219, *P*=0.148 +1.35: M 0.249, *P*=0.126; C 0.019, *P*=0.901 +1.85: M 0.281, *P*=0.083; C 0.043, *P*=0.781	Maternal blood Pb levels during the first trimester were significantly associated with increases in leading-edge a-wave amplitude, peak a-wave amplitude, and b-wave amplitude in 7 to 10-year old children
Cross-sectional Roy (2009) Chennai, India	756 elementary school children in Chennai; Years=	mean not reported Range:3-7	11.4(5.3)	Neurobehavior assessment (Conners' ADHD/	Multivariate generalized estimating equations (GEE) analysis	Multivariate GEE analysis of log blood Pb and teacher reported behavior raw scores: β (95% CI) **Anxiety β=0.27(0.05-0.51); *p* = 0.02**	Concurrent blood Pb levels were

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	2005-2006 Male=53.4%			Diagnostic and Statistical Manual for Mental Disorders, 4th Ed. (DSM-IV) Scales (CADS-T), Conners' Teacher Rating Scales-39 and Behavior Rating Inventory of Executive Function	Child's age (months), sex, hemoglobin level, family average monthly income, maternal and paternal education, number of other children, clustering at the class and school level	**Social problems β=0.20(0.02-0.038);*p* = 0.03** **ADHD index β= 0.17(0.00-0.36); *p* = 0.05** **DSM-IV inattentive β=0.24(0.05-0.43); *p* = 0.01** DSM-IV hyperactive β=0.13(-0.04-0.30); *p* = 0.13 **Global exec. func. β=0.42(0.18-0.65); *p* < 0.001** The authors reported similar value for GEE analysis by Z-score and stated there was no difference by sex	significantly associated with behavior scores indicating more anxiety, social problems, ADHD, and decreased executive function in 3-7 year old children.
Prospective Schnaas, (2000) Mexico City, Mexico *Population may overlap with Rothenberg (1989) and others*	112 children in the Mexico City Prospective Lead Study of women recruited at the National Institute of Perinatology and the General Hospital in Mexico City on or before their 36th week of pregnancy Year not stated Male = 47.3%	6-54 months	Geom. mean (range) 6-18 months: 10.1 (3.5-37.0) 24-36 months: 9.7 (3.0-42.7) 42-54 months: 8.4 (2.5-44.8) Blood Pb measured every 6 months from 6 to 54 months	Intellectual status indexed by General Cognitive Index (GCI) from McCarthy Scales of Children's Abilities (MSCA).	Repeated measures ANCOVA 5-min Apgar, birth weight, birth order, sex, socioeconomic level, maternal IQ, and maximum maternal education al level	<u>Test for interaction between blood Pb and age at which the GCI was determined (within-subject effect):</u> **6-18 month Pb: p=0.076 (linear effect p = 0.047)** **24-36 month Pb: p=0.044 quadratic effect (p = 0.019)** 42-56 month Pb: p=0.632 <u>Estimated regression coefficients and SEs of the effect of blood Pb on GCI</u> (Figure, summarized below): 6-18 month blood Pb did not have a significant effect of GCI at any age (p>0.1). **Increasing blood Pb at 24-36 months was significantly associated with a decreased GCI at 48 (p = 0.021) and 54 months (p=0.073).** **Increasing blood Pb at 42-54 months was significantly associated with a decreased GCI at 54 (p = 0.040) and 60 months (p=0.060).**	Postnatal blood Pb was significantly associated with lower GCI scores with a maximum effect approximately 1 to 3 years after Pb measurement.
Prospective Schnaas (2006) Mexico City, Mexico *Population may overlap with Rothenberg (1989) and others*	150 children the Mexico City Prospective Lead Study of women recruited at the National Institute of Perinatology and the General Hospital in Mexico City on or before their 36th week of pregnancy Year=1987-2002 Male=52.7%	mean not reported 6 - 10 years	Geometric means (5th-95th) Maternal Pb: 12-20 weeks = 8.2 (3.0, 20.7) 28-36 wks = 7.8 (2.5, 24.6) Cord Pb= not reported	Full-scale IQ (FSIQ) as assessed using the Wechsler Intelligence Scale for Children–Revised (WISC-R; Spanish version) under standardized conditions	Multivariate regression; linear mixed model Maternal IQ, SES, sex, birth weight, and an indicator variable of first FSIQ application at 6, 7, or 8 years	<u>Multivariate regression analysis of ln(blood Pb) and IQ scores</u>: β (95% CI): Maternal Pb: 12-20 weeks: -1.45 (-4.75, 2.00); p = 0.42 **28-36 weeks: -4.00 (-6.37, -1.65); p = 0.001** At delivery: -1.29 (-4.41, 1.83); p = 0.41 Cord Pb: -0.95 (-3.65, 1.75); p = 0.49	Maternal blood Pb at 28-36 weeks was significantly associated with reduced IQ at 6-10 years.
Cross sectional (Schwartz and Otto 1987)	4,519 subjects from NHANES II Year=1976-1980	mean not reported Range 4-19 yrs	mean not reported *limits utility	Elevated hearing thresholds above the standard reference	Multiple regression, logistic regression	<u>Hearing threshold (in decibels) for 4 frequencies for children (age 6-19), blood Pb estimate:</u> Coeff; p-value Left Ear:	Concurrent blood Pb was significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
USA	% male not stated			level (500, 1000, 2000, and 4000 Hz) and developmental milestones	Race, sex, current cold, ringing in ears, cold in last 2 weeks, ear discharge, ringing in ears, earache, previous running ear, other ear conditions, diagnosed hearing impairment, income, chronic ear discharge, degree of urbanization, dietary calcium, head of household education level	**500 Hz: 0.0547; p<0.0001** **1000 Hz:0.0447; p<0.0001** **2000 Hz: 0.0487; p<0.0001** **4000 Hz:0.0517; p<0.0001** Right Ear: **500 Hz: 0.0533; p<0.0001** **1000 Hz:0.0651; p<0.0001** **2000 Hz: 0.0600; p<0.0001** **4000 Hz:0.0567; p<0.0001** Developmental milestones for children (age 6-19), blood Pb estimate: Coeff; p-value **Age (in yr) of first word: 0.0024; *p* = 0.0094** **Age (in mo) when first walked: 0.0070, *p* = 0.0020** **Age (in mo) when first sat up: 0.0061, *p* = 0.0239** **Prob. of being hyperactive (logistic): 0.0116, *p* = 0.0150**	associated with elevated hearing thresholds at 500, 1000, 2000 and 4000 Hz in both ears and delays in developmental milestones, but blood Pb levels are not described and means were above 10µg/dl in other NHANES II studies.
Cross-sectional (Schwartz and Otto 1991) USA	3545 subjects from the Hispanic Health and Nutrition Survey (HHANES) Year=1982-1984; % male not stated	6-19 years	Median: 8	Elevated hearing thresholds above the standard reference level (500, 1000, 2000, and 4000 Hz)	Linear regression Covariates include family income and ethnicity; others considered include current cold, cold during past week, and sex	Hearing threshold (average of both ears, in decibels) for 4 frequencies for children (age 6-19), blood Pb estimate: Coeff; p-value Left Ear: **500 Hz: 0.0466; p=0.0.014** **1000 Hz: 0.0274; p=0.0.029** **2000 Hz: 0.044; p<0.001** **4000 Hz: 0.019; p=0.049** Right Ear: **500 Hz: 0.034; p=0.023** **1000 Hz: 0.039; p=0.007** **2000 Hz: 0.039; p=0.009** 4000 Hz: NS Hearing threshold (average of both ears, in decibels) for 4 frequencies for children (age 6-19), blood Pb estimate: Coeff; p-value **500 Hz: 0.00452; p<0.001** **1000 Hz:0.00457; p<0.001** **2000 Hz: 0.00470; p<0.001** **4000 Hz:0.00368; p<0.017** An increase in blood Pb from 6 to 18µg/dL was associated with an additional 15% of children who had hearing thresholds below the standard at 2000Hz. An increase in blood Pb from 6 to 18µg/dL was associated with a 2-dB loss in hearing at all frequencies	Concurrent blood Pb was associated with increased risk of hearing thresholds above the standard (500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz)

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Meta-analysis Schwartz (1994)	Meta-analysis of 7 studies of blood Pb and full-scale IQ in school age children: 3 longitudinal (Bellinger (1992), Dietrich (1993b), and Baghurst (1992)) and 4 cross-sectional (Hawk (1986), Hatzakis (1987), Fulton (1987), and Yule (1981)).	School aged children (mean ages not reported)	Longitudinal (Blood Pb at age 2-3 years): Bellinger, 1992: 6.5 Dietrich, 1993: 15 Baghurst, 1992: 20 Cross-sectional: Hawk, 1986: 21 Hatzakis, 1987: 23 Fulton, 1987: 12 Yule, 1981: 13 *Silva, 1988: 11 *Silva, 1988 was not included in the primary meta-analysis for analytical reasons.	Full-scale IQ (scales used varied between studies)	Predicted change in IQ as blood PB increased from 10 to 20 µg/dL. Studies were weighted by the inverse of the variances and a random effects model. Adjustments varied by study and all except Yule and Silva included parental IQ and HOME score. Also considered population SES († = disadvantaged)	Estimated decrease in IQ from an increase in blood Pb from 10 to20 µg/dL: point decrease ± SE ‡Bellinger, 1992: 5.8 ± 2.1 †‡Dietrich, 1993: 1.3 ± 0.9 Baghurst, 1992: 3.33 ± 1.46 †Hawk, 1986: 2.55 ± 1.5 Hatzakis, 1987: 2.66 ± 0.7 ‡Fulton, 1987: 2.56 ± 0.91 †‡Yule, 1981: 5.6 ± 3.2 Silva, 1988: 1.51 (SE couldn't be calculated*) **Meta-analysis: 2.56 ± 0.41, P < 0.001** Sensitivity Analyses: Exclude largest effect study (Bellinger): 2.43 ± 0.34 Exclude most sig. Study (Hatzakis): 2.52 ± 0.58 Include Silva (no weighting): 3.16 ± 0.60 Adding 8 studies with 0 effect size: ↓50%, *P* < 0.01 Longitudinal studies only: 2.96 ± 1.25 Cross-sectional studies only: 2.69 ± 0.51 Disadvantaged populations (†): 1.85 ± 0.92 Non-disadvantaged: 2.89 ± 0.50 Studies with mean blood Pb ≤ 15µg/dL (‡): 3.23 ± 0.92 Studies with mean blood Pb > 15µg/dL: 2.32 ± 0.40 Authors suggest that a threshold at 10µg/dL is implausible because effect is larger below 15µg/dL. In the study with the lowest blood Pb level (Bellinger, 1992), was examined alone using nonparametric smoothing, no evidence of a threshold was observed down to a blood Pb level of 1 µg/dL.	Blood Pb was signinficantly associated with lower IQ in school age children in this meta-analysis of 7 studies. The authors conclude that these data provide further evidence of Pb effects on cognition below 10 µg/dL - with no evidence of a threshold.
Cross-sectional Sciarillo (1992) Baltimore, MD, USA	201 African-American children aged 2-5 years recruited from the Baltimore Soil Lead Abatement Demonstration Project and the Kennedy Krieger Institute's Lead Poisoning Referral Center; Year=1989 % male not stated	mean not reported 2 - 5 years,	High (n=78, ≥15µg/dL on 2 visits): Prior: 28.6 (9.3) During: 27.8 (10.4) Low (n=123): Prior: 11.3 (4.3) During: 9.2 (2.9)	Child behavior as reported by the mother on the Achenbach Child Behavior Checklist (CBCL) and as a control measure the Center for Epidemiologic Studies Depression Scale (CES-D).	χ^2 test of difference is T-scores above the clinical 90th percentile, Odds ratio for being in the 98th percentile if exposed to high Pb Multiple linear regression including maternal education, occupation, marital status, ≥ preschool children in the home,	CBCL T-Scores (>90th): Low %/High %, χ^2, *P* value (1df) **Total:16.3%/32.0%, 6.85, *P* < 0.01** Internalizing: 10.6%/19.2%, 2.99, *P* = 0.08 **Externalizing: 14.6%/25.6%, 3.77, *P* = 0.05** Total CBCL Total Score (>98th): Low=17.9%, High=30.8%, OR=2.0 (95% CI 1.0-4.0) Multiple linear regression on CBC Total Score **Blood Pb (µg/dL): 0.18 (SE 0.073), *P* = 0.0125**	Blood Pb was significantly associated with worse behavior (on CBCL) in children age 2-5; those with blood Pb over 15µg/dL had significantly higher Externalizing scores as well.

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					CES-D, child's age, sex, and iron deficiency		
Prospective Shen (1998) Shanghai, China	133 mother/infant pairs at the Yangpu Maternal and Child Health Center: 66 in the high Pb group (blood Pb>70th percentile) and 62 in the low Pb group (blood Pb<30th percentile); Year=1993 Male=0%, mothers	3, 6, and 12 months	Cord blood Pb: All: 9.2 (8.86, 9.54) High Pb group: 13.4 (2.0) Low Pb group: 5.3 (1.4) (geometric means)	Child development as assessed by the Mental Development Index (MDI) and the Psychomotor Development Index (PDI) of the Bayley Scales of Infant Development	Single-variate analyses and multiple-variate analyses gestational age, parental occupational exposure to Pb, parity, viral infection during pregnancy, passive smoking during pregnancy, premature rupture of the membranes, father's age at birth of child, maternal Hb level at mid-term pregnancy	Comparison of developmental index of high Pb group vs. low Pb group: 3 months: **MDI: p=0.0187** PDI: p=0.0702 6 months: **MDI: p=0.0315** PDI: p=0.2706 12 months: **MDI: p=0.0279** PDI: p=0.5831	Cord blood Pb was significantly associated with MDI, but not PDI, scores at ages 3, 6, and 12 months
Prospective Shih (2006) Baltimore, MD, USA *Population may overlap with Glass (2009) and others*	985 older adults in the Baltimore Memory Study; Year not stated Male=34.1%	59.39 (5.96)	Blood Pb= 3.46 (2.23) Tibia =18.72 (11.24)µg/g	Cognitive assessment by 20 tests grouped into 7 cognitive domains: language (Boston Naming, letter fluency, and category fluency), processing speed (simple reaction time), eye-hand coordination (Purdue pegboard, Stroop C form minus A form, and trail-making test A), verbal memory and learning (Rey auditory verbal learning test), visual memory (Rey complex figure recall and symbol digit), and visuo-construction (Rey complex figure copy).	Multiple linear regression; Age, sex, technician, presence of APOE-ε4 allele	Change in domain score (β) per 1 µg/dL Blood Pb β(SE): Language β= -0.0060 (0.0118) Processing speed β= -0.0109 (0.0109) Eye-hand coordination β= -0.0110 (0.0106) Executive function β= -0.0143 (0.0099) Verbal mem. & learning β= -0.0181 (0.0124) Visual memory β= -0.0137 (0.0121) Visuconstruction β= -0.0191 (0.0138) *Further adjustment for education, wealth, and race/ethnicity did not make any statistically significant Change in domain score (β) per 1 µg/g Tibia Pb β(SE): **Language β= -0.0083 (0.0023), $p \leq 0.01$** **Processing speed β=-0.0042 (0.0021), $0.01 < p \leq 0.05$** **Eye-hand coordination β=-0.0079 (0.0020), $p \leq 0.01$** **Executive function β=-0.0075 (0.0019), $p \leq 0.01$** **Verbal mem. & learning β=-0.0078 (0.0024), $p \leq 0.01$** **Visual memory β=-0.0067 (0.0023), $p \leq 0.01$** **Visuconstruction β=-0.0122 (0.0027), $p \leq 0.01$** *After further adjustment for education, wealth, and race/ethnicity, no p-values remained < 0.05.	Tibia Pb was significantly associated with lower scores on all 7 domains of cognitive function in in older adults; while blood Pb was not significantly associated with any domain.

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Cross-sectional Silva (1988) New Zealand	579 children born in Dunedin's only obstetric hospital who were part of the 11-yr follow-up of the Dunedin Multidisciplinary Health and Development Study. Year not stated % male not stated	11 years	All children: 11.1(4.91) Boys: 11.4(4.57) Girls:10.4(4.6) (at age 11)	Intelligence was assessed using the WISC-R; behavioral problems were assessed by the Parents' and Teachers' Rutter Behavioral Scale; the Parents' and Teachers' Hyperactivity Scale; the Teachers' Inattention Scale	Pearson correlation Socio-economic status, changes of residence, frequent changes of school, solo parenting, separation of child from his or her parents, mother's age at birth of first child, maternal cognitive ability, family relations, marriage guidance, mental health symptoms, mother's age, child's sex, ordinal position in the family	Correlations between log blood Pb levels and the cognitive and behavior measures scores at age 11: Verbal IQ: r=-0.06; NS Performance IQ: r=-0.03; NS Full Scale IQ: r=-0.05; NS **Reading: r=-0.09; p<0.05** **Parents' Rutter Behavior Scale: r=0.14; p<0.001** **Teachers' Rutter Behavior Scale: r=0.14; p<0.001** **Parents' Inattention Scale: r=0.11; p<0.01** **Parents' Hyperactivity Scale: r=0.14; p<0.001** **Parents' Inattention Scale: r=0.19; p<0.001** **Parents' Hyperactivity Scale: r=0.14; p<0.001** *N.B. it is not clear from the data table in the article why "parents" rating for Inattention and Hyperactivity are listed twice, or if one should be "teachers" rating*	Concurrent blood Pb was significantly correlated with behavioral problems, but not with IQ, at age 11.
Cross-sectional Solon (2008) Visayas, Philippines	877 children aged 6 to 59 months from the Quality Improvement Demonstration Study in the central Philippines. Year=2003-2004 % male not stated	mean not stated Range = 6 to 59 months	7.1 µg/dL Concurrent blood Pb levels measured upon recruitment into study	Cognitive development in children aged 6 to 36 months measured using the Bayley Scales of Infant Development (BSID-II), consisting of a Mental Developmental Index (MDI) and a Psychomotor Development Index (PDI); Children aged 3 to 5 years were tested using the Wechsler Preschool and Primary Scales of Intelligence (WPPSI), consisting of Verbal IQ and Performance IQ	2-stage least squares regression models Roof material, water source, sex, history of breast feeding, prematurity, mother's IQ or education, maternal tobacco use during pregnancy, yearly household income.	Children aged 6 to 36 months: 1 µg/dL increase in blood Pb and change in BSID-II scores: **-3.32 (-5.02, -1.6) points; p<0.01** Children aged 3 to 5 years: 1 µg/dL increase in blood Pb and change in WPPS-III VIQ scores: **-2.47 (-4.58, -0.35) points; p=0.02**	Concurrent blood Pb was significantly associated with lower cognitive development scores in children.
Prospective Stiles (1993) Boston, MA, USA *Population may overlap with*	148 children from the Boston Lead Study born at the Brigham and Women's Hospital were re-evaluated	10 years	Low: <5µg/dL Medium: 5-9.9µg/dL High: ≥10µg/dL Measured at birth (cord), 6, 12, 18, 24,	Neuropsychological tests used were WISC-R, K-TEA, the California Verbal Learning Test for children (CVLT-C),	Multiple regression HOME score, child stress, maternal IQ, socioeconomic status, sex, and birth order	Regression coefficients (SE) associated with blood Pb at 24 months: <u>WISC-R Scores</u> **Full Scale IQ: -0.58 (0.21); p=0.007** **Verbal IQ: -0.63 (0.22); p=0.004** Performance IQ: -0.39 (0.23); p=0.091	Blood Pb at 24 months was significantly associated worse cognitive function,

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Bellinger (1984) and others	at 10 yrs of age. Year=born between 1979-1981 % male not stated		57 months and 10 years.	Wisconsin Card Sorting Test (WCST), Developmental Test of Visual-Motor Integration (VMI), Test of Visual-Motor Integration, Rey-Osterieth Complex Figure (ROCF), Story Recall, Finger Tapping, and Grooved Pegboard.		Information: -0.07 90.05); p=0.13 **Similarities: -0.13 (0.05); p=0.011** **Arithmetic: -0.12 (0.04); p=0.010** Vocabulary: -0.08 (0.04); 0.090 **Comprehension: -0.10 (0.04); p=0.018** Digit Span: -0.09 (0.05); p=0.056 **Blood design: -0.11 (0.06); p=0.043** Coding: -0.05 (0.05); p=0.35 **CVLT-C: 0.03 (0.01); p=0.013** Story Recall Delayed recall score: -0.14 (0.08); p=0.089 VMI: NS **ROCF: -0.12 (0.06); p=0.047** **Grooved pegboard: 0.04 (0.02); p=0.025**	including full scale and verbal IQ, on several subscales of WISC-R at age 10.
Prospective Surkan (2007) ME and MA, USA	New England Children's Amalgam Trial (NECAT): 511 English-speaking children with no prior or existing amalgam restorations and had two or more posterior teeth with dental caries Year= 2003 Male=46%	8.0 years (range = 6 to 11.5)	mean not reported Blood Pb measured at baseline	Primary tests: The Full-Scale IQ on the Wechsler Intelligence Scale for Children (WISC-III); Secondary outcomes: Wechsler Individual Achievement Test (WIAT); battery of additional neuropsychological tests: the Wide Range Assessment of Visual Motor Ability (WRAVMA), the Wide Range Assessment of Memory and Learning (WRAML), the Stroop Color-Word Interference Test, the Wisconsin Card Sorting Test (WCST), the Trail-making Test; Caregiver IQ measured using Kaufman-Brief Intelligence Test (K-BIT); Life Stress score	Multivariate analysis of covariance Adult IQ, age, socioeconomic status, race, and birth weight	Dose-response model of blood Pb and WISC-III: β (SE) Full-scale IQ 1-2 µg/dL: reference 3-4 µg/dL: -0.12 (1.62); p=0.941 **5-10 µg/dL: -6.04 (2.39); p=0.012** Verbal IQ 1-2 µg/dL: reference 3-4 µg/dL: -0.86 (1.66); p=0.605 **5-10 µg/dL: -5.37 (2.63); p=0.016** Performance IQ 1-2 µg/dL: reference 3-4 µg/dL: 0.05 (1.78); p=0.978 **5-10 µg/dL: -5.37 (2.63); p=0.042** Dose response model of blood Pb and WIAT: β (SE) Reading 1-2 µg/dL: reference 3-4 µg/dL: -1.01 (1.74); p=0.564 **5-10 µg/dL: -8.74 (2.57); p=0.001** Math 1-2 µg/dL: reference 3-4 µg/dL: 1.54 (1.61); p=0.340 **5-10 µg/dL: -7.92 (2.38); p=0.001** Authors also report significant effects at blood Pb of 5-10µg/dL on: WIAT scales in basic reading, reading comprehension, mathematics reasoning, numeric operations, listening comprehension WRAVMA – composite and subtest matching (not drawing or pegboard)	Blood Pb levels of 5-10 µg/dL were significantly associated with measures of compromised cognition and decreased attention and working memory, when compared to levels between 1 and 2 µg/dL.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
				measured with the Parenting Stress Index		WRAML – indices of general memory, visual memory, verbal memory (not learning index); scales finger windows and sentence memory (not other scales) WCST – preservation errors and number of categories achieved (not trials to the first category)	
Prospective Surkan (2008) Mexico City, Mexico *Population may overlap with Tellez-Rojo (2006), Gomaa (2002) and others*	379 mother-child pairs from 3 cohorts of the Harvard-Mexico Project on Fetal Pb Exposure, Risks and Intervention Strategies (FLERIS). Year=1996-2001 (n=247) and 2004-2005 (n=132) Male=57%	Assessed 12-36 months Mean maternal age at delivery: 26.0 (5.5)	At 24 months (n=319): 6.4 (4.3) Range 0.8-25.8	Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores from the Bayley Scales of Infant Development at 24, 30, and 36 months; and maternal self-esteem with the Spanish version of the Coopersmith Self-Esteem Inventory assessed at 24 months	Linear mixed effects regression model Sex, maternal age, maternal IQ, maternal education, parity, alcohol consumption, smoking, cohort, maternal self-esteem	Main effects of self-esteem and Pb on MDI and PDI repeated measures at 24, 30, and 36 months: *β* (SE), *p* Self-esteem: **MDI 0.24 (0.12), 0.04**; PDI 0.18 (0.12), 0.13 24 mon Pb: MDI -0.18 (0.14) 0.20; PDI -0.14 (0.14), 0.32 Adjusted relationship between childhood blood Pb with MDI and PDI scales at 24 months stratified by maternal self-esteem: β(SE), *p* Mental Development Index (MDI): **Lowest 3 quartiles self-esteem: -0.31 (0.15), p = 0.04** Highest quartile self-esteem: 0.36 (0.44), p = 0.44 p-value for interaction = 0.11 Quartile 1, low (n=145): -0.17 (0.25), p=0.50 Quartile 2 (n=148): -0.36 (0.25), p=0.15 Quartile 3 (n=178): -0.35 (0.44), p=0.39 Quartile 4, high (n=136): 0.38 (0.31); p=0.39 Psychomotor Development Index (PDI): Lowest 3 quartiles self-esteem: -0.25 (0.15), p = 0.10 Highest quartile self-esteem: 0.48 (0.40), p = 0.24 p-value for interaction = 0.21 Quartile 1, low (n=146): 0.21 (0.26); p=0.43 **Quartile 2 (n=147): -0.81 (0.23), p<0.01** Quartile 3 (n=178): -0.12 (0.33), p=0.71 Quartile 4, high (n=135): 0.50 (0.40); p=0.22	When mothers had low self-esteem, concurrent blood Pb was significantly associated with lower MDI and PDI score.
Prospective Tang (2008) Tongliang and Chongqing, China	110 children born to non-smoking Chinese women at one of three Tongliang county hospitals Year=2002 Male=49.1%	2 years	Cord 3.60 (1.59)	Child development measured by Gesell Developmental Schedules at 2 years of age presented as developmental quotients (DQ) in motor, adaptive, language and social areas.	Multiple regression; logistic regression Sex, gestational age, maternal education, environmental tobacco smoke (ETS)	Multiple regression analyses of GDS DQ scores at 2 years of age and cord Pb (β(95% CI): Motor: -3.72 (-7.98, 0.53); p=0.089 Adaptive: -3.59 (-9.20, 2.01); p=0.212 Language: -4.34 (-9.10, 0.43); p=0.077 **Social: -6.08 (-10.53, -1.63); p=0.009** **Average: -4.24 (-8.20, -0.29); p=0.038** Logistic regression analyses of GDS DQ scores at 2 years of age and cord Pb (OR(95% CI): **Motor: 3.85 (1.04, 14.25); p=0.043** Adaptive: 1.43 (0.43, 4.68); p=0.559 Language: 2.70 (0.70, 10.50); p=0.150 **Social: 7.29 (1.35, 39.45); p=0.021** Average: 4.25 (0.70, 25.89); p=0.116	Cord blood Pb was significantly associated with decrements in motor, social, and average developmental quotients.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Tellez-Rojo (2006) Mexico City, Mexico *Population may overlap with Surkan (2008), Gomaa (2002) and others*	294 children from 2 cohorts of the Harvard-Mexico Project on Fetal Pb Exposure, Risks and Intervention Strategies (FLERIS) with blood Pb levels < 10 µg/dL at both 12 and 24 months, Year=1994 – 2001 Male= 48%	12 months and 24 months	Cord blood = 4.85 (3.00) µg/dL 12 months = 4.27 (2.14) µg/dL 24 months = 4.28 (2.25) µg/dL	Development was assessed at 12 and 24 months by the Bayley Scales of Infant Development II (BSID II).	*t*-tests, Kruskal-Wallace test, χ^2 test, mixed-effects regression models, multivariate models, and linear regression models Mother's IQ, age and education; child's gender and birth weight.	Association between children's blood Pb levels at 24 months (<10 µg/dL) with MDI and PDI scores at 24 months **MDI: β=-1.04; p<0.01** **PDI: β=-1.18; p<0.01** Association between children's blood Pb levels at 12 months (<10 µg/dL) with MDI and PDI scores at 24 months MDI: NS **PDI: β=-3.0; p=0.01**	Concurrent blood Pb was significantly associated with lower MDI and PDI scores at 24 months, while blood Pb at 12 months was significantly associated with PDI, but not MDI, at 24 months.
Cross-sectional (Thomson *et al.* 1989) Edinburgh, Scotland *Population may overlap with Fulton (1987)*	501 children recruited from 18 primary schools in classes 3 and 4 in education authority primary schools in central Edinburgh. Year not stated, began in 1982 Male = 52%	6-9 years	Geom. mean: 10.4 (from Fulton (1987))	Behavior measured by the Rutter behavior scales, home interview with a parent	Multiple regression Child variables: age, sex, height, length of gestation, birthweight, medical history, days off school; Parent variables: mother's qualifications, working mother, parent's health, parent's mental health, smoking, parent's vocabulary, parent's matrices; Family variables: family history, birth order, family structure, parent/child communication, child's interest, parent participation; Household variables: car/phone owner, consumer goods owner, persons per room	Teachers' scores on log blood Pb: *β*; one-sided *p*-value **Total score: *β*=0.69; *p* =0.005** **Aggressive/anti-social: β=1.08; p=0.004** **Hyperactive: β=0.66; p=0.02** Neurotic: β=0.19; p=0.28 Parents' scores on log blood Pb: *β*; one-sided *p*-value Total score: *β*=0.38; *p* =0.06 Aggressive/anti-social: *β*=0.12; p=0.31 Hyperactive: *β*=0.39; *p* =0.07 Neurotic: *β*=0.33; *p* =0.08 Minimum of parents' and teachers' scores on log blood Pb: *β*; one-sided *p*-value **Total score: *β*=0.53; *p*=0.03** **Aggressive/anti-social: *β*=0.95; *p*=0.02** **Hyperactive: *β*=0.75; *p* =0.03** Neurotic: *β*=0.23; *p*=0.27	Concurrent blood Pb was significantly associated with teachers' ratings of behavior on aggressive/anti-social and hyperactive sub-scores and on total score, but not on the neurotic sub-score or parents' scores.
Prospective Tong (1996) Port Pirie, Australia	375 children living in and around the Pb smelting town of Port Pirie, South Australia, followed	mean not stated	Antenatal blood Pb: 10.1 (3.9) Cord Pb: 9.4 (3.9) Lifetime average	Children's intelligence quotient (IQ) measured at 11-13 years of age	Multivariate regression analyses	Regression of log blood Pb and IQ at age 11-13: β (SE) Cord blood: Verbal IQ: 1.0 (1.3); p=0.43 Performance IQ: 1.2 (1.8); p=0.48 Full scale IQ: 1.2 (1.5); p=0.41	Blood Pb levels measured at several ages after birth were significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Population may overlap with Wigg (1988) and others	since birth; reevaluated at age 11-13; Year = 1979-1982 (at baseline) Male=48%		blood Pb at age 7: 17.8 (5.8) 6, 15, and 24 months; 2, 4, and 7 years			15 months: **Verbal IQ: -2.9 (1.3) ; p=0.03** Performance IQ:-0.6 (1.9); p=0.76 Full scale IQ:-1.8 (1.6) ; p=0.24 3 years: Verbal IQ:-2.6(1.6) ; p=0.11 Performance IQ:-4.2(2.3) ; p=0.07 **Full scale IQ:-3.8 (1.9) ; p=0.05** 5 years: **Verbal IQ:-3.7 (1.4) ; p=0.01** Performance IQ:-3.7 (1.9) ; p=0.06 **Full scale IQ:-4.0 (1.6) ; p=0.02** 7 years: **Verbal IQ: -2.8 (1.4) ; p=0.05** Performance IQ: -3.8 (2.0) ; p=0.06 **Full scale IQ: -3.4 (1.7) ; p=0.04** 11-13 years: Verbal IQ:-2.4 (1.3) ; p=0.06 Performance IQ:-2.0 (1.8) ; p=0.12 **Full scale IQ: -3.1 (1.7); ; p=0.04** Lifetime average to age 3: **Verbal IQ: -4.6 (1.9) ; p=0.03** Performance IQ: -3.2 (2.7) ; p=0.23 Full scale IQ:-4.3 (2.2) ; p=0.06 Lifetime average to age 5: **Verbal IQ: -5.0 (2.0) ; p=0.02** Performance IQ:-4.4 (2.8) ; p=0.10 **Full scale IQ: -5.1 (2.3) ; p=0.03** Lifetime average to age 7: **Verbal IQ: -4.3 (2.1) ; p=0.03** Performance IQ: -4.3 (2.9) ; p=0.14 Full scale IQ: -4.6 (2.4) ; p=0.06 Lifetime average to age 11-13: **Verbal IQ: -3.9 (1.8) ; p=0.03** Performance IQ: -4.7 (2.6) ; p=0.07 **Full scale IQ: -4.3 (2.1) ; p=0.04**	associated with verbal and/or full scale IQ at age 11-13.
Prospective Tong (1998) Port Pirie, South Australia *Population may overlap with Baghurst (1992) and others*	326 children living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; re-evaluated at age 11-13; Year = 1979-1982	All followed from birth until age 11-13	Age 2: 21.2 µg/dL Age 11-13 (n=326): 7.9 µg/dL	Bayley Mental Development Index (BMDI) at age 2, McCarthy General Cognitive Index (MGCI) at age 4, and IQs from the Wechsler Intelligence Scale for Children-	Multiple regression models ANOVA for association of changes in cognitive scores with grouped decreases in blood Pb Correlation between	By tertile of lifetime average blood Pb [Geometric Mean (SD) concurrent blood Pb (µg/dL)]: Mean Developmental Test score Age 2 BMDI Low (n=109) [12.5(1.2)]: 113.3 Middle (n=108) [18.5 (1.1)]: 109.9 Higher (n=109) [25.9 (1.1)]: 106.7 Age 4 MGCI Low (n=109) [13.3(1.2)]: 112.5	Blood Pb was associated with poorer performance on cognitive tests throughout childhood, even after mean Pb

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
	(at baseline) %male not stated			(WISC) at ages 7 and 11-13	changes in IQ and declines in blood Pb (ungrouped) Adjusted for child's sex, birthweight, birth rank, feeding style during infancy, and duration of breast-feeding; maternal IQ and age at child's birth; socioeconomic status; Home Observation for Measurement of the Environment scores; and parental smoking habits and marital status	Middle (n=108) [19.5 (1.1)]: 107.3 Higher (n=109) [26.0 (1.2)]: 103.6 Age 7 WISC Low (n=109) [11.9(1.2)]: 109.9 Middle (n=108) [17.6 (1.2)]: 104.2 Higher (n=109) [22.8 (1.2)]: 101.4 Age 11-13 WISC Low (n=109) [11.0 (1.4)]: 104.3 Middle (n=108) [14.7 (1.3)]: 99.6 Higher (n=109) [18.6 (1.3)]: 96.9 <u>Change in IQ by decline in blood Pb (age 7 until 11-13)</u>: mean change in IQ points (95% CI) **<2.3 µg/dL: -5.4 (-3.8, -7.0)** **2.3-4.9 µg/dL: -5.0 (-3.2, -6.8)** **>4.9 µg/dL: -3.8 (-2.3, -5.3)** ANOVA >4.9 vs. <2.3: *P* = 0.45 <u>Change in cognitive function by decline in blood Pb (age 2 until 11-13)</u>: mean change in zScore (95% CI) <10.2 µg/dL: 0.03 (-0.15, 0.21) 10.2-16.2 µg/dL: 0.04 (-0.15, 0.23) >16.2 µg/dL: -0.01 (-0.20, 0.18) ANOVA >16.2 vs. <10.2: *P* = 0.74 <u>Change in cognitive function by decline in blood Pb (age 4 until 11-13)</u>: mean change in zScore (95% CI) <6.0 µg/dL: 0.05 (-0.12, 0.23) 6.0-10.3 µg/dL: 0.01 (-0.17, 0.18) >10.3 µg/dL: 0.01 (-0.17, 0.19) ANOVA >10.3 vs. <6.0: *P* = 0.42 Correlations between changes in blood Pb and cognitive function were weak and not statistically significant (data not shown). Strongest association: IQ and blood Pb decrease between ages 7 and 11 to 13: *r* = 0.12, *P* = 0.09	levels declined below 10µg/dL. Cognitive scores in those whose blood Pb levels declined the most were generally not improved relative to those who declined the least. Authors state that cognitive deficits from early childhood Pb exposure can only be partially reversed.
Cross-sectional Trope (2001) PA, USA	16 children with elevated blood levels compared to 5 non-exposed children who were siblings or cousins of exposed Year not stated Male (exp)=31% Male (unexp)=60%	Exposed: 8.75 years Unexposed: 8.5 years	Exposed: 39.93 (13.39) µg/dL Unexposed <10 µg/dL	Magnetic resonance spectroscopy (MRS) was used to evaluate the *in vivo* metabolism of the gray and white matter of the frontal cortex.	2-tailed unpaired Student's *t*-test; best fit linear regression. Covariates not reported	*N*-acetyl-aspartate/creatine and phosphocreatinine ratios in frontal gray matter (NAA/Cr ratio), mean (SD): Exposed= 1.10 (0.19) Unexposed = 1.30 (0.13) **p=0.035**	Pb exposed children had a significant decrease in the NAA/Cr ratio in frontal gray matter compared with the unexposed.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (μg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional van Wijngaarden (2009) Rochester, NY, USA	47 healthy subjects in Rochester, NY; Year =2008 Male=38.3%	61.55 (3) Range 55-67	Blood Pb not reported Bone: Calcaneus 6.1(8.5)μg/g Tibia 2.0(5.2)μg/g	Memory assessment with three tests (delayed-matching-to-sample-DMS; paired associate learning –PAL) in the of the Cambridge Neurophysiological Test Automated Battery (CANTAB) and Mild Cognitive Impairment measured with Montreal Cognitive Assessment (MoCA)	Spearman rank correlation, t-tests, continuity-corrected Wilcoxon-Mann-Whitney test, Multiple linear regression Age, education level, smoking status	Spearman rank correlation of CANTAB and MoCA by bone Pb excluding negative values (p-value): MoCA calcaneus Pb = -0.089 (0.58) MoCA tibia Pb = -0.059 (0.75) **DMS % correct all delays calcaneus Pb= -0.40 (0.0088)** **DMS % correct all delays tibia Pb= -0.43 (0.013)** **DMS % 12s delay calcaneus Pb= -0.34 (0.031)** **DMS % 12s delay tibia Pb= -0.42 (0.018)** PAL total errors adj. calcaneus Pb = 0.28 (0.082) **PAL total errors adj. tibia Pb = 0.42 (0.018)** **PAL stages completed calcaneus Pb = -0.43 (0.0056)** PAL stages completed tibia Pb = -0.19 (0.30) SRM % correct calcaneus Pb = -0.24(0.13) SRM % correct tibia Pb = 0.067(0.71) Adjusted within-group least-square means of cognitive test score (CANTAB) across bone Pb: DMS % correct all delays: Low calcaneus Pb = 86.94 (ref) Medium calcaneus Pb=86.36 (0.83) High calcaneus Pb = 80.85 (0.041); p = 0.07 p>0.1 when adjusted for hypertension p>0.1 for tibia Pb DMS % correct 12s delay: Low calcaneus Pb = 85.70 (ref) Medium calcaneus Pb=84.80 (0.83) High calcaneus Pb = 76.81 (0.051); p = 0.089 p>0.1 when adjusted for hypertension p>0.1 for tibia Pb Log PAL; total errors adjusted: Low calcaneus Pb = 2.36 (ref) Medium calcaneus Pb= 2.78 (0.23) High calcaneus Pb = 2.87 (0.18); p = 0.34 p>0.1 for tibia Pb	Tibia and calcaneus Pb were correlated with measures of memory impairment in 55-67 year olds. Calcaneus, but not tibia Pb, was borderline significant (p=0.07-0.09) for delayed matching to sample but adjusting for history of hypertension reduced the strength of the association
Case control Vinceti (1997) Northern Italy	15 ALS patients and 36 matched controls Year not stated Males: Cases=73% Controls=74%	mean not reported	Blood Pb (μg/dL): Controls: 10.8 (4.44) Cases: 12.7 (6.78)	Sporadic amyotrophic lateral sclerosis (ALS) and ALS severity scores. Blood Cd and Se also measured.	Student's t-test; Correlation; conditional logistic regression Matched by age and sex	<u>Difference in mean blood levels:</u> Pb: Controls 10.8; Cases 12.7; p = 0.383 <u>Relationship of blood Pb with ALS severity scores</u>: corr. Coeff; *P*-value Speech: -0.334; *P*=0.223 Swallowing: -0.236; *P*=0.398 Walking: -0.393; *P*=0.148 Dressing and hygiene: -0.334; *P*=0.224 Total: -0.440; *P*=0.101 Blood Cd was higher in ALS cases (*P*=0.025) but association with ALS diagnosis was not statistically significant (*P*=0.074)).	Blood Pb was not associated with ALS diagnosis or severity score.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Cross-sectional Walkowiak (1998) Germany	384 children aged 6 years in three German cities. Year=1994 %male not stated	6 years	Blood Pb at time of testing: 4.2 µg/dL 95th percentile: 8.9 µg/dL	Two subtests of the WISC (German version) vocabulary (V) and block design (BD) were combined to form a "WISC Index" which estimated IQ; Neurobehavioral Evaluation System 2 (NES2) used 5 subtests to assess motor speed, perceptual speed, reaction time, pattern memory functions, and sustained attention . *Also measured urinary Hg*	Multiple linear regression analysis Intelligence and contrast sensitivity in computerized testing	Multiple linear regression for Log blood Pb and WISC variables **WISC Vocabulary: b=-0.97; p<0.05** WISC Block Design: b=-0.43; NS WISC V+BD: b=-1.17; p<0.10 *Authors state that urinary Hg was not related to any of the neurological tests administered*	Concurrent blood Pb was significantly associated with lower scores on WISC Vocabulary test; Combined WISC index was borderline significant (p<0.1); and block design was not associated age 6 children.
Cross-sectional Wang (2002) Kaohsiung, Taiwan	934 third grade children from an area with known air and water pollution Year=1998-1999 Male= 51%	8.85 (0.41) years	5.50 (1.86) µg/dL	Child intelligence measured by ranking semester grades for Chinese (reading and writing short Chinese articles), Mathematics, History and Society, and Natural Science	Multiple regression analyses, Pearson correlation, Spearman correlation. Child's gender, father's age and socioeconomic status, mother's age and education.	<u>Correlations between class rankings and blood Pb:</u> Language (Chinese) **β(SE)= 0.37 (0.15); p < 0.05** History and Society **β (SE)= 0.43 (0.15); p < 0.05** Mathematics **β(SE) = 0.38 (0.16); p < 0.05** Natural Science **β (SE) = 0.32 (0.16); p < 0.05**	Concurrent blood Pb was significantly associated with lower child intelligence as measured by class rankings in four subjects.
Prospective Wang (2007) Boston, MA, USA *Population may overlap with Payton (1998) and others*	358 participants from the Normative Aging Study (NAS) for whom bone Pb measurements and cognitive function assessment data was available and who had been genotyped for *HFE* polymorphisms; Year=1991 – 2000 (initially enrolled in 1963) Male = 100%	67 years	Tibia: 19 µg/g Patella: 23 µg/g Measured beginning in 1991 and subsequently at 3-year intervals in a 6-year period	Cognitive function was assessed by the Mini-Mental State Examination (MMSE). Also genotyped for *HFE* polymorphisms	Multiple linear regression models Age, years of education, smoking, alcohol consumption, English as a first language, computer experience, diabetes.	Association with an interquartile (15µg/g) increase in tibia Pb biomarkers on change in MMSE score by class of *HFE* genotype <u>Binary model: Mean difference in annual rate of change in MMSE (95% CI):</u> Wild-type = -0.02 (-0.10, 0.07) **Any *HFE* variant allele = -0.22 (-0.39, -0.05)** **p-value interaction= 0.03** p-value trend: NA <u>Dose model: Mean difference in annual rate of change in MMSE (95% CI):</u> Wild-type = -0.02 (-0.10, 0.07) One *HFE* variant allele = -0.14 (-0.33, 0.04) **Two *HFE* variant alleles = -0.63 (-1.04, -0.21)** **p-value interaction: <0.01**	*HFE* polymorphisms significantly modified the association between tibia Pb and the rate of cognitive decline. Subjects with more copies of *HFE* variant alleles had greater cognitive

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						p-value trend: <0.01	decline per unit increase in tibia Pb.
Case-control Wang (2008) Anhui Province, China	1260 children, 4 – 12 years old from pediatric clinics at the Anhui Provincial Children's hospital and the Institute of Anhui Traditional Chinese Medicine: 630 ADHD cases pair-matched to 630 non-ADHD controls Years= 2003 – 2007; Male=69%	7.9 (2.1) years	ADHD = 8.77 (3.89) Control= 5.76 (3.39)	ADHD diagnosed from a structured diagnostic interview Modified to assess on the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R) criteria.	Pearson chi-square test; Student's *t*-test; conditional multiple variables logistical regression analyses with backward step-wise selection. Family history of ADHD, household composition, maternal tobacco use during pregnancy, maternal drinking during pregnancy, labor complications, cesarean delivery, perinatal distress, parents' age at birth, parents' education.	Logistical regression analysis of risk of ADHD by blood Pb: <u>Total sample</u> ≤ 5 µg/dL: reference **5 – 10 µg/dL: 4.92 (3.47, 6.99); p<0.01** **> 10 µg/dL: 6.00 (4.11, 8.77); p<0.01**	Concurrent blood Pb was significantly associated with risk of ADHD.
Cross-sectional Wang (2009) China	317 children in 1st to 6th grade from 4 rural villages in southeast China; Year = 2007 Male=51%	mean not reported Range=6-12	Blood =7.1(0.16) Urine=1.2(0.18) Hair=1.3(0.28) Nails=2.5(0.28) Measured when outcome assessed	Intelligence assessment (Revised Raven's Standard Progressive Matrices and converted to standardized intelligence scores from 0 to 100), ADHD (by Abbreviated Symptom Questionnaire of Conner's instrument for teachers), Pb symptoms (coryza dizziness, stomach ache or nausea), parental report of aggression	Student's t-test, Spearman's correlation, Binary or ordinal logistic regression Adjustments not described.	ADHD questionnaire filled in by school supervisors. Spearman's correlation coefficient of intelligence score: **Hair Pb r=0.51; p<0.01** **Urine Pb r=0.132; p<0.05** Blood and Nail Pb not reported *Binary regression* OR (95%CI) **Log Urine Pb OR= 1.79 (1.00,3.22) (*p<0.05*)** **Log Hair Pb OR=1.46 (1.06,2.03) (*p<0.05*)** *Logistic regression* OR (95%CI) **Log Urine Pb OR=1.28 (1.04-1.58) (*p<0.05*)** **Log Hair Pb OR=1.73 (1.18-2.52) (*p<0.05*)** Regression analysis and OR not reported for blood and Nail Pb data **Mental retardation** (intelligence scores below 25) rate was significantly higher (22.2%) in children with blood Pb above 10µg/dL than in those with lower blood Pb levels (9.4%) **p<0.05**). No association between Pb exposure and ADHD or Pb-related symptoms (dizziness, coryza, nausea, or aggressive behavior).	Urinary and hair Pb,but not blood or nail Pb were significantly associated with lower intelligence scores. Blood Pb was significantly associated with intelligence scores below 25 (cut-off for mental retardation) in 6-12 year olds;
Prospective Wasserman	392 infants, 208 from the Pb smelter	2 years	Total: Mid-pregnancy:	Mental Development Index (MDI), Bayley	Least squares regression analysis	Estimated change in 24-month MDI as blood Pb concentration increases from 10 to 30 µg/dl	Blood Pb at 2 years was

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
(1992) Kosovo, Yugoslavia *Population may overlap with Wasserman (1994)* and others	town of Kosovska Mitrovica and 184 from the unexposed town of Pristina; Year= initiated in 1985 Male=51.9%		13.1 (9.2) Cord: 14.4 (10.4) Exposed: Mid-pregnancy: 19.9 (7.7) Cord: 22.2 (8.1) Unexposed: Mid-pregnancy: 5.6 (2.0) Cord: 5.5 (3.3)	Scales of Infant Development	Gender, birth order, birth weight, ethnic group, HOME score, years of maternal education, maternal age, and maternal intelligence	Regression coefficient for log(blood Pb): β(SE) At birth (cord): -3.487 (2.262); p=0.1242 At 6 months: -2.373 (2.489); p=0.3412 At 12 months: -3.655 (2.654); p=0.1697 At 18 months: -3.719 (2.665); p=0.1640 **At 24 months: -5.307 (2.436); p=0.0301**	significantly associated with decrement in MDI at age 2, but early blood Pb levels were not statistically significant.
Prospective Wasserman (1994) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	332-338 infants from the Pb smelter town of Kosovska Mitrovica and the unexposed town of Pristina; Year=initiated in 1985 Male=48.5%	3 and 4 years	Mid-pregnancy: 13.0 (9.3) Cord: 14.1 (10.5)	Child developmental status at ages 3 and 4 years was assessed by the McCarthy Scales of Children's Abilities (MSCA) which provides a general measure of intellectual functioning (the GCI).	Least squares regression analysis Quality of the HOME environment; maternal age, intelligence, education, and language; birthweight and gender	Regression coefficients between blood Pb and the MSCA subscores at age 3-4: β(SE), p-value GCI Mid-pregnancy: -4.98 (2.76); p=0.072 **Cord: -7.14 (2.24); p=0.002** 6 months: -4.21 (2.36); p=0.076 **12 months: -7.53 (2.70); p=0.006** **18 months: -4.92 (2.50); p=0.05** **24 months: -10.44 (2.41); p=0.00** **30 months: -9.73 (2.59); p=0.00** **36 months: -9.25 (2.57); p=0.00** **42 months: -10.40 (2.63); p=0.00** **48 months: -9.43 (2.44); p=0.00** Perceptual Performance: **Mid-pregnancy: -4.70 (1.66); p=0.004** **Cord: -5.27 (1.36); p=0.00** 6 months: -2.39 (1.44); 0.099 **12 months: -4.38 (1.63); p=0.008** **18 months: -4.91 (1.54); p=0.002** **24 months: -6.76 (1.50); p=0.00** **30 months: -5.87 (1.62); p=0.00** **36 months: -6.92 (1.58); p=0.00** **42 months: -6.67 (1.68); p=0.00** **48 months: -7.06 (1.61); p=0.00** Verbal, Quantitative, Memory, and Motor were negatively but not significantly associated to MSCA	Blood Pb from cord, 12,18, 24, 30, 36, 42, and 48 months was significantly associated with a decrease in general intellectual functioning and the perceptual-performance subscale at age 3-4; mid-pregnancy blood Pb was also significantly associated with the perceptual-performance subscale; all other regression coefficients were negative but not statistically significant.
Prospective Wasserman (1997) Kosovo, Yugoslavia	309 7-year old children from the Pb smelter town of Kosovska Mitrovica and the unexposed	mean not reported Children were tested at 6.5,	Cord Blood: Pristina: 5.7 (3.6) Mitrovica: 23.2 (8.1) Blood Pb at 7yrs:	Wechsler Intelligence Scale for Children (WISC-III)	Ordinary least squares regression analysis. Gender, sibship size at the time of the IQ test, birth weight,	Association between Cumulative Pb and IQ at age 7: Est B (SE) β; p-value Full Scale IQ: -8.5864 (1.8868) **-0.2146; p < 0.001** Performance IQ: -9.1669 (2.0659), **-0.2177; p < 0.001** Verbal IQ -6.5931 (1.8611), **-0.1765; p < 0.001**	Cumulative Pb (7 years estimate from blood) was significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Population may overlap with Wasserman (1992) and others	town of Pristina; Year=1984-1985 Male=50.2%	7.0, or 7.5 years of age.	Pristina: 8.0 (3.1) Mitrovica: 34.0 (11.0) Cumulative Pb exposure through age 7 (AUC7): Pristina: 0.87 (0.11) Mitrovica:1.52 (0.12)		hemoglobin concentration, language spoken in the home, HOME score, years of maternal education, maternal age, and maternal Raven's test score.	Authors state that a change in lifetime blood Pb from 10 to 30 µg/dL was associated with an estimated decrease in IQ: points (959% CI) Full Scale IQ: 4.3 points (3.4, 5.1) Verbal IQ: 3.4 points (1.7, 5.0) Performance IQ : 4.5 points (2.7, 6.3)	associated with lower Full Scale, Performance, and Verbal IQ scores at age 7.
Prospective Wasserman (1998) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	293 children from from the Pb smelter town of Kosovska Mitrovica and the unexposed town of Pristina; Year= 1985 – 1989 Male=51%	mean not reported Children were assessed at their 3-year visits.	Cord Blood: Pristina: 5.5 (3.4) Mitrovica: 22.0 (8.1) Blood levels at 36 months: Pristina: 9.8 (3.4) Mitrovica: 40.9 (14.9) Blood levels also assessed at 6, 12, 18, 24, and 30 months	Destructive and withdrawn childhood behavior measured using the Child Behavior Checklist (CBCL)	Hierarchical linear regression analysis. Town, residence type, gender, ethnicity, maternal education, HOME score, parity, child's IQ, fathers education.	Correlation between levels of reported behavior problems at age 3 and blood Pb levels: *ϐ* (SE), p-value Cord blood Pb: **Anxious-Depressed: β = 1.16 (0.58); p= 0.046** **Withdrawn: β = 1.52 (0.76); p= 0.046** **Sleep Problems: β = 1.00 (0.39); p= 0.011** Somatic problems: β = 1.14 (0.60); p= 0.058 Aggressive: β = 1.25 (0.85); p= 0.145 Destructive β = 0.79 (0.48); p= 0.097 36 months blood Pb: **Anxious-Depressed: β = 1.45 (0.72); p= 0.044** **Withdrawn: β = 3.07 (0.95); p= 0.001** **Sleep Problem: β = 1.09 (0.48); p= 0.024** **Somatic problems: β = 1.71 (0.70); p= 0.016** Aggressive: β = 1.85 (1.08); p= 0.089 **Destructive: β = 2.07 (0.61); p= 0.001** Authors state that blood Pb at 6, 12, 18, 24, and 30 months were inconsistently related to behavior problems.	Cord and 36 month blood Pb levels were significantly correlated with measures of behavioral problems in 3 year old children.
Prospective Wasserman (2000b) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	283 children from the Pb smelter town of Kosovska Mitrovica and the unexposed town of Pristina; Year=initiated in 1985, assessed in 1990-1992 % male not stated	54 months (4.5 years)	mean not reported Average $\log_{10}$ blood Pb concentration from birth through 54 months estimated	Motor skills assessed by the Bruininks Oseretsky Test of Motor Proficiency (consisting of 8 subtests); The Beery Test of Visual Motor Integration assessing motor functioning, fine motor composite, gross motor composite, and visual motor integration (VMI)	Multiple regression; least squares linear regression BMI, father's education, mother's education, HOME, residence type, sex, sibship size, birth weight, no lateralization, maternal Raven (IQ)	Regression of average $\log_{10}$ blood Pb concentration (birth through 54 months) and motor proficiency: β (SE) **Fine motor composite: -0.17 (0.68); p<0.005** Gross motor composite: 0.03 (0.80); p=ns **Visual motor integration: -0.24 (0.20); p<0.001**	Average lifetime blood Pb was significantly associated with lower fine motor and visual motor integration scores at age 4.5 years, but not gross motor scores.
Prospective Wasserman (2000a)	390 children from the Pb smelter town of Kosovska	Assessments from 3 to 7 years	Mid-pregnancy: 10.0 (2.09) Cord: 10.23 (2.29)	Early intelligence as assessed by McCarthy GCI at age	Repeated measures linear regression; generalized estimating	Adjusted associations between IQ, prenatal blood Pb and postnatal increments in blood Pb: B (SE) **Prenatal blood Pb: -6.05 (1.35); p<0.001**	Elevations in both prenatal and postnatal

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	Mitrovica and the unexposed town of Pristina; Year=1985-1994 Male=51.8%	Mothers mean age at delivery 26.1 (4.6)	Average pre-natal: 10.23 (2.09) Average post-natal: Age 0-2: 13.18 (2.19) Age 2-3: 19.05 (2.14) Age 2-4: 19.50 (2.14) Age 2-5: 19.05 (2.14) Age 2-7: 17.34 (2.19) Converted from reported log_{10} Pb	3-4; Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R IQ) at age 5; and Wechsler Intelligence Scale for Children-version III (WISC-III IQ) at age 7	equation (GEE); HOME score, maternal age, intelligence, education, ethnicity, birthweight, and gender	**Postnatal blood Pb increase:** **Increase after age 2 (late): -1.78 (0.88); p<0.05** **Early and late postnatal increase: -2.71 (1.12); p<0.05** Authors state that the association between prenatal blood Pb and IQ is not linear; the strongest postnatal effects are noted at the lower levels of prenatal exposure.	blood Pb were significantly associated with small decrements in young children's IQ.
Prospective Wasserman (2001) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	199 children from the Pb smelter town of Kosovska Mitrovica and the unexposed town of Pristina; Year = recruited 1984-1985 and assessed 1989-1991; Male =51%	4-5	Cord: 5.6 (3.44) Average Pb (4 years): 7.24 (1.31) Measured semiannually from birth to the age of assessment (4, 4.5, or 5 years)	Child behavior problems were measured by the Child Behavior Checklist (CBCL): a Total Score and 8 log-transformed subscales, maternal smoking during pregnancy	Linear regression Age, smoking, HOME, birth weight, ethnicity, gender, maternal education	<u>Association between log cumulative blood Pb and log CBCL subscales</u>: β(SE) Aggressive: β(SE)= 0.08 (0.14); NS **Delinquent: β(SE)= 0.32 (0.15); p<0.05** Attention Problems: β(SE)= 0.06 (0.14); NS Thought Problems: β(SE)=0.27 (0.15); NS Social Problems: β(SE)= 0.11 (0.12); NS Anxious/Depressed: β(SE)= 0.19 (0.12); NS Somatic Complaints: β(SE)= 0.30 (0.17); NS Withdrawn: β(SE)= 0.22 (0.13); NS Maternal smoking during pregnancy was significantly positively associated with all subscales except Anxious/depressed or Somatic complaints	Average lifetime blood Pb was significantly associated with increased delinquency in 4-5 year olds; associations with other behavior subscales were positive but not statistically significant
Prospective Wasserman (2003) Kosovo, Yugoslavia *Population may overlap with Wasserman (1992) and others*	Children from the Pb smelter town of Kosovska Mitrovica and the unexposed town of Pristina; n=290 for blood analysis, n=167 for bone analysis Year=1986 – 1999 Male= 49% for blood analysis; 50% male for bone analysis	Blood Pb analysis: Pristina – 10.1 (0.1) and 12.2 (0.1) years Mitrovica – 10.1 (0.1) and 12.2 (0.2) years Bone Pb: Pristina – 11.88 (0.4) years Mitrovica – 11.96 (0.4) years	<u>Blood Pb</u> Pristina: Blood Pb: 6.1 (1.9) Concurrent tibia Pb (µg/g): 1.3 (6.6) Mitrovica: Blood Pb: 30.9 (9.6) Concurrent tibia Pb (µg/g): 39.1 (25.1) <u>Bone Pb subset</u> Pristina: Blood Pb: 6.0 (1.9) Concurrent tibia Pb (µg/g): 1.4 (6.5) Mitrovica: Blood Pb: 31.1 (9.9) Concurrent tibia Pb (µg/g): 40.1 (26.2) Measured every 6	Child intelligence measured by the Wechsler Intelligence Scale for Children (WISC–III): Full Scale IQ, Verbal IQ score and Performance IQ score at ages 10 and 12	Regression Modeling: repeated measures linear models; ordinary linear regression and a series of least squares regression models. Age, gender, sibship size at IQ test, birth weight, language, HOME score at age 9, maternal age, maternal education, maternal Raven score.	<u>Associations between average log_{10} blood Pb and IQ:</u> Full Scale IQ (age 10-12): *B* (SE), *p* Only adjusted for age: 0.90 (2.60) **Adjusted for other covariates: -5.31 (1.98), *p* < 0.01** Verbal IQ (age 10-12): *B* (SE), *p* Only adjusted for age: 0.65 (2.38) **Adjusted for other covariates: -4.84 (1.89), *p* < 0.05** Performance IQ (age 10-12): *B* (SE), *p* Only adjusted for age: 1.02 (2.71) **Adjusted for other covariates: -5.01 (2.13), *p* < 0.05** <u>Adjusted associations between log_{10} Pb and IQ (for those participating in bone Pb analyses):</u> Full Scale IQ (age 10-12): *B* (SE), *p;* standardized *β* **Model 1 (ave. blood): -5.02 (2.36), *p*<0.05; 0.1299** **Model 2 (tibia): -8.00 (2.29), p<0.01; 0.2076** **Model 3 (conc. blood): -4.48 (2.15), p<0.05; 0.1267** Model 4 (tibia x ave. blood): **Tibia: -11.16 (3.83), p<0.01; 0.2897** Ave. Blood: 3.97 (3.85), NS; 0.1027	Tibia Pb was statistically significantly associated lower full scale, verbal, and performance IQ at age 10-12. Average blood Pb was significantly associated with lower IQ scores as well, but was not statistically significant after controlling for tibia Pb in the smaller subset

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
			months (birth to 10 or 12)			Model 5 (tibia x conc. blood): **Tibia: -11.06 (3.76), p<0.01; 0.2871** Conc. Blood: 3.53 (3.43), NS; 0.0999 Verbal IQ (age 10-12): *B* (SE), *p;* standardized *β* Model 1 (ave. blood): -4.21 (2.22), *NS*; -0.1204 **Model 2 (tibia): -5.90 (2.18), p<0.01; -0.1694** Model 3 (conc. blood): -3.83 (2.02), NS; 0.1199 Model 4 (tibia x ave. blood): Tibia: -7.10 (3.65), NS; -0.2040 Ave. Blood: 1.51 (3.67), NS; 0.0433 Model 5 (tibia x conc. blood): Tibia: -6.92 (3.58),NS; -0.1989 Conc. Blood: 3.53 (3.43), NS; 0.0371 Performance IQ (age 10-12): *B* (SE), *p;* standardized *β* Model 1 (ave. blood): -5.11 (2.74), NS; -0.1209 **Model 2 (tibia): -8.88 (2.66), p<0.01; -0.2111** Model 3 (conc. blood): -4.52 (2.49), NS; 0.1170 Model 4 (tibia x ave. blood): **Tibia: -13.49 (4.44), p<0.01; -0.3207** Ave. Blood: 5.79 (4.48), NS; 0.1370 Model 5 (tibia x conc. blood): **Tibia: -13.40 (4.36), p<0.01; -0.3184** Conc. Blood: 5.21 (3.99), NS; 0.1348	with concurrent bone and blood Pb measures.
Prospective Weisskopf (2004) Boston, MA, USA *Population may overlap with Payton (1998) and others*	466 men in the Normative Aging Study; Year= 1993 – 2001 (initially enrolled in 1963) Male = 100%	67.4 (6.6) years	Patella = 23 µg/g Tibia = 19 µg/g Blood = 4 µg/dL	Cognitive decline was measured by the Mini-Mental State Examination (MMSE) scores	Generalized additive models, linear models; univariate and bivariate analyses.	Difference in change over time of MMSE score associated with one interquartile range (IQR) increase in Pb: Est. (95% CI) **Patella Pb (IQR = 20 µg/g): -0.24 (-0.44, -0.05)** Tibia Pb (IQR = 14 µg/g): -0.17 (-0.38, 0.04) Baseline blood Pb (IQR = 2 µg/dl): -0.01 (-0.13, 0.11)	Patella bone Pb was significnatly associated with a steeper decline over time in performance on the MMSE
Prospective Weisskopf (2007a) Boston, MA, USA *Population may overlap with Payton (1998) and others*	31 men from the Normative Aging Study: 15 from the lowest quartile of patella bone Pb and 16 from the highest quartile Year= 2002 – 2004 Male= 100%	Low exposure 73.2 (4.7) years High exposure 80.7 (6.1) years	Median patella Pb Low group: 9 (5 – 15) µg/g High group: 63 (43 – 86) µg/g Median tibia Pb Low group: 13 (9 – 17) µg/g High group: 41 (38 – 59) µg/g	Hippocampal levels of the metabolites N-acetylaspartate, myoinositol, and choline were assessed from Magnetic Resonance Spectroscopy (MRS) images taken ~ 6 years after Pb measured in bone.	Univariate analyses Age, renal insufficiency, diabetes, hypertension, and decline in bone Pb over time.	Effect estimate of 20 µg/g patella bone Pb concentration on myoinositol-to creatinine ratio in the hippocampus **0.09 (95% CI: 0.01, 0.17); p=0.03**	Cumulative patella Pb exposure is significantly associated with an increase in the myoinositol/creatinine ratio.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective and cross-sectional Weisskopf (2007b) Boston, MA, USA *Population may overlap with Payton (1998) and others*	1089 men in the Normative Aging Study; Year= 1993 – 2001 (initially enrolled in 1963) Male = 100%	68.7 (7.4) years	Median: Blood Pb: 5 µg/dL Patella: 5 µg/g Tibia: 20 µg/g	Participants were evaluated using: the Neurobehavioral Evaluation System 2 (NES2), the Wechsler Adult Intelligence Scale-Revised (WAIS-R), the Consortium to Establish a Registry for Alzheimer disease (CERAD) battery, the MMSE, and the developmental test of visual-motor integration (VMI).	Non-linear-spline regressions and linear repeated measures analysis; generalized extreme-studentized-deviation (ESD); ordinary least squares regression. Age, years between bone Pb measurements and date of first cognitive test, education, smoking, alcohol intake, number of years between the two tests, computer experience, English as a first language, quintile of physical activity.	Difference in cognitive test score per interquartile range (IQR = 3 µg/dL) increase in concurrent blood Pb: **Vocabulary** **-1.26 (-2.08, -0.44); p=0.003** Difference in change over time of visuospatial cognitive test scores per IQR increase in bone Pb: Patella (IQR = 20 µg/g): **Construction (# correct) -0.067 (-0.11, -0.02); p=0.0041** **Pattern (latency) 0.073 (0.04, 0.12); p=0.0008** **Pattern (# correct) 0.040 (0.002, 0.08); p=0.042** Tibia levels (IQR = 15 µg/g) Construction (# correct) -0.03 (-0.08, 0.02); p=0.22 **Pattern (latency) 0.079 (0.04, 0.12); p=0.0004** **Pattern (# correct) 0.042 (0.002, 0.08); p=0.038**	Concurrent blood Pb was significantly associated with lower vocabulary scores; cumulative bone Pb was significantly associated with declines in cognitive function over time, particularly visuospatial/ visuomotor subscales.
Case-control; Weisskopf (2010) Boston, MA, USA	330 Parkinson's disease (PD) patients in Boston, MA area and 308 acquaintance (spouse/in-law/friend), Normative Aging Study, and recruited controls; Years= 2003-2007 % Male= 65% PD 56% control	PD patients 66.5 (9.5) Control 69.4(8.8)	Tibia (µg/g) Q1-≤5 Q2 5.2-10.4 Q3 11.0-19.0 Q4 ≥19.1 No blood Pb data	Parkinson's disease (PD)	Logistical regression Age, age squared, sex, race, smoking, education, and recruitment site	Parkinson's disease and tibia bone Pb: OR (95% CI) All cases and Acq. and NAS controls (n=330/166) Q1 (<3.1µg/g): reference Q2 (3.5-9.6µg/g): 1.36 (0.70, 2.63) Q3 (10-17µg/g): 1.90 (0.90,4.01) **Q4 (>17.3µg/g): 3.21 (1.17, 8.83)** **p-trend = 0.02** Movement disorder clinics and Acq. controls(326/69) Q1 (<1µg/g): reference Q2 (1.7-7µg/g): 1.48 (0.72, 3.04) Q3 (7.8-13.1µg/g): 1.91 (0.91, 4.00) **Q4 (>13.9µg/g): 2.57 (1.11, 5.93);** **p-trend 0.03** All cases and all controls (330/308) Q1 (<3.1µg/g): reference Q2 (3.5-9µg/g): 1.30 (0.76, 2.23) Q3 (9.6-16µg/g): 1.37 (0.80, 2.36) **Q4 (>16µg/g): 1.91 (1.01, 3.60);** **p-trend 0.06** ORs for patella Pb were not statistically significant for any quartile (p-values for trend: 0.42, 0.47, 0.83)	Tibia Pb was significantly associated with a greater risk of Parkinson's disease, and patella Pb was not statistically significant.
Cross-sectional Weuve (2006) Boston, MA, USA	915 men in the Normative Aging Study with *ALAD*	68.7 *ALAD* 1-1	Blood Pb: 5.3 (1.23) *ALAD* 1-1: 5.3 (2.9) *ALAD*-2: 4.8 (2.7)	Cognitive functioning assessed by Mini-Mental State	Multivariable analyses Included interaction	Mean difference in MMSE score per IQR in Pb biomarker: Mean diff (95% CI) Blood Pb (adj for Set 1 covariates):	Higher blood Pb was significantly

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Population may overlap with Payton (1998) and others	genotype data. 149 ALAD-2 carriers and 766 wild-type non-carriers. Year= bone Pb assessed in 1991, cognitive testing began in 1993 (initially enrolled in 1963) Male = 100%	(n=766): 68.5 (7.3) *ALAD*-2 (n=149): 70.0 (7.4) 45-80 years at Pb assesment	Measured at time of cognitive testing Tibia Pb: *ALAD* 1-1: 21.7 (13.5) *ALAD*-2: 21.0 (11.1) Median: 19 µg/g Patella Pb: *ALAD* 1-1: 30.8 (19.7) *ALAD*-2: 29.7 (17.3) Median: 27 µg/g	Examination (MMSE), men began in 1993. *ALAD* rs1800435 polymorphism also genotyped.	term for blood Pb and ALAD-2 Set 1: Age at cognitive assessment, age-squared, years of education, computer experience, length of time between Pb and cognitive assessments, and timing of cognitive assessments. Set 2: all of Set 1 and smoking status, alcohol consumption, calorie adjusted calcium intake, regular energy expenditure on leisure time physical activity, and diabetes	**ALAD-2 carriers: -0.29 (-0.56, -0.02)** Wild-type: -0.05 (-0.16, 0.06) Difference in estimates: -0.24 (-0.53, 0.05) p-interaction=0.10 Blood Pb (adj for Set 2 covariates): ALAD-2 carriers: -0.26 (-0.54, 0.01) Wildtype: -0.04 (-0.16, 0.07) Difference in estimates: -0.22 (-0.51, 0.01) p-interaction=0.13 Tibia Pb (adj. for Set 1 covariates) ALAD-2 carriers: -0.20 (-0.62, 0.22) Wild-type: -0.07 (-0.23, 0.10) Difference in estimates: -0.13 (-0.58, 0.31) p-interaction=0.55 Tibia Pb (adj for Set 2 covariates): ALAD-2 carriers: -0.16 (-0.58, 0.27) Wildtype: -0.05 (-0.21, 0.12) Difference in estimates: -0.11 (-0.55, 0.33) p-interaction=0.63 Patella Pb (adj. for Set 1 covariates) ALAD-2 carriers: -0.28 (-0.66, 0.11) Wild-type: -0.08 (-0.24, 0.07) Difference in estimates: -0.19 (-0.60, 0.21) p-interaction=0.35 Patella Pb (adj for Set 2 covariates: ALAD-2 carriers: -0.26 (-0.64, 0.12) Wildtype: -0.07 (-0.23, 0.09) Difference in estimates: -0.19 (-0.59, 0.21) p-interaction=0.35	associated with poorer performance on the MMSE, among *ALAD-2* carriers. Associations between bone Pb levels and MMSE score did not vary by *ALAD-2* status.
Cross-sectional Weuve (2009) Boston, MA, USA	587 women from the Nurses Health Study; Years=1990-1994 and 2000-2004 Male=0%	61 Range 47-74	Blood: 2.9(1.9) Patella (µg/g) 12.6(11.6) Tibia (µg/g) 10.5(9.7) Bone Pb measured 5 years (on average) before outcome assessed	Cognitive assessment (by Telephone Interview for Cognitive Status-TICS),	Multiple linear regression Age and age-squared at Pb assessment, age at cognitive assessment, education, husband's education, alcohol consumption, smoking status, physical activity, aspirin use, ibuprofen use, use of vitamin E supplements, status of menopause, hormone use, Pb substudy source, and cognitive substudy source	Mean difference in overall standardized TICS score per SD increase in Pb (2µg/dL blood; 10µg/g tibia; 12µg/g patella): Blood Pb -0.015 (–0.069,0.039) (p =0.59) Patella Pb -0.012 (–0.056,0.033) (p=0.61) Tibia Pb -0.040 (–0.085,0.004) (p=0.08). Mean difference in overall standardized TICS score (excluding letter fluency) per SD increase in Pb (2µg/dL blood; 10µg/g tibia; 12µg/g patella): Blood Pb -0.016 (-0.071, 0.039) (p =0.57) Patella Pb -0.033 (-0.080, 0.014) (p=0.17) **Tibia Pb -0.051 (-0.099,-0.003) (p=0.04).**	Tibia Pb was associated with reduced cognitive function in older women; blood and patella Pb associations were not statistically significant.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Prospective Wigg (1988) Port Pirie, Australia *Population may overlap with Baghurst (1992) and others*	590 infants living in and around the Pb smelting town of Port Pirie, South Australia, followed since birth; evaluated at age 2; Year = 1979-1982 (at baseline) %male not reported	24 months	Geometric mean (95% CI) Cord: 8.3 (8.0, 8.6) 6 months: 14.4 (13.9, 14.8) 15 months: 20.9 (20.2, 21.5) 24 months: 21.2 (20.6, 21.8) Integrated postnatal: 18.1 (16.5, 19.6) Maternal exposure measured at 14-20 weeks and at delivery. Exposure measured at birth (umbilical cord)	Development as assessed by the Mental Development Index (MDI) and the Psychomotor Development Index (PDI) scores of the Bayley Scales of Infant Development	Pearson correlations; partial linear regression; blood Pb concentrations log-normally distributed Maternal age, father's secondary education, mother's secondary education, father's workplace, mother's workplace, parental relationship, mother's antenatal marital status, child's birth rank, neonatal oxygen use at birth, Apgar score at 5 minutes, neonatal jaundice, size for gestational age, mouthing activity at 15 moths, maternal IQ, and HOME score	<u>Correlations between blood Pb and age 2 Bayley scores</u>: <u>Maternal</u> 14-20 wks gestation: MDI=-0.06; PDI=-0.05 **After 20 wks gestation: MDI=-0.08 (p<0.05);**PDI=-0.02 **Average prepartum: MDI=-0.11 (p<0.05);** PDI=-0.06 At delivery: MDI=-0.03, PDI= -0.02 <u>Child</u> Umbilical cord: MDI=-0.04; PDI=-0.04 **6 months: MDI=-0.12 (p<0.05);** PDI=-0.07 **15 months: MDI=-0.12 (p<0.05);** PDI= -0.02 **24 months: MDI= -0.18 (p<0.01);** PDI=-0.02 **Integrated postnatal: MDI=-0.15 (p<0.01);** PDI=-0.01 <u>Partial linear regression coefficients for change in MDI at age 2 per unit change in blood Pb</u>: (adjusted model) β Average maternal antenatal: -0.07 Maternal at Delivery: 0.23 Cord: 0.10 6 months -0.16; p=0.07 **(unadj for HOME: -0.24, p =0.01)** **(unadj. for HOME and mat. IQ: -0.24, p =0.01)** 15 months: -0.03 24 months:-0.05 Integrated postnatal Pb: -0.12; p=0.19 **(unadj for HOME: -0.22, p =0.05)** **(unadj. for HOME and mat. IQ: -0.26, p =0.03)** Authors estimate that a child with PbB of 30 µg/dL at age 6 months will have a deficit of 3.3 points (approximately 3%) on the Bayley Mental Development Scale relative to a child with PbB of 10 µg/dl.	Blood Pb (maternal and postnatal) was significantly negatively correlated with MDI, but not PDI. Blood Pb at 6 months was associated with lower MDI scores, although not statistically significantly after adjusting for HOME score.
Cross-sectional Wright (2003) Boston,MA, USA *Population may overlap with Payton (1998) and others*	736 participants from the Normative Aging Study; Year=1991 – 2001 (initially enrolled in 1963) Male = 100%	68.2 (6.9) years	Patella = 29.5 (21.2) µg/g Tibia = 22.4 (15.3) µg/g Blood = 4.5 (2.5) µg/dL	Cognitive function was assessed by the Mini-Mental Status Exam (MMSE).	Multiple linear and logistic regression analyses. Age, education, alcohol consumption.	<u>AdjOR (95% CI) for a 1-unit change in blood, patella, or tibia Pb levels and a MMSE score below 24</u>: **Blood Pb: 1.21 (1.07, 1.36)** **Patella Pb: 1.02 (1.00, 1.03)** **Tibia Pb: 1.02 (1.00-1.04)**	Blood, patella, and tibia Pb are significantly associated with poor cognitive test performance in older men.
Prospective Wright (2008) Cincinnati, OH, USA	250 individuals recruited at birth from four prenatal clinics in the	19 - 24 years	Maternal = 8.3 (3.8) measured in 1st or early 2nd trimester:	Number of criminal arrests since turning 18 years of age	Negative binomial regression Maternal IQ, sex, SES	<u>Total arrest rates in young adults</u> <u>Rate Ratio (95% CI) for 5 µg/dL increase in blood Pb:</u> **Prenatal Pb: 1.40 (1.07-1.85)** Early childhood average Pb: 1.07 (0.88, 1.29)	Blood Pb was significantly associated with increased rates

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
Population may overlap with Dietrich (1987) and others	Cincinnati Lead Study; Years: enrolled between 1979-1984 Male=50%		Early childhood avg.: = 13.4 (6.1) Age 6 (ave. 6.5): =8.3 (4.8)		using the Hollingshead Score, and maternal education level	**Age 6 Pb: 1.27 (1.03-1.57)** Violent crime arrest rates in young adults Rate Ratio (95% CI) for 5 µg/dL increase in blood Pb: Prenatal Pb: 1.34 (0.88, 2.03) **Early childhood average Pb: 1.30 (1.03, 1.64)** **Age 6 Pb: 1.48 (1.15, 1.89)** Non-Violent crime arrest rates in young adults Rate Ratio (95% CI) for 5 µg/dL increase in blood Pb: **Prenatal Pb: 1.40 (1.06, 1.84)** Early childhood average Pb: 1.05 (0.86, 1.28) Age 6 Pb: 1.22 (0.97, 1.53)	of arrests at age 19-24: total arrests (age 6 Pb & prenatal), violent crime arrests (early childhood and age 6 Pb), and non-violent crime (prenatal Pb only).
Prospective (Yuan *et al.* 2006) Cincinnati, OH, USA *Population may overlap with Dietrich (1987) and others*	42 young adults from the Cincinnati Lead Study (CLS); Birth Cohort Year= recruited in 1979-1984 Male=52%	21 (1) years	Mean childhood blood Pb from 3 months to 78 months: 14.18 (6.52) µg/dL Measured quarterly from birth until age 5 and at age 5.5, 6.0, and 6.5 years (78 months)	Functional magnetic resonance images were collected while the subject was performing a verbal generation task using a 3-plane gradient echo scan.	Pearson's correlation coefficient; regression coefficient; multiple regression analysis. Age, gender, full scale IQ, Hollingshead four-factor total SES (TOTSES), gestational age, birth weight, marijuana usage.	Partial correlation coefficient of the mean brain activation within regions of interest (ROI) and mean childhood blood Pb (birth to 6.5 years): partial *R*; *P* **ROI1 (left frontal – near Broca's): -0.32; p<0.04** **ROI2 (right temporal): 0.35; p<0.03** **ROI3 (left temporal – incl Wernicke's): -0.31; p<0.05** ROI4 (left frontal): partial *R* = -0.30; p =0.08	Childhood blood Pb levels were significantly correlated with brain reorganization associated with language function.
Cross sectional (Yule *et al.* 1984) London, England	166 children living near leadworks in outer London with measured blood Pb levels (pilot study). Year not stated % male not stated	8.6 years	13.52 (4.13) Range: 7-32 9 to 12 months before outcome assessed	Behavior measured by teacher ratings on Needleman's Scale, Rutter B(2) Questionnaire, and the Conners Scale.	Chi-square test; ANOVA and ANCOVA Social factors not controlled for	Percentage of children receiving a negative teacher rating on Needleman Scales of four blood Pb categories: 7-10, 11-12, 13-16, 17-32 µg/dL; χ^2 or *F*; *P*-value Distractible: 35.5, 35.4, 53.1, 45.7; χ^2=4.1; NS Not persistent: 2.9, 6.3, 12.2, 14.3; χ^2=3.8; NS Dependent: 14.7, 16.7, 28.6, 25.7; χ^2=3.4; NS Disorganized: 17.6, 12.5, 24.5, 20.0; χ^2=2.4; NS Hyperactive: 5.9, 2.1, 6.1, 0.0; χ^2=3.0; NS Impulsive: 5.9, 6.3, 22.4, 14.3; χ^2=7.5; *p* = 0.06 Easily Frustrated: 23.5, 20.8, 30.6, 17.1, χ^2=2.4; NS **Day dreamer:** **17.6, 25.0, 22.4, 48.6; χ^2=10.2 ; *p*=0.02** **Does not follow simple direction:** **5.9, 0.0, 0.0, 11.4; χ^2=10.3; *p*=0.02** **Does not follow sequence of direction:** **8.8, 10.4, 26.5, 25.7; χ^2=7.6; *p*=0.05** **Low overall functioning:** **14.7, 18.8, 18.4, 40.0; χ^2=8.2; *p*=0.04** Total score: 1.53, 1.54, 2.45, 2.63; F = 2.15; p=0.096 Percent 'deviant' on B(2) Scale of Rutter Questionnaire at two blood Pb levels: 7-12 and 13-32µg/dL; χ^2; *P*-value Restless: 26.8, 33.3; χ^2=0.55; NS Truants: 6.1, 0; χ^2=3.4; *p*=0.	Blood Pb was significantly associated with several measures of behavioral problems.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Outcome measured	Statistical modeling; covariates	Findings	Observed effect
						Squirmy: 13.4, 32.1; χ^2=7.21; *p*=0.007 Destroys: 3.7, 9.5; χ^2=1.46; NS **Fights: 6.1, 20.2; χ^2=6.04; *p*=0.014** Not liked: 11.0, 16.7; χ^2=0.70; NS Worried: 30.5, 35.7; χ^2=0.30; NS Solitary: 19.5, 26.2; χ^2=0.70; NS Irritable: 8.5, 15.5; χ^2=1.29; NS Miserable: 17.1, 16.7; χ^2=0.02; NS Twitches: 6.1, 9.5; χ^2=0.28; NS Sucks thumb: 1.2, 8.3; χ^2=3.16; *p*=0.08 Bites nails: 3.7, 11.9; χ^2=2.85; *p*=0.09 Absent: 14.6, 13.1; χ^2=0.00; NS Disobedient: 9.8, 21.4; χ^2=3.44; *p*=0.06 Can't settle: 14.6, 13.1; χ^2=2.19; NS Fearful: 28.0, 35.7; χ^2=0.80; NS Fussy: 17.1, 15.5; χ^2=0.0; NS Lies: 8.5, 16.7; χ^2=1.80; NS Steals: 1.2, 6.0; χ^2=1.48; NS Inert: 9.8, 20.2; χ^2=2.79; *p*=0.09 Aches: 13.4, 10.7; χ^2=0.09; NS Tears: 11.0, 4.8; χ^2=1.44; NS Stutters: 6.1, 9.5; χ^2=0.28; NS Resentful: 11.0, 15.5; χ^2=0.39; NS Bullies: 8.5, 14.3; χ^2=0.84; NS <u>Percent with Overactivity score of 3-6 of four blood Pb catagories:</u> 7-10, 11-12, 13-16, 17-32 µg/dL; χ^2; *P*-value **5.9%, 4.2%, 20.4%, 17.1%; χ^2= 8.12; P = 0.04** <u>Conner's factor score at two blood Pb levels – summaries of ANOVA and ANCOVA adjusted for age</u>: Mean 7-12 and 13-32µg/dL; *F*; *P*-value **Conduct problems: 0.04, 0.15; *F*=4.02; *p*=0.05** **Inattentive-Passive: 0.41, 0.62; *F*=5.68; *p*=0.02** Tension-Anxiety: 0.38, 0.41; *F*=0.52; *p*=0.47 **Hyperactivity: 0.27, 0.44; *F*=5.88 *p*=0.02** **Total Score: 0.26, 0.37; *F*=4.97; *p*=0.03**	
Cross sectional Zailina (2008) Malaysia	269 children from 2 urban schools in Kuala Lumpur (n=169), and one industrial-area school (n=100); Year not stated % male not stated	Urban area: 7.5 years Industrial area: 7.25 years Range: 6.5 to 8.5	Urban area = 3.75 Industrial area = 3.56	Cognitive ability measured by McCarthy Scales of Children's Abilities (MSCA)	General Linear Model test; correlation Parents' educational level, household income, number of siblings and their sequence in the family.	<u>Correlation between blood Pb levels and total cognitive score:</u> **Urban area: r = -0.140; p<0.05** **Industrial area: r = -0.197; p<0.05**	Concurrent blood Pb was significantly correlated with lower cognitive scores in 6-8 year olds in both urban and industrial areas.

Abbreviations: β-HCH - beta-hexachlorocyclohexane; δ-ALA - δ-aminolevulinic acid;
ACHIV - achievement standard score; ADHD – attention deficit hyperactivity disorder; Adj – adjusted; AFGS - auditory figure-ground subtest; Al - aluminum; *ALAD* – aminolevulinate dehydratase; ALS - amyotrophic lateral sclerosis; ANCOVA - analysis of covariance; ANOVA - analysis of variance; *APOE* – apolipoprotein E; As - arsenic;
BAEP - brainstem auditory evoked potential; BAER - brainstem auditory evoked responses; BASC - behavior assessment system for children; BASC-PRS - behavior assessment system for children, parent rating scale; BASC-TRS - behavior assessment system for children, teach rating scale; BD - block design subtest; BMI - body mass index; BOTMP - Bruinsinks-Oseretsky test of motor proficiency; BSI - Brief Symptom Inventory; BSID - Bayley scale of infant development; BTQ - Boston teachers questionnaire;
Ca – calcium; CANTAB - Cambridge neuropsychological testing automated battery; CAT - cognitive abilities test; CBCL - child behavior checklist; CBCL-EX - child behavior checklist, externalizing scale; CCTT - children's color trails test; CD - conduct disorder; Cd – cadmium; CDC – Centers for Disease Control and Prevention; CERAD - consortium to establish a registry for Alzheimer's disease; CES-D - Center for Epidemiologic Studies–depression scale; CI - confidence interval; CLS - Cincinnati Lead Study; CPMC - Columbia-Presbyterian Medical Center; CPRS - Connors parent rating scale; CPT - continuous performance test; CR - criminal record; CRS - Conners rating scale; CRS-CP - Conners rating scale, teacher rated, conduct problems; CS - contrast sensitivity; CSID - community screening instrument for dementia; CTBS - comprehensive test of basic skills; Cu – copper; CVLT - California verbal learning test;
DDE – dichlorodiphenyldichloroethylene; DDT – dichlorodiphenyltrichloroethane; DMS - delayed-matching-to-sample; DQ - developmental quotient; *DRD4* – dopamine receptor D4; DSM - diagnostic and statistical manual of mental disorders; DTI - diffusion tensor imaging;
ELEMENT - Early Life Exposures in Mexico to Environmental Toxicants; EOG - end of grade test; ERG – electroretinographic; ET – essential tremor; ETS – environmental tobacco smoke;
Fe – iron; FLERIS - fetal lead exposure, risks and intervention strategies; FSIQ - full scale intelligence quotient; FTII - Fagan test for infant intelligence; FWS - filtered word subtest; *HFE* – hemochromatosis;
GCI - general cognitive index; GEE - generalized estimating equations; GPA – grade point average;
Hg – mercury; HHANES - Hispanic Health and Nutrition Examination Survey; HOM - home observation for measurement of the environment; HR - hazards ratio; Hz – hertz;
ICD - international classification of disease; IQ – intelligence quotient;
K-ABC - Kaufman asssessment battery for children; KEDI - Korean Educational Development Institute; KID - Kent infant development scale; KiTAP – test battery for attention performance of children (German); K-SADS-E - Kiddie schedule for affective disorders and schizophrenia; K-TEA - Kaufman test of educational achievement;
MDI - mental developmental index; MGCI - McCarthy general cognitive index; MHDS-CD - mental health diagnostic schedule; MMSE - mini-mental state examination; Mn – manganese; MoCA - Montreal cognitive assessment; MPC - mental processing composite standard score; MRI - magnetic resonance image; MRS - magnetic resonance spectroscopy; MSCA - McCarthy scales of children's abilities; *MTHFR* – methylenetetrahydrofolate reductase;
NAA - N-acetyl aspartate; NAS - Normative Aging Study; NBAS - Brazelton neonatal behavioral assessment scale; NE-NCPP - New England cohort of the National Collaborative Perinatal Project; NES - neurobehavioral evaluation system; NHANES - National Health and Nutrition Examination Survey; NICU – neonatal intensive care unit; NONVB - non-verbal standard score; NPH - neighborhood psychosocial hazards; NS – not significant; NYS - National Youth Survey;
OR - odds ratio;
P – planning; PAL - paired associate learning; PAT - progressive achievement test; PCB - polychlorinated biphenyl; PD - Parkinson's disease; PDI - psychomotor development index; PDS - Prenatal Determinants of Schizophrenia study; PIQ - performance intelligence quotient; PPVT - Peabody picture vocabulary test; PRDB - parental report of predelinquent and delinquent behavior; PSS - Perceived Stress Scale;

RAVLT - Rey auditory verbal learning test; RLR - rule learning and reversal; ROCF - Rey-Osterrieth complex figure; RR - relative risk; RS - Rutter scale, aggressive/antisocial behavior;.

SAT - standard assessment test; SCAN - screening test for auditory processing disorders; SCL-90 - symptom checklist-90; SD – standard deviation; SDB - self-reported delinquent behavior scale; Se – selenium; SE – standard error; SEQ - sequential processing standard score; SES – socioeconomic status; SIM - simultaneous processing standard score; SRA - self-reported antisocial behavior; SRD - self-reported delinquency scale; SS - spatial span; SWM - spatial working memory;

tCr - total creatinine; TICS - telephone interview for cognitive status; TONI - test of non-verbal intelligence; TOSCA - test of scholastic abilities; TRF - teacher report form; TRF-DB - teacher report form, delinquent behavior scale; TRF-Ex - Teacher Report Form, Externalizing Scale;

UPSIT - University of Pennsylvania smell identification test;

VDR – vitamin D receptor; VEP - visual-evoked potentials; VIQ – verbal intelligence quotient; VMI - visual motor integration; VRM - visual recognition memory;

WAIS - Wechsler adult intelligence scale; WCST - Wisconsin card sorting test; WHO – World Health Organization; WIAT - Wechsler individual achievement test; WISC - Wechsler intelligence scales for children; WPIC-Ag - Walker problem identification checklist, teacher version, aggressive behavior scale;WPIC-P - Walker problem identification checklist, parent version, acting out scale; WPIC-T - Walker problem identification checklist, teacher version, acting out scale; WPPSI- Wechsler preschool and primary scales of intelligence scale for children; WRAML - wide range assessment of memory and learning; WRAT - wide range achievement test; WRAVMA - wide range assessment of visual motor activity;

Zn – zinc; ZPP – zinc protoporphyrin;

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NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

June 13, 2012

APPENDIX B:
HUMAN STUDIES OF IMMUNE EFFECTS OF LEAD CONSIDERED IN DEVELOPING CONCLUSIONS

Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Low Exposure (mean blood Pb levels < 15µg/dL)							
Cross-sectional Annesi-Maesano (2003) Paris	374 mother-newborn pairs from 2 hospitals in Paris; Years= study A=1985 n=137; Study B=1991-1992 n=237 male=50%	Newborn	***Blood:*** Combined: Infant cord=6.7 (4.8) Maternal=9.6 (5.8) Study A – 1985: Infant cord=10.6 (4.8) Maternal =13.3 (6.0) Study B-1991-1992: Infant cord=3.88 (1.9) Maternal=6.16 (2.5) ***Hair (ppm):*** Infant= 1.4(1.3) Maternal= 5.2(6.1) Measured when outcome assessed Note: dose in publication contains error and should be µg/L not µg/dL.	Cord blood IgE, maternal IgE	Spearman correlation coefficient (r), linear regression analysis, ANOVA Adjustments not described.	Relationship between mean Pb measures and log cord IgE for combined cohort: Infant cord Pb =6.737 (4.8); r=-0.05; p>0.05 Maternal blood Pb =9.644(5.8); r=-0.09; p>0.05 **Infant hair =1.38(1.26); r=0.21; p<0.01** Maternal hair =5.16(6.08); r=-0.04; p>0.05 Infant hair Pb was also correlated to log cord IgE when each cohort was analyzed separately. Relationship between Pb measures and log cord IgE for combined cohort by allergic status of mother: Allergic mothers - infant hair Pb r = 0.12; p>0.05 **Non-allergic mothers –infant hair Pb r=0.21; p<0.01** Fraction of variation in log cord IgE in regression: Combined Infant cord blood Pb r^2=0.01; p>0.05 Maternal blood Pb r^2=0.01; p>0.05 **Infant hair Pb r^2=0.09; p<0.0001** Maternal hair Pb r^2=0.01; p>0.05 Study A (1985) Infant cord blood Pb r^2=0.05; p=0.08 Maternal blood Pb r^2=0.02; p>0.05 Infant hair Pb r^2=0.16; p=0.06 Maternal hair Pb r^2=0.00; p>0.05 Study B (1991-1992) Infant cord blood Pb r^2=0.01; p>0.05 **Maternal blood Pb r^2=0.06; p<0.005** **Infant hair Pb r^2=0.05; p<0.02** Maternal hair Pb r^2=0.01; p>0.05 *No functional immune tests and no other immune endpoints tested*.	Increased IgE in cord blood was associated with hair levels of Pb in infants. Cord blood IgE was not related to infant blood Pb. Cord blood IgE was related to maternal blood Pb in study B where maternal blood Pb was 6µg/dL and not study A where maternal blood Pb was 13µg/dL.
Cross-sectional Belles-Isles (2002) Quebec, Canada	Newborns from subsistence fishing families (n=48 fishing) and referents (n=60) in Quebec; Years= 1995-1997; Male=53-58%	Newborns	Cord geometric mean Fishing=1.64 Referent =1.33 SD not reported Measured when outcome assessed	WBC diff.: T-cells (CD3), helper T-cells (CD4), cytotoxic T-cells (CD8), B-cells (CD19) NK cells (CD56), IgG, IgM, mitogenic (conA) response, NK function, plasma PCBs, chlorin-ated pesticides, metals	Student's t test, chi-square test, multiple linear regression, Pearson correlation coefficient Adjustments not described.	Correlation for serum IgG and cord blood: **Pb level - IgG r=0.31; p=0.002** **Sum PCBs – IgG r=0.35; p<0.001** **DDE r=0.27; p=0.007.** No correlation between blood Pb and: -NK cell lytic function (lysis of K562 / P815 targets) -serum immunoglobulins (IgM) -lymphoproliferative (mitogen) responses to ConA -WBC differentials *No other immune endpoints tested.*	Elevated serum IgG was correlated with elevated blood Pb in newborns. NK lytic function, IgM, WBC differential, conA response did not differ.

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Cross-sectional and Case-control Boscolo (1999) Pescara, Italy	17 atopic men (case) and 17 non-allergic men (control) without occupational Pb; Years not stated; Male=100%	Mean Atopic=34 Range=19-52	11 (SD not reported) Measured when outcome assessed	WBC differential: T-cells (CD3), helper T-cells (CD4), cytotoxic T-cells (CD8), B-cells (CD19), NK cells(CD16 and CD56), non/activated (HLA-DR), IL-2 activated (CD25), naive (CD45RO-), memory (CD45RO+), serum IgG, IgM, IgA, IgE, plasma cytokines (IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ), blood Zn, urinary Cr, Ni	Pearson correlation, Spearman correlation Adjustments not described.	Correlation between blood Pb for total population: **CD4 r=0.525; p<0.001** **HLA-DR r=0.507; p<0.002** Correlation between blood Pb for atopic men: **CD4 r=0.493; p<0.05** **CD5(-)CD19 r=0.679; p<0.01** **HLA-DR r=0.508; p<0.05** **CD3(-)HLA-DR r=0.528; p<0.05** Correlation between blood Pb for nonallergic men: **lymphocytes r=0.565; p<0.05** **CD4 r=0.503; p<0.05** **CD4CD45RO(-) r=0.638; p<0.01** **HLA-DR r=0.511; p<0.05** **CD25 r=0.579; p<0.05** IgE in atopic men correlated with **CD19 r=0.531; p<0.05** **CD5(-)CD19 r=0.713, p<0.01** **CD4CD45RO r=0.590; p<0.05** **CD25 r=0.662, p<0.01** No correlation of Pb with serum IgA, IgE, IgM, IgG, cytokines, CD8, CD16/CD56 *No functional immune tests and no other immune endpoints tested*	Blood Pb was positively correlated with CD4 and HLA-DR in all men, CD19 in atopics, CD25, CD4CD45RO in nonallergics. Serum IgE, IgG, IgM, IgA, cytokines, CD8, CD16/CD56 were not correlated to blood Pb.
Cross-sectional & Case-control Boscolo (2000) Pescara and Chieti Italy	30 atopic women (case) and 30 non-allergic (control) women white collar staff and doctors of University of Chieti ; Years not stated; Male=100%	Atopic=34 Range=19-49	Mean not reported Median Control = 5.5 Atopic = 6.4 Measured when outcome assessed	WBC differential: T-cell (CD3), T-helper (CD4), T-cytotoxic (CD8), B-cells (CD19), NK cells(CD16 and CD56), non/activated (HLA-DR) IL-2 activated (CD25), naive (CD45RO-), memory (CD45RO+), serum IgE, in vitro IL-4, IFN-γ), blood Zn, Cu, urinary Cr, Ni	Pearson correlation, Spearman correlation Adjustments not described.	Correlation between blood Pb for nonallergic women: **CD4CD45RO(-) r=0.464; p<0.05** **CD3CD8 r=0.430; p<0.05** **CD3(-)HLA-DR r=0.435; p<0.05** Note CD4CD45RO(-), CD3CD8, CD3(-)HLA-DR did not correlate with blood Pb in atopics or the combined population. Although serum IgE was elevated in atopic women; authors do not specifically state if potential correlation between blood Pb and IgE was examined in atopics or nonallergic women.	Blood Pb was positively correlated with memory CD4, CD8, and HLADR lymphocytes in normal women, not atopics. CD19, CD16/CD56, in vitro IL-4 and IFN-γ were not correlated to blood Pb.
In vitro Guo (1996a) Not Applicable	Blood from health volunteers	Not reported.	Blood Pb was not measured. In vitro experiments involved Pb exposure at	TNFα secretion after LPS stimulation of peripheral blood	Friedman analysis of variance Adjustments not described.	Authors state that in vitro incubation of peripheral blood mononuclear cells with Pb: • **Increased LPS pre-treated TNF-α secretion at 10µM or 50µM Pb; p=0.025**	In vitro exposure to Pb increased TNF-α secretion as

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
			10µM or 50µM $PbCl_2$	mononuclear cells		• No effect on steady-state levels of TNF-α mRNA • **Increased TNF α (TNF-R p55) surface expression** but had no effect on TNF-Rp75 surface expression Authors state $PbCl_2$ increases TNF-α expression by posttranscriptional mechanisms and enhances reactivity and uptake of TNF-α by the receptor p55 *No functional immune tests and no other immune endpoints tested*	well as increased TNFα receptor levels in monocytes.
In vitro Guo (1996b) Not Applicable	Blood from health volunteers	Not reported.	Blood Pb was not measured. In vitro experiments involved Pb exposure at 10µM or 50µM $PbCl_2$	MHC class II antigen DR (HLA-DR) surface expression of peripheral blood mononuclear cells by ELISA, RT-PCR and Western Blot after exposure to Pb or IFNγ or IL-4	Friedman analysis of variance Adjustments not described.	Authors state that in vitro incubation of peripheral blood mononuclear cells with Pb: • **increased MHC class II antigen DR (HLA-DR) surface expression by monocytes and B cells expression at 10µM and 50µM; p<0.01** • Ii surface expression was not affected by Pb, but was enhanced by IL-4 • IFNγ increased HLA-DR and Ii on monocytes but decreased in B cells *No functional immune tests and no other immune endpoints tested.*	In vitro exposure to Pb increased MHC class II antigen surface expression.
In vitro Hemdan (2005) Not applicable	Blood from 12 healthy donors	Not reported.	Blood Pb was not measured. In vitro experiments involved Pb exposure at 14 serial doses per ml: Pb acetate:5.0mg-1.5ng Pb chloride:0.5mg-0.15ng	In vitro cytokines from peripheral blood mono-nuclear cells (IFNγ, TNF-α, IL-1β, IL-4, IL-6, IL-10) after mAb (anti-CD3, andti-CD28, anti-CD40) or *Salmonella enteritidis* (hk-SE) stimulation	Wilcoxon test for paired samples Adjustments not described.	In vitro cytokine release by mAb and Pb acetate: **TNF-α release reduced at Pb above 1.5ng/ml; p<0.05** **IL-1β release reduced at Pb above 5.0ng/ml; p<0.05** **IL-6 release reduced -Pb -150ng to 14mg/ml; p<0.05** **IFN-γ release reduced at 1.5ng to 5mg/ml; p<0.05** **IL-10 increased at all doses below 150µg/ml** **IL-4 increased at all doses below 15µg/ml** **All cytokines inhibited at does above 150µg/ml** Pb polarized response toward Th2 response In vitro cytokine release by hk-SE and Pb chloride: **TNF-α release reduced at Pb above 150pg/ml; Stimulated at 0.5µg/ml to 150µg/mlp<0.05** **IL-1β release reduced at Pb above 150pg/ml; stimulated at 50 and 150 pg/ml; p<0.05** **IL-6 release reduced -Pb -1.5ng to 0.5µg/ml; p<0.05** **IFN-γ release reduced at 150 pg to 150 ng/ml;p<0.05** IL-10 increased at lower doses and reduced at higher Doses Pb polarized response toward IL-10 from IFN-γ *No functional immune tests and no other immune endpoints tested*.	In vitro exposure to Pb increased IL-6, IL-10, IL-4, and decreased IFNγ, TNF-α, IL-1β in peripheral mononuclear cells.
Cross-sectional Hegazy (2011) Qualyobia Governate,	318 children aged 6 months to 7 years; Year=2006-2008;	Range 6 months to 7 years	Mean =9.23 Stratified by class (blood Pb in µg/dL): IA (<5µg/dL); 15.8%	Serum IgE, WBC diff.: lymphocytes, granulocytes,	Student's t test, Spearman correlation, Kruskal-Wallis test	Median (min,max) IgE (IU/ml) by Pb class (IIB, III and IV combined for analyses; age and parental tobacco smoke co-variants) IgE mean, SE or SD not reported IA (<5µg/dL); 13.0 (0.8, 892)	Serum IgE was significantly different by blood Pb level

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Egypt	Male=56.3%	% of study by age in years <2; 51.9% 2-<4.5; 38.4% 4.5-7; 8.2% >7;1.6%	IB (5-9); 47.5% IIA (10-14); 24.9% IIB (15-19); 5.5% III (20-44); 5.8% IV (45-69); <0.5%	monocytes, T-cells, B-cells (CD19)	Age, parental tobacco smoke	IB (5-9µg/dL); 12.0 (0.0, 2008) IIA (10-14µg/dL); 20.8 (0.4, 611.6) IIB (15-19µg/dL); 14.9 (4.1, 1756) III (20-44µg/dL); 20.4 (3.6, 235) **IV (45-69µg/dL); 10.2; p=0.001** Authors state IgE increased in children with Pb and parental tobacco smoke exposure. Correlation between IgE and blood Pb: With parental smoking r=0.12; p=0.24 Without parental smoking; r=-0.08; p=0.5 Children with Pb and parental smoking p=0.12; although authors only present this data in the abstract and the correlation is not presented, nor is the definition provided for "exposed to both Pb and PTS". **Correlation between blood Pb and parental tobacco smoking r=0.113; p<0.05** Percent of lymphocytes, granulocytes, monocytes, T-cells, and B-cells did not differ by Pb exposure class for total population; however authors state % lymphocytes was decreased (p=0.05) and % granulocytes was increased (p=0.06) in children of non-smokers. *No other immune endpoints tested.*	in children aged 6 months to 7 years of age; however the correlation between blood Pb and IgE was not significant. No relationship between blood Pb and lymphocytes, granulocytes, monocytes, T-cells, or B-cells was evident.
Cross-sectional Hon (2009) Hong Kong *Population may overlap with Hon (2010)*	58 new patients with eczema, aged >1 month and existing patients requiring 8-month period; Year=2008-2009; Male % not stated	Not reported Pers. Com. Author report mean age "around 10 years"	Blood Pb of eczema patients by use of traditional medicine: Ever used traditional medicine=2.07 (0.83) Never used traditional medicine=1.65 (0.62) *Combined = 1.9µg/dL-calculated by CERHR* Measured when outcome assessed	Serum IgE, eosinophils, atopic dermatitis severity (SCORAD), Nottingham eczema severity score (NESS), children's dermatology life quality index (CDLQI)	Pearson correlation Adjustments not described.	Correlation between clinical parameters: **Pb and SCORAD r=0.46; p<0.001** **Pb and NESS r=0.35; p<0.05** **Pb and CDLQI r=0.41; p=0.003** **Pb and log (IgE) r=0.34; p<0.05** *No other immune endpoints tested.*	Blood Pb in children examined for eczema were correlated with serum IgE, eczema severity score, and atopic dermatitis severity.
Cross-sectional Hon (2010, 2011) Hong Kong *Population may overlap with Hon (2009)*	110 patients with eczema and 41 with other skin conditions >1 month age sampled during 8-month period from a pediatric dermatology	Eczema=9.9 (5) Other=11.5(5)	Blood Pb Eczema=1.86 (0.83) Other=1.66 (0.62) *calculated by CERHR* Measured when outcome assessed *Note: 2011 paper corrects original table; Pb*	Serum IgE, eosinophils, atopic dermatitis severity (SCORAD), Nottingham eczema severity score (NESS), children's	Pearson or Spearman correlation, Student's t test Adjustments not described.	Correlation between clinical parameters in Eczema patients: **Pb and SCORAD r=0.329; p<0.005** **Pb and NESS r=0.203; p<0.05** **Pb and CDLQI r=0.217; p<0.05** **Log Pb and sq. root Eosinophil count r=0.29; p=0.001** **Pb and log (IgE) r=0.285; p<0.005** **Serum Cd was also correlated to IgE; r=0.216 (p<0.05**) and Cu/Zn ratio was correlated to NESS, and CDLQI; all	Blood Pb in children examined for eczema were correlated with serum IgE, eczema severity score, and atopic

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
	clinic; Year=2008-2009; Male=57% eczema and 27% other		*levels reflect whole blood levels not serum as originally stated*	dermatology life quality index (CDLQI), serum Cu, Zn, Hg, Cd, Se		other metal comparisons were not significant for IgE, or eczema scores. *No other immune endpoints tested.*	dermatitis severity.
Prospective Jedrychowski (2011) Krakow, Poland	Children of 224 women recruited in 2nd trimester; years = 2001-2004	Maternal age=27.8 (3.37)	Geometric mean Maternal Pb: =1.6 (1.52, 1.67) Cord blood: =1.16 (0.12, 1.22) Blood in 5-year olds: =2.04 (1.95, 2.12)	Atopic status (at least one positive skin prick test [SPT] to a common allergen) at 5 years of age, blood Hg, PAH	Logistic regression analysis Maternal age, child's age, gender, parity, maternal education, maternal atopy, and environmental tobacco smoke variables	Frequency of atopy by Pb exposure: **Maternal blood Pb p=0.006** **Cord blood Pb p=0.001** Pb in 5-year old (current) Pb = 0.425 Risk ratio for atopy by blood Pb measures: Maternal blood Pb RR=1.72 (0.98, 3) **Cord blood Pb RR=2.28 (1.12, 4.62)** Pb in 5-year old (current) RR= 1.10 (0.72, 1.64) *No other immune endpoints tested.* Authors state atopy not related to blood Hg or PAH	Frequency of sensitization to allergens (atopy) in 5 year olds was associated to maternal and cord blood. Cord blood Pb levels were associated with increased risk of atopy in 5 year olds.
Retrospective Joseph (2005) Southeastern Michigan, USA	4634 children in managed care screened for Pb at 1-3 years of age in Michigan; Years 1995-1998; Male=50.5%	1.2 (0.5)	Not reported: % ≥5µg/dL = 39% %≥10µg/dL= 8.7% Pb measured at age 1-3, asthma assessed in patient records	Prevalent asthma and incident asthma based on insurance records for medication dispensing events, or related hospitalization	Cox proportional hazard analysis, chi-square tests, Wilcoxon rank-sum test, logistic regression Income, birth weight, sex	Cox proportional HR (95% CI) of blood Pb to asthma: Asthma definition #1-less stringent Caucasian Pb<5µg/dL HR=– 1 – reference Caucasian Pb≥5µg/dL HR=1.4 (0.7,2.9); p=0.4 Caucasian Pb≥10µg/dL HR=1.1 (0.2,8.4); p=0.91 African American Pb<5µg/dL HR=1 – reference African American Pb≥5µg/dL HR=1.0 (0.8,1.3); p=0.94 African Amer. Pb≥10µg/dL HR=0.9 (0.5,1.4); p=0.58 Asthma definition #2-more stringent Caucasian Pb<5µg/dL HR=– 1 – reference Caucasian Pb≥5µg/dL HR=2.7 (0.9,8.1); p=0.09 African American Pb<5µg/dL HR=1 – reference African American Pb≥5µg/dL HR=1.1 (0.8,1.7); p=0.53 African Amer. Pb≥10µg/dL HR=1.3 (0.6,2.6); p=0.54 *No other immune endpoints tested.* Authors state that African Americans were at significantly increased risk of asthma regardless of blood Pb level.	Blood Pb was not related to incidence of asthma based on asthma-medication dispensing events, or related hospitalization in children 1-3 years of age.
Cross-sectional Karmaus (2005) Hesse, Germany	331 children aged 7-10 in Hesse; Year= 1995; Male=56.8%	Range 7-10 96% 7-8	Geometric mean=2.68 (SD not reported) Measured when outcome assessed	Serum Ig, WBC diff.: T-cells (CD3), T-helper (CD3/CD4), T cytotoxic (CD3/CD8), B-cells (CD3/CD5/CD19) NK (CD16/CD56)	Multiple linear regression; t test, F test; gender, age, number of infections in last 12 months, exposure to passive smoke, DDE, sum of PCBs, HCB, γ-HCH	Adjusted serum IgE (kU/L) by blood Pb: <2.2µg/dL; IgE=46 2.21-2.83µg/dL; IgE=30 2.84-3.41µg/dL; IgE=59 **>3.41µg/dL; IgE=59; F-test p=0.028** No effect of Pb levels on: serum immunoglobulins (IgA, IgG, IgM);WBC differentials (NK, T, B and subsets); eosinophils or IgE counts on basophils	Increased serum IgE was associated with increases in blood Pb in 7-10 year old children blood Pb range <2.2

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				and NK subset (CD16/CD56/ CD57), memory T (CD4/CD45RO), other toxicants (OC, DDE, HCB, γ-HCH, PCBs)		Authors report that higher blood Pb was associated with decreased B-cells, T-cells, and cytotoxic T-cells at blood Pb 2.2-2.83µg/dL compared to children in the first quartile (blood Pb<2.2µg/dL) not other quartiles; however the F-test was negative. DDE was also associated with increased IgE. The authors state that blood Pb above the median (2.8µg/dL) were associated with increased IgE in groups with lower blood DDE levels, not in groups with higher DDE. *No functional immune tests and no other immune endpoints tested.*	to >3.4µg/dL. Differential WBCs, IgA, IgG, IgM did not differ.
Cross-sectional Kim (2007) Incheon, Korea	300 University of Inha students; Year=2002; Male = 84-99% by blood Pb quartile	24	By quartile: 1.46 (0.34, 1.89) 2.22 (1.89, 2.5) 2.77 (2.5, 3.1) 3.93 (3.1, 10.5) Measured when outcome assessed	IL-6, TNF-α, WBC count, glutathione S transferase M1 (GSTM1) genotype, TNF-α genotype	Test for Hardy-Weinberg equilibrium, chi-square test, ANOVA, t test, linear regression analyses Age, BMI, smoking status	Regression coefficient (β) of Pb by WBC or cytokine: All-TNF-α – β= 0.32 (SE=0.20); p=0.108 No effect of genotype on TNF-α All-IL-6 – β= 0.08 (SE=0.07); p=0.292 No effect of genotype on IL-6 **All-WBC – β=0.22 (SE=0.10); p=0.035** WBC – GSTM1 present – β=0.18 (SE=0.15); p=0.244 **WBC – GSTM1 null – β=0.31 (SE=0.15); p=0.038** **WBC – TNF-α GG – β=0.26 (SE=0.11); p=0.020** WBC – TNF-α GA or AA – β=-0.12 (SE=0.29); p=0.691 Regression coefficient (β) of males with blood Pb (≥2.51µg/dL) by WBC or cytokine: **All-TNF-α – β= 0.75 (SE=0.31); p=0.015** TNF-α – GSTM1 present – β=0.12 (SE=0.28); p=0.655 **TNF-α – GSTM1 null – β=1.14 (SE=0.48); p=0.020** **TNF-α – TNF-α GG – β=0.80 (SE=0.33); p=0.017** TNF-α – TNF-α GA or AA – β=-0.21 (SE=0.28); p=0.470 All-IL-6 – β= 0.18 (SE=0.10); p=0.082 No effect of genotype on IL-6 **All-WBC – β=0.42 (SE=0.20); p=0.044** WBC – GSTM1 present – β=0.22 (SE=0.29); p=0.462 **WBC – GSTM1 null – β=0.75 (SE=0.30); p=0.017** WBC – TNF-α GG – β=0.38 (SE=0.22); p=0.095 WBC – TNF-α GA or AA – β=0.61 (SE=0.50); p=0.256 *No functional immune tests and no other immune endpoints tested.*	Blood Pb was significantly associated with increased WBC in 24 year olds. In men with blood Pb ≥2.51 µg/dL, Pb was significantly associated with increased TNF-α. Effects of Pb on WBC and TNF-α were modified by GSTM1 and TNF-α genotypes.
Cross-sectional Li (2005) China *Population may overlap with Sun*	Subsample of 70 children aged 3-6 years of 217 children in study; 63 children (high Pb) had blood	Range 3-6	Overall = 9.5 Immune samples taken from 35 individuals from each group: High Pb group=14.06(4) Low Pb group=6.43(1.3)	WBC differential (CD3, CD4, CD8, CD19, CD16/ CD56), height, weight	Student t test, Spearman correlation coefficients Adjustments not reported.	Mean % lymphocytes by Pb group (≥10µg/dL and <10): CD3% referent = 55.2 (6.8) CD3% high (≥10µg/dL) = 54.1 (7.5); p>0.05 **CD4% referent = 27.1(5.8)** **CD4% high (≥10µg/dL) = 23.9(4.8); p<0.05** **CD8% referent = 20.6(4.8)**	The percentage of CD4 cells was decreased and CD8 cells were increased in children with

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(2003)	Pb≥10 µg/dL and 154 had blood Pb <10 µg/dL (referent); city not stated; Year not stated; Male= 56%		Measured when outcome assessed			**CD8% high (≥10µg/dL) = 23.6(5.5);p<0.05** CD19% referent = 16.7(4.6) CD19 high (≥10µg/dL) = 17.0(6.4); p>0.05 CD16/CD56% referent = 16.7(6.3) CD16/CD56% high (≥10µg/dL) = 19.2(7.7); p>0.05 **Spearman correlation for CD4 r=-0.462; p<0.05 among children with blood Pb >10µg/dL**; other WBC differentials not significant. No functional immune tests and no other immune endpoints tested.	blood Pb levels ≥10µg/dL relative to children with Pb <10. CD19, CD16/CD56 did not differ.
Cross-sectional Lutz (1999) Springfield-Green County, MO	279 children aged 9 months to 6 years in WIC program in Springfield-Green county with preliminary elevated finger-stick Pb; Years not stated; Male=56%	Age stratified (in months): 9-24 mo: 52% 25-36 mo: 30% 37-48 mo: 10% 49-84 mo: 8%	Blood Pb stratified: <10µg/dL (64%)-class I 10-14µg/dL(22%)-classIIA 15-19 µg/dL (7%)-class IIB 20-44 µg/dL (7%)-class III Measured when outcome assessed	Serum IgE, IgG titer to Rubella vaccine, CD25 (soluble receptor for IL-2), CD27 (soluble receptor for TNF), WBC differentials, and IL-4	Kruskal-Wallis test; Spearman rank correlation coefficient (r); Spearman partial correlation coefficients Adjustments differed by endpoint and include age using residuals obtained from a regression model and Spearman partial correlation coefficients. Authors state gender and race considered an no differences noted.	Mean serum IgE (IU/ml) by blood Pb values: <10µg/dL (64%)-class I →IgE =51.8 (166) 10-14µg/dL (22%)-class IIA →IgE =74 (112) 15-19 µg/dL (7%)-class IIB →IgE =210 (441) **20-44 µg/dL (7%)-class III →IgE =64 (82); p<0.05** **Correlation of serum IgE and Pb r=0.22; p=0.0004** No effect of Pb levels on: anti-rubella IgG; WBC differentials; IL-4; CD25, and CD27 Authors list as differing by Pb class at 0.05<p<0.1: IL-4, % lymphocytes, % granulocytes, CD25, rubella titer *No other immune endpoints tested.*	Serum IgE was increased in association with blood Pb in children from 9 months to 6 years of age. IL4, WBC differentials, anti-rubella did not differ.
Cross-sectional Min (2008) Seoul, Korea	523 adult office workers in Seoul; Years not stated; Male=52%	40 Range 19-58	Total = 2.9 Male = 3.3 Female = 2.5 Measured when outcome assessed	Methacholine bronco-provocation test	Multiple regression analysis Age, sex, height, smoking, and asthma diagnosis	Significant factors in regression model for bronchial responsiveness – β (SE): **Blood Pb (µg/dL) β=0.018 (0.007); p=0.015** **FEV1 (L) β= -0.067 (0.021); p=0.0013** **Male to female β= -0.074 (0.029); p=0.012** **Smoking to non-smoking β = 0.053 (0.024); p=0.026** *No other immune endpoints tested.*	Blood Pb was significantly associated with increased bronchial responsiveness in adults.
Cross-sectional Myers (2002) Chicago, IL	151 patients of inner-city clinic with blood Pb ≥25µg/dL (high Pb) and 101 matched referents blood Pb <5µg/dL; Years 1996-1999; Male=54%	Not reported Age in months at Pb measurement: High Pb= 26.6 Referent=24.2	Not reported Blood Pb obtained before 8 years of age, asthma assessed in patient records	Medical diagnosis of asthma, or asthma symptoms, or clinical diagnosis of bronchiolitis, or report of wheezing	Matched-pairs analyses, odds ratios, and Wilcoxon signed rank tests Adjustments not reported.	Odds ratio (95% CI) for diagnosis of asthma by Pb: Blood Pb <5µg/dL 11% asthma diagnosis Blood Pb ≥25µg/dL 6% OR=0.5 (0.2,1.4) Odds ratio (95% CI) for history of symptoms by Pb: Blood Pb <5µg/dL 34% asthma symptoms Blood Pb ≥25µg/dL 26% OR=0.7 (0.4,1.3) *No other immune endpoints tested.*	Incidence of asthma based on medical records did not differ between children with blood Pb≥25 µg/dL and others <5µg/dL aged <8 at Pb measurement.
Cross-sectional Nriagu (2008) Nigeria	653 children in major cities of Nigeria with	3.7	Mean = 8.9 (4.8) Range = 1-52µg/dL By city:	Malaria, worms, disease symptoms	Spearman correlation (r), bivariate and multivariate regression	Significant bivariate association of blood Pb: **Blood Pb x malaria r = -0.149; p<0.01** Blood Pb x worms r = -0.030; p>0.05	Blood Pb was associated with a decreased

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	different levels of pollution; Year not stated; Male = 56.5%		Port Harcourt = 4.7 (2.2) Nnewi = 8.3 (3.5) Ibadan = 9.9 (5.2)	(headaches, restlessness, irritability, depressed mood, worms)	Age, gender, town, pets in house, car ownership, education level of caregiver, hours outdoor play	**Blood Pb x town r = -0.356; p<0.001** **Blood Pb x age r=0.116; p=0.004** **Blood Pb x hours outdoor play r=0.175; p<0.001** **Blood Pb x car ownership; r=0.127; p<0.01** **Blood Pb x caregiver education r=-0.240; p<0.01** **Blood Pb x pets in house; r=0.091; p=0.023** **Multiple regression of blood Pb and co-morbid malaria β=-0.108; p=0.020** *No other immune endpoints tested.*	risk of malaria in young children in Nigeria.
Cross-sectional Pizent (2008) Zagreb, Croatia	216 office workers without occupational metal exposure; Year not stated; Male= 23%	Median Men = 45 Women=43 Range Men =20.5-67 Women=19-67	Median Men = 2.16 Women= 3.17 Range Men = 0.99-7.23 Women= 0.56-7.35 Measured when outcome assessed	Serum IgE, SPT to common allergens, trace elements (Cadmium, Cu, Zn, Se), SOD, GPx, non-specific bronchial and nasal reactivity (histamine challenge), ventilatory function	Mann-Whitney U test, Pearson chi-square test, Spearman correlation, multiple regression	Authors state in women, excluding women on HRT and oral contraceptives, **a positive association was observed between total IgE and blood Pb :** **β = 0.173; p=0.046** **Regression of association between non-specific bronchial reactivity and Pb in men:** **Log blood Pb β=-0.368; p=0.016** Authors state regression showed association between positive SPT and decrease in Pb in men: OR=0.92 (0.86, 0.98) Spearman correlation between blood Pb and: **Age in men r=0.366; p<0.02** **Age in women r=0.345; p<0.0001** **Zn in men r=-0.179; p<0.05** **Zn in women r=-0.300; p<0.02** **SOD in men r=-0.219; p<0.02** **SOD in women r=-0.321; p<0.005** **Alcohol consumption in women r=0.154; p<0.05** *No other immune endpoints tested.*	Blood Pb was associated with increased IgE in female office workers. Blood Pb was associated with decease in SPT and non-specific bronchial reactivity in men.
Cross-sectional Cohort Pineda-Zavaleta (2004) Lagunera, Mexico	65 children at schools different distances from a Pb smelter; Gomez Palacio (8Km referent), Heroes de Nacozari (1.7Km Pb-1); Pedro Garcia (<1Km Pb-2); Year not stated; Male=54%	Mean not reported Range 6-11	Median Referent=7.02 Pb 1=20.6 Pb 2=30.38 Range Referent=3.47-25.27 Pb 1=10.8-49.19 Pb 2=10.3-47.49 Measured when outcome assessed	Macrophage nitric oxide (NO) and superoxide (O_2^-) production following indirect (PHA) or direct (IFNγ-LPS) stimulation, urinary As	Mann-Whitney U test, Chi-square test, multiple linear regression Age and sex	Multivariate analyses for NO by blood Pb all children: **Indirect β=-0.00089 (-0.0017, -0.00005); p=0.036** Direct – not significant Multivariate analyses for O_2^- by blood Pb all children: **Direct β=0.00389 (0.00031, 0.00748); p=0.034** Indirect – not significant Multivariate analyses for O_2^- by blood Pb by sex: **Direct boys β=0.00826 (0.00236, 0.01416); p=0.008** Direct girls – not significant **Indirect boys β=0.00792 (0.00135, 0.01449); p=0.021** Indirect girls – not significant NO and O_2^- were also negatively associated with As *No other immune endpoints tested.*	Blood Pb was negatively associated with macrophage NO production in children; Pb was also associated with increased macrophage O_2^- production in boys.
Retrospective Pugh Smith (2011) Michigan, USA	356 children with in STELLAR database; Years	Age-stratified: <3 – 32% 4-6 – 40%	Not reported 19% of children had blood Pb≥10µg/dL	Doctor diagnosis of asthma	Multivariate regression analysis, Adjustments differ by	Significant odds ratio (95% CI) for factors predicting asthma in children: **Blood Pb child ≥10µg/dL OR=7.5 (1.3,42.9); p=0.023**	Children with blood Pb≥10µg/dL

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	=1996-2003; Male=49%	7-9 – 18% 10-12 – 10%	Measured prior to and when outcome assessed		endpoint including: age, gender, income, number of stories in unit, cat, dog, problem cockroaches, # persons in home, smoker in home, clutter, candles/ incense, stove type, heating source, clutter, musty, air conditioning, peeling paint, wall damage, age of house, Pb work or hobby	**Ceiling/wall damage OR= 10.93 (2.3, 52.2); p=0.003** **Cat in home OR=10.3 (1.4, 75.5); p=0.022** Significant odds ratio (95% CI) for factors predicting elevated blood Pb (≥10µg/dL) in children: **Age OR=0.645 (0.496, 0.837); p=0.001** **Gender OR= 2.87 (1.0, 7.98); p=0.043** **Pb related work activities OR=6.8 (1.1, 40); p=0.035** **Asthmatic child OR=5.17 (1.3,21.4); p=0.023** *No other immune endpoints tested.*	had an increased odds ratio for asthma.
In vitro Pyatt (1996) Not Applicable	Blood from health volunteers	Not reported	Blood Pb was not measured. In vitro experiments involved Pb exposure at 100µM, 1 µM, 10nM, 100pM Pb acetate	NF-κB; binding of nuclear factors to the NF-κB binding site by electrophoretic mobility shift assay; lucerifase activity by NK-κB dependent luciferase reporter gene	Statistical methods not reported.	Authors state that in vitro incubation of CD4+ T cells with Pb: • activated NF-κB and stimulated translocation to the nucleus down to 1.0µM Pb • induced p50:p65 heterodymer • stimulation of luciferase gene activity indicating activation of functional gene expression Authors state that the Pb concentration resulting in NF-κB translocation corresponds to a blood Pb concentration of 20µg/dL *No functional immune tests and no other immune endpoints tested.*	In vitro exposure to Pb increased NFκ-B activation in CD4 T cells.
Retrospective Rabinowitz (1990) Boston, MA	1768 children born at Boston hospital for women 1979-to 1981; teeth submitted 1985-1987; % male not stated.	Age not reported	Mean not reported Children classified by cord blood or deciduous tooth Pb	Questionnaire for incidence of asthma, eczema, ear infections, respiratory conditions, and school absence in past year by cold, flu or other illness	Relative risk defined as incidence in the highest exposure group (cord blood Pb ≥10µg/dL or tooth ≥5µg/g)/ rest of population. Adjustments not considered.	Relative risk (95%CI) of condition for cord blood Pb>10µg/dL compared to cord blood Pb<10µg/dL: Asthma RR=1.3 (0.8, 2.0) Eczema RR=1.0 (0.6, 1.6) Ear infections – any RR=1.0 (0.9, 1.0) Ear infections - ≥5 RR=1.1 (0.9, 1.3) Ear infections ≥10 RR=1.1 (0.9, 1.3) **Ear infections severe RR=1.2 (1.0, 1.4)** **Other respiratory RR=1.5 (1.0, 2.3)** Other infections RR=1.0 (0.7, 1.5) Other immune RR=1.2 (0.8, 2.0) **School absence other than flu RR=1.3 (1.0, 1.5)** School absence flu or cold RR=1.0 (0.9, 1.1) Authors present similar data for tooth Pb. Authors report similar results for analysis split by sex. Note: Although 95% CI for severe ear infections, other respiratory infections, and school absence other than flu include 1.0 to 1.4, 1.0 to 1.5, and 1.0 to 2.3, authors state failure to demonstrate any increased occurrence of diseases in children with highest cord or tooth Pb.	Increased relative risk of severe ear infections, other respiratory infections, and school absence other than flu in children with cord blood Pb>10µg/dL. No difference in asthma, eczema, or other disease incidence.

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Cross-sectional Rabito (2010) USA	73 Latino migrant laborers identified in New Orleans 2005 followed monthly over a year; Year=2007: Male=100%	Mean not reported	Exposure determined by occupation/ job type and blood Pb determined at final time point Geometric mean = 2.67 Range =0.6 to 38.4µg/dL	Survey for symptoms including sino-nasal, respiratory, eye, skin, and headache	Multivariable logistic regression Adjustments differ by outcome including smoking, mask use, eye protection, glove use ** utility limited by lack of direct comparison of effects with blood Pb level*	Regression model for association between construction work and symptoms: Sino-nasal OR=2.62 (0.86, 7.98) Respiratory OR=2.91(0.94, 9.06) Headache OR=0.87 (0.31, 2.5) Throat OR=1.12 (0.31, 4.0) Eye OR=0.62 (0.2, 1.93) Skin OR=1.18 (0.26, 5.22) **Association of construction work with blood Pb; p=0.034 and p=0.037 after adjustment for mask use.**	Odds ratio of symptoms was not significantly associated with construction activities in migrant workers.
Cross-sectional Sarasua (2000) USA	1561 people in 4 sites near high Pb and Cd soil levels and 480 matched referents combined for analyses; Year =1991; %Male not stated	4 age groups: 6-35 months 36-71 months 6-15 years 16-75 years	6-35 mo= 7.0 (5.2) 36-71 mo= 6.0 (4.3) 6-15 yr=4.0 (2.8) 16-75 yr=4.3 (3.9) Measured when outcome assessed	IgA, IgM, IgG, lymphocytes, WBC differentials (# and % B-cell, T-cell, NK cells, CD4, CD8), urinary Cd	Pearson correlation coefficients, linear regression analysis, least square means Adjustments differ by endpoint including age, sex, study (KS, IL, MO, PA)	Regression coefficient for blood Pb for children < 3: **IgA (mg/dL) = 0.8; p<0.01** **IgG (mg/dL) = 4.8; p<0.01** **IgM (mg/dL) = 1.0; p=0.03** T-cell count = 7.2; p=0.59 **B-cell count = 16.9; p<0.01** **% T cells = -0.18; p=0.03** **% B cells = 0.19; p=0.02** No effect in children <3 of Pb levels on NK cells, CD4, or CD8 cell counts or percentages. Among children < 3 years of age: 1) IgA was increased in children with blood Pb ≥15g/dL relative to children <5µg/dL Pb. 2) IgG was increased in children with blood Pb ≥5µg/dL relative to children <5 µg/dL Pb. 3) IgM was increased in children with blood Pb ≥15g/dL relative to children <5µg/dL Pb 4) B-cell and lymphocyte count were increased in children with blood Pb ≥15g/dL relative to children <5µg/dL Pb No effect of Pb levels in children >3 years of age, or in adults on serum immunoglobulins (IgA, IgG, IgM) or WBC differentials. *No functional immune tests and no other immune endpoints tested.*	Serum IgA, IgM, IgG, and B-cell count were increased in association with blood Pb in children under 3 years of age. CD4, CD8 did not differ. No effect in children over 3 years of age or adults on serum Ig or WBC differentials.
Cross-sectional Songdej (2010) USA	9,145 individuals ≥40 years of age in NHANES 1999-2004	Population >40; mean not reported.	1.89 in entire population Measured when outcome assessed	WBC count, c-reactive protein (CRP), fibrinogen	Logistic regression Age, gender, race/ethnicity, education, income, BMI, physical activity, smoking status, diabetes status, inflammatory disease status, and cardiovascular disease status	Blood Pb was not related to CRP, fibrinogen, or WBC count when the population was analyzed together or males and females were analyzed separately. *No functional immune tests and no other immune endpoints tested.*	Blood Pb was not related to CRP, WBC count or fibrinogen in people >40.

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Cross-sectional Sun (2003) China *Population may overlap with Li (2005)*	Subsample of 72 preschool children aged 3-6 of 217 children in study; 63 children (high Pb) had blood Pb≥10µg/dL and 154 had blood Pb <10µg/dL (referent); Year not stated; Male =56%	Range 3-6	Overall =9.52 (5.59) Immune samples taken from 38 individuals from the ≥10µg/dL (high) group and 35 in the <10µg/dL (low/referent): High Pb group=14.06(4) Low Pb group=6.43(1.3) Measured when outcome assessed	Serum IgG, IgM, IgE	Mann-Whitney U test; Spearman rank correlation coefficient (r) Age, sex, weight index	**Spearman correlation for IgE r=0.48; p=0.002 among children with blood Pb >10µg/dL.** Mean rank of serum Immunoglobulin by Pb group/sex: IgG referent males (<10µg/dL) = 20.71 IgG high Pb males (>10µg/dL) = 34.76; p=0.913 IgM referent males (<10µg/dL) = 20.32 IgM high Pb males (>10µg/dL) = 19.61; p=0.596 IgE referent males (<10µg/dL) = 20.22 IgE high Pb males (>10µg/dL) = 21.61; p=0.713 **IgG referent females (<10µg/dL) = 18.41** **IgG high Pb females (>10µg/dL) = 13.60; p=0.047** **IgM referent females (<10µg/dL) = 20.44** **IgM high Pb females (>10µg/dL) = 12.03; p=0.013** **IgE referent females (<10µg/dL) = 13.06** **IgE high Pb females (>10µg/dL) = 20.40; p=0.027** Authors state multiple variable analyses of blood Pb, age, sex, and weight index showed high blood Pb level could increase serum IgE. *No functional immune tests and no other immune endpoints tested.*	Serum IgE was correlated with blood Pb in boys and girls with blood Pb>10µg/dL. Increased serum IgE and deceased IgM and IgG were associated with increased blood Pb levels in girls aged 3-6; not observed in boys.
In vitro Villanueva (2000) Not applicable	Blood from a single healthy female	Not reported.	Blood Pb was not measured. In vitro experiments involved Pb exposure at 10, 50, and 100µM using $(CH_3OO)Pb$	In vitro cytokines from peripheral blood mono-nuclear cells (IFNγ, TNF-α, IL-1β, IL-6, IL-8, IL-10); exposure to Cadmium, Cr, and Hg also examined	ANOVA; Multiple Comparison Tukey test Adjustments not described.	Production of TNF-α and IL-6: 10µM Pb – not different relative to control; p>0.05 **50µM Pb– increased relative to control; p<0.05** **100µM Pb – increased relative to control; p<0.05** The authors did not report an effect of in vitro Pb exposure on IFNγ, IL-1β, IL-8, and IL-10. *No functional immune tests and no other immune endpoints tested.*	In vitro exposure to Pb increased TNF-α and IL-6 in peripheral mononuclear cells.
Cross-sectional Zhao (2004) Zhejiang Province, China	Subsample of 72 children aged 3-6 years of 217 children in study; 63 children with blood Pb≥10 µg/dL (high Pb); and 154 had blood Pb <10 µg/dL (referent); city not stated; Year not stated; Male=44%	Not reported Range = 3-6	Children with blood Pb ≥10µg/dL: Boys=10.1(6) Girls=10.1 (5) Overall range: Authors report two different ranges: 2.32 to 43.7µg/dL 10.0 to 19.0 µg/dL and it is unclear whether data apply to entire population or subset used for immune	WBC differentials: T-cells (CD3), T-helper (CD4), T-cytotoxic (CD8), B-cell (CD19), CD35, RBC-C3b and RBC-IC rosette forming rate	t test Adjustments not described.	Mean Lymphocyte % by Pb group: CD3 – referent = 55.2 (6.77) CD3 – high Pb = 54.61 (4.81); p>0.05 **CD3CD4 – referent = 27.1 (5.83)** **CD3CD4 – high Pb = 23.68 (4.81); p<0.01** **CD3CD8-referent =20.57 (4.84)** **CD3CD8 – high Pb =23.21 (5.77); p<0.05** **CD4CD8-referent = 1.41 (0.50)** **CD4CD8- high Pb = 1.09 (0.37); p<0.01** CD19-referent = 16.58 (4.6) CD19- high Pb = 16.82 (6.64); p>0.05 **Authors report that RFIR and CD35 average fluorescence intensity was decreased p<0.05.** Authors report CD35 average fluorescence intensity	Children with blood Pb ≥10µg/dL had a decreased CD4% and CD4CD8% T-cells, and increased CD8% relative to children blood Pb<10µg/dL. CD19, CD3, CD35, RBC-C3b, RBC-IC dud bit

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
			analyses (n=35 referent; n=38-40 high Pb)			that RBC-C3b, RBC-IC, RFER, and rate of CD35 positive findings did not differ between Pb groups. *No functional immune tests and no other immune endpoints tested.*	differ.
High Exposure (mean blood Pb levels > 15µg/dL and referent group often above 10µg/dL)							
Cross-sectional Anetor (1998) Nigeria	80 workers in the Pb industry (high Pb) and 50 referents without occupational Pb exposure; Male=% not stated; Years not stated N=80 workers N=50 referents	36 (SEM 0.03) 36.6(SEM 1.2)	Pb-workers =56.3(0.95) Referent =30.4(1.4) Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	Total lymphocyte count, serum immunoglobulin, IgA, IgG, IgM, CRP	Pearson correlation, Student's t test, multiple regression analysis Adjustments not described	Immunological indices in Pb-workers and referents: Total lymphocyte count/mm^3 referent = 2515 (115) **Total lymphocyte count/mm^3 Pb= 2157 (63); p<0.01** Total globulin (g/dL) referent = 3.2 (0.07) **Total globulin (g/dL) Pb = 3.73 (0.05); p<0.001** IgA (mg/dL) referent = 187.51 (14.2) **IgA (mg/dL) Pb = 143.79 (6.76); p<0.01** IgG (mg/dL) referent = 1997.33(108.33) **IgG (mg/dL) Pb = 1187.73 (65.33); p<0.0001** IgM (mg/dL) referent = 215.43 (12.66) IgM (mg/dL) Pb = 190.87 (11.76); p>0.05 CRP (mg/dL) referent = 0.50 (0.03) **CRP (mg/dL) Pb = 0.60 (0.03); p<0.01** Multiple regression for globulin and IgA in combined Pb-workers and referents: **Total globulin p<0.01** **IgA p<0.01** Correlation between blood Pb and IgA in Pb workers: **r=-0.28; p<0.009** *No functional immune tests and no other immune endpoints tested.*	Serum levels of IgA, IgG, and total lymphocytes were decreased in Pb-workers relative to referents; and IgA was negatively associated with Pb in workers and in the referents. IgM did not differ.
Cross-sectional Ayatollahi (2002) Yazad, Iran	66 Pb-workers (n=12 car battery workers, n=12 car painters, n=12 car radiator workers, n=21 printing office workers) in Yazd; Year not stated; Male= 100%	32.02 (1.77) Range=15-70	45.52 all workers >25µg/dL – 61/66 Mean =46.77 (SE 2.14) <25µg/dL – 5/61 Measured when outcome assessed *Note: unknown source of "standard" values used; no referent group*	Serum IgG, IgM, IgA	Z test, t test, and Pearson correlation Adjustments not described. ** Statistical difference relative to "standard" decreases utility	Serum IgG (mg/dL) = 706.52 Relative to standard 1350 (mg/dL) =-643.5 p **listed as P=#0 or P~0 "significant"** Serum IgA (mg/dL) = 173.43 (SE=12.15) Relative to standard 350 (mg/dL) =-176.54 **p listed as P=#0** Serum IgM (mg/dL) = 165.6 (SE=10.48) Relative to standard 150 (mg/dL) =15.6; p=0.14 Correlations between blood Pb and: **Serum IgA r=0.31; p listed as P~0** Serum IgM r=0.14; p =0.25 Serum IgG r=-0.08; p =0.47 Authors report blood Pb by intestinal helminthes: With intestinal helminthes Pb = 54.78 **No helminthes Pb=40.89; p listed as P=0** *No functional immune tests and no other immune endpoints tested*	Serum IgA was positively related to blood Pb in Pb workers. Serum IgG was decreased and IgA was increased in Pb workers relative to "standard". IgM did not differ.
Cross-sectional	25 male Pb-	Referent =	Referent = 17 (5)	Serum IgG, IgA,	Student's t test, Mann-	Significant differences in immune values by Pb group:	Neutrophil

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Basaran (2000) Ankara, Turkey *Population may overlap with Undeger (1996)*	battery workers (high Pb) and 25 referent from university staff; Year not stated; Male=100%	33(9) High Pb=33(8.5)	High Pb = 75(18) Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	IgM, complement C3, C4, WBC differentials, neutrophil chemotaxis and neutrophil intracellular killing	Whitney U test, linear regression Adjustments not described	T-helper(CD4) # – referent=1140.3(681.2) **T-helper(CD4) # – Pb worker=858.8 (341.2); p<0.05** Serum IgG (mg/dl) – referent = 1212.1(393.6) **Serum IgG (mg/dl) – Pb = 854.6 (415.6); p<0.05** Serum IgM (mg/dl) – referent = 140.4(66.1) **Serum IgM (mg/dl) – Pb = 93.3 (39.6); p<0.05** Serum C3 (mg/dl) – referent = 61 (17.4) **Serum C3(mg/dl) – Pb = 45.1 (18.5); p<0.05** Serum C4 (mg/dl) – referent = 22.1 (7.8) **Serum C4(mg/dl) – Pb = 17.8 (8.5); p<0.05** Neutrophil chemotactic ind.–referent = 1.85(0.42) **Neutrophil chemotactic ind. Pb=1.24(0.28); p<0.001** Neutrophil random migration – referent = 19 (4.6) **Neutrophil random mig. Pb = 10 (3.2); p<0.001** No difference between workers and referents on: -serum immunoglobulins (IgA) -WBC differentials (CD3, CD8, CD20, CD56) -Neutrophil phagocytosis (NBT reduction) Complement was negatively correlated with blood Pb level; No other immune parameter was correlated with blood Pb levels. *No other immune endpoints tested*	chemotaxis was reduced in male Pb workers relative to referents and serum levels of IgG, IgM, C3, C4, and CD4 T-cells were decreased in Pb workers relative to referents. No difference in neutrophil phagocytosis, CD3, CD8, CD20, CD56, or IgA.
Cross-sectional Bener (2001) Al-Ain, United Arab Emirates	100 male industrial workers (high Pb taxi drivers, gas filling, garage, chemical, printing, building metal industry) and 100 matched referent professional workers; Year= 1999; Male= 100%	High Pb=34.6(8) Referent=8.3(6)	Geometric mean High Pb = 77.5 (42.8) Referent = 19.8 (12.3) *Note: Referent/Low Pb group over 10µg/dL*	Survey for self-reported symptoms classified by the authors as gastrointestinal, neuromuscular psychiatric, or allergic	Mantel-Haenszel test odds ratio Adjustments not described.	Relative risk of symptoms by Pb group: **Nausea/vomiting RR=1.68 (1.27, 2.22); p=0.014** Abdominal pain RR=1.08 (0.74, 1.58); p>0.05 Headache RR=1.09 (0.74, 1.48); p>0.05 Myalgia RR=1.12 (0.61, 2.04); p>0.05 **Muscular symptoms RR=1.61 (1.24, 2.08); p=0.004** Dizziness RR=1.33 (0.96, 1.86); p>0.05 **Fatigue RR=1.61 (1.22, 2.13); p=0.016** **Irritability RR=1.51 (1.13, 2.00); p=0.029** **Memory disturbances RR=1.91 (1.51, 2.43); p=0.013** Insomnia RR=1.39 (0.99, 1.95); ; p>0.05 Allergic conjunctivitis RR=1.24 (0.89, 1.73); p>0.05 **Rhinitis RR=1.78 (1.39, 2.28); p=0.0001** Dermatitis RR=1.47 (1.07, 2.0); p>0.05 Relative risk of respiratory symptoms by Pb group: Throat discomfort RR= 1.06 (0.67, 1.66); p>0.05 Cough RR= 1.11 (0.82, 1.51); p>0.05 **Phlegm RR=1.50 (1.12, 2.01)p=0.0385** Shortness of breath RR=1.33 (0.96, 1.86); p>0.05 Wheeze RR=1.08 (0.79, 1.48); p>0.05 **Diagnosed asthma RR=1.75, 2.26); p=0.002** *No other immune endpoints tested.*	Relative risk of self-reported symptoms of nausea, memory, muscular, dizziness, irritability, rhinitis, phlegm, and diagnosed asthma were elevated in industrial workers (Pb 77µg/dL) than in professional workers (Pb 20µg/dL).

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Cross-sectional Bergeret (1990) Location not stated; authors work in France	38 male Pb-battery workers (high Pb) and 34 matched referents	Referent = 38 High Pb= 40	Referents = 9.0 (4.3) High Pb=70.6 (18)	Neutrophil phagocytosis and chemotaxis	Student's t test and Chi-square test Adjustments not described.	Neutrophil Phagocytosis: Peak time – referent= 303.5(104) **Peak time – Pb worker=414.5(187); <0.01** Peak height – referent= 20.5(14.5) Peak height Pb worker= 17.7(11.1); not sig. Integral – referent =22509(16767) Integral Pb worker =19054(12015); not sig. Chemotaxis: Spontaneous –referent =42.5 (15.9) no statistics Spontaneous –Pb worker =35.5(15.8) no statistics Activated –referent =100.8(40.1) **Activated –Pb worker= 81.2(28.5); p<0.05** Differential – referent= 58.2(25.1) **Differential – Pb worker = 47.1(18.3); p<0.05** *No other immune endpoints tested*	Neutrophil phagocytosis and chemotaxis were decreased or delayed in Pb workers relative to referents.
Cross-sectional Coscia (1987) Location not stated, authors work in Italy	38 Pb-workers (13 battery workers, 9 plastics, 5 car industry, 2 ceramics, 2 Pb salts, 6 other) and 25 referents; Years not stated; % male not stated	High Pb =42.8 (11.5) Referent = 38.6 (13.3)	High Pb = 62.3 (21.6) Referent=not reported Measured when outcome assessed ***lack of blood Pb data in referents limits utility*	Leukocytes, T-cells, B-cells, CD4, CD8, IgG, IgM, IgA, complement C3 and C4,	Student's t test, Pearson correlation Adjustments not described.	Significantly different mean measures by Pb group: % lymphocytes - referents=31.2(6.6) **% lymphocytes – Pb exposed=37(8.6)** IgM – referents=182 (50.1) **IgM – Pb-exposed=144.5 (63)** C4 – referent=27.8 (8.5) **C4 – Pb workers=37.1 (15.9)** No difference by Pb-group in leukocytes, CD4, IgG, IgA, or C3 *No functional immune tests and no other immune endpoints tested*	Percentage of lymphocyte and complement C4 were increased and IgM decreased in Pb-workers relative to referents. CD4, IgG, IgA, C3 did not differ.
Cross-sectional Cohen (1989) Location not stated, authors work in Israel	10 men chronically exposed to Pb (high Pb; 7 battery workers and 3 scribes using Pb ink) and 10 hospital personal referents; Years not stated; Male=100%	High Pb=40(7) Range=22-70 Referent =not stated	Referent =≤19µg/dL High Pb=40-51µg/dL; mean not reported *Note: Referent/Low Pb group over 10µg/dL* Measured when outcome assessed	Mitogenic response to conA, PHA, WBC differentials T-helper (OKT4), T-cytotoxic (OKT8), E-rosette-forming cells	Student's t test Adjustments not described.	Percent suppression of responder cell thymidine incorporation in presence of conA-induced suppressor cells was increased in Pb workers relative to referents; **p<0.02.** No difference by Pb-group in mitogenic response to conA or PHA, or T-cell subsets (T-helper, T-cytotoxic), or E-rosette-forming cells *No functional immune tests and no other immune endpoints tested*	There was no difference between T-helper and T-cytotoxic cells # or mitogenic response to conA or PHA between 10 Pb workers and referents.
Cross-sectional Ewers (1982) West Germany	72 Pb-battery workers (high Pb) and 53 referents from various occupations;	Pb=36.4(10) Referents=35 (9)	Referent=11.6 Pb-worker =51.4 *Note: Referent/Low Pb group over 10µg/dL*	Serum IgM, IgG, IgA, complement C3, frequency colds and influenza	Student's t test, Pearson correlation, Mann Whitney U test, Kullback's 2I test Adjustments not described.	Correlation between Pb and Ig or C3 in Pb workers **Pb x log C3 r=-0.312; p=0.008** Pb x log IgM r=0.179; p>0.05 **Pb x log IgG r=-0.320; p=0.006** **Pb x log IgA r=0.256; p=0.03**	Serum IgG was negatively correlated to blood Pb in male Pb-

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	Years not stated; Male=100%				Note: Authors state Pb workers had lower salivary IgA but this contradicts a table in the publication.	Correlation between Pb and Ig or C3 in referents Pb x log C3 r=0.045; p>0.05 Pb x log IgM r=0.050; p>0.05 Pb x log IgG r=0.126; p>0.05 Pb x log IgA r=0.191; p>0.05 Correlation between Pb and Ig or C3 all subjects **Pb x log C3 r=0.231; p=0.01** Pb x log IgM r=-0.125; p>0.05 **Pb x log IgG r=-0.227; p=0.01** Pb x log IgA r=0.044; p>0.05 Authors state Pb workers had a slight tendency toward an increased frequency of colds and influenza infections, but did not demonstrate statistical relationship. *No functional immune tests and no other immune endpoints tested*	workers and combined Pb/referents. Serum IgA and complement C3 were also associated with blood Pb in Pb-workers. IgM was not affected by Pb.
Cross-sectional Fischbein (1993) USA	51 firearms instructors (Pb-1<25µg/dL, Pb-2≥25) and 36 referent industrial workers ; Years not state; Male= 100%	Referent = 47.1 (10.8) Pb-1= 48.8 (7) Pb-2=47.9 (9.4)	Referents = "tested negative" limit of detection not reported. Pb-1=14.6 (4.6) Pb-2=31.4 (4.3)	CD3, CD4, CD8, CD16, CD20, HLA-DR, spontaneous secretion of IgG (sIgG), mixed lymphocyte response (MLR), Hb, mitogenic response to PHA, PWM, and SAC	ANOVA, Pearson correlation, multiple regression Age, sex	Correlation in immune measure and Pb in Pb workers: **CD4% r=-0.45; p=0.001** **MLR r=-0.56; p=0.0001** Multiple regression of immune measures to Pb: **MLR B=-0.66 (0.21); p=0.004** CD4% B=-0.24 (0.19); p=0.2 CD8% B=0.09 (0.19); p=0.6 PHA B=-3.88(5.85); p=0.51 **Hb B=0.09 (0.03); p=0.002** **Percent and number of CD4 cells were decreased in both Pb-groups relative to referents; p<0.01 to <0.002.** **Percent of CD3 and HLA-DR were also decreased in both Pb-groups relative to referent; p<0.05 to p<0.002.** **Percent of CD20 were increased in both Pb-groups relative to referent; p<0.05 to p<0.002**. MLR and mitogenic response to PHA were decreased in Pb workers≥25µg/dL and mitogenic response PWM were decreased in both Pb-worker groups relative to referents. CD16, sIgG, and mitogenic response to SAC not related to Pb level or Pb-worker group. *No other immune endpoints tested*	Mixed lymphocyte response and % CD4 T-cells were negatively correlated to blood Pb. Mitogenic response to PHA and PWM, and % CD3 and HLA-DR were lower and CD20 was higher in firearms workers than referents. CD16 and SAC response did not differ.
Cross-sectional Garcia-Leston (2011) Portugal	70 male Pb workers (high Pb; n=34 plant 1 Pb chemical and	Referent=34.6(8) Pb=45.2(9.3)	Graphically displayed Referent ≈ 4 Pb-exposed ≈ 32 Plant 1≈ 28	WBC differential: T-cell (CD3), T-helper (CD4), T-cytotoxic (CD8),	ANOVA, Student's t test, Fisher's exact test, Bonferroni's test, Pearson correlation	Significant difference in % lymphocytes by Pb group: **CD8% - referent ≈36** **CD8% - Pb-exposed ≈ 32; p<0.05** **CD8% - plant 1 ≈ 31; p<0.05**	Percent of CD8 T-cells was decreased in Pb workers

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
	n=36 plant 2 Pb battery workers) and 38 referents; Years not stated; Male=100%		Plant 2≈37	B-cells (CD19), NK cells(CD16 and CD56)	Adjustments not described.	CD8% - plant 2 ≈ 33 No difference by Pb-group in CD3, CD4, CD19, CD16/CD56 *No functional immune tests and no other immune endpoints tested*	relative to referents. CD3, CD4, CD19, CD16/CD56 did not differ.
Cross-sectional Governa (1988) Location not stated; authors work in Italy	9 Pb battery workers (high Pb) and 18 referents with no occupational Pb; years not stated; Male= 100%	High Pb= 38(13) Referent "age-matched"	Referent = 19.2 (6.4) High Pb=63.2 (8.2) *Note: Referent/Low Pb group over 10µg/dL* Measured when outcome assessed	Polymorphonuclear leukocytes (PMNs) chemotaxis	Student's t test Adjustments not described.	Chemotactic index: Referent =75.6 (13.4) **Pb worker = 56.4 (8.7); p<0.05** Authors state PMN chemotaxis was not correlated to blood Pb levels. *No other immune endpoints tested*	PMN chemotaxis was decreased in Pb workers relative to referents.
In vitro Governa (1987) Location not stated; authors work in Italy	In vitro Pb exposure of blood from 24 health subjects years not stated; % Male not stated	Range 26 to 54	Prior to in vitro Pb exposure blood Pb ranged from 10.35 to 14.49µg/dL .5µM to 0.7 µM	Polymorphonuclear leukocyte (PMNs) phagocytosis, chemotaxis, and superoxide formation	Student's t test and linear regression analysis Adjustments not described.	Significant difference by in vitro Pb concentration: **Chemotaxis p<0.01 at Pb>2.4µM** **Phagocytosis p<0.01 at Pb>28.8µM** **Fluorescence polarization p<0.01 at Pb>57.6µM** Regression analysis: **Chemotaxis r=0.70; p<0.01** **Phagocytosis r=0.68; p<0.01** *No other immune endpoints tested*	In vitro exposure to Pb decreased PMN chemotaxis and phagocytosis.
Cross-sectional In vitro Guillard (1989) Location not stated; authors work in Belgium	25 Pb battery workers (high Pb) and 21 not occupationally exposed referents; in vitro exposure of referent PMNs also performed; years not stated; Male= 100%	Range 22 to 52	Mean Pb-workers = 60.3 Referent not reported Range Pb-workers=34.8-76.5 Referent not reported Measured when outcome assessed	Polymorphonuclear leukocytes (PMN) and monocyte respiratory burst by phorbolmyristate acetate (PMA)	Kruskal Wallis test, regression Adjustments not described.	Mean PMNs and monocytes/µl Referent = 3987 **Pb workers = 5546; p<0.05** Peak PMA respiratory burst chemiluminescence Referent = 11.57 Pb workers = 11.24; p>0.05 In vitro $PbCl_2$ exposure tested for inhibition of PMA-induced respiratory burst (referent PMN/monocytes) and Pb inhibited chemiluminescence at concentrations from 2 x 10^{-4}, 2 x 10^{-4}, and 10^{-3} mole/L and 2.8x10^{-4}M produced 50% inhibition of peak. *No other immune endpoints tested*	Respiratory burst of PMNs and monocytes was not different between Pb workers and referents.
Ecological Heinrich (1999) East Germany	2470 children aged 5-14 living in 2 industrial areas (Pb1, Pb2) or a referent area: Year=1992-1993; Male=50-51%	Range 5-14	No blood Pb data Pb emissions and Pb dustfall differ by 3 3 counties. Referent – Zebst -no emissions -dust=16-18µg/m^2/day Pb-1-Bitterfeld -no emissions -dust=18-41µg/m^2/day Pb-2-Hettstedt -0.22-.34 tons/km^2/year	Dermatological exam, test of pulmonary function, skin prick testing (SPT) for aller-gens, serum IgE, self-reported symptoms or doctor diagnosis of asthma, bronchitis,	Logistic regression analysis Adjusted for potential predictors	Odds ratio OR (95% CI) for self-reported doctor-diagnosis for lifetime prevalence rates: **Asthma Bitterfeld vs Zebst OR=4.4 (1.84,10.5)** **Bronchitis Hettstedt vs Zebst OR=1.52 (1.20,1.92)** **Allergy Hettstedt vs Zebst OR=1.69 (1.21,2.36)** Eczema Bitterfeld vs Zebst OR=1.42 (0.94,2.15) **Eczema Hettstedt vs Zebst OR=1.52 (1.03,2.24)** Bitterfeld not significant for bronchitis, allergy Hettstedt not significant for asthma Odds ratio OR (95% CI) for parent-reported symptoms lifetime prevalence rates **Wheezing Hettstedt vs Zebst OR=1.79 (1.37,2.34)**	Respiratory disease and allergy were elevated in children from a polluted area in Germany that also has higher Pb emissions and dustfall. Data include increased odds

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
			-dust=47-367µg/m^2/day * lack of blood Pb data limits utility	allergy, eczema, wheezing, cough, shortness of breath		**Short Breath Hettstedt vs Zebst OR=2.36 (1.65,3.38)** **Cough Hettstedt vs Zebst OR=1.72 (1.05,2.81)** Bitterfeld not significant Odds ratio OR (95% CI) for physical exam data Bron. React. Bitterfeld vs Zebst OR=1.69 (0.93,3.07) **SPT (sens.) Hettstedt vs Zebst OR=1.38(1.02,1.86)** **Specific IgE Hettstedt vs Zebst OR=1.75(1.31,2.33)** Bitterfeld not significant one or more positive SPT, one or more specific IgE, atopic dermatitis Hettstedt not significant for bronchial reactivity, atopic dermatitis	ratio for sensitization based on positive SPT and elevated specific IgE to common allergens, bronchitis, allergy, eczema, wheezing, shortness of breath, cough. No blood Pb data.
Cross-sectional Heo (2004) Korea	606 Pb battery factory workers; no referent population; Year not stated; Male=91%	Age-stratified: <30 (n=184) 30-39 (n=299) >40 (n=123)	Age-stratified µg/dL: <30 years = 22 (10) 30-39 years =23(11) >40 years= 24(9) Measured when outcome assessed	Serum IgE, IL-4, IFNγ,	ANOVA, Dunnett's t test, Kruskal-Wallis test, Dunn's test, Student's t test, Mann-Whitney U test Adjustments not reported.	**Correlation of serum IgE by blood Pb:** **r=0.0872; p=0.0318** Mean serum IgE level by blood Pb in factory workers: <10µg/dL blood Pb – IgE=270 (46) ng/mL 10-29µg/dL blood Pb – IgE= 536 (91) ng/mL **≥30µg/dL blood Pb – IgE= 1286 (457) ng/ml; p<0.05** The authors also reported analyses of IgE stratified by blood Pb and age groups (<30, 30-39, and ≥40 years of age) that was significant for the ≥30µg/dL blood Pb for all age groups except the 30 year-olds. Mean IL-4 level by blood Pb in <30 year-old workers: <10µg/dL blood Pb – IL-4= 22 (3) pg/mL 10-29µg/dL blood Pb – IL-4= 24 (5) pg/mL **≥30µg/dL blood Pb – IL-4= 11 (2) pg/ml; p<0.05** No effect of Pb levels on IL-4 in other age groups or on IFNγ in any age group. *No functional immune tests and no other immune endpoints tested.*	Serum IgE was correlated with blood Pb and elevated in Pb-factory workers with blood Pb levels ≥30µg/dL relative to other workers. Serum IL4 was lower in Pb-workers <30 years of age with blood Pb≥30g/dL, but IL4 and IFNγ were not associated with blood Pb in any other group.
Cross-sectional Horiguchi (1992a) Osaka, Japan	56 Pb refinery workers in Osaka; Year not stated; Male=82%	49.5 Range 18-73	Pb-workers Blood =47.4 (28.1) Urine (µg/L)=57.7 (45.7) Reference values Blood = 11 (0.28) Urine (µg/L)=35.5 (0.45) Measured when outcome assessed *Note: source of*	Frequency of colds during previous year	Chi-square test Adjustments not described.	Mean frequency of colds by Pb level in Pb workers: <20µg/dL mean=1.5 20-40µg/dL mean=1.07 40-60µg/dL mean=1.62 >60µg/dL mean=2.18 Frequency of colds by blood Pb level: Less than 1.5 cold/year – Pb<60µg/dL = 31 Less than 1.5 cold/year – Pb>60µg/dL = 7 More than 2 colds/year – Pb<60µg/dL = 8	Significantly increased frequency of colds in workers with blood Pb>60 µg/dL than other Pb workers.

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
			"reference values" not stated; reference >10µg/dL; no referent group			More than 2 colds/year – Pb>60µg/dL = 10 Chi-square=7.967>6.630 (1%)	
Cross-sectional Horiguchi (1992b) Osaka, Japan	106 Pb refinery workers in Osaka (n=47 in 1988; n=56 in 1989); Years=1988-1989; Male=100%	Mean 1988=49.9 1989=48.6 Range 1988=18-73 1989=19-74	Pb-workers Blood 1988=50.4(28) Blood 1989=43.2 (24.8) Urine 1988=60.0 (47.1) Urine 1989=53.7(40.3) Reference values Blood = 11 (0.28) Urine (µg/L)=35.5 (0.45) Measured when outcome assessed *Note: source of "reference values" not stated; reference >10 µg/dL; no referent group*	Serum IgA, IgG, IgM, IgE, complement C3	Chi-square test, correlation statistical methods not reported	Authors state in 1988 significant correlation blood Pb: Serum IgA r=0.296 Serum IgE r=0.314 Authors state significantly higher number of: Workers with IgE (400 IU/ml) had blood Pb >60µg/dL No significant correlations between blood Pb and: -serum complement C3 -serum immunoglobulins (IgG, IgM) in 1988 -serum immunoglobulins (IgG, IgA) 1989 (IgM not tested) *No functional immune tests and no other immune endpoints tested*	Significant correlation between serum IgE and blood Pb; and increased serum IgE in workers with blood Pb >60µg/dL relative to other Pb workers. IgA, IgG, IgM, C3 did not differ.
Cross-sectional Jaremin (1983a) Location not stated *Same population as Jaremin (1983b)*	80 male manufacturers (group A, n=20 Pb workers with 7-24 years of exposure and chronic Pb poisoning; B, n=30 Pb workers with 1-10 years of exposure; C, referents, no occupational Pb exposure); Year not stated; Male =100%	Range 22-62	Pb: mean (SD) µg/dL Referents = 24.06 (5.93) Pb workers-A=51.8 (16) Pb workers-B=26.6(6) Pb: range Referents = 14.3-40.6 Pb workers-A=36.4-92.1 Pb workers-B=18.2-42.1 Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	Lymphocyte count, albumen, serum immunoglobulin (IgG, IgM, IgA)	Student's t test Adjustments not described.	Mean serum Immunoglobulin mg/100ml by Pb group: IgG referent (24µg/dL) = 1075.90 (141) **IgG Pb worker A (51.8µg/dL) = 946.5 (135), p<0.01** IgG Pb worker B (26.6µg/dL) = 1047.66 (136) IgA referent (24µg/dL) = 225 (48) IgA Pb worker A (51.8µg/dL) = 230.25 (53) IgA Pb worker B (26.6µg/dL) = 238.36 (43) IgM referent (24µg/dL) = 66.4 (17) **IgM Pb worker A (51.8µg/dL) = 51.41 (13), p<0.001** IgM Pb worker B (26.6µg/dL) = 64.93 (16) Mitogenic response, rosette test, and migration inhibition test performed in Jaremin (1983b). *No other immune endpoints tested*	Serum IgG and IgM were decreased in Pb workers with a mean blood Pb of 52µg/dL relative to referents with mean blood Pb of 24µg/dL. IgA did not differ.
Cross-sectional Jaremin (1983b) Location not stated *Same population as Jaremin (1983a)*	80 male manufacturers (group A, n=20 Pb workers with 7-24 years of exposure and chronic Pb poisoning; B, n=30 Pb workers	Range 22-62	Pb: mean (SD) µg/dL Referents = 24.06 (5.93) Pb workers-A=51.8 (16) Pb workers-B=26.6(6) Pb: range Referents = 14.3-40.6 Pb workers-A=36.4-92.1 Pb workers-B=18.2-42.1 Measured when	Mitogenic transformation to PHA, rosette test, leukocyte migration inhibition test	Student's t test, linear correlation factor (r) Adjustments not described.	Mean lymphoproliferative (mitogen) responses to PHA Referents = 61.05 (7.31) **Pb workers-A = 45.94 (5.99), p<0.001** Pb workers-B = 58.86 (7.68) **Mitogenic response of Pb workers was increased relative to referents for spontaneous response, and response to Pb ions at 1-2x10^{-5}mg/ml, p<0.001** Correlation between blood Pb and mitogenic response Spontaneous r=0.917	PHA mitogenic response was decreased and spontaneous or Pb-stimulated lympho-proliferative responses were increased in Pb

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
	with 1-10 years of exposure; C, referents, no occupational Pb exposure); Year not stated; Male =100%		outcome assessed *Note: Referent/Low Pb group over 10µg/dL*			PHA-stimulated r=-0.720 No difference between Pb workers and referents on: -rosette test or migration inhibition test Serum Ig's tested in Jaremin (1983a). *No other immune endpoints tested*	workers (blood Pb of 52µg/dL) relative to referents with mean blood Pb of 24µg/dL. Rosette and migration inhibition test did not differ.
Cross-sectional Jaremin (1990) Location not stated	127 male manufacturers (Pb workers with 0.5-24 years of exposure [A1-n=41 no Pb poisoning; A2-n=32 Pb poisoning traits; A3 n=4 clinical Pb poisoning]; n=50 referents, no occupational Pb exposure); Year not stated; Male =100%	Pb worker=38 Referent=39 Range 19-59	Pb: mean (SD) µg/dL Referents = 16.4 (7.1) A1 not Pb poisoning A2 - Pb poisoning traits A3 - clinical Pb-poison Pb-A1 = 40.1 (7) Pb-A2 = 72.2 (10) Pb-A3 = 106.7 (18) Pb: range Referents = 5-35 Pb-A1 = 18-58 Pb-A2 = 60-100 Pb-A3 = 87-129 Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	Serum immunoglobulin (IgG, IgM, IgA), C_3 complement rosette test, antibody response to typhoid immunization	Student's t test Adjustments not described.	Mean absolute rosette count (SD) Referents (n=30) = 1321 (553) Pb workers-A1 (n=40) = 1218 (203) **Pb workers-A2 (n=30) = 1025 (439), p<0.02** **Pb workers-A3 (n=4) = 1080 (348), p<0.02** Mean serum Immunoglobulin mg/100ml by Pb group: IgG referent = 1213 (296) IgG Pb worker A1 = 1157 (238) **IgG Pb worker A2 = 1010 (275), p<0.02** **IgG Pb worker A3 = 906 (195), p<0.02** IgM referent = 157 (37) **IgM Pb worker A1 = 91 (34), p<0.02** **IgM Pb worker A2 = 56 (15), p<0.02** **IgM Pb worker A3 = 54 (14), p<0.02** IgA did not differ between Pb workers and referents Increase in IgG after anti-typhoid immunization: Referent (n=20) = 270 Pb worker-A1 (n=20) = 181 **Pb worker-A2 (n=20) = 42, p<0.02** Complement was significantly lower in workers with clinical Pb poisoning traits, however "n" reported as 20 when only 4 individuals were in the study. *No functional immune tests and no other immune endpoints tested*	Antibody response to typhoid immunization, rosette count, and serum IgG were decreased in workers with mean blood Pb of 70µg/dL or greater relative to referents with mean blood Pb of 16µg/dL. Serum IgM was also decreased in Pb workers with a mean blood Pb of 40µg/dL or greater. IgA and complement did not differ.
Cross-sectional Kimber (1986) Location not specified; authors located in UK	39 tetraethyl Pb plant workers (high Pb) and 21 age and sex-matched referents; Year not stated; Male=100%	Mean Referent = 38 High Pb=45 Range Referent=20-60 HighPb= 25-61	Referent=11.8(2.2) High Pb =38.4(5.6) Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	NK cell function (K562 lysis), serum IgA, IgG, IgM, mitogenic response to PHA	Correlation (r), statistical methods not reported Adjustments not described. ** lack of study and statistical information limits utility	No difference between Pb workers and referents on: -NK cell lytic function (lysis of K562 target cells) -serum immunoglobulins (IgA, IgG, IgM) -lymphoproliferative (mitogen) responses to PHA *No functional immune tests and no other immune endpoints tested*	NK cell function, serum IgG, IgM, IgA, and mitogenic response to PHA did not differ between Pb workers and referents.

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Cross-sectional Kuo (2001) Taiwan	20 Pb battery workers and 34 high school teacher referents; Years not stated; %Male=50 referent and 76% Pb workers	Mean not reported	Mean not reported for blood or urine. Authors state average blood Pb had decreased from 60µg/dL to 30µg/dL Measured when outcome assessed	WBC differential: lymphocytes, monocytes, granulocytes, T-cell (CD3), T-helper (CD4), T-cytotoxic (CD8), B-cells (CD19), NK cells(CD16 and CD56)	Chi-square test, Pearson correlation, multiple linear regression analysis Age, sex, disease status	Significant Pearson correlation for log blood Pb and: **Monocytes (% or #) r=0.4547; p<0.001** **CD8 (%) r=-0.3269; p<0.01** **B-cells (%) r=-0.3000; p<0.05** Significant difference by Pb group: **Monocytes (% or #) – referent = 4.17(0.45)** **Monocytes (% or #) – Pb = 6.00 (0.41); p=0.0013** **B-cells (%) – referent = 15.4 (1.51)** **B cells (%) – Pb = 11.17 (1.37); p=0.0246** **Lymphocytes (#/ml) – referent =1849(193)** **Lymphocytes (#/ml) – Pb =967 (140); p=0.0001** **Granulocytes (#/ml) – referent =5096(426)** **Granulocytes (#/ml) – Pb =2422 (310); p=0.0001** Authors report similar correlation to urinary Pb. *No functional immune tests and no other immune endpoints tested*	Blood Pb was correlated with % monocytes and negatively correlated to %B-cells and %CD8 T cells. Lymphocytes, granulocytes, and % B-cells were reduced in Pb workers relative to referents; # and % monocytes were increased. CD4 and NK cells did not differ.
Cross-sectional Mishra (2003) Lucknow, India *Population may overlap with Mishra (2006, 2010)*	84 male Pb-workers in Lucknow (n=34 Pb-battery workers, 30 three-wheel drivers, 20 silver jewelry makers, and 30 referents); Years not stated	29-32 by group: Range 17-65	Referent = 4.5 (2) 3-wheel drivers=6.5(4.7) Pb-battery = 128.1(105) Jewelry = 17.8 (18.5) Measured when outcome assessed	NK cell function (K562 lysis), IFN-γ production and mitogenic response to PHA of peripheral blood mononuclear cells (PBMCs)	ANOVA, Student Neuman Keuls test, Pearson correlation Adjustments not reported.	IFN-γ (pg/ml) (SD) by group: Referent-unstimulated = 63 (112) Pb-battery workers-unstimulated = 56 (95) Referent-PHA stimulated = 173 (227) **Pb-workers-PHA stimulated = 812 (778); p<0.001** Pearson correlation between blood Pb and IFN-γ in PHA stimulated lymphocytes of referent and Pb-workers combined: r=0.384; p=0.005 Stimulation Index for PHA lymphoproliferative (mitogen) response by group: Referent = 70 (55) **3-wheel drivers = 42 (28); p<0.001** **Pb-battery = 32 (22); p<0.001** **Jewelry = 36 (22); p<0.001** Authors state that PHA stimulation was not correlated to blood Pb levels despite group-related difference. Percent NK cell cytotoxicity (SD) by group at 50:1 E:T: Referent = 47 (14) 3-wheel drivers = 49 (15) Pb-battery = 42 (16) Jewelry = 41 (18) Similar results reported for 25:1 E:T ratio. *No other immune endpoints tested.*	Blood Pb was significantly associated with increased IFN-γ production in response to PHA in male adults. NK cell function and mitogenic response to PHA did not differ by blood Pb.
Cross-sectional Mishra (2006)	30 male Pb-battery workers	Median Pb =27	Pb-workers =106 (107) Referents = 4.5 (2.2)	Serum IgA, IgG, and IgM,	Mann-Whitney U test; student Neuman Keuls test,	Mean serum IgA by Pb group: Referents IgA = 138 (53) mg/dL	Serum IgA was significantly

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
Location not stated, authors work in Lucknow India *Population may overlap with Mishra (2003, 2010)*	and 27 referents; Years not stated	Referent=28 Range Pb =19-45 Referent=25-45	Measured when outcome assessed	neutrophil respiratory burst and nitric oxide (NO) production	Pearson correlation coefficient Adjustments not described.	**Pb-workers IgA = 182 (53) mg/dL; p<0.05** Authors report serum IgG and IgM did not differ between Pb-workers and referents (data shown graphically). Authors report neutrophil respiratory burst and nitric oxide (NO) production did not differ between the Pb-workers and the referents (data shown graphically). *No other immune endpoints tested.*	elevated in Pb-workers relative to referents. IgM, IgG, and neutrophil NO and respiratory burst did not differ.
Cross-sectional Mishra (2010) Location not stated, authors work in Lucknow India *Population may overlap with Mishra (2003, 2006)*	59 male Pb-workers (n=26 three-wheel drivers, n=33 Pb-battery workers) and 21 referents; Years not stated	Median 27-33 by group: Range 17-65	Referent = 4.5 (2) 3-wheel drivers=6.7(4.5) Pb-battery = 132(103) Measured when outcome assessed	Lymphocyte subsets (CD4, CD45RA [naïve], CD8, CD56)	ANOVA, Pearson correlation coefficient Adjustments not described.	Percentage of lymphocytes by Pb-group: CD4 – referent = 55 (13) **CD4 – three-wheeler = 37 (11); p<0.001** **CD4 – Pb-battery workers = 31 (8); p<0.001** CD4/CD8 – referent = 2.6 (2.3) **CD4/CD8 – three-wheeler = 1.4 (0.5); p<0.001** **CD4/CD8 – Pb-battery workers = 1.3 (0.5); p<0.001** CD45 RA – referent = 61 (15) **CD45 RA – three-wheeler = 73 (10); p<0.05** **CD45 RA – Pb-battery workers = 70 (14); p<0.05** CD8, CD16, CD25, CD45 RO did not differ by group **Correlation of blood Pb and % CD4 r=-0.374; p<0.01** **Correlation exposure time % CD4 r=-0.428; p<0.001** *No functional immune tests and no other immune endpoints tested.*	Percent of CD4 T-cells was decreased and percent of CD45RA B-cells was increased in Pb-workers relative to referents. CD8, CD16, CD25, CD45RO did not differ.
Cross-sectional Pinkerton (1998) USA	145 Pb-smelter workers (high Pb) and 84 referent workers from hardware manufacturing company; Male=100%	Pb=32.9 (8.6) Referent=30.1(9)	Median: Referent = <2 High Pb = 39 Range: Referent <2-12 High Pb= 15-55 Measured when outcome assessed Cumulative exposure also estimated by integrating blood Pb concentration over time	NK function (target lysis), serum IgG, IgM, IgA, salivary IgA, complement, WBC differentials: neutrophil, lymphocytes, monocytes, eosinophils, basophils, CD14/CD45, CD8/CD3, CD8/CD56, CD2/CD19, CD45RA (naïve) mitogenic (tetanus toxoid) response	Wilcoxon rank sum tests, chi-square tests, multivariate regression Age, race, smoking status, work shift	Geometric mean of immune parameter differing by Pb-workers and unexposed workers: **Monocytes (%) r^2 = 5.1; p=0.03** **Immature T cells (CD4/CD8) r^2 = 5.3; p=0.003** **Subset of NK cells (CD8/CD56) r^2 = 11.0; p=0.04** **Among Pb-workers the # and % of B-cells (CD19+) was positively associated (p≤0.01) with blood Pb. Among Pb-workers, negative association of cumulative Pb with IgG(p=0.03), and positive association of cumulative Pb with % and # of CD4/CD45RA(p<0.01)** No difference between Pb-workers and referents or effect of blood Pb in workers on: -serum complement -serum immunoglobulins (IgA, IgG, IgM) or-salivary IgA -lymphoproliferative responses to tetanus toxoid -WBC differentials (except effect noted above) *No functional immune tests and no other immune endpoints tested*.	Decreased percent NK cells, monocytes, and immature T cells were observed in Pb workers to referents. Increased number and percent of B-cells among Pb workers and naïve T cells were correlated with cumulative Pb exposure. Serum IgG, IgA,

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
							IgM, C3 and other lymphocyte populations were not related to Pb.
Cross-sectional Queiroz (1994b) Location not stated; authors work in Brazil *Population may overlap with Queiroz (1993, 1994a)*	33 male Pb battery workers and 20 referents from blood bank donors; Year not stated; Male= 100%	Pb=32.4 (11) Referent not stated	Referent= <10µg/dL Pb: range=12-80 <30µg/dL – 6 workers 30-40µg/dL-4 workers 40-50µg/dL-6 workers 50-60µg/dL-5 workers 60-70µg/dL-8 workers >70µg/dL-4 workers Measured when outcome assessed	Serum IgG, IgA, and IgM, mitogenic response to PHA	Student's t test Adjustments not described.	No difference between workers and referents on: -serum immunoglobulins (IgA, IgG, IgM) -lymphoproliferative (mitogen) responses to PHA *No functional immune tests and no other immune endpoints tested*	Serum IgG, IgM, IgA, and mitogenic response to PHA did not differ between Pb-workers and referents.
Cross-sectional Queiroz (1993) Location not stated; authors work in Brazil *Population may overlap with Queiroz (1994a, 1994b)*	39 male Pb battery workers and 39 referents from blood bank donors; Year not stated; Male= 100%	Pb =33.9 (12) Referent not stated	Referent= <10µg/dL Pb: range=14.8-91.4 <30µg/dL – 7 workers 30-40µg/dL-4 workers 40-50µg/dL-4 workers 50-60µg/dL-7 workers 60-70µg/dL-12 workers >70µg/dL-5 workers Measured when outcome assessed	Neutrophil chemotaxis and nitroblue tetrazolium test (NBT) reduction activity (measure of phagocytosis and respiratory burst activity)	Mann Whitney U test, ANOVA, Duncan test Adjustments not described.	Neutrophil function by Pb group: **Chemotaxis p<0.001** **NBT reduction p<0.001** Neutrophil function by Pb group > or < 60µg/dL presented graphically by median: Chemotaxis – referent≈35µm Chemotaxis Pb<60µg/dL≈9µm **Chemotaxis Pb>60µg/dL≈27µm;p<0.001** NBT positive neutrophils– referent≈51% NBT positive neutrophils Pb<60µg/dL≈22% **NBT positive neutrophils Pb>60µg/dL≈19%;p<0.001** No other immune endpoints tested	Neutrophil chemotaxis and respiratory burst activity of Pb-workers was decreased relative to referents.
Cross-sectional Queiroz (1994a) Location not stated; authors work in Brazil *Population may overlap with Queiroz (1993, 1994a)*	60 male Pb battery workers and 39 referents from blood bank donors; Year not stated; Male= 100%	Pb =33.9 (12) Referent not stated	Referent= <10µg/dL Pb: range=14.8-91.4 <30µg/dL – 8 workers 30-40µg/dL-4 workers 40-50µg/dL-7 workers 50-60µg/dL-14 workers 60-70µg/dL-12 workers >70µg/dL-15 workers Average of 33 workers in safe range (<60µg/dL) =43.2(14.9) Measured when outcome assessed	Polymorphonuclear (PMN) *Candida* phagocytosis and lytic activity, and splenic phagocyte function by quantitation of red blood cell "pits"	Mann Whitney U test, ANOVA, Duncan test Adjustments not described.	PMN function by Pb group: Candida phagocytosis p>0.05 **Candida killing/lytic activity p<0.001** **NMT reduction p<0.001** PMN function by Pb group > or < 60µg/dL presented graphically by mean: Candida killed – referent≈29 (15)% **Chemotaxis Pb<60µg/dL≈17(12)%; p<0.05** **Chemotaxis Pb>60µg/dL≈12(14)%; p<0.05** Lytic activity toward *C. albicans* was affected, but not *C. pseudotropicalis* *No other immune endpoints tested*	PMN lytic activity of Pb-workers was decreased relative to referents, but PMN phagocytic activity was not affected.
Cross-sectional Reigart (1976) Location not	19 preschool age children; 12 with blood (high Pb)	Mean not reported Range 4-6	High Pb= 45.3µg/dL Low /referent 22.6µg/dL	Recall response to soluble antigen (tetanus	Statistical methods not reported	No statistical difference between the high Pb group and the low Pb group in: -IgG-specific antibody titer for tetanus toxoid	No difference was observed in tetanus

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
stated; authors work in Charleston, SC	Pb≥40µg/dL; and 7 <30µg/dL (referent); Year not stated; Male%=unknown		Measured when outcome assessed *Note: Referent/Low Pb group over 10µg/dL*	toxoid), IgG, IgM, IgA, serum complement	Adjustments not described. * lack of study and statistical information limits utility	-serum complement -serum immunoglobulins (IgA, IgG, IgM) *No other immune endpoints tested.*	toxoid-specific antibodies, complement, serum IgG, IgM, or IgA, between 12 children with blood Pb >40 and 7 below 30µg/dL.
Cross-sectional Sata (1998) Location not stated; authors work in Japan *Population may overlap with Sata (1997)*	71 male Pb stearate workers (high Pb) and 28 referents for another chemical factory; year not stated; Male=100%	Mean High Pb=48 Referents=55	High Pb=19 Referent=not reported Measured when outcome assessed ***lack of blood Pb data in referents limits utility but correlation to blood Pb also demonstrated.*	WBC differentials T-cell (CD3), memory T(CD3CD45RO), naïve T (CD3CD45RA), T-helper (CD4), CD29A, T-cytotoxic (CD8), B-cell (CD19)	Pearson correlation, multiple regression analysis Adjustments not described.	**Regression relationship of blood Pb and memory T CD3CD45RO B=-172.4; p<0.05** **Correlation between blood Pb in Pb workers and naïve T (CD3CD45RA); p<0.05** Significantly different mean measures by Pb group: **Memory T (CD3CD45RO)# – referents = 850 (450)** **Memory T CD3CD45RO # Pb- = 740 (310);p<0.05** **Cytotoxic T (CD8) % -referents = 34(7)** **Cytotoxic T (CD8)% - Pb workers = 38(9); p<0.05** No difference by Pb-group in CD19 or CD4 lymphocytes. *No functional immune tests and no other immune endpoints tested*	Memory T cells were negatively correlated to blood Pb and naïve T cells were positively correlated to blood Pb in workers. Memory T cells were reduced and CD8 T cells were increased in Pb-sterate workers relative to referents. CD4 and CD19 did not differ.
Cross-sectional Sata (1997) Location not stated; authors work in Japan *Population may overlap with Sata (1998)*	29 male Pb stearate workers (high Pb) and 19 referents without Pb history; year not stated; Male=100%	Mean High Pb=29 Referents=55 Range High Pb=23-74	Mean Pb workers=18 Low-Pb<20µg/dL; n=19 High-Pb ≥20µg/dL; n=10 Range Pb workers= 7-35 Referent=not reported Measured when outcome assessed ***lack of blood Pb data in referents limits utility but correlation to blood Pb also demonstrated*.	WBC differentials T-cell (CD3), T-helper (CD4), T-cytotoxic (CD8), B-cell (CD19), NK (CD16 and CD57)	Students' t test, Welch's test, ANCOVA Age	Correlation between CD16 cells per mm^3 and blood Pb among Pb workers r=-0.39; p<0.05 Significantly different mean measures by Pb group: NK cell (CD16) % -referents = 32(8) NK cell (CD16) % - Pb low = 33(13) **NK cell (CD16) % - Pb high = 22 (6); p<0.05 to ref. and low Pb group; also for CD16 cell number.** Cytotoxic T (CD8) % -referents = 36(6) Cytotoxic T (CD8)% - Pb low = 35(10) **Cytotoxic T (CD8)% - Pb high = 43(6); p<0.01 to referent and p<0.05 to low Pb group** **CD3 % was increased in high Pb group relative to low Pb group at p<0.05.** No difference by Pb-group in CD3, CD4, CD19, CD57. *No functional immune tests and no other immune*	NK cell number was negatively correlated to blood Pb in Pb workers. NK cell number and percentage were reduced and CD8 T cells were increased in Pb-sterate workers relative to referents. CD3, CD4, CD19, and CD57 did not

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
						endpoints tested	differ.
Cross-sectional Undeger (1996) Ankara, Turkey *Population may overlap with Basaran (2000)*	25 male Pb-battery workers (high Pb) and 25 referents from University of Hacettepe; Years not stated; Male=100%	Referent=33(9) Pb=33 (8.5)	Referent=16.7 (5) High Pb=74.8 (17.8) *Note: Referent/Low Pb group over 10µg/dL* Measured when outcome assessed	Serum IgG, IgM, IgA, complement C3 and C4, WBC differential (CD3, CD4, CD8, CD20, CD56)	Mann-Whitney U test, linear regression Adjustments not described.	Significantly different mean measures by Pb group: T-helper (CD4) – referents=1140(681)/mm^3 **T-helper (CD4) – high Pb=858.8(341)/mm^3; p=<0.05** IgG – referents=1202(393.6) **IgG – high Pb=854.6(415.6); p<0.05** IgM – referents=140.4(66.1) **IgM – high Pb=93.3 (39.6); p<0.05** C3 – referents=61(17.4) **C3 – high Pb=45.1(18.5); p<0.005** C4 – referents=22.1(7.8) **C4 – high Pb=17.8(8.5); p<0.05** No difference by Pb-group in leukocytes, lymphocytes, B-cells, T-cells, T-suppressor, CD4/CD8 ratio, NK cells and serum IgA. *No functional immune tests and no other immune endpoints tested*	Number of CD4 T-cells and serum IgG, IgM, C3, and C4 were lower in Pb-workers than referents. Leukocytes, lymphocytes, CD8, CD20, CD56, and serum IgA did not differ.
Cross-sectional Valentino (2007) Location not stated; authors work in Italy	58 male Pb workers (Pb-1; n=14 pottery, Pb-2 n=44 foundry) and 59 alimentary plant referents ;Years not stated; Male=100%	Mean Referent=47(7) Pb-1=38.8(4) Pb-2=45.8(7) Range Referent=25-61 Pb=30-61	Blood Referent=3.9(1.8)) Pb-1=9.7(4.2) Pb-2=21.7(8.8) Urine Referent=1.9(1.2) Pb-1=12.8(12.3) Pb-2=35.7(21) Measured when outcome assessed	Plasma cytokines (IL-2, IL-4, IL-6, IL-10, TNF-α, IFN-γ), nitrates and nitrites	ANOVA, Chi-square test, Spearman correlation, multiple regression Adjustments not described.	Plasma cytokines by Pb group (pg/ml): IL-10 – referents =4.55(3.89) IL-10 – Pb- 1 = 4.68 (1.53) **IL-10 – Pb-2 = 7.37 (8); p<0.05** TNF-α – referents = 2.30 (1.39) TNF-α – Pb-1 = 3.66(2.69) **TNF-α – Pb-2 = 3.05(1.66); p<0.05** No difference by Pb-group in IFN-γ, IL-2, IL-4, IL-6, nitrates and nitrites *No functional immune tests and no other immune endpoints tested*	Plasma IL-10 and TNF-α were increased in Pb workers relative to referents. IL-2, IL-4, IL-6, IFN-γ did not differ.
Cross-sectional Valentino (1991) Location not stated; authors work in Italy	10 Pb refinery workers (high Pb) and 10 referents; Years not stated; Male=100%	Referent Pb=41.1 (7.3)	Referent = 12.4(2.5)µg/dL High Pb=33.1(5.6) *Note: Referent/Low Pb group over 10µg/dL* Measured when outcome assessed	Polymorphonuclear leukocytes (PMNs) phagocytosis, chemotaxis, and superoxide formation	Student's t test Adjustments not described.	Chemotaxis by Pb group: Toward C5a –referent =82.2 (6.0) **Toward C5a –Pb worker =65.0 (13.2); p<0.002** Toward F-MLP –referent =85.3 (12.9) **Toward F-MLP –Pb worker= 63.2 (11.8); p<0.001** LTB4 production – referent= 22.8(7.5) **LTB4 production – Pb worker = 53.8 (13.7); p<0.001** No difference by Pb-group in random migration or chemiluminescence, respiratory burst *No other immune endpoints tested*	PMN chemotaxis was decreased in Pb workers relative to referents.
Cross-sectional Wagnerova (1986) Czechoslovakia	Children living near a Pb smelter (high Pb) and referent children in a rural area followed for	11 at start of study	Presented graphically Referent boys ≈18-23 Referent girls≈12-21 Pb boys≈30-42 Pb girls≈23-41	Serum IgG, IgA, IgM, IgE	Statistical methods not reported Adjustments not described. ** lack of statistical information limits utility	Authors state IgE was significantly decreased in children during all 4 sampling times from the children living closer to the Pb smelter. Authors state IgM was significantly decreased in girls living closer to the Pb smelter during all 4 sampling times from the referents, and no difference	Decreased serum IgE in boys and girls living near a Pb smelter and decreased IgM

Study Description	Population	Age Mean (S.D)	Blood lead (µg/dl) Mean (S.D.)	Immune Measures	Statistical Modeling; Covariates	Findings	Observed effect
	every 6 months for 2 years; n varied from 53 to 92 per group per sample; Year not stated; Male=52-58%		*Note: Referent/Low Pb group over 10µg/dL* Measured when outcome assessed			in IgM in the boys. Authors state IgA was significantly increased in Pb children during the first sampling time, with no difference at the other 3 sampling times between children living closer to the Pb smelter and referents. *No functional immune tests and no other immune endpoints tested*	in girls living near a Pb smelter relative to referents. IgG did not differ and IgA was equivocal.
Cross-sectional Yucesoy (1997b) Location not stated, authors work in Turkey *Population may overlap with Yucesoy (1997a, 1997c)*	20 male Pb-battery workers (Pb-1), 20 male Pb/Cd (Pb-2)workers, and 12 age-matched referents; Years not stated; Male= 100%	Pb-1=35.9 Pb-2=41.7 Referent=36.8 Range: Pb-1=19-49 Pb-2=39-48 Referent=21-39	Referent = 4.83 (0.99) Pb-1 = 59.4 (3.2) Pb-2= no Pb data Measured when outcome assessed	Serum IL-1β, IL-2, TNF-α, γ-IFN, serum cadmium	Student's t test, Mann-Whitney U test, and Pearson correlation Adjustments not described.	Mean serum cytokine (SE) by Pb group: IL-1β -referents = 33.5 (3.09) pg/ml **IL-1β - Pb-workers = 22.67 (1.35) pg/ml; p<0.05** IL-2 -referents = 4.15 (0.78) pg/ml IL-2 - Pb-workers = 4.58 (0.52) pg/ml TNF-α -referents = 3.07 (0.86) pg/ml TNF-α - Pb-workers = 2.34 (0.58) pg/ml γ-IFN – referents = 0.59 (0.01) IU/ml **γ-IFN – Pb-workers = 0.55 (0.01) IU/ml; p<0.01** IL-1β was also lower and γ-IFN was elevated in relation to combined Pb/cadmium exposure workers. *Other immune data reported in other publications*.	Plasma IL-1β and γ-IFN levels were decreased in Pb-workers (n=20) relative to referents (n=12). IL-2 and TNF-α did not differ.
Cross-sectional Yucesoy (1997a) Location not stated, authors work in Turkey *Population may overlap with Yucesoy (1997b, c)*	20 male Pb-battery workers (high Pb) and 20 age-matched referents; Years not stated; Male= 100%	high Pb =35.9 Referent=36.8 Range: highPb =19-49 Referent=21-39	Referent = 4.5 (0.7) high Pb = 59.4 (3.2) Measured when outcome assessed	NK function (K562 lysis), mitogenic response to PHA	Student's t test, Mann-Whitney U test, and Pearson correlation Adjustments not described.	NK cell function – mean % cytotoxicity) by Pb group: Referents (12.5:1)= 31.0 (2.3) Referents (25:1)= 44.8 (2.4) Referents (50:1)= 51.8 (2.1) Pb-workers (12.5:1)= 33.8 (2.7) Pb-workers (25:1)= 42.1 (2.6) Pb-workers (50:1)= 51.6 (2.2) Mitogenic response to PHA (BrdU incorporation): Referents = 1548 (174) Pb-workers = 1462 (236) *Other immune data reported in other publications*.	NK cell function and mitogenic response to PHA did not differ between 20 Pb workers and referents.
Cross-sectional Yucesoy (1997c) Location not stated, authors work in Turkey *Population may overlap with Yucesoy (1997a, 1997b)*	50 male Pb-battery workers (n=20 Pb-1; n=30 Pb-2), 14 Pb/Cd workers (Pb-3), and 10 age-matched referents; Years not stated; Male= 100%	Pb-1=35.9 Pb-2=34 Pb-3=37.4 Referent=35.6 Range: Pb-1 =19-49 Pb-2 =24-45 Pb-3 =27-55 Referent=25-42	Referent = 4.0 (0.4) Pb-1 = 59.4 (3.2) Pb-2 = 58.4 (2.5) Pb-3 =68.7(4.7) Measured when outcome assessed	NK function (K562 lysis), CD4, and CD20	Student's t test, Mann-Whitney U test, and Pearson correlation Adjustments not described.	% mean (SE) lymphocyte surface markers by Pb group: CD4 % -referents = 30.8 (1.0) CD4 % -Pb-workers = 30.1 (1.5) CD4 % -Pb/Cd workers = 28.5 (2.3) CD20 % -referents = 15.1 (1.5) CD20 % -Pb-workers = 13.8 (0.9) **CD20 % -Pb/Cd workers = 11.1 (1.0); p<0.05** Other immune data reported in other publications. NK data reported in Yucesoy (1997a) *Other immune data reported in other publications*.	Percent of CD4 T-cells and CD20 B-cells did not differ between 20 Pb workers and referents.

Abbreviations: CD – cluster differentiation (e.g., CD3 – T cells, CD4 – helper T cells, CD8 – cytotoxic T cells); conA – concanavalin A; Cr – chromium; Cu – copper; ELISA – enzyme-linked immunosorbent assay; glutathione S transferase M1 gene (GSTM1); Hb – hemoglobin; HCB – hexachlorobenzene; γ-HCB-hexachlorocyclobenzene; Hg – mercury; HLA-DR - human leukocyte-assisted D-related antigen; IFNγ – interferon gamma; Ig – immunoglobulin; IL – interleukin; LPS – lipopolysaccharide; MHC – major histocompatibility complex; Ni – nickel; NK – natural killer cells; NO – nitric oxide; OC – organochlorine compounds; PCB – polychlorinated biphenyls; PHA – phytohemagglutanin; PMN – polymorphonuclear leukocytes; PWM – pokeweed mitogen; RT-PCR - reverse transcriptase-polymerase chain reaction; SAC – formalin-fixed *Staphylococcus aureus* Cowan Strain I antigen; Se – selenium; SOD – superoxide dismutase; SPT – skin prick test; TNF – tumor necrosis factor; WBC – white blood cell; Zn – zinc

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NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

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APPENDIX C:
HUMAN STUDIES OF CARDIOVASCULAR EFFECTS OF LEAD CONSIDERED IN DEVELOPING CONCLUSIONS

Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Blood Pressure and Hypertension							
Case-control Al-Saleh (2005) Saudi Arabia	185 Saudi women: 100 with and 85 without hypertension during or after menopausal period and not occupationally exposed to Pb; from the Polyclinic and Family Health Medicine Clinic; Year = 2001-2002; Male = 0%	45-92 years	4.66 (3.47) µg/dL Range= (1.19-28.3) µg/dL	Hypertension (based on medication use, controls had average of 3 readings ≤120/80mmHg with no reading ≥130/85 mmHg at any time in medical record)	Chi-squared test for categorical variables; binary logistic regression analysis for continuous variables; multiple regression In multiple regression only: 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, creatinine and blood Pb levels as categorized by the median value	*Binary logistic regression* Hypertension status on blood Pb levels β (SE); OR (95% CI); p Q1 (≤ 2.82 µg/dL): Ref. Q2 (>2.82 to <3.86 µg/dL): β(SE)=0.17 (0.43) OR= 1.19 (0.52-2.69) *p*=0.68 Q3 (≥3.86 to 5.08 µg/dL): β(SE)= 0.77 (0.43) OR=2.16 (0.92-5.05) *p*=0.08 Q4 (≥5.08 µg/dL): β(SE)= -0.08 (0.42) OR= 0.92 (0.41-2.09) *p*=0.84 < 3.86 vs. ≥ 3.86 µg/dL: β(SE)= 0.24(0.30) OR=1.27 (0.71-2.26) p=0.42 *Multiple Regression (median blood Pb levels)* < 3.86 vs.≥ 3.86 µg/dL: β (SE)= 1.66 (0.885) OR=5.27 (0.93-29.86) p=0.06	Concurrent blood Pb was not significantly associated with hypertension in older women.
‡Cross-sectional Apostoli (1990) Verona, Italy	525 subjects (254 men and 271 women) sampled from a general medical practice near Verona, Italy; Year not stated Male = 48%	<10µg/dl: (mean men 30.6, women 34.6) 10-20µg/dl (mean men 38.4, women 39.3) >20µg/dl (mean men 39.2, women 38.7)	<10µg/dl (n=38 men, 151 women) 10-20µg/dl (n=152 men, 112 women) >20µg/dl (n=57 men, 12 women)	Systolic and diastolic blood pressure (SBP and DBP), average of 3 readings Hypertension (≥160/95 SBP/DBP) in 88 subjects (50 men, 38 women)	Variance analysis For hypertension, Student t test Multiple logistic regression Likelihood ratio test of significance for regression coefficients No adjustment for other factors	Males Blood Pb: mean SBP (SD)/ mean DBP (SD) < 10µg/dl (n=38): 134 (12)/83 (10) 10-20µg/dl (n=152): 133 (15)/ 85 (9) > 20µg/dl (n=57): 140 (18)/ 88 (10) ***P* value: SDP <0.05, DBP <0.005** Normotensive (n=204): 15.7 (6.0) Hypertensive (n=50): 17.8 (7.2) ***P* value: <0.05** Females Blood Pb: mean SBP (SD), mean DBP (SD) < 10µg/dl (n=151): 127 (15)/ 81 (8) 10-20µg/dl (n=112): 132 (16)/ 83 (10) > 20µg/dl (n=12): 137 (13)/ 89 (10) ***P* value: SDP <0.005, DBP <0.01** Normotensive (n=233): 10.1 (3.9) Hypertensive (n=38): 12.8 (5.2) ***P* value: <0.005**	Concurrent blood Pb was significantly associated with SBP, DBP, and hypertension in both men and women.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Case-Control Bakhtiarian (2006) Tehran, Iran	160 hospital patients without a history of kidney disease, diabetes, or occupational Pb exposure (80 with hypertension and 80 normotensives); Year =2003; % male not stated	Mean not reported Range: 40-70 years	3.8 µg/dl Range: 2.6-16.5 µg/dl	Hypertension (>190/140mmHg and anti-hypertensive medication) Systolic and diastolic blood pressure (SBP and DBP)	One-way ANOVA with Tukey test of significance ("Turkey" is likely a typo) No adjustment for other factors	Hypertensive, Normotensive mean blood Pb (S.D.), p-value: **All: 5.1 (0.4) µg/dl, 2.6 (0.3) µg/dl, p<0.0001** **Women: 4.8 (0.6) µg/dl, 3.0 (0.4) µg/dl, p<0.001** **Men: 5.6 (0.6) µg/dl, 2.3 (0.5) µg/dl, p<0.001** **40-49 years: 7.2 (2.4) µg/dl, 3.1 (0.05) µg/dl, p<0.01** **50-59 years: 4.3 (2.4) µg/dl, 1.9 (0.3) µg/dl, p<0.01** 60-69 years: 5.3 (2.3) µg/dl, 4.0 (1.9) µg/dl, NS In normotensives, mean SBP (S.D.) and DBP (S.D.): 0-1.18µg/dl: 112.4 (0.8), 70.7 (0.7) 1.19-2.22µg/dl: 124.55 (0.8), 73.1 (1.2) 2.23-3.5µg/dl: 130.0 (1.8), 80.2 (0.4) 3.51-5.76µg/dl: 132.1 (1.2), 82.0 (0.5) 5.77-16.48µg/dl: 123.1 (0.8), 80.3 (1.6)	Blood Pb was significantly higher in hypertension cases, but in normotensives blood Pb was not significantly associated with SBP or DBP.
‡Cross-sectional Bost (1999) England	5,326 adults over age 16 in the Health Survey for England; Year = 1995; Male = 48%	Calc mean: 47.6 Men: 47.5 (0.34) Women: 47.7 (0.33)	Calc mean: 3.13 Men: 3.7 Women: 2.6	Systolic and diastolic blood pressure (SBP and DBP)	Stepwise multiple regression analyses. Age, BMI, smoking, social class, region of residence, and alcohol	Standardized regression coefficients for blood Pb and $\log_{10}$(BP): Men, SBP: NS **Men, DBP: 0.061 *P* < 0.001** Women, SBP: NS Women, DBP: NS A halving of blood Pb is estimated to decrease DBP in men by 0.88 mm Hg (95%CI 0.13-1.63)	Concurrent blood Pb was significantly associated with increased DBP in men.
Prospective Chen (2006) USA	780 children with had blood Pb levels of 20-44 µg/dL at age 12-33 months who were enrolled in the Treatment of Lead Exposed Children (TLC) Study and followed every 3-4 months for 5 years.; Year = 1994-1997; Male = 56%;	12-33 months at baseline	Baseline: 25 (5) µg/dl Five-year follow-up: 8 (4) µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression models. Mixed models with repeated blood Pb and blood pressure measurements. Clinical center, race, sex, parent's education, single parent, age at measurement, height, BMI.	After initiation of treatment, children in the succimer group had lower blood levels than the placebo for 9-10 months; the two groups had similar blood Pb levels until the end of the study. Adjusted regression estimates [β (95% CI)] Baseline SBP = 1.36 (-0.58, 3.30) DBP = 1.47 (-0.16, 3.10) Day 42 (1st round of chelation) SBP = 0.07 (-1.33, 1.47) DBP = 1.19 (-0.07, 2.44) 12 months SBP = 0.24 (-0.97, 1.46) DBP = -0.28 (-1.26, 0.69) 24 months SBP = -0.68 (-1.76, 0.39) DBP = 0.32 (-0.52, 1.16) 60 months SBP = 0.01 (-1.71, 1.73) DBP = 0.15 (-1.25, 1.55)	Concurrent blood Pb was not significantly associated with BP when levels were over 20µg/dL at age 12-33 months or as Pb levels dropped below 10µg/dL over 60 months of follow up.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
†Prospective Cheng (2001) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	519 men in the Normative Aging Study who were not hypertensive when baseline Pb levels were measured and followed for 3 to 6 years (n=474); Year 1991-1997; Male = 100%	At baseline: Calc. mean = 66.5 Normotensive (n=337) 65.49 (7.17) Borderline hypertension (n=182) 68.30 (7.79)	**Blood at baseline:** Calc. mean = 5.9 Norm. (n=323) 5.87 (4.01) Borderline hypertension (n=174) 6.00 (3.69) **Bone at baseline:** Tibia calc. mean = 21.4 Patella calc. mean = 30.6 Norm. (n=337) Tibia 20.27 (11.55) Patella 28.95 (18.01) Borderline hypertension (n=182) Tibia 23.46 (15.02) Patella 33.73 (21.76)	Systolic and diastolic blood pressure (SBP and DBP) and hypertension in follow-up visit.	Multivariate regression of Pb with age, age^2, BMI, and family history of hypertension, alcohol intake, and calcium intake Proportional hazards model controlled for age, age^2, BMI, and family history of hypertension	Regression coefficient (95%CI) for systolic BP (n=519) based on 1 SD increase in Pb: Blood Pb (1 SD = 4.03µg/dl): -0.13 (-1.35 to 1.09) **Tibia Pb (1 SD = 13.65µg/g): 1.37 (0.02 to 2.73)** Patella Pb (1 SD = 19.55µg/g): 0.57 (-0.71 to 1.84) Cox proportional hazards model Rate Ratio (95%CI) for incident definite hypertension in those normotensive at baseline (n=474 with follow up) based on 1 SD increase: Blood Pb (1 SD = 4.03µg/dl): 1.00 (0.76 to 1.33) Tibia Pb (1 SD = 13.65µg/g): 1.22 (0.95 to 1.57) **Patella Pb (1 SD = 19.55µg/g): 1.29 (1.04 to 1.61)** Rate ratio of hypertension for an from the midpoint of the lowest to the highest quintile: **Tibia Pb: 1.49 (95% CI 0.89 to 1.49)** **Patella Pb: 1.71 (95% CI 1.08 to 2.70)** No association with blood Pb level.	Bone Pb was significantly associated with higher BP 3 to 6 years later, but blood Pb was not associated.
‡Cross-sectional Chu (1999) Taiwan	2,800 subjects who had lived in Taiwan for at least 6 months; Year= 1993-1994; Male = 53%	44.3 (15.4) years Range= 15 – 85 years	6.5 (4.7) Range: (0.1 – 69.1)	Systolic and diastolic blood pressure (SBP and DBP)	Pearson's correlation coefficients; multiple regression analyses; Univariate analyses – backward elimination Age, BMI, milk intake, alcohol intake, smoking	Regression analyses of blood Pb and BP: **SBP Male (p = 0.015)** β = 0.185 (0.076) R^2 = 0.241 SBP Female (p = 0.603) β = -0.057 (0.109) R^2 = 0.274 DBP Male (p = 0.159) β = 0.075 (0.053) R^2 = 0.117 DBP Female (p = 0.250) β = -0.083 (0.072) R^2 = 0.171	Concurrent blood Pb was significantly associated with higher DBP in men, but not with SBP or in women.
‡Cross-sectional Den Hond (2002) USA	13,781 adults age 20 or older (46.8% male) in NHANES III; Year= 1988-1994	White Males (n=4685): 44.3 (16.6) years	MEDIAN (interquartile range):	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression analysis by race and sex. Adjustments included	Change in SBP for a doubling of blood Pb: (95% CI), P White male = 0.3 (-0.2 to 0.7), P=0.29 White female = 0.1 (-0.4 to 0.5), P=0.8 **Black male = 0.9 (0.04 to 1.8), P=0.04**	Concurrent blood Pb was significantly associated with

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Population may overlap with Vupputuri (2003)		White Females (n=5138): 46.2 (17.8) years Black Males (n=1761): 40.5 (15.3) Black Females (n=2197): 41.5 (16.3)	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)		age, age^2, BMI, smoking, alcohol consumption, coffee consumption, dietary calcium, dietary sodium/potassium ratio, hematocrit, serum total calcium, serum total protein, anti-hypertensive drug use, and diabetes.	**Black female = 1.2 (0.4 to 2.0), *P*=0.004** Change in DBP for a doubling of blood Pb: (95% CI), *P* **White male = -0.6 (-0.9 to -0.3), *P*=0.0003** White female = -0.2 (-0.5 to 0.1), *P*=0.13 Black male = 0.3 (-0.3 to 1.0), *P*=0.28 **Black female = 0.5 (0.01 to 1.1), *P*=0.047**	higher SBP in black subjects and DBP in white males and black females.
Cross sectional Dolenc (1993) and Staessen (1995) Belguim *Population may overlap with Staessen (1991)*	1648 adults (827 men, 821 women; Cadmium in Belgium (Cadmibel) Study; Year: 1985-1989; Male = 50%	45 (15) years Range: 20-88 Men: 46 (15) years Women: 44 (15) years	OHAT calc. 8.3 µg/dl Range: (2.1-29.2) Men: 0.5 µmol/l (Range: 0.2-1.4) OHAT calc. 10.4 µg/dl (4.2-29.2) Women: 0.3µmol/l (Range: 0.1-0.8) OHAT calc. 6.25 µg/dl (2.1-16.7)	Systolic and diastolic blood pressure (SBP and DBP)	Free-running stepwise multiple regression Adjusted for: age, age^2, BMI, pulse rate, log γ-glutamyltranspeptidase, log serum creatinine, serum calcium, urinary potassium, smoking, alcohol intake, contraceptive pill intake*, and menopause* *in women only	Partial regression coefficients of BP and log blood Pb: **Men, SBP: -5.2 ± 2.4, partial r= -0.07, *P*=0.04** Men, DBP: -1.1 ± 1.6, NS Women, SBP: 0.5 ± 2.8, NS Women, DBP: -0.3 ± 1.7, NS 1.5mmHg decrease in SBP for a doubling of blood Pb Some indication of an interaction with serum calcium	Concurrent blood Pb was not associated with increased BP.
Cross sectional Elmarsafawy (2006) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	471 men from the Normative Aging Study (Low calcium ≤800 mg/d n=259, high calcium >800 mg/d n=212); Year=1991-1996; Male = 100%	351 <70 years, 140 ≥ 70 years (enrolled 1963-1968 with an average age of 42, range 21-80)	Blood: 6.6 ± 4.3 µg/dL Tibia: 21.6 ± 12.0 µg/g, Patella: 31.7 ± 18.3 µg/g	Hypertension (systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg or a physician's diagnosis with use of antihypertensive medications), systolic and diastolic blood pressure (SBP and DBP)	Logistic regression models stratified by dietary calcium intake and linear regression with blood pressure. Age, family history of hypertension, history of smoking, and BMI	Odds Ratio of Hypertension (95% CI): Low calcium intake (≤800 mg/day) **Blood Pb (µg/dL): 1.07 (1.00-1.15)** **Tibia Pb (µg/g): 1.02 (1.00-1.04)** **Patella Pb (µg/g): 1.01 (1.00-1.03)** High calcium intake (>800 mg/day) Blood Pb (µg/dL): 1.03 (0.97-1.11) Tibia Pb (µg/g): 1.01 (0.97-1.04) Patella Pb (µg/g): 1.01 (0.99-1.03) OR for hypertension from a 1 SD increase in tibia Pb in the high calcium group = 1.3 (95% CI 0.97-1.74) Linear regression for hypertension with a 1µg/g increase in tibia Pb: **Low calcium = 0.19mmHg (95% CI 0.01-0.37)** **High calcium = 0.40mmHg (95% CI 0.11-0.70)** Blood and Patella Pb linear regressions N.S. (data not shown)	Blood Pb, tibia Pb, and patella Pb were significantly associated with hypertension which may be modified by dietary calcium intake.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
‡Cross sectional Elwood (1988a) and Elwood (1988b) Wales, England *Both papers included the Welsh Heart Programme as well.*	1,136 (1,137 in other paper) men from the Caerphilly Collaborative Heart Disease Studies, living in Caerphilly, South Wales; Year= 1985 Male = 100%	Range: 49-63 years	12.7 (6-26)	Systolic and diastolic blood pressure (SBP and DBP) Cold Pressor Test: the hand and wrist are immersed in water at 4°C for 1 min. The consequent rise in blood pressure has been shown to be predictive of ischemic heart disease.	Regression coefficients, partial regression coefficients, and correlation coefficients (*r*). The only covariant was age.	Regression coefficients of blood pressure on blood Pb (±SE) [NOT in the Cold Pressor Test]: SBP = 0.077 (±0.126) DBP = 0.049 (±0.068) Regression coefficients between resting blood pressure and the rise in log blood pressure in the Cold Pressor Test on log blood Pb (age adjusted): Resting blood pressure: SBP = 1.112 (±1.830) DBP = 0.879 (±0.984) Rise in cold pressor test: SBP = 0.0006 (±0.0006) DBP = 0.0002 (±0.0007) Correlation coefficients (*r*) between log blood Pb and log resting BP and the rise in log blood pressure in the Cold Pressor Test (age adjusted) [if r>0.06, p <0.05]: Resting blood pressure: SBP = 0.0183 DBP = 0.0230 Rise in Cold Pressor Test: SBP = 0.0342 DBP = 0.0078	Blood Pb was not significantly associated with blood pressure or blood pressure change after a cold pressor test.
‡Cross sectional Elwood (1988a) and Elwood (1988b) Wales, England *Both papers included the Caerphilly Collaborative Heart Disease Studies as well.*	1,721 adults from the Welsh Heart Programme (865 men and 856 women); Year= 1985 Male = 50%	18–64 years	Men (n=865): 11.6 (5.7- 23.3 Women (n=856): 9 (4.5-18.3) OHAT calc. mean: 10.3µg/dL	Systolic and diastolic blood pressure (SBP and DBP)	Regression coefficients, partial regression coefficients, and correlation coefficients (*r*). The only covariant was age.	Regression coefficients of blood pressure on blood Pb (±SE): Men: SBP = 0.050 (±0.108) DBP = 0.068 (±0.069) Women: SBP = 0.0 (± 0.135) DBP = 0.048 (±0.093) Partial regression coefficient between resting blood pressure and log blood Pb, adjusted for age: β(SE) Men: SBP = 0.82 (1.49) DBP = 1.29 (0.95) Women: SBP = 0.19 (1.46) DBP = 0.58 (1.00)	Blood Pb was not significantly associated with blood pressure.
Cross-sectional Factor-Litvak (1996) Kosovo, Yugoslavia	144 children residing in an unexposed town (Pristina), from a study of 281* children of women	5.5 years	Age 5.5: Unexposed 8.7 (2.8) [Exposed 37.3 (12.0)]	Systolic and diastolic blood pressure (SBP and DBP), mean of last two measures at the end of physical exam	Linear regression analysis SBP adjusted for: height, BMI, gender, ethnic group (Albanian, Serbian, other), and birth order	In the unexposed town with low blood Pb levels, estimated coefficient related to BPb: SBP: 0.17 (95% CI -0.47, 0.8) mmHg DBP: 0.052 (95% CI -0.37, 0.47) mmHg	Concurrent blood Pb was not significantly associated with BP in 5 year old children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Population may overlap with Factor-Litvak (1999)	recruited during pregnancy; here, we did not consider 137 children in the exposed town (Kosovska Mitrovica); Year=1985-1986 *abstract says 282		(12 measures of blood Pb from birth to age 5.5)		DBP adjusted for: waist circumference, ethnic group (Albanian, Serbian, other), and birth order		
Cross-sectional Factor-Litvak (1999) Kosovo, Yugoslavia *Population may overlap with Factor-Litvak (1996)*	577 children of women recruited during pregnancy from an exposed and an unexposed town. Year not stated % male not stated	Infants followed every 6 months until 7.5 years of age	mean not reported Range: 1 to 70 µg/dl	Systolic and diastolic blood pressure (SBP and DBP) K. Mitrovica: SBP: 100.5 ± 10.7 mm Hg DBP: 59.1 ± 7.5 mm Hg Pristina: SBP: 98.4 ± 10.0 mm Hg DBP: 58.4 ± 6.7 mm Hg	Least-squares regression (continuous variables) and unconditional maximum likelihood logistic regression (categorical variables) Covariates: SES (maternal education and intelligence), ethnicity, and quality of childrearing environment.	<u>At 5.5 years of age:</u> Association between BPb concentration and BP: SBP: β=0.054 (-0.024-0.13) DBP: β=0.042 (-0.010-0.090) 10µg/dl increase in BPb associated with adjusted increases in BP: SBP: 0.5 mm Hg (CI, -0.2-1.3) DBP: 0.4 mm Hg (CI, -0.1-0.9)	Blood Pb and BP were not significantly associated with BP in in 7 year old children.
‡Cross-sectional Gartside (1988) USA	20,325 subjects from the NHANES II; Year= 1976-1980; % male not stated	mean not reported Range: 21-65 years	mean not reported **limits utility*	Systolic and diastolic blood pressure (SBP and DBP)	Forward stepwise regression Demographic, socioeconomic dietary variables and other likely confounders details not provided	For all ages combined the increase in blood pressure for a doubling of blood Pb: White men: Systolic BP 2.777 mm Hg (SD = 0.972) Diastolic BP 1.323 mm Hg (SD = 0.476) White women: Systolic BP -0.335 mm Hg (SD = 0.374) Diastolic BP 0.700 mm Hg (SD = 0.276) Blacks: Systolic BP 0.915 mm Hg (SD = 3.730) Diastolic BP 2.88 mm Hg (SD = 3.088) Reports changes in SBP and DBP by gender and race showing how sensitive the significance is to age group categories.	Mean blood Pb was higher than 10µg/dl and was not significantly associated with increases in BP with a doubling of blood Pb levels.
†Cross-sectional Gerr (2002) WA, USA	508 participants with bone and BP Five-town cohort (exposed): 281 young adults (47% male) who had lived in one of 5 towns around a Pb smelter	24* 19-29 years in 1994 *from Navas-Acien (2008)	2.3 (1.9)* Bone Pb: <1 µg/g (n=210): 1.91 1-5 µg/g (n=126): 2.31	Systolic and diastolic blood pressure (SBP and DBP)	General linear regression models Age, sex, height, BMI, smoking, alcohol intake, use of birth control pills, hemoglobin, serum albumin, childhood residence group, recent	Mean BP by bone Pb content: Mean SBP (S.D.) by bone Pb (p=0.054): <1 µg Pb/g = 116.69 (12.23) 1 – 5 µg Pb/g = 116.63 (12.46) >5 – 10 µg Pb/g = 114.50 (10.80) >10 µg Pb/ = 119.72 (12.66) Mean DBP (S.D.) by bone Pb (p=0.080): <1 µg Pb/g = 73.10 (8.95)	Bone Pb was significantly associated with SBP and DBP in young adults some of which were exposure to environmental Pb as children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
	in Idaho as children in 1974/75 and a non-five-town cohort (unexposed): 287 young adults in Spokane WA; Year= 1994;		>5-10 µg/g (n=102): 2.43 >10µg/g (n=67): 3.15 *from Navas-Acien (2008)		Pb exposure, income category. Separate models with bone Pb as a four-ordinal variable (<1, 1 – 5, >5 – 10, >10 µgPb/g bone mineral) and as a continuous variable.	1 – 5 µg Pb/g = 72.75 (9.44) >5 – 10 µg Pb/g = 71.43 (8.12) >10 µg Pb/g = 75.00 (8.67) SBP by bone Pb estimate (S.E.) (<1 µg Pb/g = ref.): 1 – 5 µg Pb/g = 0.10 (1.11), p=0.93 >5 – 10 µg Pb/g = 0.98 (1.22), p=0.42 **>10 µg Pb/g = 4.26 (1.48), p=0.004** DBP by bone Pb estimate (S.E.) (<1 µg Pb/g = ref.): 1 – 5 µg Pb/g = -0.16 (0.94) p=0.868 >5 – 10 µg Pb/g = -0.01 (1.04), p=0.99 **> 10 µg Pb/g = 2.80 (1.25), p=0.03**	
†Prospective Glenn (2003) USA	496 men previously employed at a chemical-manufacturing facility on or after January 1, 1950 exposed to tetramethyl and tetraethyl Pb; Year= 1994 (baseline) followed until 1998; Male = 100%	55.8 (7.4) years at baseline Range 40-70 years	Baseline (1994) blood Pb = 4.6 (2.6) µg/dl Tibia Pb in 1997 = 14.7 (9.4) µg/g	Systolic and diastolic blood pressure (SBP and DBP)	Generalized estimating equation (GEE) SBP: baseline age, BMI, antihypertensive medications, smoking, education, technician, and years to each BP measurement DBP: baseline age; age^2; BMI; diabetes, arthritis or thyroid disease; race; education; technician; and years to each BP measurement	Average annual change in BP from 1994-1998 with one SD increase in Pb dose (blood Pb=2.6µg/dl, tibia Pb=9.4µg/g, peak tibia Pb=18.1µg/g): SBP: **Blood Pb (1994) β = 0.64 (0.14, 1.14)** **Tibia Pb (1997) β = 0.73 (0.23, 1.23)** **Peak Past Tibia Pb β = 0.61 (0.09, 1.13)** DBP: Blood Pb (1994) β = 0.09 (-0.24, 0.43) Tibia Pb (1997) β = 0.07 (-0.29, 0.42) Peak Past Tibia Pb β = 0.02 (-0.35, 0.39)	Blood and tibia Pb were significantly associated with increases in SBP but not DBP.
‡Prospective and cross-sectional Grandjean (1989) Denmark *Population may overlap with Møller (1992)*	861 adults with complete follow-up; born in 1936 and living in the 4 municipalities served by the Glostrup Hospital (Glostrup Population Study); Year = Baseline: 1976 (age 40); 5-year follow up: 1981 (age 45); Male = 42%	40 years old for first examination, 45 years old for second examination	Median (µg/dL) At 40 years: Men = 13 Women = 9 At 45 years: Men = 9 Women = 6	Systolic and diastolic blood pressure (SBP and DBP) Hypertension (SBP ≥160mmHg and/or DBP ≥95mmHg)	Multiple regression analysis. Adjusted for hemoglobin and alcohol	<u>Prospective</u> Increase in blood pressure at age 45 with a doubling in blood Pb at age 40, adjusted for age 45 confounders: SBP, age 40: Men: Unadj= 3.0*, Adj =1.4 Women: Unadj=2.3, Adj =p>0.5 DBP, age 40: Men: Unadj=1.1, Adj =p>0.5 Women: Unadj=0.7, Adj =p>0.5 <u>Cross-sectional</u> Increase in blood pressure with a doubling in blood Pb (multiplied regression coefficient by 0.3010): SBP, age 40: Men: Unadj= 2.6*, Adj =1.1 Women: Unadj=3.1*, Adj =p>0.5 DBP, age 40:	Blood Pb was not associated with BP or hypertension in prospective or cross-sectional analyses.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						Men: Unadj=p>0.5, Adj =-1.6 Women: Unadj=2.1*, Adj =1.2 SBP, age 45: Men: Unadj= 2.2, Adj =p>0.5 Women: no change (p>0.5 for all) DBP, age 45: Men: Adj hemo.=1.1, Adj =p>0.5 Women: Unadj=1.3, Adj =1.0 No difference in blood Pb levels between normotensive, increased (but not hypertensive) blood pressure, untreated, and treated hypertensives	
Prospective Gump (2005) NY, USA *Population may overlap with Gump (2007)* *Also listed for ECG Conduction Abnormalities*	122 children from Oswego Children's Study with established early childhood blood Pb levels; Year not stated Male = 45.9%	9.5	Cord = 2.97 (1.75) Childhood blood= 4.62 (2.51)* *Gump (2007) states this was abstracted from health records at average age of 2.6 years Correlation of cord and childhood Pb: *r* = 0.11, *p*>0.50	Systolic and diastolic blood pressure (SBP and DBP)	Linear regression Adjusted for: psychosocial variables, other toxicants, emotional response to tasks, *exact adjustment variables not reported*	<u>Cord blood Pb level µg/dL and BP:</u> **SBP: β=12.16 (4.96), p=0.016** DBP: β=8.45 (4.54), p=0.066 <u>Childhood blood Pb (µg/dL) and BP:</u> SBP and DBP had p-values >0.15 <u>Childhood blood Pb (µg/dL) and BP responses to acute stress tasks:</u> (β (95% CI), Standardized β, p-value) SBP: β= -0.009 (-.074 to .055), Std β=-0.026, p=0.773 **DBP: β= 0 .069 (-.001 to .138), Std β=0.182, p=0.052** (Cord blood and childhood blood Pb were not correlated (r=0.11, p>0.50)	Higher cord blood Pb levels were significantly associated with higher SBP while early childhood Pb levels were significantly associated with DBP response to acute stress.
Prospective Gump (2007) NY, USA *Population may overlap with Gump (2005)* *Also listed for ECG Conduction Abnormalities*	122 children from the Oswego Children's Study with established early childhood blood Pb levels; Year not stated Male = 45.9%	9.5	Cord = 2.97 (1.75) Childhood blood at age 2.6= 4.62 (2.51) *abstracted from health records	Includes family SES in evaluations of blood pressure	Sobel tests to evaluate mediation Linear regression Adjusted for: family SES, blood Pb levels, interaction of SES and blood Pb	<u>SES in relation to children's CV responses (β ; R^2; p-value of SES and Pb interaction)</u> SBP (mmHg): β=-1.192; R^2=0.102; p=0.007 DBP (mmHg): β=-0.701; R^2=0.037; p=0.013 <u>With SES X Pb interaction term</u>: SBP β=0.007, SE=0.003, *p*<0.01 DBP β=0.007, SE=0.003, *p*<0.05	Lower family SES was significantly associated with higher early childhood blood Pb levels and heightened BP responses to acute stress tasks at age 9-11 years.
Cross-sectional Gump (2011) NY, USA *Population may overlap with Gump (2005)*	140 children from the Oswego Children's Study Year not stated Male = 55%	10.21 (0.75) Range: 9-11	Median: 0.94 Range: 0-3.76	Systolic and diastolic blood pressure (SBP and DBP)	Generalized linear model with a linear contract test Adjusted for gender, age, race, BMI percentile standing, SES, family history of cardiovascular disease, and Hg level	<u>Adjusted associations of blood Pb and BP at baseline:</u> SBP (n=139): *p* linear trend = 0.51 Pb Q1 (0.14-0.68µg/dL): 106.10 Pb Q2 (0.69-0.93µg/dL): 102.60 Pb Q3 (0.94-1.20µg/dL): 107.34 Pb Q4 (1.21-3.76µg/dL): 102.47 DBP (n=139): *p* linear trend = 0.36 Pb Q1 (0.14-0.68µg/dL): 56.14	Concurrent blood Pb was not associated with statistically significant increases in SBP or DBP at baseline and in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Also listed for HRV and ECG Conduction Abnormalities						Pb Q2 (0.69-0.93µg/dL): 54.28 Pb Q3 (0.94-1.20µg/dL): 56.97 Pb Q4 (1.21-3.76µg/dL): 53.42 **BP significantly increased in response to acute stress tasks (SBP 106 to 113, *p*<0.0001 and DBP 57 to 61, *p*<0.0001).** Adjusted associations of blood Pb and BP reactivity to acute stress: SBP (n=139): *p* linear trend = 0.31 Pb Q1 (0.14-0.68µg/dL): 5.30 Pb Q2 (0.69-0.93µg/dL): 7.33 Pb Q3 (0.94-1.20µg/dL): 7.07 Pb Q4 (1.21-3.76µg/dL): 7.23 DBP (n=139): *p* linear trend = 0.29 Pb Q1 (0.14-0.68µg/dL): 4.02 Pb Q2 (0.69-0.93µg/dL): 5.64 Pb Q3 (0.94-1.20µg/dL): 5.09 Pb Q4 (1.21-3.76µg/dL): 5.53	response to acute stress tasks in children age 9-11.
‡ Cross-sectional Hense (1993) Germany *Population may overlap with Hense (1994)*	3,364 subjects participating in the WHO MONICA Project: Augsburg cohort first follow-up; Year= 1987-1988; Male = 50.6%	Range: 28 to 67 years	Median: Men = 8.3 µg/dL Women = 6.0 µg/dL	Systolic and diastolic blood pressure (SBP and DBP)	Linear regression with blood Pb as a continuous variable in univariate and multivariate models; Adjusted for: age, BMI, alcohol consumption, hematocrit Authors conclusion: Hematocrit and alcohol consumptions should always be considered confounders	Coefficients (95% CI) of the regressions of systolic and diastolic blood pressure on blood Pb concentrations: Men: **SBP: β (95% CI)=Unadj. 0.55 (0.34-0.76)** **Adj. 0.29 (0.08-0.49)** DBP: β (95% CI)= **Unadj. 0.27 (0.13-0.41)** Adj. 0.08 (-0.06-0.23) Women: SBP: β (95% CI)= **Unadj. 0.67 (0.34-1.00)** Adj. 0.17 (-0.14-0.48) **DBP: β (95% CI)= Unadj. 0.54 (0.35-0.73)** **Adj. 0.29 (0.09-0.49)**	Concurrent blood Pb was significantly associated with SBP and DBP in men and women, but adjustment for covariates including hematocrit and alcohol decreased the significance of the findings.
Cross-sectional Hense (1994) Germany *Population may overlap with Hense (1993)*	3,364 subjects participating in the WHO MONICA Project: Augsburg cohort first follow-up; Year= 1987-1988; Male = 50.6%	Range 28-67 years	Median: Men:8.3 µg/dL Women: 6.0 µg/dL	Systolic and diastolic blood pressure (SBP and DBP)	Linear regression with separate slopes model Stratified by drinking status: abstainers, moderate drinkers (0-40gm/day), and heavy drinkers (40+ gm/day) Adjusted for age, hematocrit, body mass index, place of residence,	Regressions of systolic and diastolic blood pressure on blood Pb concentrations: Women SBP: adjusted β (95% CI) Abstain (n=701): β=0.07 (-0.48-0.62) Moderate (n=877): β=0.12 (-0.28-0.52) **Heavy (n=83): β=1.30 (0.45-2.15)** Women DBP: adjusted β (95% CI) Abstain (n=701): β=0.21 (-0.14-0.56) **Moderate (n=877): β=0.27 (0.02-0.52)** **Heavy (n=83): β=0.86 (0.33-1.39)** Men, urban SBP: adjusted β (95% CI) Abstain (n=118): β=0.28 (-0.63-1.20)	Moderate and heavy drinkers had significant associations between concurrent blood Pb and BP in women and men residing in rural but not urban areas.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
					and smoking In men, further stratified by place of residence	Moderate (n=379): β=-0.2 (-0.46-0.42) Heavy (n=240): β=-0.16 (-0.65-0.33) Men, urban DBP: adjusted β (95% CI) Abstain (n=118): β=-0.23 (-0.85-0.39) Moderate (n=379): β=-0.08 (-0.38-0.22) Heavy (n=240): β=-0.22 (-0.55-0.11) Men, rural SBP: adjusted β (95% CI) Abstain (n=147): β=0.35 (-0.30-1.00) **Moderate (n=463): β=0.65 (0.21-1.09)** **Heavy (n=356): β=0.45 (0.05-0.99)** Men, rural DBP: adjusted β (95% CI) Abstain (n=147): β=0.03 (-0.41-0.47) **Moderate (n=463): β=0.39 (0.09-0.69)** **Heavy (n=356): β=0.30 (0.03-0.57)**	
†Cross-sectional Hu (1996) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	590 men in the Normative Aging Study; Year=1991-1994; Male = 100%	66.6 (7.2) years Range: 48-92	6.3 (4.1) Range <1-28 Tibia: 21.6 (12.1) µg/g Patella: 32.1 (18.7) µg/g	Hypertension (SBP >160mmHg or DBP ≥96mmHg at exam) or daily antihypertensive medication	*t* test Multiple logistic regression adjusted for age, race, BMI, family history of hypertension, pack-years of smoking, alcohol intake, dietary sodium, and dietary calcium	Mean Pb level for hypertensives (n=146)/normotensives (n=444) and *t* test *P*-value **Blood Pb: 6.9/6.1 µg/dl *P*<0.05** **Tibia Pb: 23.7/20.9 µg/g *P*<0.05** **Patella Pb: 35.1/31.1 µg/g *P*<0.05** Hypertension and Pb biomarkers: Adj. β (SE) *P* value Blood Pb: β=0.0344 (0.0237) *P*=0.15 Tibia Pb: β=0.136 (0.0085) *P*=0.11 Patella Pb: β=0.0087 (0.0055) *P*=0.11 Final backward elimination logistic regression model including BMI and family history of hypertension: **Tibia OR=1.019 (95% CI 1.004-1.035)** **χ^2 for covariates in final model=39.9 (3 *df*,) *P*<0.001** Odds Ratio of hypertension from an increase in tibia Pb from 8 to 37µg/g (middle of lowest to middle of highest quintile): **Tibia OR=1.5 (95%% CI: 1.1-1.8)**	Blood and bone Pb levels were significantly higher in hypertensives than nonhyper-tensives, and tibia Pb was associated with a significant increase in risk of hypertension.
Cross-sectional Kaewboonchoo (2007) Bangkok, Thailand *Population may overlap with Kaewboonchoo (2010) listed in Clinical Cardiovascular Disease*	438 male bus drivers in Bangkok Thailand; Year= 2002	41.5 (7.8) years Range = 23 – 59 years	6.3 (2.2) Range 2.5 – 16.2µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Student's *t*-test comparison of low and high Pb Pearson's correlation coefficient (*r*) Multiple regression analyses adjusting for age, BMI, alcohol intake, smoking, and physical exercise	**Mean SBP (SD), p=0.012** Low Pb (≤4.1µg/dL, n=62) = 128 (14) High Pb (≥ 8.5µg/dL, n=70) = 135 (19) **Mean DBP (SD), p=0.001** Low Pb (≤4.1µg/dL, n=62) = 78 (9) High Pb (≥ 8.5µg/dL, n=70) = 84 (11) Correlation with blood Pb: **SBP *r* = 0.176, p<0.01** **DBP *r* = 0.196, p<0.01** Univariate linear regression with blood Pb: **SBP *β*=0.902, p<0.01** **DBP *β*=0.648, p<0.01**	Concurrent blood Pb was significantly associated with increases in SBP and DBP.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Kim (2008) South Korea *Also listed for Clinical Cardiovascular Disease*	13,043 Pb workers in the Special Health Surveillance Program; Year = 2003 Male 69%	33.7 (10.0) years	Geometric mean 6.08 (2.53) Range: 0.002–123.22 70% of workers <10µg/dl women had lower levels than men	Blood pressure and Hypertension	*t*-test; ANOVA; Relative risk was calculated ala Lawes et al, 2003. No adjustment for other factors	Estimated increase in blood pressure (mmHg): 5 µg/dl ≤ PbB < 10 µg/dl = 0.458 (men) 0.266 (women) 10 µg/dl ≤ PbB < 15 µg/dl = 1.800 (men) 1.088 (women) 15 µg/dl ≤ PbB < 20 µg/dl = 3.050 (men) 1.952 (women) 20 µg/dl ≤ PbB = 3.750 (men) 2.400 (women) Relative Risk for Hypertension: PbB <5µg/dL (referent) 5 µg/dl ≤ PbB < 10 µg/dl = 1.055 (men) 1.045 (women) 10 µg/dl ≤ PbB < 15 µg/dl = 1.380 (men) 1.198 (women) 15 µg/dl ≤ PbB < 20 µg/dl = 1.683 (men) 1.358 (women) 20 µg/dl ≤ PbB = 1.853 (men) 1.441 (women) Significance tests or 95% CI not reported	Concurrent blood Pb was not statistically significantly associated with BP and risk of hypertension.
Case-control Korrick (1999) Boston, MA, USA	284 women in the Nurses' Health Study (Hypertension cases, n=89; Normotensive controls, n= 195) Year = 1993-1995 Male = 0%	58.7 (7.2) years	Blood Pb: 3.125 µg/dl Tibia Pb: 13.3 (9.0) µg/g Patella Pb: 17.3 (11.1) µg/g	Hypertension: physician diagnosed between 1988 and 1994 or measured SBP ≥140 or DBP ≥90mmHg	Ordinal regression modeling Adjusted for: age, menopausal status, job status, alcohol intake, serum creatinine, hemoglobin, hematocrit, and caffeine intake.	Risk of hypertension and Pb: Blood (µmol/L): β (SE)= 0.972 (1.055); p-value=0.36 Tibia (µg/g): β (SE)= 0.003 (0.013); p-value=0.85 **Patella (µg/g): β (SE)= 0.025 (0.011); p-value=0.03** No significant interactions by alcohol, age, or postmenopausal status An increase from the 10th to the 90th % patella Pb (25µg/g) was associated with 2-fold increase in risk of hypertension **(95% CI: 1.1-3.2)**	Patella Pb was significantly associated with increased risk of hypertension, but blood and tibia Pb were not.
Cross-sectional Kuo (2006) Taiwan	2,565 adults, Hsin-yi County in rural Central Taiwan, annual health exams after age 40, 51.4% aboriginals (97.5% Bunnun tribe) Year not stated Male = 48%	≥ 40 years	Non-aboriginals Male (n=638) 5.3 (±1.2) Female (n=609) 5.3 (±1.1), Aboriginals: Male (n=588) 5.6 ±1.4 Female (n=730) 5.4 ±1.2;	Systolic and diastolic blood pressure (SBP and DBP)	Multiple linear regression models Adjusted for age, gender, BMI, alcohol, and ethnic group	Regression coefficient for Blood Pb and BP: **SBP: β = 0.85 mmHg/µg/dl (SE = 0.33) p<0.05** **DBP: β = 0.48 mmHg/µg/dl ((SE = 0.2) p<0.05** Odds Ratio of Hypertension with blood Pb: Non-aboriginals: <5ug/dL = ref. 5-7.5ug/dL= 1.09 **7.5ug/dL = 2.97 p<0.05** Aboriginals: <5ug/dL = ref. 5-7.5ug/dL = 0.94 7.5ug/dL = 0.9	Concurrent blood Pb was significantly associated with SBP and DBP; and with risk of hypertension in non-Aboriginal Taiwanese.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Magri (2003) Malta	143 primigravid women in their third trimester without a history of hypertension, a family history of gestational hypertension, gestational diabetes, renal disease, or on medication; Year not stated Male = 0%	Calc. mean = 29 Normotensive (n=110): 30 (6) years Gestational hypertension cases (n=33): 27 (6) years	Calc. mean = 6.7 Normotensive (n=93): 5.8 (3) Gestational hypertension cases (n=30): 9.6 (6)	Systolic and diastolic blood pressure (SBP and DBP)	Mann-Whitney *U*-test (hematocrit adjusted) Pearson correlation (Age, BMI, and hematocrit adjusted)	**Hematocrit adjusted mean blood Pb (p=0.009)** Normotensive (n=93) = 16.6 ± 7 Gestational hypertension (n=30) = 26.7 ± 17 Pearson correlation of blood Pb and BP (adjusted): **SBP = 0.210 (*p*=0.047)** **DBP = 0.208 (*p*=0.049)** Pearson correlation of blood Pb: ionized calcium ratio and BP (adjusted): **SBP = 0.355 (*p*=0.002)** **DBP = 0.297 (*p*=0.011)**	Third trimester blood Pb was significantly higher in gestational hypertension cases and significantly correlated with SBP and DBP.
† Cross-sectional Martin (2006) Baltimore, MD, USA	964 adults from the Baltimore Memory Study; Year=2001-2004; Male = 44.5%	59.4 (5.9) Range= 50-70 years	Blood Pb: 3.5 (2.3) µg/dL Tibia Pb (2002-2004): 18.8 (12.4) µg/g	Systolic and diastolic blood pressure (SBP and DBP) and hypertension (SBP > 140mmHg, DBP > 90 mmHg or antihypertensive medication)	Multiple linear regression (BP); Multiple logistic regression (hypertension) Adjusted for age, sex, BMI, antihypertensive medication use, dietary sodium intake, dietary potassium intake, time of day, testing technician, serum total cholesterol, race/ethnicity and socioeconomic status (model 4)	SBP adjusted coefficient from linear regression: **Blood Pb: β(95% CI)= 0.99 (0.47-1.51); p<0.01** Tibia Pb: β (95% CI)= 0.02 (-0.08-0.11); NS DBP adjusted coefficient from linear regression: **Blood Pb: β(95% CI)= 0.51 (0.24-0.79); p<0.01** Tibia Pb: β (95% CI)= 0.02 (-0.03-0.07); NS Hypertension adjusted odds ratio from logistic regression: Blood Pb: AdjOR (95% CI)= 1.01 (0.86-1.19); NS Tibia Pb: AdjOR (95% CI)= 1.16 (0.98-1.37); p=0.09	Blood Pb was significantly associated with increased SBP and DBP, while tibia Pb was higher (but not statistically significant) in hypertension cases.
‡ Cross-sectional; Menditto (1994) Rome, Italy	1,319 men in the New Risk Factors Project (participants in the 1979-1981 study). Year = 1989-1990; Male = 100%	63 (5) years Range: 55-75	Median = 11.3 Range: 4.0- 44.2	Systolic and diastolic blood pressure (SBP and DBP) and BP category: Normal (SBP≤140mmHg and DBP≤90), Borderline (SBP 140-160 or DBP 90-95), or High (SBP≥160mmHg or DBP≥95)	Kruskall-Wallis test of differences in BP category Linear correlation and multiple step-wise regression analyses. BMI, age, heart rate, skinfold thickness, smoking, serum lipids, and glucose levels	Median blood Pb values in BP categories: **(*p*=0.004)** Normal (n=668): 11.1 µg/dL Borderline (n=373): 11.35 µg/dL High (n=278): 12.0 µg/dL Log-normal blood Pb linear correlation: **SBP: r=0.1332, p<0.001** **DBP: r=0.0737, p=0.007** Adjusted linear regression coefficient with blood Pb: SBP: 5.6 mmHg/ln(ug/l) (6.8 unadjusted) DBP: 1.7 mmHg/ln(ug/l) (1.8 unadjusted) Alcohol Drinkers (n=1068)	Concurrent blood Pb was significantly associated with increased SBP and DBP in all the men and in the subset who drank alcohol.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
					DBP model did not adjust for skinfold thickness, non-HDL-cholesterol, or glucose levels	Log-normal blood Pb linear correlation: **SBP: r=0.1449, p<0.001** **DBP: r=0.1042, p<0.001** Adjusted linear regression coefficient with blood Pb: SBP: 5.6 mmHg/ln(ug/l) (7.5 unadjusted) DBP: 2.5 mmHg/ln(ug/l) (2.6 unadjusted) Non-drinkers (n=251) No significant relationships between blood Pb and BP Statistical significance of the regression coefficients was not included	
‡ Prospective and cross-sectional Møller (1992) Denmark *Population may overlap with Grandjean (1989)* *Also listed for Clinical Cardiovascular Disease and Cardiovascular Mortality*	1052 adults born in 1936 and living in the 4 municipalities served by the Glostrup Hospital (Glostrup Population Study); Year = Baseline: 1976; 5-year follow up: 1981 (both sexes); 11-year follow up: 1987 (men only) Male 48%	40 years at baseline	Baseline Calc. mean=11.5 Men (n=504): 13.6 (5.7) Range=5 – 60 Women (n=546): 9.6 (3.8) Range=4 – 39 1981 (age 45) Men (n=463): 9.6 (4.3) Range: 3 – 39 Women (n=430): 6.8 (3.5) Range: 2 – 41 1987 (age 51) Men (n=439): 8.3 (4.1) Range=2 – 62	Systolic and diastolic blood pressure (SBP and DBP)	Multiple linear regression Tobacco, BMI, physical activity, alcohol, hemoglobin† *1987 results are not adjusted for hemoglobin	Regression of BP on ln(blood Pb): SBP: Unadjusted; Multiply adjusted Men, 1976: β=3.88 (*p*=0.02); β=1.29 (*p*=0.45) Men, 1981: β=2.38 (*p*=0.11); β=0.88 (*p*=0.54) Men, 1987: β=2.35 (*p*=0.21); β=0.25 (*p*=0.89)* Women, 1976: β=4.21 (*p*=0.02); β=1.18 (*p*=0.51) Women, 1981: β=1.08 (*p*=0.45); β=1.62 (*p*=0.27) DBP: Unadjusted; Multiply adjusted Men, 1976: β=1.08 (*p*=0.44); β=-1.37 (*p*=0.33) Men, 1981: β=0.92 (*p*=0.44); β=0.59 (*p*=0.61) Men, 1987: β=-0.48 (*p*=0.68); β=-0.12 (*p*=0.32)* Women, 1976: β=3.49 (*p*=0.01); β=2.65 (*p*=0.07) Women, 1981: β=1.98 (*p*=0.07); β=2.78 (*p*=0.01) Regression of change in blood pressure on change in blood Pb in men from age 40 to age 51: SBP: Unadj. β=0.26 (*p*=0.03); Adj. β=0.16 (*p*=0.28) DBP: Unadj. β=0.03 (*p*=0.74); Adj. β =-0.06 (*p*=0.54)	Blood Pb was not significantly associated with SBP or DBP at baseline, or after 5 or 11 years of follow up; and change in blood Pb levels over time were not associated with SBP or DBP.
‡Cross-sectional Morris (1990) USA	251 adults without secondary hypertension, or antihypertensive mediations 1 month prior; Year = enrollment began in 1984 Male = 58%	23-79	Calc. mean: 7.5µg/dL Men: 8.0 (4.4) Women: 6.9 (3.6)	Systolic and diastolic blood pressure (SBP and DBP), after >5 minutes of supine rest and >2 minutes of standing, measured once a week for 4 weeks A 12 week calcium supplement intervention did not significantly change blood Pb levels.	Correlations Coefficients (*r*) Multiple linear regression (unadjusted reported here)	Correlation of blood Pb with BP (*p<0.05) Men (unadjusted): SBP: **Supine *r* = 0.16***, Standing *r* = 0.12 DBP: Supine *r* = 0.12**, Standing *r* = 0.15*** A 10µg/dL increase in blood Pb is related to a 5mmHg increase in supine SBP and a 2.9mmHg increase in standing DBP in men. Women (unadjusted): SBP: Supine *r* = 0.02, Standing *r* = -0.06 DBP: Supine *r* = -0.04, Standing *r* = -0.12 Multiple regression of Supine BP **SBP, Men (with age and Ca):** **Pb β=0.14; r=0.47, *P*<0.001**	Concurrent blood Pb levels were related to blood pressure in men, but not women.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						DBP, Men (with age smoking and hemoglobin): **Pb β=0.09; r=0.43, *P*<0.001** SBP, Women: blood Pb not in model DBP, Women: blood Pb not in model	
Cross-sectional Muntner (2005) USA *Also listed for Clinical Cardiovascular Disease*	9,961 adults in NHANES 1999-2002; Year = 199-2002; % male not stated	mean not reported all ≥18	1.64µg.dl (95% CI 1.59-1.68)	Hypertension: SBP/DBP ≥ 140/90mmHg and/or current antihypertensive medication	Multivariable logistic regression, χ^2 test for trend, Adjusted for age, sex, diabetes, BMI, current and former smoking, alcohol consumption, having a high school education, and having health insurance	Adjusted Odds Ratio (95% CI) of Hypertension by Quartile of Blood Pb: OR (95% CI); Disease % (SE) Non-Hispanic white Q1 (<1.06 µg/dl)=ref.; 18.7% (1.6) Q2 (1.06-1.63 µg/dl) OR=1.12 (0.83-1.50); 26.4% (1.6) Q3 (1.63-2.47 µg/dl) OR=1.03 (0.78-1.37); 32.0% (1.7) Q4 (≥2.47 µg/dl) OR=1.10 (0.87-1.41); 38.9% (1.9) *P* Value for Trend OR 0.61;**Prevalence <0.001** Non-Hispanic black Q1 (<1.06 µg/dl)=ref.; 20.9% (3.0) Q2 (1.06-1.63 µg/dl) OR=1.03 (0.63-1.67); 29.4% (2.4) Q3 (1.63-2.47 µg/dl) OR=1.12 (0.77-1.64); 37.5% (3.5) Q4 (≥2.47 µg/dl) OR=1.44 (0.89-2.32); 47.2% (2.0) *P* Value for Trend OR 0.06; **Prevalence <0.001** Mexican American Q1 (<1.06 µg/dl)=ref.; 10.3% (1.8) Q2 (1.06-1.63 µg/dl) OR=1.42 (0.75-2.71); 16.8% (1.7) Q3 (1.63-2.47 µg/dl) OR=1.48 (0.89-2.48); 17.8% (2.1) Q4 (≥2.47 µg/dl) OR=1.54 (0.99-2.39); 18.2% (1.7) ***P* Value for Trend OR 0.04; Prevalence <0.001**	Blood Pb and the prevalence of hypertension increased in all ethnicities and in non-Hispanic blacks and Mexican Americans there was a near statistically significant increase in the risk of hypertension.
Cross-sectional Nash (2003) USA *Population may overlap with Den Hond (2002) and others*	2,165 women aged 40-59 years from NHANES III; non-Hispanic black, non-Hispanic white, and Hispanic only; Year= 1988 – 1994 Male = 0%	48.2 (0.2) years	2.9 µg/dl Range = 0.50 – 31.1 µg/dl	Systolic and diastolic blood pressure (SBP and DBP) and Hypertension (SBP >140, DBP >90mmHg, or treatment with antihypertensive medication)	Multiple linear regression models; multiple logistic regression; Age, race and ethnicity, alcohol, smoking history, BMI, and serum creatinine family income, education,	Mean Blood pressure (SE) by blood Pb quartile: **SBP (χ^2 p=0.03, *p*<0.001 for trend)** **Q1 (0.5-1.6µg/dl) = 117.2 (0.95) mmHg** **Q2 (1.7-2.5µg/dl)= 117.7 (0.83) mmHg** **Q3 (2.6-3.9µg/dl)= 119.3 (1.10) mmHg** **Q4 (4.0-31.1µg/dl)= 121.2 (0.92) mmHg** DBP (χ^2 p=0.86, *p*= 0.79 for trend) Q1 (0.5-1.6µg/dl)= 73.7 (0.51) mmHg Q2 (1.7-2.5µg/dl)= 74.2 (0.53) mmHg Q3 (2.6-3.9µg/dl)= 74.2 (0.62) mmHg Q4 (4.0-31.1µg/dl)= 74.3 (0.62) mmHg Regression coefficient (SE), *P* value in women not treated for hypertension: All women (n=1786): **SBP: 0.32 (0.16), p=0.03** **DBP: 0.25 (0.09), p=0.009** Premenopausal women (n=1084): SBP: 0.14 (0.26), p=0.59 DBP: 0.38 (0.25), p=0.12	Blood Pb levels in middle aged women were significantly associated with increased BP and risk of hypertension. This association was strongest in postmenopausal women.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						Postmenopausal women (n=633): SBP: 0.42 (0.21), p=0.29 **DBP: 0.14 (0.13), p=0.04** <u>Adjusted odds ratio of general hypertension</u> (95% CI): All women (n=2165): Q1 = ref. Q2 (1.7-2.5µg/dl)= 1.0 (0.63-1.6) Q3 (2.6-3.9µg/dl)= 1.3 (0.87-2.0) Q4 (4.0-31.1µg/dl)= 1.4 (0.92-2.0) Premenopausal (n=1214): Q1 (0.5-1.4µg/dl)= ref. Q2 (1.5-2.1µg/dl)= 0.78 (0.38, 1.6) Q3 (2.2-3.3µg/dl)= 1.4 (0.82, 2.4) Q4 (3.4-28.7µg/dl)= 1.5 (0.78, 2.8) Postmenopausal (n=850): Q1 (0.5-1.9µg/dl)= ref. Q2 (2.0-3.1µg/dl)= = 0.73 (0.40, 1.3) Q3 (3.2-4.6µg/dl)= 1.3 (0.75, 2.2) Q4 (4.7-31.1µg/dl)= 1.3 (0.68, 2.3) <u>Premenopausal women untreated for hypertension, adjusted odds ratio of hypertension</u> (95% CI): Systolic hypertension (n=1084): Q1 (0.5-1.4µg/dl)= ref. Q2 (1.5-2.1µg/dl)= 0.88 (0.29-2.7) Q3 (2.2-3.3µg/dl)= 1.4 (0.49-3.7) Q4 (3.4-28.7µg/dl)= 1.6 (0.62-4.2) Diastolic hypertension (n=1084): Q1 (0.5-1.4µg/dl)= ref. Q2 (1.5-2.1µg/dl)= 1.1 (0.31-3.6) Q3 (2.2-3.3µg/dl)= 1.8 (0.76-4.2) Q4 (3.4-28.7µg/dl)= 3.5 (0.89-13.4) <u>Postmenopausal women untreated for hypertension, adjusted odds ratio of hypertension</u> (95% CI): Systolic hypertension (n=633): Q1 (0.5-2.0µg/dl)= ref. **Q2 (2.1-3.0µg/dl)= 3.0 (1.3-6.9)** **Q3 (3.1-4.6µg/dl)= 2.7 (1.2-6.2)** Q4 (4.7-31.1µg/dl)= 2.6 (0.89-7.5) Diastolic hypertension (n=633): Q1 (0.5-2.0µg/dl)= ref. **Q2 (2.1-3.0µg/dl)= 4.6 (1.1-19.2)** **Q3 (3.1-4.6µg/dl)= 5.9 (1.5-23.1)** **Q4 (4.7-31.1µg/dl)= 8.1 (2.6-24.7)**	

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Meta-analysis; Navas-Acien (2008) [†, below, denotes study included in this meta-analysis]	Meta-analysis of data from 3 prospective cohort studies and 7 cross-sectional studies with bone Pb measurements. One prospective and one cross-sectional study had mean blood Pb levels above 15µg/dl and were not included in this evaluation.	≥18 years	Range of Mean Blood Pb levels (µg/dL) 2.3 - 32.0 Range of Mean Tibia Bone Pb levels (µg/g): 4.2 - 38.4 Range of Mean Patella Bone Pb levels in 3 studies (µg/g): 17.3 - 32.1	Systolic and diastolic blood pressure (SBP and DBP); hypertension	Summary measures of association were calculated using inverse-variance weighted random-effects models. Not all seven studies were included in the cross-sectional analyses presented here.	Cross-sectional study summary: Associations with a 10 µg/g increase in tibia Pb: **SBP: 0.26 mm Hg (95% CI 0.02-0.50)** DBP: 0.02 mm Hg (95% CI -0.15-0.19) **Hypertension: OR (95% CI)= 1.04 (1.01-1.07)** Associations with a 10 µg/g increase patella Pb: Hypertension: OR (95% CI)= 1.04 (0.96-1.12) *Associations with 5 µg/dL increase of blood Pb:* SBP: 1.53 mmHg (-0.19-3.25) DBP: 1.19 mmHg (-0.69-3.08) Hypertension: OR (95% CI) = 1.02 (0.93-1.13) Prospective study summary: *Associations with a 10 µg/g increase in tibia Pb:* SBP: 0.33 mm Hg (-0.44-1.11) *Associations with 5 µg/dL increase of blood Pb:* **SBP: 0.71 mm Hg (0.01-1.43)**	A significant positive association was found between 10µg/g increase in tibia Pb and hypertension in a summary of cross-sectional studies. In tibia bone Pb levels the majority of the studies found a positive association with blood pressure and the risk of hypertension.
Meta-analysis; Nawrot (2002) [‡, below, denotes study included in this meta-analysis]	Meta-analysis of 31 studies (19 general population surveys and 12 occupationally exposed surveys) including 58,518 total subjects. 8 studies had mean blood Pb levels above 15µg/dl and one was not in English and were not included	Not all studies included age, most in adults	Range of Mean Blood Pb levels 2.3-64 µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Estimation of association from a doubling of blood Pb at the mean of the study Combined *P*-values using Fisher's method with unweighted *P*-value between parentheses (χ^2) and Stouffer's method with one-sided *P*-value between parentheses (Z-score)	For a two-fold increase of the blood Pb concentration: Both sexes, all studies: **SBP (n=58518): 1.0 mmHg (0.5-1.4, *P*<0.001)** **DBP (n=58491): 0.6 (0.4-0.8, *P*<0.001)** Men, all studies: **SBP (n=32268): 1.2 mmHg (0.6-1.7, *P*<0.001)** **DBP (n=32263): 0.6 (0.4-0.8, *P*<0.001)** Women, all studies: **SBP (n=24057): 0.8 mmHg (0.2-1.4, *P*=0.003, 0.004)** **DBP (n=24035): 0.6 (0.3-0.9, *P*<0.001)**	This meta-analysis concludes a small but consistent association between BP and blood Pb, with no differences between genders.
Cross-sectional Nordberg (2000) Stockholm, Sweden	762 subjects in the Kungsholmen longitudinal study; Years (follow-up)= 1994-1996; Male=23%	87.3 (4.9) (all ≥75 years)	3.7 (2.3)µg/dl Men: 4.6µg/dl Women: 3.5µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression Specific adjustments to Pb and BP analyses are unclear.	Different multiple regression models with Pb as the dependent variable were tested and no relation to SBP or DBP was found (data not shown).	Blood Pb was not associated with SBP or DBP in these elderly subjects

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
‡Cross-sectional Orssaud (1985) Paris, France	431 men attached to a section of the Paris civil service living in the same urban area and not occupationally exposed to Pb; Year not stated Male = 100%	41.4 years Range: 24-55	Mean not reported <12.4: n=46 12.5-18.4: n=212 18.5-24.4: n=126 24.5-30.8: n=34 30.9-36.9: n=7 ≥37: n=6	Systolic and diastolic blood pressure (SBP and DBP)	Correlation coefficients using logarithms of blood Pb values. Adjusted for age, BMI, and alcohol consumption	Correlation coefficient between SBP and blood Pb: **All subjects: 0.23 ($p < 0.001$)** **Age 24-34 (n=145): 0.29 ($p < 0.001$)** **Age 35-44 (n=143): 0.20 ($p < 0.05$)** Age 45-55 (n=143): 0.14 (NS) DBP not included in the study. Adjusting for alcohol consumption and BMI did not modify the results.	Concurrent blood Pb was significant associated with SBP, particularly in younger men, but blood Pb levels >10µg/dL limit the utility to this evaluation.
Cross-sectional Perlstein (2007) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	593 men in the Normative Aging Study not treated with antihypertensive medication; Year = 1991-1997 Male = 100%	Calc. mean 66.6 By tibia Pb quintile: Q1 (n=111) 63.0±7.0 Q2 (n=119) 64.4±6.9 Q3 (n=122) 66.8±7.4 Q4 (n=119) 68±7.3 Q5 (n=122) 70.5±6.7	6.12 (4.03)	Systolic and diastolic blood pressure (SBP and DBP) and Pulse Pressure (the difference between systolic and diastolic blood pressure)	Spearman correlations, multiple linear regression, and test of linear trend Adjusting for age, age^2, height, race, heart rate, waist circumference, diabetes, family history of hypertension, education, smoking history, alcohol intake, fasting plasma glucose, and total cholesterol-to-HDL ratio	Spearman correlations (r) of Pb and BP: Tibia SBP: **unadj. r=0.13, p<0.01**, adj. r=0.06, p=0.15 Tibia DBP: **unadj. r=-0.14, p<0.01**, adj. r=-0.02, p=0.63 Blood SBP: **unadj. r=0.08, p=0.05**, adj. r=0.05, p=0.28 **Blood DBP: unadj. r=0.09, p=0.03, adj. r=0.12, p=0.01** Multivariate adjusted quintile mean differences in pulse pressure (Q1 ref): *P* for linear trend: Tibia Pb (*P*=0.02): Q5: 2.58 (95% CI -1.15 to 6.33) Q4: 2.64 (95% CI -0.93 to 6.21) Q3: -0.73 (95% CI -4.27 to 2.82) Q2: -3.02 (95% CI -6.48 to 0.44) Blood Pb (*P*=0.82): Q5: -1.49 (95% CI -4.93 to 1.94) Q4: -1.39 (95% CI -4.94 to 2.15) Q3: -2.56 (95% CI -5.78 to 0.67) Q2: -4.37 (95% CI -7.88 to -0.86) **Tibia Pb above the median had 4.2mmHg (95%CI 1.9-6.5) higher pulse pressure.**	Concurrent blood Pb was significantly correlated with DBP, and tibia Pb over the median was significantly associated with an increase in pulse pressure.
Cross-sectional Peters (2007) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	513 participants with baseline hypertension and 237 without hypertension from the Normative Aging Study Year = 1991-1996 Male = 100%	*Hypertensives:* 67.5 (6.8) years *Non-hypertensives:* 66.2 (7.4) years	Blood Pb: *Hypertensive* 6.3 (4) µg/dL *Non-hypertensive* 6.2 (4.2) µg/dL Patella Pb: *Hypertensive* 32.5 (20.1) µg/g *Non-Hypertensive* 30.3 (18.3) µg/g	Systolic and diastolic blood pressure (SBP and DBP)	Logistic regression Age, age^2, BMI, family history of hypertension, education, pack-years smoking; alcohol intake, physical activity, and sodium, calcium, and potassium intake	Tibia Pb OR (95% CI): Non-hypertensives: Referent Hypertensives: 1.17 (0.88-1.42) Patella Pb OR (95% CI) Non-hypertensives: Referent Hypertensives: 1.08 (0.85-1.38)	Bone Pb was not statistically significantly associated with hypertension.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Pizent (2001) Croatia	267 peasant women, residents of two rural areas in Croatia: Istra (low calcium intake, n=100) and Podravina (high calcium intake, n=167); Year not stated Male = 0%	Calc. mean: 60.5 Istra (Low Ca): 58 (40-86) Podravina (High Ca): 62 (41-85)	Calc. mean: 6.46µg/dl Istra (Low Ca): 7.4 (2.9-25.1) µg/dL Podravina (High Ca): 5.9 (2.1-26.3) µg/dL	Systolic and diastolic blood pressure (SBP and DBP), sitting after 10 min rest	Spearman's rank correlation Forward stepwise multiple regression Mann Whitney U-test (z, p) No adjustment for other factors	Correlation coefficient of blood Pb: *r*, *p*-value SBP: 0.070, NS DBP: 0.087, NS BP regression models did not include blood Pb Mean Blood Pb (µg/dl), Range Group 1 Low Ca, No alcohol (n=34): 6.4 (2.9-13.7) Group 2 Low Ca, Any alcohol (n=66): 7.8 (4.2-25.1) Group 3 High Ca, No alcohol (n=107): 5.1 (2.2-19.2) Group 4: High Ca, Any alcohol (n=60): 7.4 (2.1-26.3) **Group 2 vs. 1: p-value<0.01** **Group 3 vs. 2: p-value<10^{-8}** **Group 3 vs. 1: p-value<0.05** **Group 4 vs 3: p-value<10^{-5}**	Blood Pb was not statistically significantly associated with BP in this population, but low calcium and/or alcohol consumption was associated with higher Pb levels.
‡Cross-sectional Pocock (1984) England *Population may overlap with Pocock (1988)*	7,371 men randomly selected from general practices in 24 British towns (The Regional Heart Study); Year not stated Male = 100%	mean not reported 40-59 years	mean not reported <12.4 – 37.3 **limits utility*	Systolic and diastolic blood pressure (SBP and DBP)	Statistical methods not reported but statistics were presented as correlation coefficients (β); Alcohol consumption	Blood Pb was not associated with increased hypertension Correlation coefficients (r) of blood Pb: SBP = 0.03 DBP = 0.01 There was no significant trend in the proportion of men with hypertension across the blood Pb concentration groups.	Blood Pb was not associated with SBP, DBP or hypertension; but lack of mean blood Pb levels in this study limits the utility.
Cross-sectional Pocock (1988) England *Population may overlap with Pocock (1984)]*	7,371 randomly selected from general practices in 24 British towns (The Regional Heart Study); Year not stated Male = 100%	mean not reported 40-59 years	mean not reported **limits utility*	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression analyses Age, BMI, alcohol intake, smoking, social class, town of residence.	Regression coefficient of blood pressure on ln (blood Pb) [standard errors not given]: **SBP = 2.089 (*p*=0.003)** **DBP = 1.809 (*p*=0.001)** *Authors note that these significant results are due to the large sample size as the adjusted statistical associations are very weak, partial correlation coefficients being 0.04 and 0.05 for the SBP-blood Pb and DBP-blood Pb associations.*	Blood Pb was significantly associated with SBP and DBP; but lack of mean blood Pb levels in this study limits the utility.
‡Cross-sectional Proctor (1996) Boston, MA, USA *Population may overlap with Cheng (1998) and others*	798 men from the Normative Aging Study; Year= 1991-1993 Male = 100%	66.1 (7.4) Range: 43 – 93 years	6.5 (4) Median (range): 5.6 (0.5 – 35)	Systolic and diastolic blood pressure (SBP and DBP)	Multivariate linear regression analyses with systolic and diastolic pressure as continuous outcome variables. Age, BMI, dietary calcium (adjusted for total calorie intake), alcohol, sitting heart rate, weekly exercise, hematocrit, and smoking.	β (95% CI) for unit increase in ln blood Pb: Whole cohort: SBP: 0.85 (-1.1, 2.7); *P*>0.05 **DBP: 1.2 (0.1, 2.2) mmHg; *P*=0.03** ≤74 years (n=681): SBP: 1.2 (-0.86, 3.2); *P*>0.05 **DBP: 1.6 (0.42, 2.7) mmHg; *P*=0.007** *When men on anti-hypertensive medication were removed from the analysis the associations with DBP became non-significant.*	Blood Pb was significantly associated with DBP with a large effect in men under 74, but when men taking anti-hyper-tensives were excluded it was no longer statistically significant.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
‡Cross-sectional Rabinowitz (1987) Boston, MA, USA	3,851 women whose babies were delivered consecutively at the Boston Hospital for Women; Year= 1979-1981 Male = 0%	28 (5) years	Umbilical cord blood: 6.9 ± 3.3 (range: 0-35)	Systolic and diastolic blood pressure (SBP and DBP) during labor (last recorded), pregnancy hypertension, and preeclampsia	Multiple linear regression analyses; Maternal age, parity, hematocrit, BMI, race, and diabetes.	High (mean 11.24µg/dl) vs. Low (mean = 3.50µg/dl) quartile of cord blood Pb: **SBP: F = 9.39, df = 3, p<0.001** **DBP: F = 4.75, df = 3, p<0.003** **Pregnancy hypertension: χ^2 (3 df) = 12.38, P<0.01** Pearson correlation coefficient for blood Pb and BP during labor: **SBP: r = 0.081 (p=0.0001)** **DBP: r = 0.051 (p=0.002)** Relative risk of hypertension during pregnancy at selected blood Pb levels (% with greater Pb levels) β = 0.34, SE = 0.12: **0.7 µg/dL (98.7%) = ref.** **6.3 µg/dL (50.0%) RR = 1.7 (1.3-2.1)** **15 µg/dL (1.7%) RR = 2.2 (1.5-2.9)** **25 µg/dL (0.2%) RR = 2.5 (1.5-3.5)**	Umbilical cord blood Pb was significantly associated with SBP, DBP, and pregnancy hypertension, but not preeclampsia.
‡Cross-sectional Rothenberg (1999) Los Angeles, CA, USA *Population may overlap with Rothenberg (2002)*	1,627 women in their 3rd trimester of pregnancy recruited at the King-Drew Medical Center prenatal care clinics; Year= 1995-1998 Male = 0%	Immigrants (n=1,188, 98% Latin counties): 27.7 (0.2) years Non-immigrants (n=439): 24.7 (0.3) years	Immigrants: 2.3 (0.04) µg/dL Non-immigrants: 1.9 (0.06) µg/dL	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression models Age, BMI, coffee intake, iron supplement, and job stress.	Multiple Regression Model of blood Pb and BP: Robust HC3 coefficients Immigrants: **SBP = 1.708 (SE=.536, p=0.001) 95%CI 0.656-2.758** **DBP = 1.476 (SE=.399, p<0.001) 95%CI 0.531-1.939** Non-Immigrants: SBP = 0.367 (SE=.968, p=0.705) 95%CI -1.535-2.269 DBP = 0.086 (SE=.985, p=0.93) 95%CI -1.849-2.021 In the immigrant group between the 5th and 95th percentiles (0.9-6.2µg/dl), each natural-log increase in blood Pb was associated with an increase of 2.8 mmHg in SBP and 2.4 mmHg in DBP	A statistically significant association between blood Pb and blood pressure during late pregnancy was only found in the immigrant, predominantly Hispanic, group.
†Cross-sectional Rothenberg (2002) Los Angeles, CA, USA *Population may overlap with Rothenberg (1999)*	667 third trimester and postpartum women recruited at the King-Drew Medical Center prenatal care clinics; Year= 1995-2001 Male = 0%	31.0 (7.7)	Prenatal Blood (geometric mean) = 1.9 (+3.6/-1.0) Postnatal Blood (geometric mean) = 2.3 (+4.3/-1.2) Tibia (µg/g) = 8.0 (11.4) Calcaneus (µg/g)	Systolic and diastolic blood pressure (SBP and DBP) and third trimester hypertension (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg)	*t*-tests; Fishers exact tests, logistic regression analyses; multiple regression models. Postpartum hypertension, education, immigrant status, current smoking, parity, age, BMI	Adjusted odds ratio for third trimester hypertension from a 1µg/dl blood or 10µg/g bone increase: Third trimester: Concurrent lnBlood Pb: OR = 0.75 (0.21, 2.65) Tibia Pb: OR = 0.98 (0.92, 1.04) **Calcaneus Pb OR = 1.86 (1.04, 3.32)** Postpartum: Concurrent lnBlood Pb: OR = 1.24 (0.64, 2.42) Tibia Pb: OR = 1.00 (0.96, 1.04) Calcaneus Pb: OR = 1.22 (0.86, 1.73) Multiple regression analysis in normotensive women for a 1µg/dl blood or 10µg/g bone increase: Third trimester: Concurrent lnBlood Pb:	Calcaneus Pb was significantly associated with risk of gestational hypertension and with third trimester SBP and DBP in normotensive women. Significant associations between

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
			= 10.7 (11.9)			SBP β = -0.04 (-1.26, 1.18) DBP β = 0.20 (-0.78, 1.18) Tibia Pb: SBP β = 0.07 (-0.62, 0.77) DBP β = 0.18 (-0.38, 0.74) **Calcaneus Pb:** **SBP β = 0.70 (0.04, 1.36)** **DBP β = 0.54 (0.01, 1.08)** Postpartum: **Concurrent lnBlood Pb:** **SBP β = -1.52 (-2.83, -0.20)** **DBP β = -1.67 (-2.85, -0.50)** Tibia Pb: SBP β = 0.10 (-0.64, 0.84) DBP β = 0.14 (-0.43, 0.70) Calcaneus Pb: SBP β = 0.36 (-0.32, 1.03) DBP β = 0.23 (-0.29, 0.75)	postpartum blood Pb and lower SBP and DBP are not in the expected direction.
Cross-sectional Schuhmacher (1994) Barcelona, Spain	36 workers occupationally exposed to Pb (welders and PCV-workers) and 40 workers not occupationally exposed to Pb or cadmium; Year not stated Male = 100%	Exposed: 43.7 (6.7) Unexposed: 46.3 (3.2)	Exposed: 39.5 µg/dL Range 18.3-119.3 Unexposed: 9.8 µg/dL Range: 2.4-17.9	Systolic and diastolic blood pressure (SBP and DBP)	Kruskal-Wallis test No adjustment for other factors	In the controls: Blood Pb by BP: geometric mean (SD) SBP <140 (n=31): 9.5 (1.5) µg/dl SBP >140 (n=9): 10.9 (1.7) µg/dl *p*, not significant DBP <90 (n=36): 9.7 (1.6) µg/dl DBP >90 (n=4): 10.6 (1.7) µg/dl *p*, not significant	In unexposed workers, blood Pb was not significantly higher in subjects with higher SBP and DBP.
Cross-sectional Schwartz (1991) USA *Also listed for Clinical Cardiovascular Disease*	9,932 participants from NHANES II; Year= 1976 - 1980; % male not stated	mean not reported Range = 20 – 74 years	mean not reported **limits utility*	Diastolic blood pressure (DBP)	Step-wise regression; SURREGR; RTILOGIT Age, BMI, race, family history, cholesterol, height, smoking, serum zinc, triceps skin fold thickness	Regression results for DBP: **Men = β (SE): 2.928 (1.002); *p*= 0.0063** **Women = β(SE): 1.640 (0.6963); *p*= 0.0247**	Blood Pb was significantly associated with DBP, but lack of mean blood Pb levels in this study limits the utility to the evaluation.
Cross-sectional Scinicariello (2010) USA *Population may overlap with Den*	6,016 participants in NHANES III with available DNA; Year=1988-1994; Male = 47.9%	44 years	All: 2.99 (0.09) Non-Hispanic Whites (n=2,387): 2.87 (0.09)	Systolic and diastolic blood pressure (SBP and DBP) in subjects not on antihypertensive medication and hypertension (SBP ≥140mmHg, DBP ≥	Multivariable logistic and linear regression stratified by race/ethnicity. OR adjusted for age, sex, BMI, alcohol, smoking,	Adjusted Prevalence OR for hypertension: (95%CI) Blood Pb Quartile (ref=0.7-1.4 µg/dL) Non-Hispanic Whites: 1.5-2.3 µg/dL=1.21 (0.66-2.24) 2.4-3.7 µg/dL=1.57 (0.88-2.80) 3.8-52.9 µg/dL=1.52 (0.80-2.88) **Non-Hispanic Blacks:**	Blood Pb was significantly associated with increased SBP and DBP and risk of hypertension, particularly in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Hond (2002) and others			Non-Hispanic Blacks (n=1,670): 3.59 (0.20) Mexican Americans (n=1,746): 3.33 (0.11)	90mmHg, or antihypertensive medication). *ALAD* polymorphism was also genotyped.	education, serum creatinine, serum total calcium, glycosylated hemoglobin, and hematocrit β-coefficient adjusted for age, sex, BMI, alcohol, smoking, education, serum creatinine, serum total calcium, glycosylated hemoglobin, and hematocrit	**1.5-2.3 µg/dL=1.83 (1.08-3.09)** **2.4-3.7 µg/dL=2.38 (1.40-4.06)** **3.8-52.9 µg/dL=2.92 (1.58-5.41)** Mexican Americans: 1.5-2.3 µg/dL=0.74 (0.24-2.23) 2.4-3.7 µg/dL=1.43 (0.61-3.38) 3.8-52.9 µg/dL=1.27 (0.59-2.75) *ALAD* genotype was not significantly associated with hypertension. Linear regression models of Ln blood Pb and BP: β-coefficient ± SE: **Non-Hispanic Whites, SBP: 1.05 ± 0.37, *P*=0.01** Non-Hispanic Whites, DBP: -0.14 ± 0.49, *P*=0.77 **Non-Hispanic Blacks, SBP: 2.55 ± 0.49, *P*=0.001** **Non-Hispanic Blacks, DBP: 1.99 ± 0.44, *P*=0.0002** Mexican Americans, SBP: 0.84 ± 0.46, *P*=0.08 Mexican Americans, DBP: 0.74 ± 0.38, *P*=0.06 Including interaction of *ALAD* 2 allele in the model reduced the statistical significance of the β estimates all $p > 0.05$.	non-Hispanic blacks. Genetic variation in *ALAD* may modify this association.
Cross-sectional Scinicariello (2011) USA *Population may overlap with Den Hond (2002) and others*	16,222 participants in NHANES ≥20 years old (pregnant and nursing mothers excluded) and blood Pb ≤10µg/dL; Year=1999-2006; Male = 50.7%	44 years	All race/ethnicity and gender geom. mean (SE) 99-00: 1.75(0.03) 01-02: 1.56(0.03) 03-04: 1.52(0.04) 05-06: 1.41(0.03) White men (n=4538) 99-00: 2.16(0.05) 01-02: 1.95(0.05) 03-04: 1.79(0.05) 05-06: 1.69(0.07) White women (n=4319) 99-00: 1.38(0.03) 01-02: 1.24(0.03) 03-04: 1.23(0.04) 05-06: 1.18(0.04) Black men (n=1767) 99-00: 2.29(0.09) 01-02: 2.22(0.13)	Systolic and diastolic blood pressure (SBP and DBP) in subjects not on antihypertensive medication, pulse pressure, and hypertension (SBP ≥140mmHg, DBP ≥ 90mmHg, or antihypertensive medication). Serum creatinine and blood Cd were also measured.	Multivariable linear and logistic regression stratified by race/ethnicity. Adjusted for age, education, smoking status, alcohol intake, BMI, self-reported diabetes, serum creatinine levels (as a marker of kidney function), serum Ca, serum Na, hematocrit, and blood Cd	Multivariable linear regression coefficient and SE for lnBlood Pb (≤10µg/dL) and BP outcomes: Systolic BP **All Subjects: 1.07 (0.35), *p* <0.05** White Men: 0.87 (0.53) White Women: 0.89 (0.55) **Black men:2.30 (0.71), *p* <0.05** **Black Women: 2.40 (1.14), *p* <0.05** Mex-Amer. Men: 0.10 (0.70) Mex-Amer. Women: -0.03 (0.64) Diastolic BP **All Subjects: 0.71 (0.27), *p* <0.05** **White Men: 0.90 (0.45) *p* <0.05** **White Women: 0.95 (0.38), *p* <0.05** **Black Men: 2.75 (0.82), *p* <0.05** Black Women: 0.30 (0.81) **Mex-Amer. Men: -1.34 (0.66), *p* <0.05** Mex-Amer. Women: -0.74 (0.44) Pulse Pressure All Subjects: 0.37 (0.34) White Men: -0.02 (0.55) White Women: -0.03 (0.62) Black Men: -0.42 (0.93) Black Women: 2.21 (1.17) **Mex-Amer. Men: 1.42 (0.70), *p* <0.05**	Only including subjects ≤10µg/dL, blood Pb was significantly associated with increased SBP and DBP in white and black subjects, but not in Mexican-Americans. Blood Pb was significantly associated with an increased prevalence odds ratio of hypertension in black men.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
			03-04: 2.07(0.10) 05-06: 1.80(0.08) Black women (n=1854) 99-00: 1.61(0.07) 01-02: 1.35(0.07) 03-04: 1.48(0.12) 05-06: 1.24(0.06) Mex-Amer. men (n=1925) 99-00: 2.56(0.07) 01-02: 2.17(0.11) 03-04: 2.07(0.11) 05-06: 1.87(0.09) Mex-Amer. women (n=1819) 99-00: 1.53(0.06) 01-02: 1.18(0.06) 03-04: 1.32(0.06) 05-06: 1.09(0.04)			Mex-Amer. Women: 0.70 (0.63) Adjusted prevalence odds ratios for hypertension with blood Pb: POR (95% CI) Q2 (1.01-1.59µg/dL) vs. Q1 (≤ 1.00µg/dL) All Subjects: 1.00 (0.82 - 1.21) White Men: 1.05 (0.76 – 1.47) White Women: 0.85 (0.65 – 1.12) Black Men: 1.36 (0.73 – 2.52) **Black Women: 0.58 (0.40 – 0.84)** Mex-Amer. Men: Mex-Amer. Women: Q3 (1.60-2.39µg/dL) vs. Q1 (≤ 1.00µg/dL) All Subjects: 1.01 (0.81 – 1.27) White Men: 0.93 (0.67 – 1.34) White Women: 0.93 (0.67 – 1.29) Black Men: 1.38 (0.81 – 2.36) Black Women: 0.85 (0.53 – 1.37) Mex-Amer. Men: 1.26 (0.67 – 2.37) Mex-Amer. Women: 0.87 (0.57 – 1.32) Q4 (2.40-10µg/dL) vs. Q1 (≤ 1.00µg/dL) All Subjects: 0.97 (0.77 – 1.22) White Men: 0.97 (0.69 – 1.36) White Women: 0.82 (0.58 – 1.15) Black Men: 1.71 (0.94 – 3.10) Black Women: 1.02 (0.60 – 1.74) Mex-Amer. Men: 0.86 (0.46 – 1.60) Mex-Amer. Women: 0.87 (0.51 – 1.47) 90^{th} (≥3.50 µg/dL) vs 10^{th} (≤0.70 µg/dL) percentile All Subjects: 1.26 (0.98 – 1.61) White Men: 1.20 (0.74 – 1.96) White Women: 1.07 (0.69 – 1.66) **Black Men: 2.69 (1.08 – 6.72)** Black Women: 1.04 (0.50 – 2.16) Mex-Amer. Men: 1.03 (0.23 – 4.59) Mex-Amer. Women: 0.67 (0.37 – 1.20) LN blood Pb All Subjects: 0.99 (0.89 – 1.11) White Men: 0.97 (0.84 – 1.13) White Women: 0.94 (0.77 – 1.14) **Black Men: 1.41 (1.05 – 1.88)** Black Women: 1.04 (0.76 – 1.42) Mex-Amer. Men: 0.91 (0.67 – 1.24) Mex-Amer. Women: 0.89 (0.69 – 1.16) Blood Pb All Subjects: 0.99 (0.95 – 1.03)	

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						White Men: 0.99 (0.94 – 1.05) White Women: 0.98 (0.89 – 1.08) **Black Men: 1.11 (1.00 – 1.22)** Black Women: 1.02 (0.90 – 1.16) Mex-Amer. Men: 0.97 (0.87 – 1.07) Mex-Amer. Women: 0.98 (0.86 – 1.11)	
‡Cross-sectional Sharp (1988) San Francisco, CA, USA *Population may overlap with Sharp (1990)*	288 bus drivers not being treated for hypertension; Year = 1986 (from Sharp (1990)) Male = 91%	Men 42.7 (7.13) Range: 30.6-64.7 Women 40.3 (6.89) Range: 27.9-54.5	Median: 6.4µg/dl Range: 2-15µg/dl	Systolic and diastolic blood pressure (SBP and DBP); Average of 3 measures (AVESYS, AVEDIA in paper)	Multiple regression models Adjusted for age, BMI, sex, caffeine use, and race	Regression coefficient of BP and lnBlood Pb (adjusted model with outlier removed): SBP: β =0.79 mm Hg/ln (µg/dL) [95% CI: -2.68, 4.27] **DBP: β = 2.45 mm Hg/ln (µg/dL) [90% CI: 0.10, 4.80]**	Concurrent blood Pb was significantly associated with DBP in these bus drivers.
‡Cross-sectional; San Francisco, CA, USA; Sharp (1990) *Population may overlap with Sharp (1988)*	249 bus drivers not being treated for hypertension; drivers; Year= 1986; Male = 100%	Blacks (n=132): 42.6 (7.05) Range 30.8 - 64.7 years Nonblacks (n=117): 42.7 (7.22) Range 30.6 - 58.9 years	Blacks (n=132): 6.9 (2.63) Range 3-21 µg/dl Nonblacks (n=117): 6.6 (2.32) Range 2-15 µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Multiple regression models Age, age2, BMI, caffeine use, tobacco use, and race (in nonblacks).	Adjusted regression coefficient of BP and lnBlood Pb (outliers removed): Blacks (n=130): **SBP β = 6.92 (95% CI 0.67 to 13.2)** **DBP β = 5.08 (95% CI 0.88 to 9.27)** Black infrequent caffeine users (n=52): **SBP β = 12.14 (95% CI 1.34 to 22.9)** DBP β = 7.34 (95% CI -0.51 to 15.2) Black habitual caffeine users (n=78): SBP β = 3.22 (95% CI -4.7 to 11.1) DBP β = 2.55 (95% CI -2.5 to 7.6) Nonblacks (n=117): SBP β = -5.71 (95% CI -12.0 to 0.6) DBP β = 0.76 (95% CI -3.4 to 4.9) Nonblack infrequent caffeine users (n=33): SBP β = -1.98 (95% CI -17.1 to 13.1) DBP β = 1.39 (95% CI -7.87 to 10.6) Nonblack habitual caffeine users (n=84): SBP β = -4.55 (95% CI -12.2 to 3.0) DBP β = 2.55 (95% CI -2.54 to 7.63)	Concurrent blood Pb was significantly associated with SBP and DBP in blacks, but not in non-blacks. The effect in blacks was stronger in infrequent caffeine users than in habitual caffeine users.
Cross-sectional Sirivarasai (2004) Bangkok, Thailand	212 men without known exposures to Cd and Pb; Year not stated Male = 100%	41.1 (4.81) Range: 34-53	Calc mean: 7.48µg/dl	Systolic and diastolic blood pressure (SBP and DBP)	Pearson's correlation coefficient Stepwise multiple regression Adjusted for age, weight, BMI, blood cadmium, serum uric acid, current smoking, and current alcohol consumption	Correlation between Blood Pb and BP: **SBP: 0.342, p < 0.001** DBP: 0.209, NS β-coefficient ± S.D. (square partial corr. coefficient) **SBP: 15.67 ± 3.00 µmol/L (r^2 = 2.6), p<0.001** DBP: (data not shown), NS	Concurrent blood Pb was significantly associated SBP but not DBP.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
‡Cross-sectional Sokas (1997) MD, USA	264 unionized Maryland construction workers not known to currently be performing Pb work; Year= 1989-1990 Male = 99%	43 years Range = 18 – 79 years	Mean= 8.0 Median: 7 Range: 2 – 30	Systolic and diastolic blood pressure (SBP and DBP)	Multiple linear regression; t test; simple Pearson correlations. Age, BMI, hematocrit, race, smoking, alcohol consumption, years of education.	<u>Regression coefficients of blood Pb and BP:</u> SBP = -0.49 [SE not reported] (p=0.13) DBP = -0.18 [SE not reported] (p=0.38)	Blood Pb levels were not significantly associated with SBP or DBP.
Prospective Sowers (2002) Camden, NJ, USA	705 pregnant women followed through pregnancy without serious nonobstetric conditions including chronic hypertension; Year not stated Male = 0%	20.5 (SE=0.2) Range 12-34 years	1.2 (SE = ±0.03)	Hypertension in pregnancy (HIP), preeclampsia, or toxemia based on >140/90mmHg Data and blood collections in each trimester, at delivery, and first postpartum visit.	Longitudinal regression with mixed models Age, race/ethnicity, and in-pregnancy dietary calcium	<u>Association of change in Pb concentration across pregnancy and HIP/toxemia</u>: HIP/toxemia (n=71): β=1.02 (SE=0.02) No HIP/toxemia (n=631): β=0.98 (SE=0.01) **Adjusted p=0.03** Maternal blood Pb levels were not associated with other reproductive outcomes: preterm delivery, small for gestational age, low birth weight, or Apgar scores.	Increases in blood Pb across pregnancy was significantly associated with hypertension in pregnancy/toxemia.
‡Cross-sectional Staessen (1990) London, England	531 London civil servants without industrial exposure to heavy metals; Year= 1982; Male = 75%	Calc. mean: 47.7 years <u>Men</u>: 47.8 (5.8) years Range: 37 – 58 <u>Women</u>: 47.5 (5.7) years Range: 38 – 57	Calc. mean: 11.8 µg/dl <u>Men</u>: 12.5 (4.37) Range: 6.25-35.4 <u>Women</u>: 10.2(3.96) Range: 4.17-31.25	Systolic and diastolic blood pressure (SBP and DBP)	Linear regression; t tests; step wise multiple regression. Age, sex, body weight, BMI, pulse rate, employment grade, smoking, alcohol consumption, serum creatine, serum calcium, γ-glutamyltranspep-tidase.	<u>Correlation between BP and log blood Pb:</u> Men: SBP r=0.05 (N.S.), DBP r=0.08 (N.S.) Women: SBP r=0.12 (N.S.), DBP r=-0.01 (N.S.) **All: SBP r=0.11 (p<0.02) DBP r=0.11 (p<0.02)** In the step wise multiple regression, the correlation between blood Pb and SBP or DBP did not approach statistical significance (data shown in figure only).	Correlations between blood Pb and SBP and DBP were not significant after adjustment for covariates.
Cross-sectional Staessen (1991) Belgium *Population may overlap with Dolenc (1993) and Staessen (1995)*	1,982 Belgians selected from a stratified random sample of the population of 4 Belgian districts; Cadmium in Belgium (Cadmibel) Study; Year: 1985-1989 (from Staessen (1995)) Male = 49%	48 Range: 20-80	Calc. mean: 9.5 Men: 11.6 Women: 7.5	Systolic and diastolic blood pressure (SBP and DBP)	Univariate analysis, stepwise regression Adjusted for age, age^2, BMI, pulse rate, log γ-glutamyltranspeptidase, smoking habits, and contraceptive pill use in women	<u>Univariate analysis, adjusted partial correlation coefficient:</u> Men (n=963): **SBP: 0.07, p-value=0.03** DBP: 0.01, p-value=0.80 Women (n=1019) SBP: 0.01, p-value=0.87 DBP: 0.04, p-value=0.18 <u>Multiple regression analysis</u> (348 subjects on hypotensive medication, such as diuretics, removed): Men (n=824) **SBP: β= -5.904 (sig. level for inclus. not reported)** DBP: NS Women (n=810) SBP: NS DBP: NS	Blood Pb was not significantly associated with increases in SBP or DBP.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
‡Prospective Staessen (1996) Belgium	728 adults from 2 regions, 1 of which was polluted by the emissions of non-ferrous smelters; Year= Baseline 1985-1989 and follow up 1991-1995 (mean 5.2 years between) Male = 49%	Men (n=359) Baseline: 46.3 (14.6) years Follow-up: 51.5 (14.6) years Women (n=369) Baseline: 45.7 (14.3) years Follow-up: 50.9 (14.3) years	Baseline: 8.7µg/dl Men Baseline: 11.4 Follow-up: 7.7 Women Baseline: 6.6 Follow-up: 4.8	Systolic and diastolic blood pressure (SBP and DBP) – 15 readings at home per subject Normotension: ≤140 mm Hg SBP and ≤90 mm Hg DBP Borderline Hypertension: 141-159 SBP OR 91-94 DBP Hypertension: ≥160 SBP OR ≥95 DBP, or medication	Multivariate analyses of time-integrated estimates of BP and Pb Adjusted for age, BMI, hematocrit or hemoglobin, γ-glutamyltransferase activity, and menopausal status (if applicable)	Correlation with stepwise adjustments: DBP in women (all others NS) **Unadjusted: β=5.37 mmHg, SE=2.05, p=0.009** Adj. hematocrit: β=4.14 mmHg, SE=2.25, p=0.06 Adj. hemoglobin: β=3.69 mmHg SE=2.05, p=0.07 Risk ratio of becoming hypertensive with a doubling of baseline blood Pb (adjusting for sex, age and BMI): All: RR=1.01 (95% CI 0.69-1.46) Excluding borderline hypertension: RR=1.21(0.72-2.03)	Blood Pb was not significantly associated with SBP, DBP, or with increased risk of hypertension after adjusting for relevant covariates.
Cross-sectional Telisman (2001) Croatia	154 Croatian men without occupational Pb exposure; Year = 1998-1999 Male = 100%	Median = 31.2 Range: 19.3-52.8	Median = 5.7 Range: 2.5-25.4	Systolic and diastolic blood pressure (SBP and DBP) Also measured erythrocyte protoporphyrin, blood Cd and serum Cu, Zn, and Se	Spearman's rank correlation and stepwise multiple regression Covariates included in the model: BMI, alcohol, smoking, serum Cu,	Spearman's rank correlation coefficient with blood Pb: **SBP: *r* = 0.229, *P*<0.005** **DBP: *r* = 0.207, *P*<0.01** BMI and erythrocyte protoporphyrin were also significantly correlated. Multiple regression coefficient of log blood Pb and BP (including a Pb x serum Se interaction term): SBP model (plus BMI): **logPb (*B*=12.9, *P*<0.02),** **logPb*SSe (*β*=-1.16, *P*<0.007)** DBP model (plus BMI and alcohol): **logPb (*B*=7.02, *P*<0.04),** **logPb*SSe (*β*= -0.95, *P*<0.0007)**	Concurrent blood Pb was significantly associated with SBP and DBP.
Case-control Vigeh (2004) Tehran, Iran	110 pregnant women not occupationally exposed to Pb (55 cases with pregnancy-induced hypertension and 55 age-and gravidity-matched normotensive controls) Year = 2001 Male = 0%	27 (5.6) years Range: 17-40 years	Cases: 5.7(2) Range 2.2-12.6 Controls: 4.8(1.9) Range 1.9-10.6 (blood collected 24 hours after delivery)	Systolic and diastolic blood pressure (SBP and DBP)	Wilcoxon signed-rank test or McNemar test; Spearman's correlation coefficient; logistic regression analysis	LnBlood Pb and hypertension during pregnancy (case vs. control): **β=1.37; p<0.05** **Odds Ratio (95% CI): 3.9 (1.3-11.7)** Correlations of lnblood Pb and BP in hypertensive cases: **SBP: r_s = 0.01, p>0.05** **DBP: r_s = 0.18, p>0.05** No significant differences in blood Pb concentrations among hypertensive subjects with proteinuria and those without proteinuria.	Blood Pb was significantly associated with hypertension during pregnancy and SBP and DBP in cases.
Cross-sectional Vupputuri (2003) USA *Population may*	14,952 subjects in NHANES III (including whites and blacks ≥18 years old and excluding	White men = 43.9 (0.5) years Black men = 39.9 (0.5) years	White men = 4.4 (0.1) µg/dl Black men = 5.4 (0.2) µg/dl	Systolic and diastolic blood pressure (SBP and DBP) and hypertension	Multivariate-adjusted linear regression models; linear and logistic regression models.	Differences in BP associated with one SD (3.3µg/dl) increase in blood Pb: SBP: White men = 0.29 (-0.24, 0.83) **Black men = 0.82 (0.19, 1.44) (*p*< 0.05)**	Concurrent blood Pb was significantly associated with SBP and DBP in

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
overlap with Den Hond (2002) and others	non-black, non-white, and those taking anti-hypertension medication); Year= 1988 – 1994 Male = 50%	White women = 47.4 (0.6) years Black women = 42.0 (0.4)	White women = 3.0 (0.1) µg/dl Black women = 3.4 (0.1) µg/dl		Age, high school education, BMI, alcohol intake, leisure-time physical activity, dietary intake of sodium, potassium, and total energy.	White women = 0.34 (-0.49, 1.17) **Black women = 1.55 (0.47, 2.64) (*p*< 0.01)** DBP: White men = 0.01 (-0.38, 0.40) **Black men = 0.64 (0.08, 1.20) (*p*< 0.05)** White women = -0.04 (-0.56, 0.47) **Black women = 1.07 (0.37, 1.77) (*p*< 0.01)** Odds Ratio and 95% CI of Hypertension associated with a 1-SD increase in blood Pb: White men = 1.04 (0.93, 1.16) Black men = 1.08 (0.99, 1.19) (*p*= 0.08) **White women = 1.32 (1.14, 1.52) (p<0.001)** **Black women = 1.39 (1.21, 1.61) (p<0.001)**	blacks, but not whites; and with risk of hypertension in women, but not men.
Cross-sectional Wells (2011) Baltimore, MD, USA	285 pregnant women who gave birth at Johns Hopkins Hospital in the Baltimore THREE Study; Year = 2004-2005 Male = 0%	Age at delivery: 26 years Range:14-43	Cord blood Pb: 0.66 µg/dL (95% CI: 0.61-0.70)	Systolic and diastolic blood pressure (SBP and DBP) during pregnancy, gestational hypertension (GH), preeclampsia, and any hypertension	Multivariate regression Age, race, median household income, parity, smoking during pregnancy, prepregnancy BMI, and anemia	Change in SBP at Admission by cord blood Pb quartile: Q1 (≤0.46 µg/dL): referent Q2 (0.47-0.65 µg/dL): 2.89 (-2.16, 7.94) Q3 (0.66-0.95 µg/dL): 1.05 (-4.04, 6.14) **Q4 (≥0.96 µg/dL): 6.87 (1.51, 12.21)** **p-trend= 0.033** Change in DBP at Admission by cord blood Pb quartile: Q1 (≤0.46 µg/dL): referent Q2 (0.47-0.65 µg/dL): 0.00 (-3.95, 3.96) Q3 (0.66-0.95 µg/dL): 0.81 (-3.17, 4.80) **Q4 (≥0.96 µg/dL): 4.40 (0.21, 8.59)** **p-trend= 0.036** Change in maximum SBP by cord blood Pb quartile: Q1 (≤0.46 µg/dL): referent Q2 (0.47-0.65 µg/dL): 2.47 (-3.08, 8.02) Q3 (0.66-0.95 µg/dL): -1.76 (-7.36, 3.85) **Q4 (≥0.96 µg/dL): 7.72 (1.83, 12.60)** p-trend= 0.055 Change in maximum DBP by cord blood Pb quartile: Q1 (≤0.46 µg/dL): referent Q2 (0.47-0.65 µg/dL): 3.93 (-2.86, 10.72) Q3 (0.66-0.95 µg/dL): -0.42 (-7.27, 6.43) **Q4 (≥0.96 µg/dL): 8.33 (1.14, 15.53)** p-trend= 0.086 There were no significant associations between Pb and GH, preeclampsia, or hypertension (data not shown).	Umbilical cord blood Pb was significantly associated with elevations in maternal BP during labor and delivery, but not other BP related conditions.
Cross-sectional Wolf (1995) Austria	507 law enforcement agents without occupational exposure to Pb; Year not stated	44.9 (8.2)	8.0 (3.5)	Systolic and diastolic blood pressure (SBP and DBP); after sitting for at least 3 minutes	Stepwise linear regression Age, height, weight, nicotine consumption, alcohol intake, blood Pb,	Standardized estimates (STE) and p-value for logPb in regression model (with BMI, age and alcohol): SBP: STE=0.02, p=0.6418, R^2=0.1978 **DBP: STE=0.09, p=0.0355, R^2=0.1798** Standardized estimates (STE) and p-value for logPb in	Concurrent blood Pb was significantly associated with DBP, but not SBP.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
	Male = 100%				SBP, DBP, erythrocyte count	regression model (excluding alcohol intake): SBP: STE= 0.05, p=0.2096, R^2=0.1887 **DBP: STE= 0.12, p=0.0049, R^2=0.1742** Standardized estimates (STE) and p-value for logPb in regression model (including erythrocyte count): SBP: STE= 0.02, p=0.6170, R^2=0.1986 **DBP: STE= 0.09, p=0.0323, R^2=0.1827**	
Cross-sectional Yazbeck (2009) France	971 pregnant women enrolled at two French maternity wards before 24 weeks of gestation with no history of chronic hypertension; The EDEN study; Year= 2003, 2005; Male = 0%	29.3 (4.9)	At 24-28 wks Calc. mean: 1.9µg/dl PIH cases (n=106): 2.2 (1.4) No PIH (n=865): 1.9 (1.2) Measured 24-28 weeks gestation	Pregnancy induced hypertension (PIH): SBP ≥140 mmHg and/or DBP ≥90 mmHg averaged over visits before 24wks (P1); 24-36 wks (P2), and after 36 weeks (P3)	Multivariable logistic regression Maternal age, cadmium, manganese and selenium blood levels, hematocrit, parity, BMI, gestational diabetes, education level, socioeconomic status, geographic residence, and smoking status during pregnancy Additionally alcohol consumption for PIH according to parity analysis	Difference in mean blood Pb between PIH and no PIH: PIH cases 2.2 (1.4); No PIH (n=865): 1.9 (1.2) **Adj. p-value=0.02** Adj. Odds ratios (95% CI) for PIH by maternal blood Pb distribution: **Log Pb (continuous): 3.29 (1.11-9.74), *p*=0.03** Q1 (<1.20 µg/dl): referent Q2 (1.20-1.70 µg/dl): 1.84 (0.77-4.41), *p*=0.84 Q3 (1.71-2.30 µg/dl): 2.07 (0.83-5.13), *p*=0.50 Q4 (>2.30 µg/dl): **2.56 (1.05-6.22)**, *p*=0.09 Adj.ORs (95% CI) for PHI according to parity (per unit increase in blood Pb level): Nulliparous (10.7% with PIH): 2.9 (0.6-15.7) **Multiparous (11.4% with PIH): 4.6 (1.0-21.6)** Correlation of BP and log blood Pb: **24-36 wks, SBP: *r*=0.08, *p*=0.03** **24-36 wks, DBP: *r*=0.07, *p*=0.03** After 36 weeks also significantly associated (data not shown) Each decimal-log increase in blood Pb was associated with a 3.5 mmHg SBP and 2.5 mmHg DBP increase.	Blood Pb levels at mid-pregnancy were significantly associated with risk of pregnancy induced hypertension, particularly in multiparous women.
Cross-sectional Zhang (2010) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	619 men from the Normative Aging Study; Year = 1991-1995 Male = 100%	Calc. mean: 66.6 Wild type (n=409): 66.4 (7.0) *C282Y* (n=72): 66.9 (7.1) *H63D* (n=138): 66.9 (6.8)	Median (interquartile range) Tibia: 19 (13-27) µg/g Patella: 26 (18-37) µg/g	Pulse Pressure (PP, the difference between systolic and diastolic blood pressure) *HFE H63D* and *C282Y* polymorphisms also genotyped.	Mixed model Adjusted for age; education; alcohol intake; smoking; daily intakes of calcium, sodium, and potassium; total calories; family history of hypertension; diabetes; height; heart rate; high-density lipoprotein (HDL); total cholesterol:HDL ratio; and waist circumference	Adjusted estimators in the difference in PP for an IQR increase in bone Pb by *HFE* genotype: β (95% CI) Tibia Pb (IQR= 13 µg/g): **Wild type: 0.38 (0-1.96)** ***H63D*: 3.30 (0.16-6.46)** ***C282Y*: 0.89 (0-5.24)** **Any *HFE* variant: 2.90 (0.31-5.51)** Patella Pb (IQR= 19 µg/g): **Wild type: 0.26 (0-1.78)** ***H63D*: 2.95 (0-5.92)** ***C282Y*: 0.55 (0-1.66)** **Any *HFE* variant: 2.83 (0.32-5.37)** *HFE* variants were not independently associated with pulse pressure or bone Pb levels.	Bone Pb was significantly associated with pulse pressure and this association was modified by genetic variation in the *HFE* gene.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Heart Rate Variability (HRV)							
Cross-sectional Gump (2011) NY, USA *Population may overlap with Gump (2005)* *Also listed for ECG Conduction Abnormalities*	140 children from Oswego Children's Study (n=95 for high frequency HRV measurement) Year not stated Male = 55%	10.21 (0.75) Range: 9-11	Median: 0.94 Range: 0-3.76	Heart Rate Variability (HRV) in response to acute stress tasks: Pre-ejection period (PEP, decreases = ↑ sympathetic), high frequency (HF-HRV, ↑ with parasympathetic), cardiac autonomic regulation (CAR) and cardiac autonomic balance (CAB)	Generalized linear model with a linear contract test For Pb as a continuous measure: partial correlation of log transformed blood Pb Adjusted for gender, age, race, BMI percentile standing, SES, family history of cardiovascular disease, and Hg level	<u>Adjusted associations of blood Pb and HRV at baseline:</u> PEP (n=140): *p* linear trend = 0.11 Pb Q1 (0.14-0.68µg/dL): 107.75 Pb Q2 (0.69-0.93µg/dL): 108.39 Pb Q3 (0.94-1.20µg/dL): 105.17 Pb Q4 (1.21-3.76µg/dL): 104.45 HF-HRV (n=95): *p* linear trend = 0.12 Pb Q1 (0.14-0.68µg/dL): 5775.77 Pb Q2 (0.69-0.93µg/dL): 5237.09 Pb Q3 (0.94-1.20µg/dL): 5014.43 Pb Q4 (1.21-3.76µg/dL): 8798.16 CAR (↑HF↓PEP, n=95): *p* linear trend = 0.07 Pb Q1 (0.14-0.68µg/dL): 0.00 Pb Q2 (0.69-0.93µg/dL): -0.09 Pb Q3 (0.94-1.20µg/dL): 0.07 Pb Q4 (1.21-3.76µg/dL): 0.85 CAB (↓HF↓PEP, n=95): *p* linear trend = 0.80 Pb Q1 (0.14-0.68µg/dL): 0.27 Pb Q2 (0.69-0.93µg/dL): 0.17 Pb Q3 (0.94-1.20µg/dL): -0.06 Pb Q4 (1.21-3.76µg/dL): 0.47 **PEP and HF-HRV significantly decreased in response to acute stress tasks (PEP 105.6 to 104, *p*<0.0001 and HF-HRV 5002 to 2267, *p*<0.0001).** <u>Blood Pb in quartiles and cardiac responses to acute stress</u>: *F* (degress of freedom), *p*-value **Smaller ↓ in PEP: 4.11 (1,130), *p* < 0.05** **Greater ↓ in HF-HRV: 4.59 (1,85), *p* < 0.05** **↓ CAR (↑HF-HRV↓PEP): 6.33 (1,85), *p* < 0.05** ↔ CAB (↓HF-HRV↓PEP): 2.31 (1,84), p>0.10 <u>Continuous blood Pb and cardiac responses to acute stress</u>: *r*, *p*-value **PEP: *r*=0.17, *p* = 0.05** **HF-HRV: *r*=-0.22, *p* < 0.05** **CAR (↑HF-HRV↓PEP): *r*=-0.24, *p* < 0.05** CAB (↓HF-HRV↓PEP): data not shown	Concurrent blood Pb was significantly associated with impaired autonomic response to acute stress in children aged 9-11 years as assessed by heart rate variability measures.
Cross-sectional Jhun (2005) Seoul, Korea	331 public officials and their family members in Seoul with no history of occupational exposure to Pb; Year not stated	37.9 (17.3) years Range <10 (n=27) to ≥60 (n=29)	2.34 (0.86) µg/dl Median: 2.16µg/dl	Heart Rate Variability (HRV) at low frequency (0.04-0.15 Hz), high frequency (0.15-0.30 Hz), and total power spectrum (0.04-0.30)	ANOVA; Univariate association followed by step-wise multiple regression analyses Models included age, heart rate, alcohol	<u>Univariate analysis of blood Pb related to heart rate variability measures</u>: **ln Low Frequency = -0.53 (*p*<0.01)** **ln High Frequency = -0.98 (*p*<0.01)** **ln Total Power Spectrum = -0.57 (*p*<0.01)** Other metals were also examined: As and Cd were	Blood Pb was significantly associated with decreased low and high frequency heart rate variability,

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
	Male = 55%			Low: sympathetic/ parasympathetic mediation; High: only parasympathetic mediation	drinking, blood As or Cd, and serum Co or Zn.	significantly associated, but Al, Co, Cu, and Zn were not. Pb was not included in multiple regression analyses of HRV, while As, Cd, Co, and/or Zn were retained in the models.	but it may confounded by correlation with other metals.
Cross-sectional Park (2006) Boston, MA, USA *Population may overlap with Park (2008) and others*	413 participants in the Normative Aging Study; Year 2000-2004; Male = 100%	72.9 (6.5)	Patella bone Pb: 23 (15-34) µg/g Tibia bone Pb: 19 (11-28) µg/g	Heart rate variability (HRV) High-frequency (HF) Low-frequency (LF)	Linear regression Age, BMI, fasting blood glucose, HDL, triglyceride, cigarette smoking, alcohol consumption, use of beta-blockers, use of calcium channel blockers, use of angiotensin converting enzyme (ACE) inhibitors, room temperature, and season	Estimated change (95% CI) in HRV parameters associated with one IQR increase in bone Pb markers: Tibia (µg/g) High-frequency: -0.9 (-3.8 to 2.1) Low-frequency: 0.9 (-2.0 to 3.9) Log_{10} LF/HF (%): 3.3 (-10.7 to 19.5) Patella (µg/g) High-frequency: -0.6 (-3.1 to 1.9) Low-frequency: 0.6 (-1.9 to 3.1) Log_{10} LF/HF (%): 3.0 (-8.7-16.2)	Bone Pb was not significantly associated with changes in heart rate variability.
Cross-sectional Park (2008) Boston, MA, USA *Population may overlap with Park (2006) and others*	384 participants in the Normative Aging Study; Year= 2000 – 2004 Male = 100%	73 (6.5) years	Median bone Pb (µg/g) Tibia Pb: 19 Patella Pb: 23	Heart Rate Variability (HRV) Air pollutants also measured	Linear regression analyses; cubic spline; linear trend. Age, BMI, fasting blood glucose, antihypertensive medication, smoking, alcohol intake, season, apparent temperature, mean arterial pressure, temperature of the room where the heart rate was measured, education, cumulative traffic.	Tibia: Estimated changes in Heart Rate Variability (high and low frequency) associated with air pollution, by quartiles of Pb: **High Frequency, Sulfate (p<0.01 for trend)** **1st quartile = 50.7 (5.4, 115.5)** 2nd quartile = 1.4 (-30.1, 47.1) 3rd quartile = -8.4 (-35.9, 30.9) 4th quartile = -22.2 (-40.4, 1.6) **High Frequency, Ozone (p<0.01 for trend)** 1st quartile = 16.1 (-18.9, 66.2) 2nd quartile = -3.2 (-29.7, 33.2) 3rd quartile = -22.4 (-45.4, 10.3) 4th quartile = -37.9 (-54.6, -14.9) **Low Frequency, Sulfate (p=0.04 for trend)** 1st quartile = 28.3 (-3.6, 70.6) 2nd quartile = -2.6 (-27.6, 31.1) 3rd quartile = -10.6 (-32.8, 18.8) 4th quartile = -11.7 (-28.6, 9.3) **Low Frequency, Ozone (p<0.01 for trend)** 1st quartile = 4.2 (-21.8, 38.8) 2nd quartile = -14.5 (-33.8, 10.4) 3rd quartile = -24.3 (-42.9, 0.2) 4th quartile = -38.1 (-51.9, -20.4) Patella: Estimated changes in Heart Rate Variability (high and low frequency) associated with air pollution, by quartiles of Pb: **High Frequency, Ozone (p=0.01 for trend)**	Bone Pb significantly modified associations between cardiac autonomic function and short-term exposure to air pollutants.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						1st quartile =6.8 (-21.8, 45.8) 2nd quartile = -14.1 (-39.9, 22.9) 3rd quartile = -19.3 (-44.0, 16.4) 4th quartile = -41.4 (-59.9, -15.0) **Low Frequency, Ozone (*p*<0.01 for trend)** 1st quartile = 2.1 (-20.4, 31.1) 2nd quartile = -12.2 (-34.1, 16.9) 3rd quartile = -28.2 (-46.4, -3.6) 4th quartile = -36.4 (-52.8, -14.3)	
Electrocardiographic (ECG) Conduction Abnormalities							
Cross-sectional Cheng (1998) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	775 men from the Bone Pb Substudy of the Normative Aging Study; Excluded those with a history of heart disease, hypertension, diabetes, cancer, peptic ulcer, gout, recurrent asthma, bronchitis, sinusitis Year= 1991 – 1995 Male = 100%	67.8 (7.3) years Range = 48 – 93 years	Blood = 5.8 (3.44) µg/dl Tibia = 22.2 (13.4) µg/g Patella = 30.8 (19.2) µg/g	QT and QRS intervals, intraventricular conduction defect (IVCD), atrioventricular conductive defect (AVCD), other arrhythmias	Multivariate linear and logistic regression models Age, alcohol intake, BMI, diastolic pressure, fasting glucose, serum HDL	<u>Multivariate-adjusted parameter estimates of heart rate-corrected QT and QRS intervals associated with a 10-unit increase in Pb</u>: QT (ms) (< 65 years old, n=277) Blood Pb: β = -0.65 (-10.40, 9.10) (p= 0.90) **Tibia Pb: β = 5.03 (0.83, 9.22) (p= 0.02)** **Patella Pb: β = 3.00 (0.16, 5.84) (p= 0.04)** QRS (ms) (< 65 years old) Blood Pb: β = -3.49 (-10.72, 3.75) (p= 0.35) **Tibia Pb: β = 4.83 (1.83, 7.83) (p < 0.01)** **Patella Pb: β = 2.23 (0.10, 4.36) (p= 0.04)** Not sig. in ≥65 population (n=498) <u>Multivariate-adjusted parameter estimates of IVCD and AVCD associated with a 10-unit increase in Pb:</u> IVCD (< 65 years old, not sig in ≥65) Blood Pb: OR = 0.63 (0.12, 3.31) (p= 0.59) **Tibia Pb: OR = 2.33 (1.28, 3.90) (p < 0.01)** Patella Pb: OR = 1.32 (0.90, 1.95) (p= 0.16) AVCD (≥ 65 years old, not sig in < 65) Blood Pb: OR = 1.19 (0.41, 3.47) (p= 0.75) **Tibia Pb: OR = 1.22 (1.02, 1.47) (p= 0.03)** Patella Pb: OR = 1.14 (1.00, 1.29) (p= 0.06) Not sig. for Arrhythmia	Tibia and patella Pb were significantly associated with longer QT and QRS intervals in subjects under age 65 and tibia Pb was significantly associated with increased risk of conduction defects, but not arrhythmias, at any age. Blood Pb was not significantly associated with any outcome.
Prospective Eum (2011) USA *Population may overlap with Proctor (1996) and others*	496 men in the Normative Aging Study free of ECG abnormalities at baseline Year = Pb was measured (1991-1995) with a follow up ECG 8 years later, on average Male = 100%	Baseline: 66.7 (7.0) years	5.8 (3.6) <u>Patella</u>: 30.3µg/g (17.7) <u>Tibia</u>: 21.6µg/g (12.0)	Intraventricular conduction defect (IVCD), atrioventricular conduction defect (AVCD), other arrhythmia, heart rate corrected QTc interval (≥440 ms), QRSc durations, JTc interval (>360 ms); classified by the Minnesota code, on	Multiple regression Adjusted for age, age^2, education, BMI, smoking, diabetes, albumin-adjusted serum calcium (mg/dL) at baseline, years between ECG tests, and QT-prolongation medications at the time of ECG	<u>Adjusted 8 year change (95% CI) in ECG by baseline Pb:</u> QTc Interval Tibia Pb (µg/g) ***P* for trend = 0.03** <16 (n=191) ref. **16.0-23 (n=208) 7.49 (1.42-13.75)** **23+ (n=195) 7.94 (1.42-14.45)** Patella Pb (µg/g) *P* for trend = 0.45 <22 (n=207) ref. 22-33 (n=190) 4.14 (-2.19-10.46) 33+ (n=202) 2.69 (-3.68-9.06) QRSc Duration	Tibia Pb was significantly associated with increases over 8 years of follow up in QT interval, QRS duration, and increased risk of QT and JT prolongation. Results were

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
				average 8.1 (SD=3.1) years after Pb measurement		Tibia Pb (µg/g) ***P* for trend = 0.005** <16 (n=191) ref. 16.0-23 (n=208) 0.52 (-3.60-4.65) **23+ (n=195) 5.94 (1.66-10.22)** Patella Pb (µg/g) *P* for trend = 0.20 <22 (n=207) ref. 22-33 (n=190) 2.87 (-1.02-7.33) 33+ (n=202) 3.16 (-1.34-7.07) None sig. for JTc interval None sig. with Blood Pb <u>Adjusted Odds Ratio (95% CI) for incident cardiac abnormality at follow-up by Pb at baseline:</u> QT prolongation (≥ 440ms) Tibia Pb (µg/g), 67 case/387 cont., ***P*-trend = 0.003** 16.0-23 vs. <16 OR=0.86 (0.39-1.88) **23+ vs. <16 OR= 2.53 (1.22-5.25)** Patella Pb (µg/g), 68 case/391 cont., *P*-trend = 0.14 **22-33 vs. <22 OR=2.67 (1.28-5.56)** 33+ vs. <22 OR=2.10 (0.96-4.60) JT Prolongation (≥360 ms) Tibia Pb (µg/g), 32 case/425 cont., ***P*-trend = 0.04** 16.0-23 vs. <16 OR=0.93 (0.32-2.72) 23+ vs. <16 OR=2.53 (0.93-6.91) Patella Pb (µg/g), 32 case/429 cont., *P*-trend = 0.21 22-33 vs. <22 OR=2.24 (0.81-6.20) 33+ vs. <22 OR=2.18 (0.75-6.35) IVCD (MN codes 7-1-1, 7-2-1, 7-4) Tibia Pb (µg/g), 33 case/458 cont., *P*-trend = 0.55 16.0-23 vs. <16 OR=1.46 (0.56-3.85) 23+ vs. <16 OR=1.45 (0.52-4.08) Patella Pb (µg/g), 33 case/463 cont., *P*-trend = 0.75 **22-33 vs. <22 OR=3.77 (1.37-10.33)** 33+ vs. <22 OR=1.57 (0.49-5.00) No increased risk of AVCD No increased risk of Arrhythmia No increased risk with Blood Pb	similar, but weaker, for patella Pb and there was no association with blood Pb. There were no associations between Pb and JT interval, IVCD, AVCD or other arrhythmias.
Prospective and Cross-sectional Gump (2005) NY, USA *Population may overlap with Gump (2007)*	122 children from Oswego Children's Study (n=202) with established early childhood blood Pb levels. Year not stated Male= 45.9%	9.5	Cord = 2.97 (1.75) Age 2.6 blood= 4.62 (2.51)* *Gump (2007) states this was abstracted from	ECG measured stroke volume (SV), heart rate, cardiac output (CO: meanSV*meanHR for a time period), total peripheral resistance (TPR: [(SBP-DBP)/3+DBP]/CO*80), and mean successive	Linear regression Adjusted for: psychosocial variables, other toxicants, emotional response to tasks, *exact adjustment variables not reported*	<u>Childhood blood Pb (µg/dL) and cardiovascular functioning:</u> Heart Rate: β=-0.62 (0.35), p<0.10 Stroke Volume, CO, and TPR had p-values >0.15 <u>Childhood blood Pb (µg/dL) and cardiovascular responses to acute stress tasks:</u> β (95% CI), Standardized β, p-value **Stroke Volume (mL): β=-0.069 (-.124 to -.015), Std β=-**	Blood Pb in early childhood was significantly associated with decreased SV and increased TPR in response to acute stress at age 9-11 years,

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Also listed for Blood Pressure and Hypertension			health records Correlation of cord and childhood Pb: r = 0.11, p>0.50	difference for each data series/time period (MSD)		**0.219, p=0.013** Heart rate (beats/min): β=0.013 (-.046 to .072), Std β=0.038, p=0.659 CO (L/min): β=-0.0056 (-.113 to .001), Std β=-0.170, p=0.054 **TPR (dyn-s/cm5): β=0.088 (.024 to .152), Std β=0.241, p=0.007** MSD (ms): β=-0.028 (-.098 to .042), Std β=-0.078, p=0.424 Cord blood was not associated with responses to acute stress tasks	but cord blood Pb was not.
Cross-sectional Gump (2007) NY, USA *Population may overlap with Gump (2005)* *Also listed for Blood Pressure and Hypertension*	122 children from Oswego Children's Study (N=202) with established early childhood blood Pb levels; Year not stated Male= 45.9%	9.5	Cord = 2.97 (1.75) Age 2.6 blood = 4.62 (2.51) abstracted from health records	ECG measured stroke volume (SV), heart rate, cardiac output (CO: meanSV*meanHR for a time period), total peripheral resistance (TPR: ([(SBP-DBP)/3+DBP]/CO*80), and mean successive difference for each data series/time period (MSD)	Sobel tests to evaluate mediation Linear regression Adjusted for: family socioeconomic status (SES), blood Pb levels, interactor for SES and blood Pb	<u>SES in relation to children's CV responses (β ; R^2; p-value of SES and Pb interaction)</u> Heart rate (beats/min): β=0.048; R^2=0.001; p=0.232 SV (mL): β=-0.176; R^2=0.003; p=0.663 CO (L/min): β=-0.319; R^2=0.019; p=0.279 TPR (dyne-s/cm^5): β=-0.398; R^2=0.017; p=0.070 MSD (seconds): β=-0.269; R^2=0.016; p=0.191 Responses to acute stress tasks With SES X Pb interaction term: TPR β=0.005, SE=0.003, p<0.10	Lower family SES was associated with higher blood Pb levels in early childhood and heightened TPR responses to acute stress tasks, but the interaction was not statistically significant.
Cross-sectional Gump (2011) NY, USA *Population may overlap with Gump (2005)* *Also listed for Blood Pressure and Hypertension and Heart Rate Variability*	140 children from the Oswego Children's Study; Year not stated Male= 55%	10.21 (0.75) Range: 9-11	Median: 0.94 Range: 0-3.76	ECG measured heart rate , stroke volume (SV), cardiac output (CO: meanSV*meanHR for a time period), total peripheral resistance (TPR: [(SBP-DBP)/3+DBP]/CO*80)	Generalized linear model with a linear contract test Adjusted for gender, age, race, BMI percentile standing, SES, family history of cardiovascular disease, and Hg level	<u>Adjusted associations of blood Pb and HR at baseline:</u> Heart Rate (n=140): p linear trend = 0.16 Pb Q1 (0.14-0.68µg/dL): 82.47 Pb Q2 (0.69-0.93µg/dL): 83.24 Pb Q3 (0.94-1.20µg/dL): 83.69 Pb Q4 (1.21-3.76µg/dL): 78.55 **Heart rate significantly increased in response to acute stress tasks (85.3 to 86.1, p<0.05).** <u>Adjusted associations of blood Pb and reactivity to acute stress:</u> Heart Rate (n=140): p linear trend = 0.85 Pb Q1 (0.14-0.68µg/dL): 0.91 Pb Q2 (0.69-0.93µg/dL): 0.19 Pb Q3 (0.94-1.20µg/dL): 0.86 Pb Q4 (1.21-3.76µg/dL): 0.58 **Stroke Volume (n=140): p linear trend = 0.04** **Pb Q1 (0.14-0.68µg/dL): 2.23** **Pb Q2 (0.69-0.93µg/dL): 0.91**	Concurrent blood Pb was significantly associated with decreased stroke volume, decreased cardiac output, and increased total peripheral resistance in response to acute stress tasks in children.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
						Pb Q3 (0.94-1.20µg/dL): -3.47 **Pb Q4 (1.21-3.76µg/dL): -0.89** **Cardiac Output (n=140): *p* linear trend = 0.05** **Pb Q1 (0.14-0.68µg/dL): 3.26** **Pb Q2 (0.69-0.93µg/dL): 1.19** **Pb Q3 (0.94-1.20µg/dL): -2.31** **Pb Q4 (1.21-3.76µg/dL): -0.20** **Total Peripheral Resist. (n=140): *p* linear trend = 0.03** **Pb Q1 (0.14-0.68µg/dL): 2.91** **Pb Q2 (0.69-0.93µg/dL): 8.18** **Pb Q3 (0.94-1.20µg/dL): 9.55** **Pb Q4 (1.21-3.76µg/dL): 9.51**	
Cross-sectional Park (2009) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	613 older men in the Normative Aging Study with bone Pb and gene polymorphisms measured; Year 1991-1995; Male = 100%	67.3 (7.2) years	Blood median: 5µg/dl (IQR 4-7) Tibia median: 19µg/g (IQR 14-27) Patella median: 26µg/g (IQR 18-37)	QTc interval (time from start of the Q wave to end of the T wave) Genotyped polymorphisms in iron metabolism genes: hemochromatosis (*HFE*), transferrin C2 (*TFC2*), and heme oxygenase-1 (*HMOX-1*)	Linear regression Adjusted for age, BMI, albumin-adjusted serum calcium, smoking status, and diabetes status	Difference in QTc interval per IQR increase in Pb, stratified by number of gene variants: β (95% CI) Blood Pb (IQR=3µg/dl) All (n=613): β=1.30 (-0.76-3.36) 0 variants (n=237): β=-0.82 (-4.35-2.71) 1 variant (n=276): β=2.65 (-0.66-5.96) 2 or 3 variants (n=100): β=6.71 (-0.70-14.13) ***p* for trend=0.04** Tibia Pb (IQR=13µg/g) **All (n=613): β=2.85 (0.29-5.40)** 0 variants (n=237): β=-2.43 (-7.05-2.37) **1 variant (n=276): β=5.17 (2.02-8.32)** 2 or 3 variants (n=100): β=7.26 (-0.72-15.25) ***p* for trend=0.01** Patella Pb (IQR=19µg/g) **All (n=613): β=2.64 (0.13-5.15)** 0 variants (n=237): β=-0.53 (-5.23-4.18) **1 variant (n=276): β=3.77 (0.57-6.98)** 2 or 3 variants (n=100): β=5.38 (-1.74-12.49) *p* for trend=0.10	BonePb was significantly associated with increases in QT interval, which was stronger in carriers of iron metabolism gene polymorphisms. Concurrent blood was only significantly associated in with QT interval carriers of one iron metabolism gene variant.
Clinical Cardiovascular Disease							
Case-control Afridi (2010a) Hyderabad, Pakistan	130 patients admitted with myocardial infarction and 61 healthy controls in the same city, matched by age group and SES with no history of CVD or family history of MI or cardiac death	Range: 45-60	No blood Pb Hair Pb: Range of group means 6.4-18.6µg/g Estimated range: 2-6 µg/dl based on children with blood and hair Pb available	Number of myocardial infarction (MI) attack and survival (32 patients were admitted for their 3rd MI attack and 25 of them died.) Excluded renal or hepatic disease,	Linear regression, pearson correlation coefficient, unpaired student *t* test of mean differences	Hair Pb levels: mean (SD); Regression, Correlation **Men, *p* <0.001** Controls: 7.5 (0.4) µg/g; (ref.) 1st MI: 9.7 (1.2) µg/g; β=0.214, r=0.065 2nd MI: 13.6 (6.7)µg/g; β=8.59, r=0.33 3rd MI: 18.6 (5.4) µg/g; β=10.4, r=0.53 **Women, *p* <0.001** Controls: 6.4 (1.6) µg/g; (ref.) 1st MI: 7.9 (0.7) µg/g; β=0.028, r=0.06 2nd MI: 11.2 (5.3) µg/g; β=1.12, r=0.33 3rd MI: 14.5 (3.9) µg/g; β=0.912, r=0.50	Hair Pb levels increased with number of heart attacks and patients who died after a third MI had higher Pb levels.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
	before age 55 Year = 2007-2008; Male = 59% cases, 54% controls		(Afridi *et al.* 2010b)	vascular disease, and antioxidant or aspirin treatment			
Cross-sectional Guallar (2006) USA	4,447 participants over age 40 from NHANES without missing data, including cadmium; Year= 1999-2002; Male = 48.3%	OHAT calc mean: 56.4 Cases: 68.5 (0.6) Noncases: 55.5 (0.2)	OHAT calc mean: 1.95µg/dl Cases: 2.56 (95% CI 2.41-2.72) Noncases: 1.91 (95% CI 1.86-1.97)	Peripheral arterial disease (PAD, n=310 cases): ankle-brachial index lower than 0.9 in at least one leg	Multivariable logistic regression, χ^2 test for trend, Adjusted for age, sex, race/ethnicity, education, smoking status, alcohol intake, BMI, C-reactive protein, serum folate and/or vitamin B12 and blood cadmium level PAD models further adjusted for diabetes, hypertension, hypercholesterolemia, estimated glomerular filtration rate, and homocysteine	Ratio (95% CI) of geometric mean plasma homocysteine levels by quintile of Blood Pb (fully adjusted model): Q1 (<1.1 µg/dl): ref. **Q2 (1.1-1.6 µg/dl): 1.03 (1.00-1.06)** **Q3 (1.6-2.2 µg/dl): 1.06 (1.03-1.19)** **Q4 (2.2-3.2 µg/dl): 1.10 (1.07-1.13)** **Q5 (≥3.2 µg/dl): 1.12 (1.09-1.17)** **P_{trend} <0.001** Adjusted Odds Ratio (95% CI) for PAD by quintile of blood Pb (n=cases/noncases); Q1 (<1.1 µg/dl, n=43/939): ref. Q2 (1.1-1.6 µg/dl, n=41/821): 0.99 (0.53-1.85) Q3 (1.6-2.2 µg/dl, n=53/811): 1.19 (0.74-1.92) **Q4 (2.2-3.2 µg/dl, n=73/809): 1.64 (1.02-2.61)** **Q5 (≥3.2 µg/dl, n=100/757): 1.65 (1.07-2.56)** **P_{trend} = 0.045**	Concurrent blood Pb was significantly associated with risk of PAD, independent of plasma homocysteine.
Cross-sectional Ishida (1996) Japan	128 ceramic painters not on medications; 26.6% of the area's ceramic painters; Year not stated Male = 45%	53.3 years Range: 29-75 Men: 55 yrs Women: 52 yrs	13.3µg/dl Range: 2.1-69.5 Men 16.5 (2.1) Range: 3.5-69.5 Women 11.1 (1.7) Range: 2.1-31.5	Median nerve maximal conduction velocity (MCV, measure of motor nerve function), coefficient of variation of R-R interval on electrocardiography (supine= CVRR, while breathing deeply=D-CVRR; measures of parasympathetic function), postural changes in finger blood flow volume (ΔFBF), and changes in finger blood flow drop velocity (FDV) from the supine to standing position (sympathetic function)	Analysis of variance and correlation Stepwise multiple regression analysis: ΔFBF model included age, BMI, smoking, and alchol	ΔFBF mean (SD) by Pb concentration: All subjects: **ANOVA p=0.002** **r=-0.313, p<0.001** **β=0.213; p=0.010** Men: ≤9.9 µg/dl (n=15): 0.42 (0.27) 10.0-19.9 µg/dl (n=19): 0.39 (0.25) 20.0-29.9 µg/dl (n=10): 0.21 (0.25) ≥30 µg/dl (n=11): 0.31 (0.20) r=-0.296, **p=0.032** Women: ≤9.9µg/dl (n=28): 0.47 (0.19) 10.0-19.9 µg/dl (n=32): 0.47 (0.17) 20.0-29.9 µg/dl (n=4): 0.35 (0.11) ≥30 µg/dl (n=1): 0.65 r=-0.208, p=0.097 No significant differences with blood Pb in the other physiological tests: MCV, CVRR, D-CVRR, and FDV	Concurrent blood Pb was significantly associated with decreases in postural changes in finger blood flow volume is consistent with an atherosclerotic effect.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Prospective Jain (2007) Boston, MA, USA; *Population may overlap with Proctor (1996) and others*	837 men in the Normative Aging Study without a history of ischemic heart disease at time of Pb measurement. Year = 1991-2001; Male = 100%	Noncases (n=754): <60=162, 60-69=378, ≥70=214 Cases (n=83): <60=10, 60-69=48, ≥70=25	Calc. mean = 6.3 Noncases (n=738): 6.2 (4.3) Cases (n=80): 7.0 (3.8) Patella Pb Noncases (n=487): 30.6 (19.7) µg/g Cases (n=63): 36.8 (20.8) µg/g TIbia Pb Noncases (n=486): 21.4 (13.6) µg/g Cases (n=63): 24.2 (15.9) µg/g	Coronary Artery Disease (described as ischemic heart disease by diagnosis of myocardial infarction or angina pectoris)	Cox proportional hazards model including age, race, and serum high density lipids	Age, blood and patella Pb were significantly higher in cases than noncases (p<0.05 for all 3). Unadjusted Cox proportional HR (95%CI): **Blood Pb ≥ 5 µg/dl: 1.64 (1.00-2.68)** Log Blood Pb: 1.40 (0.99-1.98) **Log Patella Pb: 3.27 (1.41-7.58)** Log Tibia Pb: 2.76 (0.94-8.12) Adjusted Cox proportional HR (95%CI): **Blood Pb ≥ 5 µg/dl: 1.73 (1.05-2.87), p=0.05** **Log Blood Pb: 1.45 (1.01-2.06), p=0.05** **Log Patella Pb: 2.64 (1.09-6.37), p=0.05** Log Tibia Pb: 1.84 (0.57-5.90), p=0.31	Blood and patella Pb were significantly associated with increased risk of coronary artery disease in this prospective study.
Cross-sectional Kaewboonchoo (2010) Bangkok, Thailand *Population may overlap with Kaewboonchoo (2007) listed in Blood Pressure and Hypertension*	420 bus drivers without a history of hypertension, heart disease, or tachycardia at the time of SDPTG measurement; Year not stated Male = 100%	41.6 (7.7) Range: 20 - 60 years	6.3 (2.2) Range: 2.5-16.2µg/dl	Second derivative finger photoplethysmogram waveform (SDPTG) and a mean aging index of SDPTG (SDPTG-AI) Higher values of SDPTG-AI indicate lower central and peripheral arterial functions	Mean comparison by Student's *t* test Pearson's correlation coeffieicient (*r*) Multiple regression analysis adjusted for age, BMI, smoking, alcohol, physical exercise	Mean SDPTG-AI (SD): **p=0.015** Low Pb (<4.1µg/dl, n=54) = -0.56 (0.30) High Pb (>8.5µg/dl, n=83) = -0.42 (0.30) Correlation of SDPTG-AI and Log blood Pb: ***r* = 0.185, p<0.01** Blood Pb regression with SDPTG-AI: ***β* = 0.017 (p=0.003)** Age, BMI, and smoking also included in model	Concurrent blood Pb was significantly associated with higher mean aging index of SDPTG – a marker of poor arterial function.
Cross-sectional Kim (2008) South Korea *Also listed for Blood Pressure and Hypertension*	13,043 Pb workers in the Special Health Surveillance Program; Year = 2003; Male = 69%	33.7 (10.0) years	Geometric mean 6.08 (2.53) Range; 0.002 - 123.22 70% of workers <10µg/dl	Coronary Artery Disease (described as ischemic heart disease) and Cerebral Vascular Disease,	Relative risk was calculated as in Lawes (2003). No adjustment for other factors	Relative Risk [95% CI not reported] for Ischemic Heart Disease: PbB <5µg/dL (referent) 5 µg/dl ≤ PbB < 10 µg/dl = 1.026 (men) 1.017 (women) 10 µg/dl ≤ PbB < 15 µg/dl = 1.122 (men) 1.070 (women) 15 µg/dl ≤ PbB < 20 µg/dl = 1.210 (men) 1.125 (women) 20 µg/dl ≤ PbB = 1.260 (men) 1.154 (women) Relative Risk [95% CI not reported] for Cerebral Vascular Disease: PbB <5µg/dL (referent) 5 µg/dl ≤ PbB < 10 µg/dl = 1.034 (men) 1.022 (women) 10 µg/dl ≤ PbB < 15 µg/dl = 1.168 (men) 1.095 (women) 15 µg/dl ≤ PbB < 20 µg/dl = 1.292 (men) 1.172 (women) 20 µg/dl ≤ PbB = 1.362 (men) 1.212 (women) The impact fractions for cardiac diseases among Pb workers from increases in blood pressure were estimated 4.9 to 12.8 times the general population.	Blood Pb was not significantly associated with increased risk of coronary artery disease or cerebral vascular disease in these Pb exposed workers.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Prospective Møller (1992) Denmark *Population may overlap with Grandjean (1989)* *Also listed for Blood Pressure and Hypertension and Cardiovascular Mortality*	1, 050 adults born in 1936 and living in the 4 municipalities served by the Glostrup Hospital (Glostrup Population Study); Year = Baseline 1976, Follow up through 1990; Male = 48%	40 years at baseline	Baseline Calc. mean=11.5 Men (n=504): 13.6 (5.7) Range=5 – 60 Women (n=546): 9.6 (3.8) Range=4 – 39	Coronary heart disease and cardiovascular disease (fatal and non-fatal cases)	Multiple regression analyses and Cox proportional hazards model. Tobacco, cholesterol, physical activity, sex, SBP, and alcohol	<u>Regression of cardiovascular endpoints on ln(blood Pb) from 1976 – 1990</u>: β, Relative Hazard (RH), *p* value Coronary heart disease for a 1 ln blood Pb unit change: **Unadjusted β=1.10, RH=2.14, *p*=0.003** Fully adjusted β=0.66, RH=1.58, *p*=0.15 Cardiovascular disease for a 1 ln blood Pb unit change: **Unadjusted β=0.66, RH=1.58, *p*=0.05** Fully adjusted β=0.14, RH=1.10, *p*=0.74	After adjustment there was no significant association between blood Pb and coronary heart disease or cardiovascular disease.
Cross-sectional Muntner (2005) USA *Population may overlap with Den Hond (2002) and others* *Also listed for Blood Pressure and Hypertension*	9,961 participants from NHANES; Year= 1999-2002 Male = 50.3%	mean not reported all ≥ 18	1.64µg/dl 95% CI: 1.59-1.68	Peripheral artery disease (PAD): ankle-brachial index lower than 0.9	Multivariable logistic regression, χ^2 test for trend, Adjusted for age, sex, diabetes, BMI, current and former smoking, alcohol consumption, having a high school education, and having health insurance	<u>Adjusted Odds Ratio (95% CI) of Peripheral Artery Disease by Quartile of Blood Pb</u>: Disease % (SE) Q1 (<1.06 µg/dl)=ref.; 2.6% (0.6) Q2 (1.06-1.63 µg/dl) OR=1.00 (0.45-2.22); 3.0% (0.5) Q3 (1.63-2.47 µg/dl) OR=1.21 (0.66-2.23); 4.8% (0.6) **Q4 (≥2.47 µg/dl) OR=1.92 (1.02-3.61); 7.7% (0.6)** ***P* Value for Trend <0.001;**	Concurrent blood Pb was significantly associated with increased risk of PAD.
Cross-sectional Navas-Acien (2004) USA *Population may overlap with Den Hond (2002) and others*	2,125 participants from NHANES 40 years and older; Year= 1999-2000 Male = 50.3%	40-49 (n=556), 50-59 (n=447), 60-69 (n=583), ≥70 (n=539)	Geometric mean: 2.1 µg/dL	Peripheral artery disease (PAD)	Adjusted odds ratios; regression models. Sex, age, BMI, education, race, smoking, serum cotinine, alcohol intake, hypertension, diabetes, hypercholesterolemia, glomerular filtration rate, C-reactive protein, blood cadmium levels	Subjects with Peripheral Artery Disease (PAD) had **13.8% (95% CI 5.9, 12.9)** higher mean levels of blood Pb. <u>Odds ratios (95% CI) of PAD by quartile of blood Pb:</u> 1st quartile (<1.4µg/dL) = ref. 2nd quartile (1.4-2.1µg/dL) = 1.63 (0.51, 5.15) 3rd quartile (2.1-2.9µg/dL) = 1.92 (0.62, 9.47) 4th quartile (>2.9µg/dL) = 2.88 (0.87, 9.47) ***p*= 0.02 for trend, but 0.05 after adjusting for cadmium**	Blood Pb was significantly associated with increased prevalence of PAD, but adjustment for blood cadmium reduced statistical significance.
Prospective Pocock (1988) England	7,371 men randomly selected from general practices in 24 British towns (The Regional Heart Study); Year not stated Male =100%	[mean not provided] Range = 40 – 59 years.	mean not reported **limits utility*	Coronary Artery Disease (described as ischemic heart disease)	Multiple regression analyses Age, BMI, alcohol intake, smoking, social class, town of residence.	Mean blood Pb for men with Ischemic heart disease: 16.3 µg/dL Others: 15.22µg/dL Mean blood Pb for men with Stroke: 16.7µg/dL Others: 15.3 µg/dL	Lack of information on blood Pb levels in this study limits the utility in this evaluation.
Cross-sectional Schwartz (1991) USA	9,932 participants from NHANES II; Year= 1976 – 1980; % male not stated	mean not reported Range = 20 – 74	mean not reported **limits utility*	Left ventricular hypertrophy	Step-wise regression; SURREGR; RTILOGIT Age, BMI, race, family	Regression of blood Pb and left ventricular hypertrophy: **β(SE): 0.0283 (0.0100); *p*= 0.0087**	Blood Pb was significantly associated with left ventricular

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Also listed for Blood Pressure and Hypertension		years			history, cholesterol, height, smoking, serum zinc, tricep skin fold thickness		hypertrophy, but the mean levels are above 10µg/dl.
Cross-sectional Zeller (2010) Innsbruck, Austria	197 women, Atherosclerosis Risk Factors in Female Youngsters study Year = 2005; Male = 0%	mean not reported 18-22 years	mean not reported Tertiles: <0.72µg/dl, 0.72-0.82µg/dl, and >0.82µg/dl	Intima-media thickness of the common and carotid arteries *most of this paper focused on in vivo and in vitro studies of mechanism	Multivariate logistic regression Systolic blood pressure, smoking, fasting glucose, insulin resistance, cholesterol, waist circumference, social status family history for hypertension, GOT, lipoprotein(a), C-reactive protein, homocysteine, T-cell reactivity against human Hsp60, soluble Hsp60 in serum, asthma and oral contraceptives	<u>Increased serum Pb levels and intima-media thickness for 1 SD increase</u>: **OR = 1.6 (1.1, 2.4) p=0.01** The risk increased over tertile groups (**p<0.05 for linear trend**) 8 other metals tested were not significantly associated	Concurrent serum Pb levels in healthy young women were significantly associated with an increased risk for high intima-media thickness.
Cardiovascular Mortality							
Prospective Lin (2011) Taiwan	927 patients on maintenance hemodialysis for 6 months without previous Pb exposure, malignancies, infections, or hospitalization or surgery in the last 3 months; 803 completed follow-up for 18 months; Year not stated Male = 51%	55.7 (13.4) Range: 18-93 years	Median: 10.4µg/dl Range: 1.1-41.8) Tertile 1 (<8.51) median = 6.3µg/dl Tertile 2 (8.51-12.64) median = 10.4µg/dl Tertile 3 (>12.64) median = 16.4µg/dl	Mortality and cause of death (59 patients died after 18 months of follow up) *Figure says 36-month infection cause, but text says 18-month, and there is no other mention of 36 months of follow up	Kaplan Meier survival analysis Cox multivariable analysis adjusted for age, diabetes, education, hemodialysis vintage, using biocompatible membrane of dialyzers, normalized protein catabolic rate, daily residual urine<100 mL, hemoglobin, serum albumin, HDL, creatinine, phosphate, cardiothoracic ratio, logarithmic transformation of ferritin, intact parathyroid hormone, and high-sensitivity C-reactive protein	<u>All-cause mortality</u>: Kaplan Meyer survival **Tertile 3 (10.0%) vs 1 (2.6%): χ^2 =14.51, p<0.001** Tertile 2 not formally tested (mortality est. 6.5% Fig 2) <u>All-cause mortality</u> Hazard Ratio (95% CI): Blood Pb (Tertile 1=ref.): Tertile 2 vs. 1: HR=2.69 (0.47-3.44) **Tertile 3 vs. 1: HR=4.70 (1.92-11.49)** Hemoglobin Corrected Blood Pb: (Tertile 1=ref.): Tertile 2 vs. 1: HR=3.52 (0.41-5.01) **Tertile 3 vs. 1: HR=4.98 (1.86-13.33)** <u>Cardiovascular-cause mortality</u> HR (95% CI): Blood Pb (Tertile 1=ref.): **Tertile 2 vs. 1: HR=3.70 (2.06-6.48)** **Tertile 3 vs. 1: HR=9.71 (2.11-23.26)** Hemoglobin Corrected Blood Pb: (Tertile 1=ref.): Tertile 2 vs. 1: HR=3.52 (0.51-6.33) **Tertile 3 vs. 1: HR=7.35 (1.64-33.33)** <u>Infection-cause mortality*</u> HR (95% CI): Blood Pb (Tertile 1=ref.): Tertile 2 vs. 1: HR=4.33 (0.35-6.54) **Tertile 3 vs. 1: HR=5.35 (1.38-20.83)** Hemoglobin Corrected Blood Pb: (Tertile 1=ref.): Tertile 2 vs. 1: HR=3.02 (0.23-2.07) **Tertile 3 vs. 1: HR=4.72 (1.27-17.54)**	Blood Pb was significantly associated with increase risk of death due to cardiovascular or infection causes in dialysis patients.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Prospective Møller (1992) Denmark *Population may overlap with Grandjean (1989) Also listed for, Blood Pressure and Hypertension and Clinical Cardiovascular Disease.*	11, 050 adults born in 1936 and living in the 4 municipalities served by the Glostrup Hospital (Glostrup Population Study); Baseline: 1976 Follow up through 1990; Male = 48%	40 years at baseline	Baseline Calc. mean=11.5 Men (n=504): 13.6 (5.7) Range=5 – 60 Women (n=546): 9.6 (3.8) Range=4 – 39	Total Mortality	Multiple regression analyses and Cox proportional hazards model. Tobacco, cholesterol, physical activity, sex, SBP, and alcohol	Regression of total mortality on ln(blood Pb) from 1976 – 1990: β, Relative Hazard (RH), *p* value (n=1050): Total mortality **Unadjusted β=1.11, RH=2.16, *p*=0.001** Fully adjusted β=0.66, RH=1.58, *p*=0.12 Analyses of coronary heart disease and cardiovascular disease included fatal and non-fatal cases	After adjustment there was no significant association between blood Pb and total mortality
Prospective Menke (2006) USA *Population may overlap with Den Hond (2002) and others*	13,946 adult participants of NHANES III (≥17 years of age at baseline and matched to the National Death Index records for up to 12 years for all-cause and cause-specific mortality); Year= Baseline was 1988 – 1994; follow-up through 2000; Male= 47%	44.4 (0.5) years	Geometric mean at baseline: 2.58 µg/dl	Mortality by all cause, cardiovascular disease, myocardial infarction, stroke, and cancer	Cox regression analyses with Schoenfeld residuals; restricted quadratic splines. Age, race-ethnicity, sex, urban residence, smoking, alcohol intake, education, physical activity, household income, menopausal status, BMI, CRP, total cholesterol, diabetes mellitus.	Hazards ratio by tertile of blood Pb at baseline Tertile 1: ≤1.03 µg/dL (reference) Tertile 2: 1.94-3.62 µg/dL Tertile 3 ≥3.63 µg/dL **All-cause mortality (p=0.002 for trend)** Tertile 2 vs. 1: HR (95% CI) = 0.91 (0.72, 1.15) **Tertile 3 vs. 1: HR (95% CI) = 1.25 (1.04, 1.51)** **Cardiovascular Disease (*p*=0.003 for tend)** Tertile 2 vs. 1: HR (95% CI) = 1.03 (0.69, 1.55) **Tertile 3 vs. 1: HR (95% CI) = 1.55 (1.08, 2.24)** **Myocardial infarction (*p*=0.007 for tend)** Tertile 2 vs. 1: HR (95% CI) = 1.02 (0.55, 1.89) **Tertile 3 vs. 1: HR (95% CI) = 1.89 (1.04, 3.43)** **Stroke (*p*=0.017 for tend)** Tertile 2 vs. 1: HR (95% CI) = 2.19 (0.87, 5.53) **Tertile 3 vs. 1: HR (95% CI) = 2.51 (1.20, 5.26)** Cancer (*p*=0.101 for tend) Tertile 2 vs. 1: HR (95% CI) = 0.72 (0.46, 1.12) Tertile 3 vs. 1: HR (95% CI) = 1.10 (0.82, 1.47)	Blood Pb was significantly associated with all cause mortality and mortality from cardiovascular disease, myocardial infarction, and stroke, but not cancer over 12 years of follow-up in adults.
Cross-sectional Schober (2006) USA *Population may overlap with Den Hond (2002) and others*	9,757 participants ≥40 years at baseline from the NHANES III matched to the 2000 National Death Index records; Year= Baseline was 1988 – 1994; follow-up through 2000; Male = 48%	Calc. overall mean: 58.6 <5µg/dL (n=6608): 57.0 5-9µg/dL (n=2532): 60.6 >10µg/dL (n=617): 62.0	mean not reported <5µg/dL n=6608 5-9µg/dL n=2532 >10µg/dL n=617	Mortality from all causes, cancer, and cardiovascular disease	Cox proportional hazard regression analysis; multivariate proportional hazard models Sex, race/ethnicity, education, and smoking status	Relative risk (95% CI): <5 µg/dL = ref. All causes **5-9 µg/dL: 1.24 (1.05-1.48)** **≥10 µg/dL: 1.59 (1.28-1.98)** **P-value for trend <0.001** Cardiovascular disease 5-9 µg/dL: 1.20 (0.93-1.55) **≥10 µg/dL: 1.55 (1.16-2.07)** **P-value for trend <0.01** Cancer **<5 µg/dL: 1.44 (1.12-1.86)** **≥10 µg/dL: 1.69 (1.14-2.52)** **P-value for trend <0.01**	Blood Pb was significantly association with increased risk of death from all causes, cardiovascular disease, and cancer over 12 years of follow-up of adults over age 40.

Study Description	Population	Age (yr) Mean (S.D.)	Blood Pb (µg/dl) Mean (S.D.)	Cardiovascular Measures	Statistical Modeling; Covariates	Findings	Observed Effect
Prospective Weisskopf (2009) Boston, MA, USA *Population may overlap with Proctor (1996) and others*	860 men with valid patella bone Pb from the Normative Aging Study; Year = bone Pb began in 1994 and follow up continued through 2007; Male = 100%	67.3 (7.3) years in 1994	Patella Pb = 31.2 (19.4) µg/g bone mineral Blood Pb = 5.6 (3.4) µg/dl	All-cause mortality, cardiovascular disease mortality, and cancer mortality	Cox proportional hazards regression with multivariable models Results presented adjusted for age, smoking, and education. Those with disease at baseline excluded.	Hazards ratio and 95% CI by tertile of patella Pb (<22 µg/g served as reference) All-cause (***p*=0.02 for trend**) 22 – 35 µg/g, HR = 1.75 (0.82, 3.75) **>35 µg/g, HR = 2.52 (1.17, 5.41)** All-cardiovascular (***p*=0.003 for trend**) 22 – 35 µg/g, HR = 1.63 (0.51, 5.18) **>5 µg/g, HR = 5.63 (1.73, 18.3)** Cancer (*p*=0.14 for trend) 22 – 35 µg/g, HR = 0.82 (0.26, 2.59) >35 µg/g, HR = 0.32 (0.08, 1.35) Hazards ratio and 95% CI by tertile of blood Pb (<4 µg/dl served as reference) All-cause (*p*=0.67 for trend) 4 – 6 µg/dl, HR = 0.69 (0.41, 1.19) >6 µg/dl, HR = 0.84 (0.50, 1.42) All-cardiovascular (*p*=0.44 for trend) 4 – 6 µg/dl, HR = 0.63 (0.29, 1.38) >6 µg/dl, HR = 0.69 (0.33, 1.47) Cancer (*p*=0.15 for trend) 4 – 6 µg/dl, HR = 1.03 (0.42, 2.55) >6 µg/dl, HR = 0.53 (0.20, 1.39)	Bone Pb, but not blood Pb, was significantly associated with all-cause and cardiovascular mortality, but not cancer mortality in men.

Abbreviations: ΔFBF - changes in finger blood flow volume; Adj – adjusted; Al - aluminum; ANOVA - analysis of variance; As - arsenic; AVCD - atrioventricular conduction defect; BMI - body mass index; BP - blood pressure; CAB - cardiac autonomic balance; CAR - cardiac autonomic regulation; Cd – cadmium; CI - confidence interval; Co – cobalt; CO - cardiac output; Cu- copper; CVRR - coefficient of variation of R-R interval on electrocardiography; DBP - diastolic blood pressure; ECG - electrocardiographic; FDV - flow drop velocity; GH – gestational hypertension; GOT - glutamic oxalic transaminase; HDL – high-density lipoprotein; HF-HRV – high frequency heart rate variability; HF - high-frequency; *HFE* – hemochromatosis; Hg – mercury; *HMOX-1* - heme oxygenase-1; HR - hazards ratio; HRV - heart rate variability; Hz - hertz; IVCD - intraventricular conduction defect; LF - low-frequency; MCV - maximal conduction velocity; MI - myocardial infarction; MSD - mean successive difference; NS – not significant; OR - odds ratio; PAD – peripheral artery disease; PP - pulse pressure; RR - relative risk; PEP - pre-ejection period; SBP - systolic blood pressure; SD – standard deviation; SDPTG - second derivative finger photoplethysmogram waveform; SDPTG-AI - mean aging index of SDPTG Se – selenium; SE – standard error; SES – socioeconomic status; SV - stroke volume; *TFC2* - transferrin C2; TPR - total peripheral resistance; Zn – zinc;

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NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

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APPENDIX D:
HUMAN STUDIES OF RENAL EFFECTS OF LEAD CONSIDERED IN DEVELOPING CONCLUSIONS

Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Cross-sectional Akesson (2005) Sweden	816 Swedish women from the Women's Health in the Lund Area (WHILA), 726 with blood Pb available; Year= 1999-2000 Male = 0%	Median (5-95% percentiles): 58 (53-64)	Median (5-95% percentiles): 2.2 (1.1-4.6)	GFR (based on cystatin C); creatinine clearance; α1-microglobulin; NAG *Primary exposure assessed in study was Cd*	Multiple linear regression; Age, BMI, diabetes, hypertension, and regular use of nephrotoxic drug, blood and urinary Cd (in separate models), smoking status by stratification	<u>Multiple logistic regression with blood Pb, β (95%CI):</u> **GFR (mL/min; adjusted for urinary Cd)** **All (n=816): -0.20 (-0.32 to -0.09)** **Never-smokers: -0.26 (-0.43 to -0.09)** **GFR (mL/min; adjusted for blood Cd)** **All (n=816): -0.20 (-0.30 to -0.07)** **Never-smokers: -0.20 (-0.4 to -0.07); significant interaction with diabetes** **creatinine clearance (mL/min; adjusted for urinary Cd)** **All (n=816): -0.18 (-0.30 to -0.06)** **Never-smokers: -0.30 (-0.5 to -0.1)** **creatinine clearance (mL/min; adjusted for blood Cd)** **All (n=816): -0.18(-0.30 to -0.07)** **Never-smokers: -0.30 (-0.5 to -0.1)** urinary α1-microglobulin (µg/L; adjusted for urinary Cd) All (n=816); NS (data not reported) Never-smokers: NS (data not reported) urinary α1-microglobulin (µg/L; adjusted for blood Cd) All (n=816); NS (data not reported) Never-smokers: NS (data not reported) urinary NAG (U/L; adjusted for urinary Cd) All (n=816): NS (data not reported) Never-smokers: NS (data not reported) urinary NAG (U/L; adjusted for blood Cd) All (n=816): NS (data not reported) Never-smokers: NS (data not reported)	Blood Pb is negatively correlated with GFR and creatinine clearance, but not α1-microglobulin and NAG.
Cross-sectional Alfven (2002) Sweden	1,021 individuals living near two battery plants (479 men, 542 women); 117 participants were current or former workers from plants. Part of the OSCAR (osteoporosis-cadmium as a risk factor study Year not stated Male = 47%	Men = 54 (10^{th} and 90^{th} percentiles: 18-81) Women = 52 (10^{th} and 90^{th} percentiles: 16-81)	male: 3.3 µg/dL female: 2.3 µg/dL	Urinary α_1-microglobulin	Multiple linear regression Age, smoking status, blood cadmium	men: 0.015 (-0.80 to 0.83) women: -0.19 (-0.99 to 0.60)	No association between blood Pb and urinary α_1- microglobulin
Cross-sectional Bernard (1995) Czech Republic	195 children aged 12-15 years referent area (n=51), "polluted" area 1 (n=91), "polluted"	12-15	Referent site: male: 8.7 µg/dL female: 8.39µg/dL Area 1:	β_2-microglobulin; urine RBP, Clara cell protein, urinary NAG activity, albumin	ANOVA on log-transformed data; Scheffe's multiple comparison test RBP and blood Pb	<u>Polluted areas relative to referents:</u> **β_2-microglobulin: ↑ area 1 (89.1 vs 60.3 µg/g creatinine); p<0.05** **Clara cell protein: ↑ area 1 (1.18 vs 0.62 µg/g creatinine); p<0.05**	↑ RBP in two polluted areas; increases in β_2-microglobulin, Clara cell

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
	area 2 (n=53); Year not stated % male not stated		male:10.9 µg/dL female: 9.44 µg/dL Area 2: male: 14.9 µg/dL female: 12.9 µg/dL		multivariate analysis adjusted for age, sex, and other metals	**RBP: ↑ area 1 (109.4 vs 73.8 µg/g creatinine), ↑ area 2 (117.8 vs 73.8 µg/g creatinine); both p<0.05** **NAG: ↑ area 1 (2.32 vs 1.56 UI/g creatinine); p<0.05** Albumin: no differences <u>Continuous variable analysis:</u> RBP: significant correlation between urinary excretion and blood Pb (partial r^2=0.046, regression coefficient=0.302, p=0.005)	protein, and NAG were only noted in the "polluted" area with lower blood Pb levels. Albumin was not different in either area. Significant correlation between urinary excretion of RBP and blood Pb
Cross-sectional de Burbure (2003) France	600 adults living near two nonferrous smelters for ≥8 years compared to age (n=399) and gender-matched referents living in neighboring municipalities with unpolluted soil; Year not stated Male = 50%	Men: Polluted area= 34.6 (8.9) Referent = 35.2 (9.2) Women: Polluted area= 35.9 (9.6) Referent= 34.9 (8.6)	Polluted Area = male:6.8 (range: 1-24) female: 5.3 (range: 0.6-19) Referents = male: 7.1 (range: 1.1-26.2) female:4.2 (range: 0.2-15.4)	serum creatinine, urinary total protein, albumin, transferrin, β2-microblobulin, RBP, brush border antigen, NAG *Study assessed exposure to Pb, Cd, and Hg*	Multiple linear regression, t-test, and ANOVA Age, sex, BMI, area of residence, log urine Hg, log blood Cd and urinary creatinine	No statistically significant difference in any renal parameters (geometric means) in adults living in referent area (n= 86-91 men; 78-82 women) and "polluted" area (n= 147-155 men; 156-169 women) No significant correlations in multiple regression model (data not shown) Selected renal findings: Serum creatinine (mg/L) male: 14.3 (referent) vs 13.8 (polluted) female: 13.3 (referent) vs 12.6 (polluted) β2 microglobulin (µg/g creatinine) male: 68.16 (referent) vs 76.29 (polluted) female: 63.79 (referent) vs 71.98 (polluted)	No difference in renal parameters was observed, however blood Pb was higher in men from the "unpolluted" referent region compared to the "polluted" region
Cross-sectional de Burbure (2003) France *Population may overlap with de Burbure (2006)*	400 children living near two nonferrous smelters for ≥8 years compared to age and gender-matched referents living in neighboring municipalities with unpolluted soil; exclusionary criteria; obesity, diabetes and puberty; Year not stated Male = 50%	Range: 8.5-12.3	Exposed = male:4.2 (range: 0.5-14.8) female:3.7 (range: 0.8-16.6) Referents = male: 3.4 (range: 0.2-10.7) female: 2.7 (range: 0.2-12.6)	Urinary total protein, albumin, transferrin, β2-microblobulin, RBP, brush border antigen, NAG *Study assessed exposure to Pb, Cd, and Hg*	Multiple linear regression, t-test, and ANOVA Age, sex, BMI, area of residence, log urine Hg, log blood Cd and urinary creatinine	No significant correlations in multiple regression model Selected renal findings: β2 microglobulin (µg/g creatinine) male: 87.8 (referent) vs. 97.3 (polluted) female: 88.2 (referent) vs. 94.8 (polluted area)	No significant correlations between blood Pb and renal markers

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Cross-sectional de Burbure (2006) France, Czech Republic, and Poland *Population may overlap with de Burbure (2003)*	804 children from 3 countries living near two nonferrous smelters for ≥8 years compared to age and gender-matched referents living in neighboring municipalities with unpolluted soil in the same region of each country. Year not stated Male = 49.3%	8-5-12.3	382 French children: Exposed male(n=100): 4.2 (0.2) Referent male(n=94): 3.4 (0.2) Exposed female(n=94): 3.6 (0.2) Referent female (n=94): 2.8 (0.2) 174 Polish children: Exposed male (n=42): 6.5 (0.2) Referent male(n=35): 3.8 (0.1)- Exposed female(n=47): 5.7 (0.2) Referent female (n=50): 3.4 (0.1) 160 Czech children: Exposed male (n=42): 5.0 (0.1) Referent male(n=43): 3.6 (0.1) Exposed female(n=39): 4.1 (0.2) Referent female (n=36): 3.4 (0.1)	Serum creatinine, serum cystatin C, serum β2-microglogulin *Study assessed exposure to Pb, Cd, Hg, and As*	Step-wise multiple regression using logPb (blood), rank Cd (blood), rank Hg (urine), and log As (urine), log creatinine (urine), log BMI, age, sex, and area of residence Standardizations Serum Creatinine (1): creatinine (urine), sex, rank Cd (blood) x rank Hg (urine), and Pb (blood) x rank Hg (urine) Serum Creatinine (2): Cd (urine), creatinine (urine), sex, and Pb (blood) x rank Hg (urine) Serum $\beta_2$microglobulin: rank Hg (urine) and creatinine (urine) Serum Cystatin C: none	Regression coefficients for renal measures (log transformed) with Pb as independent variable: **creatinine (serum) = -0.026, p=0.007** **serum cystatin C = -0.056; p=0.02** **$\beta_2$microglobulin (serum) = -0.095; p=0.01** *similar results when blood or urine Cd included Differences in biomarkers by quartiles of blood Pb (µg/dL) standardized for other cofactors: Serum Creatinine (1): <2.85 (ref, n=150) 2.85-4.07 (n=149): p=NS 4.08-5.59 (n=151): p=NS **>5.59 (n=150): p =<0.01, lower than referent** Serum Creatinine (2): <28.4 (ref, n=149) 2.84-4.06 (n=151): p=NS 4.07-5.56 (n=148): p=NS **>5.56 (n=150): p =<0.01, lower than referent** Serum $\beta_2$microglobulin: <3.10 (ref, n=82); 3.10-4.14 (n=80): p=NS; 4.15-5.86 (n=81): p=NS; **>5.86 (n=81): p =<0.001, lower than referent** Serum Cystatin C: <3.09 (ref, n=81); 3.09-4.17 (n=82): p=NS; 4.18-5.86 (n=79): p=NS; >5.86 (n=81) p=0.065, lower than referent	Three renal measures decreased with increasing levels of blood Pb, in these children with low Pb levels
Prospective Factor-Litvak (1993) Yugoslavia	1,465 pregnant women in two Yugoslavian towns, one near a smelter [K. Mitrovica (n=587)], and the other considered less exposed [Pristina (n=878)] Year not stated Male = 0%	*K.Mitrovica* 26.3 (5.2) *Pristina* 26.9 (4.9)	*K.Mitrovica* 17.1 (geometric mean) *Pristina* 5.1 (geometric mean)	urinary protein	logistic regression ≥1 + proteinuria: smoking, height, age, milk consumption, gestational age, number of previous live births, meat consumption, hemoglobin trace proteinuria: smoking, ethnic group, age, milk consumption, gestational age, consumption, hemoglobin	Risk of proteinuria (in entire sample) Pb (µg/dL) ≥1+ proteinuria: Higher adjusted ORs in groups with higher blood Pb (mostly statistically significant in groups with >6.9 µg/dL Pb) trace proteinuria: Adjusted ORs mostly statistically significant in groups with >8.7µg/dL Pb	Association with blood and increased odds ratio for trace and 1+ proteinuria

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Cross-sectional Fadrowski (2010) USA *Population may overlap with Munter (2003)*	769 adolescents aged 12-20 in NHANES Year = 1988-1994 Male = 50.4%	12-20	Median: 1.5 (IQR: 0.7-2.9)	GFR based on serum cystatin C (Filler and Lepage method) and serum creatinine (Schwartz method)	Linear regression Age, sex, race/ethnicity, urban vs rural, tobacco smoke exposure, obesity, annual household income, educational level of family reference person	Mean difference in estimated GFR (mL/min/1.73 m^2) associated with blood Pb Pb (µg/dL) / **Cystatin C-based** / Creatinine-based 1 (<1.0) / **1 (reference)** / 1 (reference) 2 (1.0-1.5) / **-1.4 (-7.4 to 4.5)** / -0.5 (-6.1 to 5.1) 3 (1.6-2.9) / **-2.6 (-7.3 to 2.2)** / -1.7 (-6.9 to 3.5) 4 (>2.9) / **-6.6 (-12.6 to -0.7)** / -1.9 (-7.4 to 3.5) p-trend / **0.009** / 0.31 Per doubling of blood Pb / **-2.9 (-5.0 to -0.7)** / -1.0 (-2.8 to 0.9)	A negative correlation between blood Pb and GFR is strongest for the cystatin C-based measure compared to the serum creatinine-based measure
Cross-sectional Fels (1998) Poland *Population may overlap with de Burbure (2006)*	112 children recruited from 3 schools in the area of Katowice, Poland. "Exposed" children (n=62, 44 boys) lived in the vicinity of Pb-producing factories and "referents" (n=50, 28 boys) lived in the same province but without Pb emission into neighborhood; Year=1995 Male = 64%	Exposed: 10.6 (1.2) Referents: 9.9 (0.4)	1995 referents : 3.9 (1.3) exposed: 13.3 (6.2) Previous screening in "exposed" only 1992 (n=21): 18.2 (2.6) 1993 (n=21): 21.0 (4.3) 1994 (n=10): 20.8 (8.9) 1994 (n=39): 17.4 (5.4)	Kidney function markers in serum (3) and urine (26). Urinary biomarkers include glomerular (5), proximal tubular enzymes (6), proximal tubular serum-derived proteins (5), proximal tubular antigens (3), distal tubular (2), collecting duct, interstitial cells (1), and general markers (4)	t test, Mann Whitney U test	Serum kidney function creatinine (↔), **β_2-microglobulin (↑, p<0.01)**, Clara cell protein (↔) Urinary Biomarkers: Glomerular: HMW (↔) , **transferrin (↑, p<0.05)**, fibronectin (↔), **6-keto-PGF1$_\alpha$ (↑, p<0.01)**, **TXB_2 (↑, p<0.01)** Enzyme, proximal tubular: αGST (↔), AAP (↔), γGT (↔), NAG_{TOTAL} (↔), **NAG B (↓, p<0.01)**, IAP (↔) Serum-derived protein, proximal tubular: α_1-microglobulin (↔), **β_2-microglobulin (↑, p<0.025)**, RBP (↔), **Clara cell protein (↑, p<0.025)**, LMW (↔) Tubular antigens: CB7 (↔), CG9 (↔), HF5 (↔) Distal tubular: :πGST (↔), **EGF (↑, p<0.001)** Collecting duct, interstitial cells: **PGE_2 (↑, p<0.01)** General markers: total protein (↔), albumin (↔), laminin (↔), LTE_4 (↔)	Children with Pb exposure have significant differences from unexposed children in urinary markers of kidney function in a pattern similar to observations in adults, but at a lower blood Pb level.
Cross-sectional Khan (2010) Pakistan	246 children recruited from families of lead smelters/battery recycle plant workers living close to the industries at Wah/Gujranwala (n=123), Pakistan and those living 30 km away from the industrial area as controls (n=123) Year not stated Male = 56%	Median (range): 4 (1-6)	Median (range): Exposed= 8.1 (1-20.9) Referents= 6.7 (1.4-13.3)	serum creatinine urea total protein	Mann Whitney test and Spearman correlation	Exposed vs Reference group comparisons total protein (↔, p=0.08) **urea (↑, p≤0.01)** **serum creatinine (↑, p≤0.01)** Correlations protein (r = -0.07; p=0.27) urea (r = 0.10, p = 0.12) serum creatinine (r = 0.13, p = 0.05)	Children with higher Pb exposure have higher serum creatinine levels

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Retrospective cohort with cross-sectional data at baseline Kim (1996) Boston, MA, USA *Population may overlap with Payton (1994) and others*	459 men randomly selected from the Normative Aging Study (healthy veterans in the greater Boston area, recruited in 1961); Years= 1979-1994 Male = 100%	56.9 (8.3) at baseline Median:56.7 Range: 37.7-87.5	9.9 (6.1) at baseline Median: 8.6 Range: 0.2-54.1	Serum creatinine concentration measured 1979-1994	Random-effects model Baseline age, time since initial visit, BMI, current smoking status, daily alcohol consumption, educational level, hypertension For change in creatinine, also includes: time between visits and current creatinine In longitudinal analysis, serum creatinine at the beginning of the follow-up interval and time between evaluations	**Serum creatinine (µmol/L) by Pb:** **β (SE)= 2.89 (1.04); p=0.005 (n=1671 observations)** **Change in serum creatinine (µmol/L) by Pb:** **β (SE)= 1.75 (1.09); p=0.11 (n=1212 observations)** **A 10-fold increase in blood Pb level predicted an increase of 7 µmol/L (95% CI: 2-12) in serum creatinine** Serum creatinine (µmol/L) by Pb tertile: ≤40 µg/dL: β (SE)= **2.78 (1.06); p=0.08** (452 subjects, 1647 observations) ≤25 µg/dL: β (SE)=**3.23 (1.18); p=0.007** (428 subjects, 1558 observations) **≤10 µg/dL: β(SE)= 5.29 (1.71); p=0.002** (141 subjects, 508 observations) Change in serum creatinine (µmol/L) by Pb tertile: ≤40 µg/dL: β (SE)= 1.96 (1.06); p= 0.07 (n=452 subjects, 1195 observations) ≤25µg/dL, β (SE)= 2.38 (1.22); p=0.05 (428 subjects, 1130 observations) **≤10µg/dL**, β (SE)=3.43 (2.24); p=0.13 (141 subjects, 367 observations)	Elevated serum creatinine was associated with long-term low-level Pb exposure
Cross-sectional Lai (2008) Taiwan	2565 subjects: 1,318 aboriginals and 1,247 non-aboriginals from Hsinyi County, a rural area of central Taiwan; Year not stated Male = 48% aboriginals 52% non-aboriginals	>40 years	Aboriginal: male:5.6 (1.4) female:5.4 (1.2) Non-Aboriginals: male: 5.3 (1.2) female: 5.3 (1.1)	Renal dysfunction Serum creatinine levels >1.2 mg/dL considered dysfunctional	Linear regression, logistic regression Age, gender, occupation, education, marital status, smoking, alcohol consumption, betel nut chewing, hypertension, high lipid level	Serum creatinine >1.2 mg/dL [Odds Ratio (95% CI)] Aboriginals: <5 µg/dL: Reference 5-7.5 µg/dL: 1.15 (0.79-1.68) >7.5 µg/dL: 2.45 (1.28-4.69) **p-trend <0.05** Non-aboriginals: <5 µg/dL: Reference 5-7.5 µg/dL: 1.24 (0.90-1.73) >7.5 µg/dL: 2.62 (1.25-5.52) **p-trend<0.05** All ≤ 7.5 µg/dL: Reference > 7.5 µg/dL: 1.92 (1.18-3.10)	Elevated serum creatinine positively associated with increased blood Pb
Prospective Lin (2003) Taiwan	202 patients with chronic renal insufficiency followed for 2 years. 64 patients with "high	baseline: 56.6 25-80 (range) "chelation	baseline: 5.3 (2.9) "chelation group" 6.1 (2.5)	primary outcome: increase in serum creatinine to 1.25 times baseline	Cox proportional-hazards to determine significance of the variables in predicting the primary end point (increase in serum	In a Cox multivariate regression analysis, baseline chelatable Pb was significantly associated with overall risk for the primary endpoint (increase in serum creatinine to 1.5 times baseline) during months 0-24 HR(95%CI) = 1.03(1.00, 1.07); p 0.03	Low level Pb associated with accelerated deterioration of renal function in

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
	normal" EDTA chelatable Pb levels [body lead burden, or BLB) at study start: (≥80 to <600 µg/72 h; n=32] during the observation period (months 0-24) were randomly assigned to EDTA chelation (n=31 completed) or placebo (n=30 completed) group for months 24-51 Year not stated % male not stated	group" 57.9 (39-79) "control group" 57.6 (27-80)	"control group" 5.9 (3.0)	secondary outcome: estimated GFR following chelation therapy	creatinine to 1.5 times baseline) during the observation period. Generalized estimating equations for associations between baseline chelatable Pb or blood Pb level and longitudinal change in GFR Age, gender, baseline BMI, smoking, baseline serum creatinine, proteinuria, hypertension, hyperlipidemia, daily protein intake, and underlying renal disease	Change in glomerular filtration rate improved in patients receiving chelation therapy (2.1±5.7 ml per minute per 1.73 m^2 of body-surface area, as compared with –6.0±5.8 ml per minute per 1.73 m^2 of body-surface area in the controls, p<0.001)	chronic renal insufficiency patients
Prospective Lin (2006a) Taiwan *Population may overlap with Yu (2004)*	108 CKD patients followed for 2 years, 32 patients with "low normal" EDTA chelatable Pb levels [body lead burden at study start: ≥20 to <80 µg/72 h; n=32] during the observation period (months 0-24) were randomly assigned to EDTA chelation (n=16) or placebo (n=16) group for months 24-51 Year not stated % male not stated	baseline: 56.2 30-80 (range) "chelation group" 58.6 (48-74) "control group" 54.8 (31-76)	baseline: 2.9 (1.4) "chelation group" 2.6 (1.0) "control group" 3.0 (1.1)	primary outcome: increase in serum creatinine to 1.25 times baseline secondary outcome: estimated GFR following chelation therapy	Cox proportional-hazards to determine significance of the variables in predicting the primary end point (increase in serum creatinine to 1.25 times baseline) during the observation period. Generalized estimating equations were applied in longitudinal multivariate analyses to investigate association between baseline chelatable Pb or blood Pb level and longitudinal change in GFR	1 µg/dL higher blood Pb at baseline associated with increased risk of achieving an increase in serum creatinine to 1.25 times baseline during months 0-24 HR(95%CI) = 1.03(1.00, 1.07) **The mean GFR change in the chelation group patients was 6.6±10.7 mL/min/1.73m^2, compared with -4.6±4.3 mL/min/1.73m^2 in control group patients (*P* <0.001) at the end of the intervention period.**	Low level Pb associated with accelerated deterioration of renal insufficiency in CKD patients; less decline in function in CKD patients on EDTA chelation therapy
Prospective Taiwan Lin (2006b)	82 patients with diabetes and diabetic nephropathy followed for 1 year. 30 patients with "high normal" EDTA chelatable Pb levels [body lead burden at study start:	baseline: 60.0 33-79 (range) "chelation group" 59.5 (33-79)	baseline: 6.5 (3.4) "chelation group" 7.5 (4.6) "control group" 5.9 (2.2)	primary outcome: increase in serum creatinine to 1.25 times baseline secondary outcome: estimated GFR following chelation	Cox proportional-hazards to determine significance of the variables in predicting the primary end point (increase in serum creatinine to 1.25 times baseline) during the observation period.	1 µg/dL higher blood Pb at baseline associated with increased risk of achieving an increase in serum creatinine to 1.25 times baseline during months 0-24 HR(95%CI) = 1.01(1.01, 1.02); p = 0.0011 The mean GFR rates of decline in the chelation group patients was 5.0±5.7 mL/min/1.73m^2, compared with -11.8±7.0 mL/min/1.73m^2 in control group patients (*P*	Low level Pb associated with accelerated deterioration of renal insufficiency in diabetic patients; less decline in

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
	≥80 to <600 µg/72 h; n=32] during the observation period (months 0-24) were randomly assigned to EDTA chelation (n=15 completed) or placebo (n=15 completed) group for months 13-24 Year not stated % male not stated	"control group" 57.9 (47-66)		therapy	Generalized estimating equations were applied in longitudinal multivariate analyses to investigate association between baseline chelatable Pb or blood Pb level and longitudinal change in GFR	<0.001) at the end of the intervention period.	function in diabetic patients on EDTA chelation therapy
Cross-sectional Mortada (2004) Egypt	68 men (35 smokers, 33 non-smokers); Year=not stated Male = 100%	Smokers: 31.8 (range: 25-38) Non-smokers: 30 (range: 25-35)	Smokers: 14.4 (3.4) Non-smokers 10.2 (3.1)	Urine: β_2-microglobulin, NAG, γ-glutamyltransferase, and alkaline phosphatase, albumin, Serum: creatinine, β_2-microglobulin, and BUN *Study assessed exposure to Pb, Cd, and Hg*	Spearman rank correlation coefficient (r)	Smokers had higher blood Pb levels than non-smokers, but did not have elevated markers of kidney damage; and no significant correlations were found between exposure indices of Pb (blood, urine, hair) and markers of kidney damage (data not shown)	Markers of kidney damage did not correlate with Pb exposure in smokers with higher blood Pb levels than non-smokers.
Cross-sectional Munter (2003) USA *Population may overlap with Fadrowski (2010)*	NHANES III with 15,211 participants with hypertension (n=4,813) and without hypertension (n=10,398) Year = 1988-1994 Male = 48%	≥20 years	Hypertension: 4.21 (0.14) Without hypertension: 3.30 (0.10)	Elevated serum creatinine: defined as ≥99th percentile of each race-gender-specific distribution for participants aged 20-39 years without hypertension or diabetes Chronic Kidney Disease (CKD): defined as estimated GFR <60ml/min/1.73m^2	Multiple logistic regression Age, race, gender, diabetes, systolic blood pressure, smoking status, history of cardiovascular disease, BMI, alcohol consumption, household income, education level, marital status, and health insurance	Elevated Creatinine; adjusted OR (95% CI): *With Hypertension:* With each twofold higher blood Pb: 1.43 (1.20-1.72) Quartile blood Pb (µg/dL) Quartile1 (0.7-2.4); 1.00 Quartile2 (2.5-3.8); 1.47 (1.03-2.10) Quartile3 (3.9-5.9); 1.80 (1.34-2.42) Quartile4 (6.0-56.0); 2.41 (1.46-3.97) P trend<0.001 *Without hypertension*: With each twofold higher blood Pb: 1.07 (0.81-1.41) Quartile blood Pb (µg/dL); adj. OR (95% CI) Q1 (0.7-1.6); 1.00 Q2 (1.7-2.8); 1.11 (0.56-2.21) Q3 (2.9-4.6); 1.19 (0.62-2.25)	Elevated serum creatinine and chronic kidney disease (CKD) is positively associated with blood Pb in subjects with hypertension only

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
						Q4 (4.7-52.9); 1.09 (0.53-2.22) P trend= 0.79 <u>Elevated Creatinine; adjOR (95% CI):</u> *Hypertension* With each twofold higher blood Pb: 1.38 (1.15-1.66) Quartile (blood Pb (µg/dL) Q1 (0.7-2.4); 1.00 Q2 (2.5-3.8); 1.44 (1.00-2.09) Q3 (3.9-5.9); 1.85 (1.32-2.59) Q4 (6.0-56.0); 2.60 (1.52-4.45) P trend<0.001 *Without hypertension*: With each twofold higher blood Pb: 1.04 (0.72-1.38) Quartile blood Pb (µg/dL); adjusted OR (95% CI) Q1 (0.7-1.6); 1.00 Q2 (1.7-2.8); 0.90 (0.37-2.16) Q3 (2.9-4.6); 1.00 (0.45-2.22) Q4 (4.7-52.9); 1.09 (0.41-2.89) P trend= 0.36	
Cross-sectional Muntner (2005) USA *Population may overlap with Navas-Acien (2009)*	9,961 adults from NHANES Year = 1999-2002 % male not stated	NHANES 1999-2002: 18-75 years	NHANES 1999-2002: 1.64 (95% CI: 1.59-1.68)	Chronic kidney disease (GFR <60 mL/min)	Multiple logistic regression Age, race/ethnicity, gender, diabetes, smoking status, alcohol, BMI, education, and health insurance	<u>NHANES 1999-2002:</u> Adjusted OR (95% CI) of chronic kidney disease by quartile of blood Pb Q1: <1.06 µg/dL (prevalence 1.8%); 1.00 (Reference) Q2: 1.06-1.63 µg/dL (prevalence 3.4%); Adjusted OR = 1.49 (0.75-2.98) Q3: 1.63-2.47 µg/dL (prevalence 5.6%); Adjusted OR =1.89 (1.09-3.30) Q4: ≥2.47 µg/dL (prevalence 8.1%); Adjusted OR = 2.72 (1.47-5.04) P trend=<0.001	Increased risk of CKD with blood Pb ≥1.63 µg/mL
Cross-sectional Navas-Acien (2009) USA *Population may overlap with Muntner (2005)*	14,778 adults from the NHANES Year = 1999-2006 % male not stated	≥20	1.58 (geometric mean)	Albuminuria (≥30 mg/g creatinine), reduced e stimated GFR (<60 mL/minute/1.73 m^2) Described in study but not summarized here are kidney	Logistic regression; Model 3: Survey year, age, race/ethnicity, gender, smoking status, alcohol intake, BMI, education, cotinine, hypertension, diabetes mellitus, menopausal status, and	Albuminuria, OR (95% CI) by quartile of blood Pb (µg/dL) (median) Q1: ≤1.1; 1.0 (Reference) Q2: >1.1-1.6; adjusted OR = 0.83(0.66-1.04) Q3: >1.6-2.4; adjusted OR = 0.92 (0.76-1.12) Q4: >2.4; adjusted OR = 1.19 (0.96-1.47) **p-trend<0.001** Reduced estimated GFR, OR (95% CI) by quartile of	Increased risk of reduced estimated GFR in highest quartile for Pb exposure; significant trend for albuminuria

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
				effects related to Cd	blood Cd	blood Pb (µg/dL) (median) Q1: ≤1.1; 1.0 (Reference) Q2: >1.1-1.6; adjusted OR = 1.10 (0.80-1.51) Q3: >1.6-2.4; adjusted OR = 1.36 (0.99-1.85) **Q4: >2.4; adjusted OR = 1.56 (1.17-2.08)** **p-trend<0.001** *Association with estimated GFR stronger when people more highly exposed to both Pb and Cd compared to those less exposed	
Cross-sectional Payton (1994) Boston, MA, USA *Population may overlap with Kim (1996) and others*	744 adults participating in the Normative Aging Study; Year= 1988-1991 Male = 100%	64 (7.4)	8.1 (3.9)	Log- transformed (ln) creatinine clearance (both measured and estimated from serum creatinine)	Multivariate linear regression Age, BMI, analgesic & diuretic use, alcohol consumption, smoking status, systolic/diastolic blood pressure	Rate of ln creatinine clearance (mL/min) was significantly and negatively associated with increasing levels of ln blood: Adjusted β between ln Pb and ln measured creatinine clearance =-0.0403 (0.0198) µg/dl; p-value= 0.0426 A 10µg/dl rise in blood Pb was associated with a decrease in creatinine clearance rate of 10.4 mL/minute	Low-level Pb associated with decreased renal function
Cross-sectional Pocock (1984) England	7,364 men randomly selected from general practices in 24 British towns (The Regional Heart Study); Year not stated Male = 100%	40-59 (mean not reported)	<12.4 – 37.3 (mean not reported) *limits utility of the study in this evaluation	Serum creatine, urate, urea	Statistical methods not reported but statistics were presented as correlation coefficients (β) Alcohol consumption	β for blood Pb and log transformed urine level: serum urate (β = 0.06)* serum urea (β = -0.05)* serum creatinine: no association (β=0.00) Authors state that the magnitude of the changes are small and unlikely to be of biological importance	Lack of information on blood Pb levels in this study limits the utility in this evaluation
Cross-sectional Satarug (2004a) Thailand	118 Thai adults; Year not stated Male = 45%	*Men,* 36.7 (range: 21-57) *Women,* 38.1 (range: 23-55)	Males: 0.42 Females: 0.3 (reported as "serum" Pb)	Serum creatinine, urinary NAG and β2-microglobulin, BUN, total urinary protein,	Spearman rank correlation adjusted for urine cadmium	correlations with kidney filtration markers and urine Pb (correlations with blood Pb not reported) NAG (r = 0.39; p < 0.001) protein (r = 0.09, p = 0.47) β2-microglobulin (r = 0.16, p = 0.19)	Lack of information on correlations with blood Pb levels in this study limits the utility in this evaluation
Cross-sectional Satarug (2004b) Thailand	96 Thai men subdivided into nonsmokers (n = 53), current smokers (n = 27), and ex-smokers (n = 16) Year not stated Male = 100%	*Non-smokers,* 36.7 (range: 21-57) *Current Smokers,* 35.8 (range: 19-53) *Ex-Smokers,* 38.5	*Non-smokers,* 0.42 (0.54) *Current Smokers,* 0.9 (0.12) *Ex-Smokers,* 0.61 (0.63)	Serum creatinine, urinary NAG and β2-microglobulin, BUN, total urinary protein, urinary Cd	Spearman rank correlation	correlations with kidney filtration markers and urine Pb (correlations with blood Pb not reported) *Non-smokers,* NAG (r = 0.08; p=0.27) protein (r = 0.22, p = 0.06) β2-microglobulin (r = 0.12, p = 0.19) *Current Smokers,* NAG (r = -0.02; p=0.47)	Lack of information on correlations with blood Pb levels in this study limits the utility

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
		(range: 20-57)				protein (r = 0.49, p = 0.004) β2-microglobulin (r = 0.09, p = 0.32) *Ex-Smokers,* NAG (r = 0.27; p < 0.16) protein (r = -0.14, p = 0.31) β2-microglobulin (r = 0.39, p = 0.06)	
Retrospective Shadick (2000) Boston, MA, USA *Population may overlap with Payton (1994) and others*	777 participants in all male Normative Aging Study Year = 1991 and 1996 Male = 100%	66.9 (7.3)	5.9 (3.5)	Uric acid	Logistic regression Age, BMI, diastolic blood pressure, alcohol intake, serum creatinine	Significant association between patella Pb and uric acid (β= 0.0007 [95% CI: 0.001, 0.013]; p = 0.02); borderline significant associations between tibia (p = 0.06) and blood Pb (p = 0.1) and uric acid were also observed.	Lack of information on correlations with blood Pb levels in this study limits the utility in this evaluation
Cross-sectional Staessen (1990) London, England	531 adult London civil servants; Year not stated Male = 75%	37-58	Male (n=398): 12.4 Female (n=133): 10.2	Serum creatinine	t-test for comparison of means and linear multiple regression analysis (step wise)	In male, significant correlation between serum creatinine and log blood Pb (r = 0.10, p=0.04)* In female, no correlation with serum creatinine and log blood Pb (r=0.03, p= NS) The predicted increase in serum creatinine concentration per 25% increase in blood Pb was β = 0.6 µmol/L (95% CI, -0.2, 1.36). *The association was no longer significant after excluding two subjects from the analysis who had serum creatinine concentrations exceeding 180 µmol/L (2 mg/dL).	Blood Pb was associated with increased serum creatinine in men when 2 individuals with >180µmol/L creatinine were included. Blood Pb was not associated with serum creatinine in women or men when the individuals with high serum creatinine were excluded.
Cross-sectional Staessen (1992) Belgium	1,981 residents participating in the ≥8 years study; Year= 1985-1989 Male = 48%	48 (16) (range: 20-88)	male: 11.4 (range 2.3-72.5) female: 7.5 (range 1.7-60.3)	<u>Impaired renal function:</u> creatinine clearance <43 ml/min in non-diabetic women and <52 ml/min in non-diabetic men Serum creatinine; urine creatinine; creatinine clearance	Analysis of variance, single and multiple linear regression, and logistic-regression Age, diabetes, use of analgesic and diuretic drugs	<u>β (±SE) with ln blood Pb:</u> Ln creatinine clearance (mL/min, measured) male: -13.1 (±4.0); female: -9.5 (±4.4) Ln β2-microglobulin (mg/L) male: 0.04 (±0.02); female: -0.01 (±0.02) Ln serum creatinine (mg/dL) male: 0.01 (±0.01); female: 0.01 (±0.01) adjOR (95%CI) for 10-fold increase in blood Pb and impaired renal function = 3.76 (1.37, 10.4)	10-fold increase in blood Pb associated with reduction of 10 (female) to 13 (male) ml/min creatinine clearance

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Cross-sectional Staessen (2001) Belgium	200 children aged 17 (Pb exposed n=42 from Wilrijk and n=58 from Hoboken both considered Pb- and chemical-industrial areas; n=100 referent); Year=1999 Male = referent=40%; Wilrijk=50%; Hoboken=33%	17	Referent 1.49µg/dL Wilrijk 1.8µg/dL Hoboken 2.7µg/dL	serum cystatin C and urinary β2 microglobulin	ANOVA and Fisher's exact test, linear regression and logistic regression Adjustments included sex, smoking, and initial urinary pH (for β2 microglobulin)	Geometric Mean Blood Pb: Referent 1.49µg/dL Wilrijk 1.8µg/dL; p=0.04 to referent Holboken 2.7µg/dL; p<0.0001 to referent Serum cystatin C (mg/L): Referent 0.65 Wilrijk 0.63; p=NS Holboken 0.71; p=<0.0001 Urinary β2 microglobulin (µg/mmol creatinine): Referent 5.22 Wilrijk 5.30; p=NS Holboken 9.09; p=<0.0001	Serum cystatin-C and β2 microglobulin were higher in children living in areas with higher blood Pb (2.7µg/dL) compared to referents
Prospective cohort with cross-sectional data at baseline Tsaih (2004) Boston, MA, USA *Population may overlap with Payton (1994) and others*	448 men participating in the Normative Aging Study Year recruited during 1991-1995 were followed for 6 years Male = 100%	At baseline: 66 (6.6) At baseline: 72 (6.5)	Baseline: 6.5 (4.2) Followup: 4.5 (2.5)	Serum creatinine	Multiple linear regression Age, BMI, baseline serum creatinine (SCr), SCr squared, diabetic status, hypertensive status, smoking history, alcohol consumption, and ue of analgesic medication and diuretic medication	β(SE) of baseline blood Pb with change in serum creatinine: diabetics (n=26): 0.076 (0.023); p-value = <0.05 non-diabetics (n=422): 0.006 (0.005); p-value = NS hypertensive (n=115): 0.008 (0.010); p-value = NS normotensives (n=333): 0.009 (0.006); p-value = NS	Significant associations blood Pb and change in serum creatinine in diabetics
Cross-sectional Wu (2003) Boston, MA, USA *Population may overlap with Payton (1994) and others*	709 adults (100% male) participating in the Normative Aging Study; objective of study was to investigate whether an *ALAD* polymorphism has a modifying effect on the association of blood or bone Pb level with uricemia and indices of renal function; Year= 1991-1995 Male = 100%	67 (7.4) years	6.2 (4.1)	Serum creatinine, serum uric levels, estimated creatinine clearance	Multiple linear regression; Age, BMI, hypertension, smoking status, alcohol ingestion, analgesic medication use	<u>Estimated creatinine clearance (mL/min)</u> Significant negative association between patella Pb and estimated creatinine clearance: Patella: β=-0.069; p-value=0.024 Tibia: β=-0.078; p-value=0.082 <u>Serum creatinine (mg/dL)</u> Bone Pb levels were not associated with serum creatinine Patella: β=0.0004; p-value=0.41 Tibia: β=0.0006; p-value= 0.354 <u>Uric Acid (mg/dL)</u> Patella: β=0.005; p-value=0.078 Tibia: β=0.005; p-value=0.190 Authors state that no significant association was detected between blood Pb or its interaction with genotype to serum uric acid.	Creatinine clearance inversely significantly associated with patella Pb, not blood Pb. Serum creatinine and uric acid not significantly associated with any lead measure.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Kidney measures	Statistical modeling; covariates	Findings	Observed Effect
Prospective Yu (2004) Taiwan *Population may overlap with Lin (2006a)*	121 CKD patients (77% male) followed for 4 years, patients were divided into 2 groups based on EDTA chelatable Pb levels (body lead burden (BLB) at study start: "low normal" (<80 µg/72 h; n=58) and "high normal" (≥80 to <600 µg/72 h; n=63) Year not stated % male not stated	Baseline= 25-82 (range) "low normal" BLB= 54.8 (mean) "high normal" BLB= 59 (mean)	baseline: 4.2 (2.2) "low normal" BLB: 3.4 (1.3) "high normal" BLB: 4.9 (2.6)	Estimated GFR (MDRD equation)	Cox proportional-hazards to determine significance of the variables in predicting the primary end point (doubling of serum creatinine over the 4 yr study period or need for hemodialysis) during the observation period. Generalized estimating equations were applied in longitudinal multivariate analyses to investigate association between baseline chelatable Pb or blood Pb level and longitudinal change in GFR	1 µg/dL higher blood Pb at baseline associated with a 4.0 mL/min/1.73 m^2 reduction in eGFR over 4 years Fifteen patients in the "high-normal" BLB group reached the primary endpoint (doubling of serum creatinine over the 4 yr study period or need for hemodialysis) compared to only two in the "low-normal" group (p = 0.001 by Kaplan-Meier analysis)	Low level Pb associated with accelerated deterioration of renal insufficiency in CKD patients

Abbreviations: AAP – alanine aminopeptidase; ALAD – γ-aminolevulinic acid dehydratase; ANOVA – analysis of variance; As – arsenic; BMI - body mass index; BLB – body lead burden; BUN – blood urea nitrogen; Cd – cadmium; CI – confidence interval; CKD - chronic kidney disease; CRI - chronic renal insufficiency; EDTA – edetate calcium disodium; EGF – epidermal growth factor; GFR - glomerular filtration rate; αGST – α-glutathione-S-transferase; γGT – γ-glutamyl transferase; Hg – mercury; HMW –high molecular weight; HR – hazard ratio; IQR - interquartile range; IAP – intestine alkaline phosphatase; ln – natural log; min – minute; LMW – low molecular weight; LTE_4 – leukotriene E_4; NAG - N-acetyl-β-D-glucosaminidase; NAG B – isoform B of NAG; NHANES – National Health and Nutrition Examination Survey; NS – not significant; OR – odds ratio; Pb – lead; PG - prostaglandin (i.e. PGE_2 , $PGF_{1\alpha}$); RBP - retinol binding protein; SE – standard error; TXB_2 – thromboxane; UI – international unit; vs – versus

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NTP
National Toxicology Program
U.S. Department of Health and Human Services

NTP MONOGRAPH ON HEALTH EFFECTS OF LOW-LEVEL LEAD

June 13, 2012

APPENDIX E:
HUMAN STUDIES OF REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF LEAD CONSIDERED IN DEVELOPING CONCLUSIONS

Office of Health Assessment and Translation

Division of the National Toxicology Program

National Institute of Environmental Health Sciences

National Institutes of Health

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Repro: Reproductive Development/Puberty							
Cross-sectional Denham (2005) Akwesasne Mohawk Nation	Akwesasne girls age 10-16.9 (n= 138); Years not stated; Male=0%	12.9 (1.92)	0.49 (0.905)	Attainment of menarche	Probit and Binary logistic regression models for predictors of menarche status; Age, socioeconomic status, BMI, and other pollutants (p,p'-DDE, HCB, PCBs, mirex, mercury)	Binary Logistic Regression predicting menarcheal status β (SE): **Mean Pb (0.49μg/dL) β=-1.29 (0.49); p=0.01** Pb squared β=-1.01 (0.57) p=0.08 **75th %tile Pb (1.66μg/dL) β=-3.75 (1.8); p=0.04** The effect of Pb was not significant below the mean blood Pb level of 0.49μg/dL. Predicted age at menarche (95% CI): Blood Pb <1.2 μg/dL 11.8 years (9.9-12.8) Blood Pb ≥1.2 μg/dL 12.7 years (12.2-13.1) Increasing PCB levels were associated with a greater likelihood of having reached menarche; other pollutants did not have a significant effect.	Akwesansne girls with blood Pb≥0.49μg/dL had a significantly reduced likelihood of reaching menarche.
Cross-sectional Gollenberg (2010) USA *Same population as Selevan (2003) and Wu (2003)* *Also listed for endocrine*	Girls aged 6-11 in NHANES III (n=705 girls with exposure inhibin B, and LH data); Male=0%	6-11	Median 2.5 (range 0.07-29.4)	Pubertal status by Inhibin B and Tanner stage of breast development stage, Tanner pubic-hair stage, urinary Cd, blood iron	Chi-square, ANOVA, logistic regression BMI, race/ethnicity, census region, poverty-income ratio (PIR), age	Association between blood Pb and odds ratio (95% CI) of exceeding inhibin B (35pg/mL ~ puberty): <1μg/dL reference 1-4.99μg/dL OR=0.38 (0.12, 1.15) **≥5 μg/dL OR=0.26 (0.11, 0.60); p<0.05** **Log Pb continuous OR=0.51 (0.34, 0.78); p<0.05** Association between blood Pb and OR (95% CI) of exceeding LH (0.4mIU/mL ~ puberty): <1μg/dL reference 1-4.99μg/dL OR=0.98 (0.48, 1.99) **≥5 μg/dL OR=0.83 (0.37, 1.87); p>0.05** **Girls with inhibin >35pg/dl were more likely to have Tanner stage≥2 (puberty) for pubic hair and breast development (p<0.0001)**	US girls with higher blood Pb (≥5μg/dL) had a lower likelihood of having inhibin B levels indicative of puberty.
Cross-sectional Hauser (2008) Chapaevsk, Russia *Population later used in Williams (2010)* *Also listed for growth*	Boys aged 8-9 (n=489); Years=2003-2005 Male=100%	8.41 (0.49)	Median (25th-75th percentile) 3 (2-5) Exposure measured when outcome assessed	Puberty onset (by testicular volume [onset TV>3 ml], Tanner staging - pubic hair stage [onset for P≥2], genital staging [onset for G≥2]), height, weight, penile length	Multiple linear regression; Adjustments depended on variable modeled including: birth weight, gestational age, age at examination, height, weight, BMI, penile length Multivariable logistic regression; Adjustments depended on variable and included: birth weight, gestational age, height, BMI, age at examination; and sensitivity analysis done to discount socioeconomic status, weight, height, and excluding subjects with blood Pb ≥10	Odds ratio (95% CI) for association of blood Pb (natural log) with onset of puberty: Models for effect of Pb with puberty: Testicular volume all six levels; OR 0.90(0.67-01.20); p=0.47 Testicular volume (>3ml) pubertal onset; OR 1.08(0.69-1.70); p=0.74 Tanner stage≥G2; OR 0.75(0.53-1.06); p=0.10 Tanner stage≥P2; OR 1.08(0.60-1.93); p=0.81 Models for effect of high Pb (≥5μg/dL)with puberty: Testicular volume all six levels; OR 0.72(0.48-01.07); p=0.11 Testicular volume (>3ml) pubertal onset; OR 0.83(0.43-1.59); p=0.58 **Tanner stage≥G2; OR 0.57(0.34-0.95); p=0.03** Tanner stage≥P2; OR 0.74(0.34-1.60); p=0.44	Boys with blood Pb ≥5μg/dL had significantly later puberty onset (defined by Tanner genital staging and marginally significant testicular volume-p=0.05).

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
					*Also for macronutrients	Additional adjustment for dietary macronutrients in models for effect of high Pb (≥5μg/dL)with puberty: **Tanner stage≥G2; OR 0.52(0.31-0.88); p=0.01** **Testes vol. (>3ml); OR 0.66(0.44-1.00); p=0.05**	
Cross-sectional Naicker (2010) Johannesburg/ Soweto, South Africa	Girls from the Birth to Twenty longitudinal birth cohort n=725-682 depending on endpoint; Years not stated; Male=0%	13	4.9 (1.9) Exposure measured at age 13 when outcome was assessed	Puberty (Tanner breast development stage, Tanner pubic-hair stage, age a menarche), height, weight	Trend analyses and logistic regression Authors state socio-economic status (SES) and BMI not significantly associated with any measure of puberty and that attainment of puberty stages across dichotomized blood Pb categories was adjusted for SES and anthropometric measures. However, only BMI is listed as adjustment for trend or regression analyses.	Trend analysis for developmental measure and mean blood Pb level for: **Tanner breast stage; p<0.001** **Tanner pubic hair growth; p<0.001** **Attainment of menarche; p<0.001** OR (95%CI) for effect of blood Pb 5≥μg/dL compared with <5μg/dL for a delay in puberty as determined by: **Breast development: 2.34 (1.45,3.79); p=0.001** **Pubic hair development: 1.81(1.15,2.84); p=0.01** **Attainment of menarche: 2.01(1.4,2.9); p<0.001**	South African girls with blood Pb≥5 μg/dL had significantly delayed onset of puberty as determined by pubic hair stage, breast development stage, and age at menarche.
Cross-sectional Selevan (2003) USA *Same population as Wu (2003)* *Also listed for growth*	Girls aged 8-16 in NHANES III (n=600 non-Hispanic whites; n=805 African Americans; n=781 Mexican Americans) Male=0%	13.4 for all groups	Mean (95% CI) non-Hispanic whites 1.4 (1.2-1.5) African Americans 2.1 (1.9-2.3) Mexican Americans 1.7(1.6-1.9)	Puberty (Tanner breast development stage, Tanner pubic-hair stage, age a menarche), height, weight	Ordinal logistic regression was used to assess progression of tanner stage for breast and pubic hair development which calculated the odds ratio of reaching higher stages with changes in blood Pb. Mean age for each Tanner stage was estimated from the model. Age of menarche data obtained by interview. Adjustments depended on endpoint and included: Age at examination, age squared, height, BMI, family income, smoking status, dietary calcium, iron, vitamin C, total fat, anemia	Effect of blood Pb concentration of 3μg/dL compared with 1μg/dL on: Beast development OR (95%CI) Non-Hispanic Whites 0.82 (0.47-1.42) **African Americans 0.64 (0.42-0.97); p<0.05** **Mexican Americans 0.76 (0.63-0.91); p<0.05** Pubic-hair development OR (95%CI) Non-Hispanic Whites 0.75 (0.37-1.51) **African Americans 0.62 (0.41-0.96); p<0.05** **Mexican Americans 0.70 (0.54-0.91); p<0.05** Age at menarche HR(95%CI) Non-Hispanic Whites 0.74 (0.55-1.002) **African Americans 0.78 (0.63-0.98); p<0.05** Mexican Americans 0.90 (0.73-1.11) Delay in reaching successive developmental stages associated with blood Pb ≥3 compared to 1μg/dL depended on endpoint but ranged from: Non-Hispanic Whites 0.7-3.0 months African Americans 2.1-6.0 months Mexican Americans 0.4-3.0 months	African American and Mexican American girls with blood Pb≥3 μg/dL had significantly delayed pubertal development. These effects were not significant in non-Hispanic whites.
Cross-sectional Staessen (2001) Belgium	200 children aged 17 (Pb exposed n=42 from Wilrijk and n=58 from Hoboken both considered Pb- and chemical-industrial areas; n=100	17	Referent 1.49μg/dL Wilrijk 1.8μg/dL Hoboken 2.7μg/dL	Puberty and sexual development (boys-testicular volume, Tanner genital stage; girls- Tanner breast	ANOVA and Fisher's exact test, linear regression and logistic regression Adjustments depended on endpoint and included: sex, smoking, BMI, parental social class, use of oral contraceptives	Geometric Mean Blood Pb: Referent 1.49μg/dL **Wilrijk 1.8μg/dL; p=0.04 to referent** **Holboken 2.7μg/dL; p<0.0001 to referent** Testicular volume: Referent 47.3 (6.5) **Wilrijk 42.8 (6.7); p=0.02** **Holboken 42.1 (6.3); p=0.004**	Testicular volume was lower in boys living in areas with higher blood Pb levels. More boys and girls living in

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
	referent); Year=1999; Male-referent=40%; Wilrijk=50%; Hoboken=33%			development stage), heavy metal, PCB, and other levels in urine or blood, cystatin C and other kidney measures	** lack of reporting on direct comparison with testicular stage or Tanner genital or breast stage and blood Pb limits utility	Boys with genital stage G3-G4; not adult stage: Referent 8% **Wilrijk 38%; p=0.003** Holboken 0; p=0.96 Girls with breast stage B3-B4; not adult stage: Referent 10% **Wilrijk 33%; p=0.03** Holboken 21%; p=0.10 **Breast stage in girls was associated with dioxin-like compounds in serum OR=2.26(1.2,4.5); p=0.02**	Wilrijk (an area with higher blood Pb) had not reached adult stage of genital or breast development; however this was not the case for Holboken (another area with higher Pb).
Cross-sectional Tomoum (2010) Cairo, Egypt *Also listed for endocrine and growth*	41 children living in Pb contaminated areas of Cairo and areas with no obvious Pb pollution; Year = 2007; Male=51%	11.98 (1.13) Range = 10-13	9.46 (3.08) Range=3-15	Puberty/sexual development (Tanner stage pubic hair, testicular size, penile growth in boys; Tanner pubic hair and breast development in girls), serum FSH, LH, E_2 (girls), T (boys), height and weight	Student's t test, Mann-Whitney U test, chi-squared test, Spearman correlation Adjustments not described.	Tanner stage 1(S1)/stage2(S2)/stage3(S3) by blood Pb above and below 10µg/dL: Male Testes Pb<10→S1=0%; S2=44%; S3=56% **Testes Pb≥10→S1=33%; S2=67%; S3=0%; p<0.01** Pubic hair Pb<10→S1=0%; S2=56%; S3=44% **Pubic h. Pb≥10→S1=33%; S2=67%; S3=0%; p<0.05** Penile stage Pb<10→S1=11%;S2=44%; S3=44% **Penile s. Pb≥10→S1=78%;S2=22%; S3=0%; p<0.05** Female Breast Pb<10→S1=0%; S2=36%; S3=64% **Breast Pb≥10→S1=0%; S2=100%; S3=0%; p<0.01** Pubic hair Pb<10→S1=0%; S2=36%; S3=64% Pubic h. Pb≥10→S1=0%; S2=78%; S3=22%; p>0.05 Both boys and girls had reduced FSH and LH; T was reduced in boys, and E2 did not differ. Full results listed under endocrine in table below.	Boys with blood Pb ≥10µg/dL had significant-ly delayed puberty (by testicular size or Tanner pubic hair and penile staging); girls had delayed Tanner breast staging, not pubic hair development.
Prospective Williams (2010) Chapaevsk, Russia *Follow up of Hauser (2008)*	Boys studied for pubertal onset from ages 8-12 (n=481 of original 489 enrolled); Years=enrolled at age 8-9 in 2003-2005 Male=100%	Individuals followed from ages 8-9 to age 11-12	Median (25-75%tile) 3 (2-5) Exposure measured at age 8-9; outcome assessed through age 12	Puberty onset (defined as testicular volume of >3ml; Tanner genital (G)stage ≥2; or Tanner pubic hair (P) ≥2), height, weight, penile length	Cox proportional hazard models for time to pubertal onset; Birth weight, gestational age, nutritional status, maternal alcohol consumption during pregnancy, socioeconomic measures, height and BMI at study entry Repeated-measures models using generalized estimating equations (GEEs) were also applied; Sensitivity analysis done to	Cox-proportional-Hazard ratio (95% CI) for association of blood Pb with onset of puberty: Testicular volume (>3 ml): **Blood Pb≥5 µg/dL; HR 0.73(0.55-0.97); p=0.03** Log Blood Pb; HR 0.90(0.75-1.09)p=0.27 Tanner stage≥G2 **Blood Pb≥5 µg/dL; HR 0.76(0.59-0.98); p=0.04** Log Blood Pb; HR 0.95(0.81-1.12)p=0.57 Tanner stage≥P2 Blood Pb≥5 µg/dL; HR 0.69(0.44-1.07); p=0.10 Log Blood Pb; HR 0.80(0.59-1.05); p=0.14 GEE repeated-measures models odds ratio (95% CI) for association of blood Pb with onset of puberty: Testicular volume (>3 ml):	Boys with blood Pb ≥5µg/dL had significantly later puberty onset (defined by testicular volume or Tanner genital staging)

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
					discount mothers age at menarche, inclusion of 4 sets of twins and 3 sets of siblings status, weight, height, and excluding subjects with blood Pb ≥10	Blood Pb≥5 μg/dL; HR 0.75(CI not rep.)p=0.16 Tanner stage≥G2 **Blood Pb≥5 μg/dL; HR 0.61(0.41-0.91); p=0.01** Tanner stage≥P2 Blood Pb≥5 μg/dL; HR 0.57(0.32-1.02); p=0.06 Median age of pubertal onset (testicular volume >3) Blood Pb 0-2 μg/dL 10.5 years Blood Pb 3-4 μg/dL 10.5 years Blood Pb ≥5 μg/dL 11.5 years Long-rank test P values for Kaplan-Meir estimates for distribution of age at pubertal onset according to blood Pb category**; p=0.0042**	
Cross-sectional Wolff (2008) New York City, NY	139 healthy girls aged 9 at Mount Sinai Hospital; Years = recruited 1996-1997	9.5 (0.3)	Median 2μg/dL	Puberty (Tanner breast development stage, pubic-hair stage), height, weight, phytoestrogen, BPA, DDE, PCB exposure	Modified Poisson regression models Adjustments depended on endpoint and included: age, BMI, black race, height, private clinic	Prevalence ratio (95%CI) for Tanner stage ≥2 vs stage 1 for blood Pb: Breast development: PR=1.01 (0.79-1.30) Pubic hair development: PR=1.25(0.83-1.88)	Blood Pb had no effect on puberty (in 9-year old girls in New York.
Cross-sectional Wu (2003) USA *Same population as Selevan (2003) and (Gollenberg et al. 2010)*	Girls in NHANES III Population 1: aged 8-16 n=1,706 (n=600 non-Hispanic whites; n=805 African Americans; n=781 Mexican Americans) Population 1: aged 10-16 n=1,235 Male=0%	8-16	2.5 (2.2) Range 0.7-21.7μg/dL	Puberty (Tanner stage of breast development stage, Tanner pubic-hair stage, age a menarche), height, weight	Cochran Mantel Haenszel chi-square test controlling for age with application of weights was used to test percentage difference by category of blood Pb ANOVA to compare girls who attained a puberty level compared to those that did not with weighting and adjustments by SUDAAN statistical software Logistic regression adjusted for race/ethnicity, age, family size, residence, poverty income ratio, and BMI with weighting and adjustments by SUDAAN statistical software	Likelihood of having attained pubertal marker by blood Pb level OR (95% CI): Attainment of menarche 0.7-2.0μg/dL: 1.00 – reference 2.1-4.9μg/dL: 0.42 (0.18-0.97) 5.0-21.7μg/dL: 0.19(0.08-0.43) Log transformed: 0.52(0.28-0.97) Pubic Hair 0.7-2.0μg/dL: 1.00 – reference 2.1-4.9μg/dL: 0.48(0.25-0.92) 5.0-21.7μg/dL: 0.27(0.08-0.93) Log transformed: 0.54(0.32-0.91) Breast development 0.7-2.0μg/dL: 1.00 – reference 2.1-4.9μg/dL: 1.51 (0.90-2.53) 5.0-21.7μg/dL: 1.20(0.51-2.85) Log transformed: 1.20(0.76-1.92) **Blood Pb level was higher in girls with pubic hair stage ≥2 (p=0.013 by ANOVA and 0.022 by chi-square)** and in girls that attained menarche (p=0.053 by ANOVA and 0.091 by chi-square), but not in girls with breast development stage≥2 (p=0.552 by ANOVA and 0.520 by chi-square).	US girls with blood Pb ≥2μg/dL had significantly delayed puberty as determined by pubic hair stage or age at menarche.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Repro: postnatal growth (height and head circumference)							
Retrospective cohort Angle (1989) Omaha, Nebraska	54 children from Omaha Led Paint Poison Prevention Program (n=24 blood Pb<30μg/dL; n=30 blood Pb≥30μg/dL); Years 1978-1982; % Male not stated	Birth through 48 months	12-23 months Low=17 (1.7) High=46.9 (3.5) 35-48 months Low=18.5 (3.5) High 40.5 (2.4)	Height, weight	t test, chi-square analyses Adjustments not described.	**Monthly change in weight % (0- 3 years) showed fewer upward shifts in ≥30μg/dL group (p<0.01).** **Monthly change in height % (0- 3 years) showed fewer upward shifts in ≥30μg/dL group (p<0.01).** Height and weight did not differ between infants with blood Pb levels above and below 30μg/dL, except for a higher weight velocity at 15 months and weight at 24 months in the ≥30μg/dL group.	Change in height and weight showed fewer upward shifts in the high blood Pb group from 0-3 years.
Cross-sectional Ballew (1999) USA	4391 children aged 1 to 7 in NHANES III (n=1266 non-Hispanic whites; n=1452 black; n=1673 Mexican-Americans); Male=50%	White =4.7 Black =4.5 Mexican-American =4.6	Overall mean =3.6 White =3.14(0.16) Black =5.71(0.32) Mexican-American =4.0 (0.22)	Height, head circumference, weight	Regression analyses Age, sex, race/ethnicity, household income, anemia, dietary vitamin C, iron, calcium	**Regression model of height and blood Pb: β= -0.157 (SE=0.032)cm; p<0.0001** **Regression model of head circumference-blood Pb: β= -0.052 (SE=0.008)cm; p<0.0001** Authors state blood Pb was not significantly associated with weight or BMI.	Current blood Pb in children 1-7 years of age was negatively associated with height and head circumference.
Prospective Factor-Litvak (1999) Kosovo, Yugoslavia *Same population as Murphy (1990), Loiacono (1992), Factor-Litvak {, 1991 #635*	706 infants born to women recruited at mid-pregnancy: 394 lived in an area with high environmental Pb (exposed) and 312 lived in an area with low Pb exposure (referent); %male not stated; Years= 1985-1986	Height taken at 4 years of age. (n=156 from Pb-exposed area and n=175 from referent area)	Individual means by year reported graphically: Exposed=20-40μg/dL Referent = 4-10μg/dL	Height	Ordinary least squares regression analysis and maximum likelihood logistic regression analysis. Maternal height, HOME score, ethnic group, maternal age, sex	Mean height by town (Pb-exposed town of Titova Mitrovica, a Pb smelter town, and referent town of Pristina): Pb exposed (higher Pb) = 100.9 (4.6) Referent (lower Pb) = 101.0 (4.9) cm Regression coefficient (95% CI) relating log current blood Pb (μg/dL) level to height at 4 years of age in Pristina, the town with lower blood Pb levels: β = -7.3 (cm) (-12.8, -1.8)	Current blood Pb (<15μg/dL) in 4-year olds from referent town was negatively associated with height. Blood Pb was not associated to height in children from a Pb smelter town.
Cross-sectional Frisancho (1991) USA	1454 Mexican-American children aged 5-12 in NHANES II; Years= 1982-1984; Male=50%	Range: 5-12	Male = 10.56 (0.21) Female= 9.3(0.21)	Height	Multiple regression analyses Adjustments differ by sex including: age, poverty index ratio, hematocrit	**Relationship between height and blood Pb:** **Males coefficient (μg/dL) = -0.01; p=0.011** **Females coefficient (μg/dL) = -0.01; p=0.0078** Height in children above and below mean blood Pb: Male height low Pb: 133.6 (SE=0.59) **Male height high Pb: 132.1 (SE=1.04); p<0.001** Female height low Pb: 134.5 (SE=0.41) **Female height high Pb: 133.3 (SE=0.55); p<0.001**	Current blood Pb in Mexican-American children aged 5-12 years of age was negatively associated with height.
Prospective Greene (1991) Cleveland, USA	Follow up of Ernhart (1986) Cleveland prospective study;	4 years 10 months	Maternal at delivery 6.49(1.88) Cord	Weight, length, head circumference	Pearson correlation, Spearman correlation, multivariate regression	Relation of blood Pb with concurrent and subsequent (1, 2, 3, 4 years) size outcomes: Blood Pb at 6 months:	Blood Pb at 6 months of age was related to

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Same population as Ernhart (1986)	359 mother-infant pairs (n=162 with cord Pb; n=185 maternal Pb); Enrolled Years= 1980-1981		5.97 (2.09) 6 months 10.05 (3.3) 2 years 16.74 (6.5) 3 years 16.7 (5.93) 4 years 10 months 15.62 (6.55)		Race, sex, parity, maternal age at delivery, gestational age, duration of gestation at first visit, date of first visit, smoking, Michigan Alcoholism Screening Test (MAST), average number of ounces of alcohol consumed per day through pregnancy (AA), drugs during pregnancy, maternal IQ, parental education, maternal pre-pregnancy weight, maternal height, maternal head circumference, paternal size, HOME indices	**Head circumference β= -0.05 (SE=0.03); p=0.05** Length β= -3.91 (SE=2.07); p=0.06 Weight β= -3.74 (SE=2.11); p=0.08 Blood Pb at 2 years: Head circumference β= -0.01 (SE=0.02); p=0.56 Length β= -0.95 (SE=1.22); p=0.43 Weight β= +0.29 (SE=1.35); p=0.83 Blood Pb at 3 years: Head circumference β= -0.03 (SE=1.81); p=0.11 Length β= +0.06 (SE=1.39); p=0.96 Weight β= +0.17 (SE=1.44); p=0.91 Blood Pb at 4 years 10 months: Head circumference β= +0.01 (SE=0.02); p=0.75 Length β= +1.62 (SE=1.40); p=0.25 Weight β= +1.41 (SE=1.29); p=0.19 Cumulative blood Pb: Head circumference β= -0.01 (SE=0.02); p=0.62 Length β= +1.91 (SE=1.56); p=0.22 Weight β= +1.41 (SE=1.68); p=0.62	subsequent head circumference and marginally related to subsequent length (p=0.06) and weight (p=0.08).
Cross-sectional Hauser (2008) Chapaevsk, Russia *Also listed for puberty*	Boys aged 8-9 (n=489) in Chapaevsk; Years=2003-2005 Male=100%	8.41(0.49)	Median (25-75%tile) 3 (2-5) Exposure measured when outcome assessed	Height, weight, penile length, puberty onset	Multiple linear regression Adjustments depended on variable modeled including: birth weight, gestational age, age at examination, height, weight, BMI, penile length	Adjusted regression coefficient (95% CI) for association of blood Pb (natural log): **Height (cm) -1.439 (-2.25 to -0.63) p<0.001** Weight(kg) -0.761 (-1.54 to 0.02) p=0.67 BMI -0.107 (-0.44 to 0.23) p=0.53	Current blood Pb in 8-year old boys was negatively related to height.
Cross-sectional Ignasiak (2006) Silesia, Poland *Same population in Ignasiak (2007)*	899 children 7-15 years old living in Silesia, near copper smelters; Year=1995; Male=52%	Range 7-15	7.7 (3.5)	Height, weight, trunk length, arm length, leg length	Multiple regression Age, mother's education	Regression analysis for growth by log blood Pb: **Male height B=-6.26 (SE=1.4); p=0.002** Male weight B=-4.00 (SE=2.5); p=0.1 **Male trunk length B=-2.21 (SE=0.97);p=0.02** **Male leg length B=-4.05 (SE=1.27); p=0.002** **Male arm length B=-3.20 (SE=0.97); p=0.0001** **Female height B=-5.54 (SE=2.05); p=0.007** **Female weight B=-6.59 (SE=2.1); p=0.001** Female trunk length B=-1.47 (SE=1.00);NS **Female leg length B=-4.08 (SE=1.27); p=0.0001** **Female arm length B=-2.61 (SE=0.98); p=0.008** B= unstandardized regression slope	Current blood Pb in children 7-15 years of age was negatively associated with height, leg length, and arm length in both sexes, trunk length in boys, and weight in girls; not trunk length in girls or weight in boys.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Ignasiak (2007) Silesia, Poland *Same population as Ignasiak (2006)*	899 children 7-15 years old living in Silesia, near copper smelters; Year=1995; Male=52%	Range 7-15	7.7 (3.5)	Grip strength, timed sit-ups, flexed arm hang, plate tapping, shuttle run, standing long jump, ball throw	Multiple regression Age, mother's education	Regression analysis for indicators of physical fitness by log blood Pb: **Sum R + L grip β=0.05; p=0.02** Sit ups, ball throw, shuttle run, flexed arm hang; p>0.05 Authors state direct effect of blood Pb on physical fitness are not evident. Blood Pb adversely affects physical fitness indirectly through growth stunting.	Current blood Pb in children 7-15 years of age was not associated with physical fitness.
Cross-sectional Kafourou (1997) Greece	522 children 6-9 years of age; in Greece; Years not stated; Male=52%	Range 6-9	12.3 (8.9)	Height, head circumference, chest circumference	Multiple regression analysis Sex, father's height, father's job, age, Hb, city	Regression effect of blood Pb on height (b= regression coefficient): **Height b=-0.086 (SE=0.037); p=0.020** **Head circumference b=-0.033 (SE=0.011); p=0.002** Chest circumference b=-0.040 (SE=0.032); p=0.207	Current blood Pb in children 6-9 years of age was negatively associated with height, head circumference, and chest circumference.
Prospective and cross-sectional Kim (1995) Chelsea and Somerville, USA	236 children 1st and 2nd graders Years=recruited in 1975-1978; follow up n=58 in 1989-1990; Male=53% in 1975; 47% in 1989	1975-8:=7.4 1989-90=20.5	No blood Pb data Exposure determined by dentin and bone Pb ** lack of blood Pb data limits utility	Height, weight, bone Pb, dentin Pb	Multiple linear regression Age, sex, mother's socioeconomic status, birth weight	Association between log dentin Pb and size at 7 years of age: **BMI β=1.02 (0.12, 1.93); p=0.03** Weight and height p>0.05 Association between log dentin Pb and size change from 7 to 20 years of age: **BMI β=2.65 (0.33, 4.97); p=0.03** Weight and height p>0.05 Authors state there was no association between bone Pb in 1989-1990 with any change in growth.	Dentin Pb in 7 year old children was not associated with height or weight at age 7 or age 20; bone Pb in 20 year olds was not associated with height or weight. Dentin Pb at age 7 was associated with increased BMI at age 7 and 20.
Cross-sectional Kordas (2004) Torreon, Mexico	602 children in first grade near metal foundry in Torreon; Year=2001; Male=54%	7.0 (0.4)	11.5(6.1) Exposure measured when outcome assessed	Head circumference, weight, height for age	Spearman correlation, linear and logistic regression Adjustments not described.	Correlation between blood Pb and size: **Height for age Z-score Spearman ρ=-0.16, p<0.01** **Head circumference Spearman ρ=0.35, p<0.01** Study designed to test cognitive function. Unclear if regression analyses were applied to Pb and size.	Current blood Pb was negatively associated with height & positively with head circumference in 7 year olds.
Prospective Lamb (2008) Kosovo, Yugoslavia	309 children assessed at birth, 1, 4, 6.5, and 10 years of age; 161 women	Children assessed at birth, 1, 4, 6.5, and 10 years of	Median Pb smelter town = 20.2 (7.4) Median referent = 5.6µg/dL (2.0)	Height, weight, BMI, maternal free T_4, maternal TSH	Linear regression analysis Sex, ethnicity, parity, maternal height, maternal education,	Effect of living in the Pb-exposed (Titova Mitrovica a Pb smelter town) and referent (Pristina) areas: Estimated regression coefficient relating mid-pregnancy blood Pb to height in referent area:	Maternal blood Pb was not correlated to height or

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Same population as Murphy (1990), Factor-Litvak (1991, 1999) *Also for endocrine*	recruited at mid-pregnancy; 106 lived in an area with environmental Pb (exposed) and 55 lived in an area without significant Pb (referents); children n=156 Pb and 153 referent; % male not stated; Years not stated	age plus or minus 3 months			gestational age at delivery, gestational age at blood sample, HOME score	Birth β=0.35 (-0.94, 1.34) 1 year β=-0.61 (-2.24, 1.03) 4 years β=0.79 (-1.71, 3.29) 6.5 years β=0.15 (-2.43, 2.74) 10 years β=-0.09 (-3.69, 3.52) Estimated regression coefficient relating mid-pregnancy blood Pb to height in Pb-exposed area: Birth β=0.43 (-0.83, 1.69) 1 year β=-0.30 (-2.55, 1.96) 4 years β=-0.72 (-3.26, 1.82) 6.5 years β=-1.87 (-4.38, 0.64) 10 years β=-2.87 (-6.21, 0.47) Regression data for BMI and rate of change per month also not significant.	weight in children aged 1-10.
Cross-sectional Little (1990) Dallas, USA	139 children 1-10 years old at Dallas Children's Medical Center; Years = 1981-1988; Male=47%	1-10	23.6 (SE=1.3) High dose group 34.6 (5.6) Low dose group 11.6 (3.3)	Height, weight, head circumference	Chi-square, ANOVA, and Fisher's exact test, multiple regression models Age, sex	Regression of growth status on blood Pb: **Height B=-0.16 (SE=0.08); p<0.05** **Weight B=-0.14 (SE=0.06); p<0.05** **Head circumference B=-0.06 (SE=0.02); p<0.05** B= unstandardized regression coefficient	Current blood Pb in children 1-10 years of age was negatively associated with height, weight, head circumference.
Cross-sectional Little (2009) Dallas, USA	794 children in 2 cohorts (n=404 in 1980s, n=390 in 2002) aged 2-12 at Dallas Children's Medical Center; Years = 1980-1989, and 2002; Male=47%	2-12	1980s= 24.8 (11) 2002 = 1.8 (1.8)	Height, weight, head circumference	MANCOVA, multiple regression models Age, sex, cohort	Regression effect of log blood Pb on Z-scores for: B= unstandardized regression coefficient by cohort: 1980s <6 years Height B=-0.11 (SE=0.04) 1980s >6 years Height B=-0.21 (SE=0.33) 2002 <6 years Height B=-0.09 (SE=0.13) 2002 >6 years Height B=-0.19 (SE=0.11) Regression effect of log blood Pb on Z-scores for: B= unstandardized regression coefficient **Height B=-0.52 (SE=0.09); p=0.0001** **Weight B=-0.68 (SE=0.09); p=0.0001** **Head circumference B=-0.32 (SE=0.09); p=0.0001** Cohort effect p=0.20, 0.13, 0.58 and authors state cohort effect was negligible (no effect study year) β= standardized regression coefficient **Height β=-0.30; p=0.0001** **Weight β=-0.36; p=0.0001** **Head circumference β=-0.19; p=0.005** Cohort effect p=0.20, 0.33, 0.71 and authors state cohort effect was negligible (no effect study year)	Current blood Pb in children 2-12 years of age was negatively associated with height, weight, head circum-ference; height-Pb relationship did not differ between children in 1980s (mean= 24.8µg/dL) or 2002 (mean= 1.8µg/dL).
Cross-sectional Mahram (2007) Zanjan province	45 children from a Pb mining area (high Pb) and 36	Range 7-11	High Pb = 37(25) Referent=16(13)	Height, weight	Mann-Whitney U test Adjustments not described.	Ratio of height to standard height for age between high Pb area and referent area: Referent relative height = 1.018 (0.052)	Children living in a Pb mining area had higher

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Iran	from a referent area in the same province; 52% male; Years not stated				* Lack of corrections for sex or other adjustments in the analysis of height and weight limits utility	Pb-area relative height = 1.011 (0.050); p=0.52 Ratio of weight to standard weight for age between high Pb area and referent area: Referent relative weight = 0.94 (0.16) Pb-area relative weight = 0.93 (0.18); p=0.8	blood Pb, but did not differ from referents in height or weight.
Cross-sectional Min (2008) Seoul Korea	108 children of white-collar civil servants in Seoul; 57% male; Years not stated	= 9 (2.7) Range 5-13	2.4 (0.7)	Height, arm length, weight, body mass index	Multiple linear regression, generalized estimating equations (GEE) Age, sex, father's education	Multiple linear regression estimate (SE) for height, arm length, weight, and body mass index by Pb: **Height x blood Pb = -1.449 (0.639); p=0.026** **Arm length x blood Pb = -1.804 (0.702); p=0.012** Weight x blood Pb = -0.646 (0.718); p=0.81 BMI x blood Pb = -0.006 (0.272); p=0.982	Current blood Pb in children 5-13 years of age was negatively associated with height and arm length.
Treatment-control Peterson (2004) Baltimore, Newark, Philadelphia, Cincinnati/ Columbus	780 children with blood Pb 20-40µg/dL in the treatment of Pb-exposed children (TLC) trial group, given succimer or placebo; 55-57% male; enrolled in 1998	12-33 months	Baseline placebo =25.9 (4.8) Succimer treatment baseline=26.5 (5.4) Difference from placebo after 6-months=-4.7 12-months=-2.7 >12 months = no difference from placebo	Height, weight	Locally weighted regression, ANCOVA	Mean (95% CI) difference in height between succimer and placebo groups by study month: 6 months = -0.2 (-0.32, -0.09) 9 months = -0.27 (0.42, -0.11) 12 months = -0.28 (-0.46, -0.1) 18 months = -0.37 (-0.60, -0.13) 24 months =-0.36 (-0.64, -0.09) 34 months =-0.43 (-0.77, -0.09) Mean (95% CI) difference in weight between succimer and placebo groups by study month: 6 months = -0.02 (-0.07, 0.04) 9 months = -0.02 (-0.10, 0.05) 12 months = -0.05 (-0.14, 0.03) 18 months = -0.10 (-0.22, 0.02) 24 months =-0.14 (-0.29, 0.02) 34 months =-0.12 (-0.35, 0.10)	Growth rate for height and weight were slower for children on succimer compared with placebo; although blood Pb was lowered during 6-12 months of follow up.
Prospective Rothenberg (1999) Mexico City, Mexico *Follow up on population in Rothenberg, (1993)*	119 to 199 children measured at 6-month intervals through 4 years of age from the Mexico City Prospective Pb Study (502 pregnant women recruited in 1st trimester in Mexico City); Years not stated	Children: every 6 months to 4 years of age Maternal range = 15-42	Median reported graphically Prenatal≈7.5-9 Postnatal≈7-10 Maternal sampled during pregnancy at 36 weeks	Head circumference	Multiple regression Gender, head circumference at birth, head circumference of mom, fetal suffering	Multiple regression for head circumference At 6 months and ln maternal Pb at 36 weeks **β=-0.54 (SE=0.15); p=0.0004** At 36 months and ln infant Pb at 12 months **β=-0.46 (SE=0.16); p=0.0042** NOT significant at other times	Maternal blood Pb (at 36 weeks) and infant blood Pb (at 12 months) was associated with smaller head circumference at later age.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Prospective Rothenberg (1993) Mexico City, Mexico *Same population followed to 4-years in Rothenberg, 1999 (1999)*	50 to 111 children measured at 6, 18, and 36 months of age from the Mexico City Prospective Pb Study of pregnant women recruited in 1st trimester in Mexico City; Years not stated	Children: every 6 months to 4 years of age Maternal range = 15-42	Median reported graphically Prenatal≈7.5-9 Postnatal≈7-10 Maternal sampled during pregnancy at 36 weeks	Head circumference	ANOVA, Spearman rank-order correlation, Pearson correlation, multiple regression analysis Adjustments differed by endpoint including: sex, head circumference at birth, fetal suffering, mother married, HOME score, birth weight, breast-feeding	Multiple regression for head circumference At 6 months and log maternal Pb at 36 weeks **β=-0.43 (SE=0.14); p=0.0027** At 18 months and log cord Pb **β=-0.47 (SE=0.16); p=0.0035** At 36 months and log infant Pb at 12 months **β=-0.98 (SE=0.27); p=0.0009** NOT significant at other times	Maternal blood Pb (at 36 weeks) and infant blood Pb (at 12 months) was associated with smaller head circumference at later age.
Prospective Rothenberg (2000) Mexico City, Mexico *Also in Appendix A: Neural Effects*	100 children from the Mexico City Prospective Lead Study; Years not stated % Male not stated	5.5 years Range: 5-6 years	Geometric means Maternal (20 weeks of gestation) = 8.1(+8.1/-4.0) Infant Cord=8.7(+8.4/-4.3) 12 mo not stated 18 mo=10.8(+9.4/-5.2) 48 mo not stated 60 mo=8.0 (+6.2/-3.7) Abstract presents different mean for maternal Pb (7.7; range 1–30.5)	Head circumference, Brainstem auditory evoked response (BAER)	Linear multiple regression, ANOVA, t test Head circumference, age at time of testing, and sex	Effect of ln blood Pb on head circumference (cm) at 72 months β (95% CI): **Maternal Pb β=-0.415(-0.764, -0.066); p=0.020** **Postnatal 12mo β=-0.414(-0.790, -0.039);p=0.031** **Postnatal 48mo β=-0.517(-0.935, -0.098);p=0.016** Authors also report association between blood Pb and BAER interval.	Maternal blood Pb (20 weeks of gestation) and postnatal blood Pb (12 and 48 months) was associated with changes in the BAER I-V and III-V inter-peak intervals by a linear relationship.
Prospective and Cross-sectional Sanin (2001) Mexico City, Mexico *Population may overlap with Hernandez-Avila (2002) and others*	329 mother-infant pairs of women attending one of three hospitals in Mexico City; Years 1994-1995	Mean age mothers = 24.4 years	Blood Pb Maternal = 9.7 (4.1) Cord = 6.8 (3.8) Infant at 1 month = 5.6 (3.0) Maternal bone μg/g Tibia = 10.1 (10.3) Patella= 15.3 (15.2) Maternal blood at delivery; bone Pb within 1 month	Weight gain from birth to 1 month and weight at 1 month	Univariate and bivariate statistics and distribution plots, multiple regression analyses Infant's age, sex, hospital visit, breastfeeding maternal education, first pregnancy, maternal height, calf circumference	Relationship between Pb and infant weight gain; multiple regression coefficient (95% CI): Maternal patella Pb -0.31 (-2.94 to 2.3) Maternal tibia Pb -0.24 (-4.13 to 3.6) Cord Pb -5.6 (-15.9 to 4.7) **Infant blood Pb -15.1 (-28.3 to -1.8); p<0.05** Maternal blood Pb -4.9 (-12.6 to 2.6) Relationship between Pb and weight; multiple regression coefficient (95% CI): **Maternal patella Pb -3.69(-7.2 to -0.16);p<0.05** Maternal tibia Pb -0.4.8 (-10.1 to 0.36) Cord Pb -6.67 (-20.6 to 7.1) Infant blood Pb -8.2 (-26.1 to 9.7) Maternal blood Pb -1.0 (-11.3 to 9.3) Ordinary least-squares multiple regression model for weight gain β (95% CI): **Infant blood Pb -15.6 (-27.9 to -3.34); p=0.01**	Infant blood Pb and maternal bone Pb were associated with infant growth (weight or weight gain) through 12 months of age; maternal and cord Pb were not.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Maternal patella Pb 1.77 (-1.34 to 4.90);p=0.26 Ordinary least-squares multiple regression model for weight attained β (95% CI): **Maternal patella Pb -3.65(-7.2 to -0.16);p=0.04**	
Prospective Schell (2009) Albany, USA	211 mother-infant pairs from Albany Pregnancy Infancy Pb Study; Years = 1992-1998	6 and 12 months	Geometric mean Maternal Pb 2nd trimester=2.8(2.6) 3rd trimester=2.6(2.2) at delivery= 2.8(2.4) Infant Pb At delivery = 2.3(2.7) 6 months = 3.3 (3.3) 12months=6.3(4.8)	Length, weight, head circumference	Multivariate regression models Sex, birth weight, nutrition, mother's age, marital status, employment, race, mother's height, parity, smoking, education	Regression effect of log maternal blood Pb in second trimester on Z-scores for: B= unstandardized regression coefficient **6 months of age-total** Length-for-age B=0.149 (SE=0.076); p=0.05 Weight-for-age B=0.013 (SE=0.098); p=0.89 **Head circ.-for age B=-0.242 (SE=0.09); p=0.01** 12 months of age-total Length-for-age B=0.073 (SE=0.083); p=0.38 Weight-for-age B=0.124 (SE=0.107); p=0.25 Head circ.-for age B=-0.220 (SE=0.109); p=0.05 **6 months of age; higher Pb≥3μg/dL** Length-for-age B=0.457 (SE=0.271); p=0.10 **Weight-for-age B=-0.771 (SE=0.344); p=0.03** **Head circ.-for age B=-0.846 (SE=0.338); p=0.01** **12 months of age; higher Pb≥3μg/dL** Length-for-age B=-0.076 (SE=0.301); p=0.80 Weight-for-age B=-0.475 (SE=0.403); p=0.24 **Head circ.-for age B=-1.163 (SE=0.376); p<0.01** 6 or 12 months of age; lower Pb<3μg/dL: p>0.05 for length, weight, or head circumference for age	Maternal blood Pb was negatively associated with head circumference in children 6 and 12 months of age; not for length or weight. Effects may be limited to blood Pb ≥3μg/dL.
Cross-sectional Schwartz (1986) USA	2695 Children aged 6 months to 7years in NHANES II; Years= 1976-1980	0.5-7 years	Not reported Range 5-35μg/dL	Height, weight, chest circumference	Multiple linear regression Adjustments differed by endpoint including: age, race, sex, calories, protein, hematocrit	Relationship between Pb and endpoint β (SE): **Height β= -0.12±0.0005cm; p<0.0001** **Weight β= -1.02 (0.08); p<0.001** **Chest circumference β= -0.65 (0.08)cm; p<0.026**	Current blood Pb in children <7 years of age was negatively related to height, weight, and chest circumference.
Cross-sectional Selevan (2003) USA *Also listed for puberty*	Girls aged 8-16 in NHANES III (n=600 non-Hispanic whites; n=805 African Americans; n=781 Mexican Americans): Males=0%	13.4 for all groups	Mean (95% CI) non-Hispanic whites 1.4 (1.2-1.5) African Americans 2.1 (1.9-2.3) Mexican Americans 1.7(1.6-1.9)	Height, weight, puberty (breast development stage, pubic-hair stage, age a menarche)	Multivariable linear regression Age at examination, age squared, race and ethnic group, family income, dietary calcium, iron, vitamin C, anemia	**Blood Pb≥3 was associated with decreased height (r=-0.51, p<0.001)** compared to individuals with blood Pb of 1μg/dL in girls aged 8-16 across racial groups. Blood Pb was not associated with weight or BMI.	Blood Pb≥3 was associated with decreased height in US girls aged 8-16.
Prospective Shukla (1989) Cincinnati, USA *Same population*	Cincinnati Pb study; 260 infants prospectively followed from birth	15 months	Geometric means Maternal=7.5 (1.6) Infant (months) 3 mo= 5.3 (1.8)	Birth length, length at 3 months, growth rate	Pearson correlation, stepwise multiple regression Adjustments differed by	Relationship between higher postnatal blood Pb (>median of 3.4μg/dL) increase and growth rate: Infants of mothers ≤7.7μg/dL (median) blood Pb regression slope = -0.007cm per μg/dL; p=0.19	Current blood Pb was negatively associated with

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
as (Shukla et al. 1991)	in high Pb neighborhood; Enrolled Years= 1980-1985; Male =48%		15 mo=14.6 (1.6) Change in average from 3 to 15 months 3.7 (3.0) Maternal sampled during pregnancy		endpoint including: race, smoking, sex, gestational age, maternal height, postnatal complications, socioeconomic status, HOME score	**Infants of mothers >7.7µg/dL (median) blood Pb regression slope = -0.015cm per µg/dL; p=0.013**	growth rate in 15 month old children with higher maternal blood Pb during pregnancy.
Prospective Shukla (1991) Cincinnati, USA *Same population as Shukla (1989)*	Follow-up of Shukla (1991) Cincinnati Pb study; n=235 of 260 original infants prospectively followed from birth in high Pb neighborhood; Enrolled Years= 1980-1985; Male =48%	33 months	Maternal 7.5 (1.6) Infant (months) 18 mo= 17.3(9.1) 33 mo = 15.9(7.8) mo 3-15=11.8(5.4) mo 18-33= 17.1(8) Maternal sampled during pregnancy	Length, growth rate indicated by slope of least squares regression for length	Pearson correlation for bivariate correlations, stepwise multiple regression analysis Smoking, child's race, sex, maternal height, total iron-binding capacity, length at 18 months	Relationship between blood Pb during 18-33 months of age and length at 33 months: **Infants with high blood Pb (>mean 10.77µg/dL) during 3 to 15 months of age; p=0.002** Infants with low blood Pb (<mean 10.77µg/dL) during 3 to 15 months of age; p=0.85 **Regression coefficient= -1.81 (SE=0.80) cm;p=0.025 for length at 33 months of age with the blood Pb from 3-15 months of age interaction with blood Pb from 18-33 months of age.**	Blood Pb from 18 to 33 months of age was negatively associated with length at 33 months of age in children with higher blood Pb (>10.77µg/dL) from 3 to 15 months of age.
Cross-sectional Stanek (1998) Omaha, USA	21 children aged 18-36 months living in Omaha in an area with high Pb levels;	18-36 months	6.39	Head circumference	Pearson correlation coefficients, multiple regression analyses Sex, race, income, age	**Relationship between blood Pb and head circumference: r=-0.48, p<0.027**	Current blood Pb in children 18-36 months of age was negatively associated with head circumference.
Cross-sectional Tomoum (2010) Cairo, Egypt *Also listed for endocrine and puberty*	41 children living in Pb contaminated areas of Cairo and areas with no obvious Pb pollution; Year = 2007; Male=51%	11.98 (1.13) Range = 10-13	9.46 (3.08) Range=3-15	Height, weight, serum FSH, LH, E_2 (girls), T (boys), puberty /sexual development (Tanner stage pubic hair, testicular size, penile growth in boys; Tanner pubic hair and breast in girls)	Student's t test, Mann-Whitney U test, chi-squared test, Spearman correlation Adjustments not described.	Mean of height and weight as percentage of median for age and sex by below Pb above and below 10µg/dL: Boys weight Pb<10= 127.56% (16.26) Boys weight Pb≥10= 122.0% (16.71) Boys height Pb<10= 98.06% (13.19) Boys height Pb≥10= 99.5% (5.04) Girls weight Pb<10= 114.8% (10.8) Girls weight Pb≥10= 123.11% (12.52) Girls height Pb<10= 96.75% (2.91) Girls height Pb≥10= 100.33% (4.53)	Height and weight did not differ in 12 year old boys and girls with blood Pb above and below 10µg/dL.
Cross-sectional Vivoli (1993) Trento, Italy *Also for endocrine*	418 children 11-13 years of age in Trento; Years not stated; Male=48%	Range:11-13	Male= 8.54 Female=7.01	Height, weight, LH, FSH, T, E_2, DHA-S	Pearson correlation, multiple regression analysis Adjustments differed by sex including: mother's height, father's height, menarche date,	Linear correlation between height and log blood Pb: 11 year old males r=0.023; p=0.841 12 year old males r=0.011;p=0.925 **13 year old males r=-0.353; p=0.009** Total males r=-0.063; p=0.371 11 year old females r=-0.097; p=0.416	Current blood Pb was negatively associated with height and weight in 13

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
					T	12 year old females r=-0.209;p=0.064 13 year old females r=-0.026; p=0.636 **Total females r=-0.162; p=0.017** Relationship between height and blood Pb: **Males aged 13 β= -27.4 (SE=11.5) cm; p=0.02** **Females aged 12 β= -13.2 (SE=4.1) cm; p=0.002** Linear correlation between weight & log blood Pb: 11 year old males r=0.007; p=0.955 12 year old males r=0.064; p=0.598 **13 year old males r=-0.368; p=0.006** Total males r=-0.048; p=0.498 Females of all ages p>0.05 for weight and blood Pb	year old boys and height in 12 year old girls, not other children aged 11-13.
Cross-sectional Zailina (2008) Malaysia	269 children from 2 urban schools in Kuala Lumpur (n=169), and one industrial-area school (n=100); authors indicate stratified random sampling according to sex, but % male not stated; Year not stated	Urban area = 7.5 years Industrial area = 7.25 years Range = 6.5 to 8.5 years	Urban area = 3.75 µg/dL Industrial area = 3.56 µg/dL Blood Pb measured when other outcomes assessed	Height, weight, arm circumference	Correlation analysis Relative height and weight compared to National Center for Health Statistics (NCHS). Adjustments not described. **lack of reported adjustment for sex limits utility	Correlation between blood Pb levels and relative anthropometric measures for total population: Height for age r=-0.071; p=0.244 Weight for age r=-0.011; p=0.856 Weight for height r=0.060; p=0.328 Arm circumference r=0.007; p=0.907 Similar analyses also did not show statistical relationship between blood Pb and anthropometric data for separate urban and industrial populations.	Current blood Pb was not correlated to relative height or weight in 6-8 year olds.
Repro: Sperm							
Retrospective Alexander (1996b) Trail, British Columbia *Population overlap with Alexander (1998)* *Also listed for endocrine*	152 male employees (n=119 who donated semen) of the Cominco smelter; Years= employed in 1993	39.7	28.7	Sperm count, concentration, sperm motility, serum T, FSH, LH	Least-square means regression model Age and smoking status	Odds ratio (95% CI) for below normal sperm concentration (<20 mil./ml) by blood Pb: <15µg/dL) (reference) 15-24µg/dL OR = 4.3 (0.8, 23.3) 25-39µg/dL OR= 2.1 (0.3, 14.5) **≥40µg/dL OR= 8.2 (1.2, 57.9)** Odds ratio (95% CI) for sperm count (<40mil) by blood Pb: <15µg/dL) (reference) 15-24µg/dL OR = 1.7 (0.4, 7.3) 25-39µg/dL OR= 1.0 (0.2, 5.6) ≥40µg/dL OR=2.6 (0.4, 15.7) Odds ratio (95% CI) for normal morphology (%) (<50) by blood Pb: <15µg/dL) (reference) 15-24µg/dL OR = 1.3 (0.4, 4.0) 25-39µg/dL OR= 1.6 (0.5, 5.3) ≥40µg/dL OR= 1.6 (0.3, 8.4)	Blood Pb levels (>40µg/dL) were associated with decreased sperm concentration; not motility or morphology.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Odds ratio (95% CI) for motile sperm (%) (<50) by blood Pb: <15μg/dL) (reference) 15-24μg/dL OR = 0.4 (0.2, 1.0) 25-39μg/dL OR= 0.5 (0.2, 1.5) ≥40μg/dL OR= 0.8 (0.2, 3.1) Mean FSH, LH, and T did not differ by blood Pb.	
Retrospective Alexander (1998) Trail, British Columbia *Population overlap with Alexander (1996b)* *Also listed for endocrine*	81 male employees of original 119 in Alexander (1996b) of the Cominco smelter; Years= employed in 1993	39.7	Blood=22.8 Semen Pb=1.9 Range Blood=5-58 Semen=0.1-17.6	Sperm count, sperm motility, serum T, FSH, LH	Least-square means regression model Age and smoking status	Regression models blood Pb for sperm count with ejaculate volume as covariate: **Blood Pb β=-0.034 (SE=0.011); p=0.003** p=0.008 when ejaculate is added to model **Semen Pb β=-0.244 (SE=.122); p=0.049** p=0.583 when ejaculate is added to model Regression models blood Pb sperm concentration: **Blood Pb β=-0.027 (SE=0.01); p=0.009** p=0.009 when ejaculate is added to model Semen Pb β=-0.046 (SE=.108); p=0.669 p=0.632 when ejaculate is added to model No association was found between blood Pb and sperm motility, morphology.	Blood Pb was associated with decreased sperm count and concentration. Semen Pb was associated with decreased sperm count; not motility or morphology.
Cross-sectional Apostoli (1999)	10 men with occupational Pb exposure (high Pb) and 18 men not-occupationally exposed to metals (referent); Male = 100%; Years not stated	Referents=32.5 Pb-workers: =33.1	No blood Pb data Seminal plasma(μg/dL): Referents=0.28(0.3) Pb-workers=3(1.9) Spermatozoa (μg/Kg) Referents=4.0(2.9) Pb-workers=39.2(28) ** lack of blood Pb data limits utility	Metals in seminal plasma and spermatozoa	Student's t test Adjustments not described. ** only metal concentrations were measured, lack of sperm counts or functional data limits utility	Mean Pb in seminal plasma and spermatozoa: Seminal plasma – referents = 0.28 (0.3) Seminal plasma – Pb-workers = 3 (1.9) Spermatozoa – referents = 4.0(2.9) Spermatozoa – Pb-workers =39.2(28)	Sperm parameters not reported; Pb concentrations were higher in sperm and seminal plasma of Pb-workers than referents.
Cross-sectional Assennato (1986, 1987) Italy *Also listed for endocrine*	39 male employees at a Pb battery plant (high Pb) and 81 workers at a cement plant (referent); Year not stated	Pb=38 (10) Referent=37 (10)	Blood Pb High Pb= 61 (20) Referent= 18 (5) Semen Pb (ppb) High Pb= 79 (36) Referent= 22 (9) Urinary Pb (μg/L) High Pb= 79 (37) Referent= 18 (8)	Sperm count, T, PRL, GSH, LH, seminal Pb, urinary Pb	Pearson correlation, t test, Kolmogorov-Smirnov test, and chi-square test Adjustments not described. Effect of alcohol, cigarette, and coffee consumption, frequency of intercourse, and days of abstinence prior to semen donation examined separately.	Pearson correlation coefficient between Pb and sperm count: **Blood Pb r = -0.385; p=0.010** Semen Pb r = -0.026; p=0.440 Urinary Pb r = -0.266; p=0.058 Authors report 3-fold increase in oligospermia in Pb battery workers (16.7% vs 5.5%).	Blood Pb levels were associated with decreased sperm count.
Cross-sectional Benoff (2003a) Rochester, New York *Also for fertility*	96 men selected from couples undergoing IVF at North Shore University Hospital;	Not reported	No blood Pb data Exposure determined by Pb in semen Seminal Pb =39.5 (28.3)μg/dL	Sperm count, concentration, motility, acrosome reaction,	Spearman correlation, receiver operating characteristic (ROC) analysis Adjustments not described.	Spearman correlation between seminal plasma Pb: **Sperm concentration r=-0.277; p<0.017** **% normal oval morphology r=-0.306; p<0.008** **% sperm motility r=-0.282; p<0.015** **% increase in mannose rec. r=-0.383; p<0.001**	Semen Pb levels were associated with decreases in sperm motility,

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
	Years=1995-1996		** lack of blood Pb data limits utility	morphological assessment , seminal Pb, Cd, Zn, plasma FSH, LH, T	Effect of alcohol consumption, smoking, and age examined separately.	**% premature acrosome loss r=0.265; p<0.05** **%increase in man.-ind. ac. loss r=-0.423; p<0.003** Authors state plasma LH, FSH, T were not related to seminal plasma Pb.	concentration, and other characteristics; blood Pb not reported.
Cross-sectional Benoff (2003b) Rochester, New York *Also for fertility*	15 semen donors in an artificial insemination program at University of Rochester Medical Center; Years= 1998-2000	Range 19-39	No blood Pb data Exposure determined by Pb in semen Range – seminal plasma: <10 to >150µg/dL ** lack of blood Pb data limits utility	Sperm count, concentration, motility, acrosome reaction, morphological assessment	Spearman correlation Adjustments not described. Effect of alcohol consumption, smoking, and age examined separately.	Spearman correlation between seminal plasma Pb: Sperm concentration r=-0.048; p=0.8 Normal oval morphology r=0.044; p=0.8 **Sperm motility r=-0.404; p<0.05** **Premature acrosome loss r=0.697; p<0.02** **P-stimulated ac. loss r=-0.643; p<0.05**	Semen Pb levels were associated with decreases in sperm motility, premature acrosome loss, but not sperm concentration; blood Pb not reported.
Cross-sectional Bonde (2002) United Kingdom, Italy, Belgium The Belgium population was also published in Mahmoud (2005)	486 male workers with (high Pb n=306) and without (referent n=197) occupational exposure to Pb; Years=1996-1997	Range 18-55	Workers=31.0 Reference=4.4	Sperm count, sperm density, sperm chromatin	ANOVA, multiple linear regression Adjustments differed by endpoint including: genital disorders, shorter period of abstinence, age, smoking, season, marihuana	**Mean sperm density and sperm count were reduced in workers with blood Pb ≥50µg/dL relative to individuals with blood Pb ≤10 µg/dL (p<0.05).** OR (95% CI) of sperm count≤50 mil/ml by blood Pb: <10 µg/dL reference 10.1-20 µg/dL OR=1.6 (0.7, 3.5) 20.1-30 µg/dL OR=1.3 (0.7, 3.7) 30.1-40 µg/dL OR=1.2 (0.6, 2.5) 40.1-50 µg/dL OR=0.9 (0.4, 2.1) **≥50 µg/dL OR=4.4 (1.6, 11.6)** OR of reduced sperm volume (≤1.5 ml), sperm density≤20 mil/ml, mean sperm chromatin, and proportion of sperm cells outside the main population were not significantly affected by blood Pb concentrations of 10 to >50 µg/dL relative to the reference <10µg/dL blood Pb. **Authors suggest 44 µg/dL blood Pb level as a threshold for decreased sperm concentration.** **β=-0.037; p=0.038.**	Blood Pb levels (>44-50µg/dL) were associated with decreases in sperm count and sperm density; not sperm volume, chromatin, or sperm density ≤20mil./ml.
Case report Braunstein (1978) Location not stated *Also listed for endocrine*	10 men with chronic high occupational Pb exposure (n=6 judged Pb-poisoned by symptoms; n= 4 exposed without symptoms) and 9 referents; Year not stated	Not reported	Referent= 16.1 (1.7) Poisoned=38.7(3) Exposed=29(5)	Sperm volume, motility, abnormal sperm, testicular histology, FSH, LH, T, E_2, PRL	t test Adjustments not described. * lack of study and statistical information and small sample size limits utility	Authors state no significant difference in volume, motility, or percentage of abnormal sperm in Pb-exposed individuals relative to referents. Authors state testicular biopsies in two most severely Pb-poisoned men demonstrated peritubular fibrosis, oligospermia, and Sertoli cell vacuolization.	Occupational Pb exposure was not associated with sperm parameters.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Chia (1992) Singapore, China	35 males attending an andrology clinic at Singapore General Hospital; Years= 1987 to 1988	37.7 (5)	6.5 (5.4)	Sperm parameters, serum; blood levels of Cd, Mg, Cu, Zn	Statistical methods not reported Adjustments not described.	Blood Pb for subjects by sperm motility: **Individuals < 40% motility Pb=7.2 (6.2)** Individuals ≥40% motility Pb=5.1 (2.4); **p=0.0034** Individuals <40% motility also higher Cd**; p=0.025**	Blood Pb was elevated in men with <40% sperm motility among males attending an andrology clinic.
Cross-sectional Chowdhury (1986) India	10 male workers with chronic occupational exposure in Ahmedabad (Pb exposed) and 10 administrative employees (referent); Years not stated	30	Exposed Blood=42.5 Semen=14.8 ** lack of blood Pb data on referents limits utility	Sperm count, motility, abnormal, seminal acid phosphatase, succinic dehydrogenase, and fructose	Statistical methods not reported Adjustments not described.	Authors state sperm counts and percentage of motile sperm were significantly lower in Pb-exposed workers and percentage of abnormal sperm was increased. Authors state seminal levels of acid phosphatase, succinic dehydrogenase, and fructose were lower in exposed workers	Occupational Pb exposure was associated with higher blood Pb and decreases in sperm count motility and increases in % abnormal sperm.
Case series Cullen (1984) New Haven, Connecticut *Also listed for endocrine*	7 men with occupational Pb intoxication referred to Yale Occupational Medicine Clinic; Years not stated	35	73 (19)	Sperm count, motility, morphology, semen volume, Plasma T_4, TBG, T_3, TSH, FSH, LH, PRL, T, free T, urinary cortisol	Observational study, comparisons made to reference values. Statistical methods not utilized. * small sample size and observational nature limits utility of study	Authors list the following observations for the 7: 5 had defects in spermatogenesis 2 men had oligospermia (low sperm count) 2 men had azoospermia (lack of motile sperm) 3 of 4 men with sperm had motility <50% Depressed spermatogenesis, Leydig cell hyperplasia, and tubular interstitial fibrosis was observed in both testicular biopsies	Some of the 7 men with occupational Pb intoxication had deceases in sperm count, sperm density, and motility.
Cross-sectional De Rosa (2003) Location not stated, authors work in Naples Italy *Also listed for fertility and endocrine*	85 men working at a tollgate (exposed) and 85 reference men recruited from clerks, drivers, students and doctors; Year 2000-2002	Range 23-62 Exposed = 38.6 Referent= 39.6	Exposed=20(SE=0.6) Referent=7.4(SE=0.5)	Sperm count and motility, semen volume, eosin test, acridine orange test; hypo-osmotic swelling (HOS), penetration (CMPT), sperm velocity (VSL, VCL, LIN, ALH), serum FSH, LH, T, air levels of CO, NO, SO, Pb, Zn, Met-, Sulp-, and Carboxy-	Linear regression, t test, chi-square, Pearson correlation Adjustments not described.	Linear regression by blood Pb for significant effects: Total population (n=85) **Sperm count β=-0.8622 (-1.66,-0.07);p<0.05** 52 men with sperm motility <WHO criteria: **Sperm count β=-1.325 (-2.18,-0.47);p<0.01** **Viability (Eosin) β=-0.8937 (-1.6,-0.15);p<0.05** Pb and sperm measures by exposure group (SE): Sperm count(x10^6/ml).–referent = 33.7(1.6) Sperm count –exposed= 32.4(2.4);p>0.05 Semen volume (ml)- referent = 2.7(0.1) Semen volume (ml) –expose= 2.5(0.1);p>0.05 Sperm total motility–referent = 56.8(0.8) **Sperm total motility–exposed= 34.7(2.2);p<0.0001** Forward progression–referent = 28.7(0.5) **Forward progression–exposed= 12.3(1.2);p<0.0001**	Sperm count was negatively correlated with blood Pb. Sperm motility, viability, penetration, hypo-osmotic swelling, and velocity were decreased in exposed men (20µg/dL blood Pb) relative to referents with lower blood Pb.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
				haemaglobin, time to pregnancy		Viability-Eosin–referent = 80.7(0.6) **Viability-Eosin –exposed= 51.7(2.5);p<0.0001** HOS–referent = 65.4(0.6) **HOS –expose= 43.4(2.2);p<0.0001** Acridine orange–referent = 75.7(0.6) **Acridine orange –exposed= 48.5(2.2);p<0.0001** CMPT–referent = 30.3(0.2) **CMPT –exposed= 15.9(1.2);p<0.0001** Velocity (VSL, VCL, LIN, ALH)–referent = 34.4(0.6) **Velocity –exposed= 16.1(1.3);p<0.0001** Blood Pb – referent = 7.4 (0.5) **Blood Pb – exposed = 20.1 (0.6); p<0.0001** Methaemaglobin, sulphaemaglobin, Zn-protoporphyrin, and air levels of NO, SO, CO, and Pb were all significantly higher in the study group. Metheamaglobin was significant associated by linear regression with sperm motility, viability, HOS, acridine orange, CMPT, and linear velocity.	
Case report Fisher-Fischbein (1987) Location not stated; authors work in New York	A 41-year old firearms instructor presenting with Pb-poisoning symptoms in 1983 and followed through chelation therapy until 1986	41 at start of study	1983=88 1986 (Post chelation therapy)=30	Sperm density, sperm count, morphology	Statistical methods not reported Adjustments not described.	Blood Pb and sperm parameters over time and chelation therapy (initial – 1983; final – 1986): Blood Pb 1983 = 88 µg/dL Blood Pb 1986 =30µg/dL from figure Sperm density (x10^{-8}/mL) 1983 = 9.6 Sperm density (x10^{-8}/mL) 1986 = 158 Sperm count (x10^{-6}/ejaculate) 1983 = 12.5 Sperm count (x10^{-6}/ejaculate) 1986 = 110 Normal morphology (%) 1983 = 40 Normal morphology (%) 1986 = 61 Head Defects (%) 1983 = 30 Head Defects (%) 1986 = 22	A case report of increases in sperm density, total sperm count, and decreases in abnormal morphology in parallel with decreasing blood Pb with treatment.
Cross-sectional Hernandez-Ochoa (2005) Region Lagunera, Mexico	68 men living near a smelter in Region Lagunera; Years not stated	34 (8)	Geometric mean blood Pb = 9.31 Range (1.9-24.4) Seminal fluid=0.2 Range (0.114-1.24) Sperm(ng/10^6 cells) =0.047 Range (0.032-0.245)	Sperm count, density, motility, viability, morphology, nuclear chromatin condensation (NCD)	Linear regression analysis Adjustments differed by endpoint including: smoking, drug consumption	Multivariate analysis between Pb-semen quality: Blood Pb – no significant association with volume, motility, morphology, viability, concentration, or nuclear chromatin condensation (NCD) **Seminal Fluid – volume β=-0.183;p<0.05** **Seminal Fluid – NCD β=0.264;p<0.05** Seminal Fluid – no significant association with motility, morphology, viability, concentration **Sperm Pb – motility β=-2.12 ;p<0.05** **Sperm Pb – morphology β=-1.42; p<0.05** **Sperm Pb- viability β=-0.130; p<0.05** **Sperm Pb-log sperm conc. β=-17.2; p<0.05** Sperm Pb-volume β=-0.006; p>0.05 Sperm Pb-NCD β=0.486; p>0.05	Sperm Pb was associated with lower sperm concentration, morphology, viability, motility; seminal Pb was associated with volume and NCD; blood Pb was not associated with sperm parameters.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Hsu (2009) Taiwan	80 male workers in a battery plant; Year not stated	29.2 (3.9)	40.2 (12.8)	Sperm count, motility, morphology, extent DNA denaturation	t test, ANOVA, and Tukey test, multiple linear regression Smoking propensity	Association between blood Pb and sperm morphology and chromatin DNA adjusted for smoking β (SE): **Morph. abnormal.% β=0.271 (0.06); p<0.0001** **Head abnormality % β=0.237(0.07); p=0.0002** Extent DNA denaturation/ cell **β=1.469 (0.56); p=0.011** % sperm with > sensitivity to DNA denaturation **β=0.233(0.10); p=0.021** Morphologic abnormality (%) by blood Pb: <25μg/dL =30.4% (6.2) 25-45μg/dL =34.4% (7.7) **>45μg/dL=39.4%(6.9); p<0.05 to <25μg/dL ;p<0.05 relative to 25-45 μg/dL groups** Extent DNA denaturation/ cell by blood Pb: <25μg/dL =429.4 (58) **25-45μg/dL=480.6(63) p<0.05 to <25μg/dL** **>45μg/dL =488 (60); p<0.05 relative to <25μg/dL** % sperm with >sensitivity to DNA denatur. by Pb: <25μg/dL =65.2 (8.9) **25-45μg/dL =77.0 (12) p<0.05 to <25μg/dL** **>45μg/dL =75.6 (9); p<0.05 relative to <25μg/dL** Authors state blood Pb was not statistically correlated with semen volume, sperm count, sperm tail abnormalities, immaturity, motility, velocity, or H_2O_2 production.	Blood Pb levels were associated with increased percentage abnormal sperm morphology and DNA denaturation; not sperm count or motility.
Case-control Jockenhovel (1990) Germany *Also for fertility*	172 infertile men (case) attending fertility clinic and 18 men (control) that had fathered a child within 15 months; Years=1987-1988	Not reported	Exposure determined by seminal fluid Pb (μg/dL): Infertile =1.18(0.06) Fertile=0.56(0.05) ** lack of blood Pb data limits utility	Sperm concentration, motility, morphology, seminal Cu	Student's t test Adjustments not described. Note: infertile men were sampled in 1987 and fertile men were sampled in 1988 during a time when the use of leadfree gasoline increased from 28% to almost 50%.	When grouped by sperm concentration, motility, and % normal morphology, no differences existed between groups in semen Pb concentration. **A significant correlation was reported between seminal Cu and sperm concentration, motility, and % normal morphology.**	When grouped by sperm parameters, there were no differences in semen Pb; blood Pb not reported.
Cross-sectional Kasperczyk (2008) Poland	63 male employees of a metal plant (n=29 high blood Pb >40μg/dL; n=20 moderate <40μg/dL and 14 referent office workers with lower blood Pb); Years not stated	Referent = 34(2) High=39 (2) Mod. =36(2)	Referent=8.5(SE=0.5) Mod. = 34.7(SE=0.83) High= 53.1(SE=2) Seminal Plasma Referent=1.7(SE=0.2) Mod. = 2.02(SE=0.23) High= 2.06(SE=0.4)	Sperm count, motility, morphology, seminal volume, sperm cell density, blood and seminal Cd and Zn	ANOVA, Mann-Whitney U test, Spearman correlation Adjustments not described.	Percentage of motile sperm after 1 hour by group (estimated mean and SE from figure 1 in Kasperczyk, 2008): Referent 43 (SE=7) Moderate Pb 41 (SE=6) **High Pb 29 (SE=5); p=0.034 to referent(8.5μg/dL) ;p=0.048 to moderate (34.7μg/dL)** Spearman's correlation between blood Pb and: Sperm cell motility after 1 hour **r= -0.32; p<0.001**	The percentage of motile sperm was decreased in workers with mean blood Pb of 53μg/dL; semen volume, sperm count and morphology

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Malondialdehyde (MDA) in seminal plasma **r= 0.43; p<0.01** δ-aminolevulinic acid (ALA) in urine **r=0.48; p<0.001** **Authors state blood Pb is significantly higher in Pb exposed group (p<0.001)** but seminal plasma Pb did not differ from controls (p=0.894). Authors state no difference in Cd, Zn, sperm volume, sperm cell count, percent normal morphology, percentage of progressively motile sperm after 1 hour, and motility after 24 hours	were not different. Sperm cell motility was negatively correlated to blood Pb.
Cross-sectional Lancranjan (1975) location not stated	150 male Pb battery workers (100 plant workers and 50 technicians and office workers) and 50 non-Pb occupational exposed referents (source of referents not stated); Years not stated	Not stated	Pb-plant workers: Pb-poisoned =74.5 (26)µg/dL; n=23 Pb-moderate =53.8 (21)µg/dL; n=42 Pb-slight increase=41 (12)µg/dL; n=35 Technicians =23 (14)µg/dL; n=23 Lack of blood Pb for non-exposed referents	Sperm count, motility, morphology, semen volume, pH, urinary 17-ketosteroids	Chi square test, t test Adjustments not described.	Incidence of asthenospermia (reduced motility): **Pb-poisoned workers = 50%; p<0.001** **Pb-moderate increase workers=51%; p<0.001** **Pb-slight increase workers=42%; p<0.01** Technician and office workers=24%;p>0.05 Incidence of hypospermia (low semen volume): **Pb-poisoned workers = 50%; p<0.001** **Pb-moderate increase workers=44%; p<0.001** **Pb-slight increase workers=42%; p<0.01** Technician and office workers=28%;p>0.05 Incidence of teratospermia (abnormal morphology): **Pb-poisoned workers = 86%; p<0.001** **Pb-moderate increase workers=58%; p<0.001** Pb-slight increase workers=31%; p>0.05 Technician and office workers=16%;p>0.05 Authors state absence of any relationship between Pb absorption and 17-ketosteroid elimination.	Men with occupational Pb and blood Pb levels ≥41µg/dL show sperm alterations relative to non-Pb exposed referents.
Cross-sectional Lerda (1992) location not stated, author works in Argentina	38 male battery workers (high Pb) and 30 non-Pb exposed referents; Years not stated	Pb = 36 Referent = 35	Pb-exposed workers: A-87(0.6)µg/dL; n=12 B-66(1.6)µg/dL; n=11 C-49(4.2)µg/dL; n=15 Referents: 24(1.4)µg/dL; n=30	Sperm count, motility, morphology, semen volume	Pearson correlation coefficients, ANOVA and Dunnett's test Adjustments not described.	Sperm count (mill/ml) for workers and referents: Referents = 11.5 **Pb-worker group A = 69.2; p<0.05** **Pb-worker group B = 67.2; p<0.05** **Pb-worker group C = 68.0; p<0.05** Sperm motility (%) for workers and referents: Referents = 70.4 **Pb-worker group A = 49.0; p<0.05** **Pb-worker group B = 49.9; p<0.05** **Pb-worker group C = 51.5; p<0.05** Sperm anomalies (%) for workers and referents: Referents = 33.4 **Pb-worker group A = 72.9; p<0.05** **Pb-worker group B = 72.2; p<0.05** **Pb-worker group C = 72.1; p<0.05** Semen volume (ml) for workers and referents: Referents = 4.1	Men with occupational Pb and blood Pb levels ≥49µg/dL show sperm alterations relative to non-Pb exposed referents.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Pb-worker group A = 3.8; p<0.05 **Pb-worker group B = 4.0; p<0.05** **Pb-worker group C = 3.9; p<0.05** Percent live sperm for workers and referents: Referents = 82.9 **Pb-worker group A = 68.1; p<0.05** **Pb-worker group B = 65.7; p<0.05** **Pb-worker group C = 71.2; p<0.05**	
Cross-sectional Mahmoud (2005) Belgium *This study was subset of European study in Bonde (2002)* *Also listed for endocrine*	68 male workers (high Pb) in a Pb smelter in Hoboken and 91 hospital personnel (referent) in Ghent Belgium; Years = 1996-1997	Workers=37.4 Referents=32.5	Pb workers=30.9 Referents=3.4 Pb levels measured concurrently with other parameters	Sperm concentration (count/semen volume), serum levels of inhibin B, FSH, E_2	Multiple regression analysis, Spearman rank correlations, Wilcoxon test Adjustments depended on endpoint including: age, period of abstinence, smoking, FSH, BMI	Median sperm values (95% CI) by Pb exposure: Blood Pb referent (hospital staff) = 3.4 (0.5, 9.0) **Blood Pb -Pb worker = 30.9 (10.2, 59.1); p<0.0001** Sperm conc. (mil/ml)- referent= 51 (1,255) **Sperm conc. - Pb worker= 35 (0,177); p=0.028** Semen vol. (ml) - referent= 2.7 (0.4,8.4) Semen vol. Pb worker = 3.0 (0.1, 5.5); p=0.6235 Authors state the difference in sperm concentration remained significant after correction for age and period of abstinence.	Sperm concentration was significantly reduced in Pb workers compared to hospital staff (referents); not semen volume.
Cross-sectional Meeker (2008) Michigan *Same population as Meeker (2010)*	219 men recruited from infertility clinics; Years not stated	34.2 (5.6)	Median 1.5(IRQ 1, 2) 10th percentile=0.80 25th percentile=1.10 50th percentile=1.50 75th percentile=2.00 95th percentile=4.20	Sperm count, volume, concentration, motility, morphology, serum As, Cd, Cr, Cu, Mg, Hg, molybdenum, thallium, Se, Zn	Multiple logistic regression Age, smoking, other metals	Regression model for sperm concentration below reference (<20 mil/ml) by blood Pb when considering multiple metals and covariates: **25-50th percentile OR=0.89(0.27, 2.89)** **50-75th percentile OR=3.94(1.15, 13.6)** >75th percentile OR=2.48(0.59, 10.4); **p trend=0.07** Regression model for sperm parameters by blood Pb when considering Pb (not other metals): OR (95% CI) of sperm conc.<20 mil/ml by blood Pb: <25th percentile reference 25-50th percentile OR=1.04(0.43, 2.44) 50-75th percentile OR=2.58(0.86, 7.73) >75th percentile OR=1.16(0.37, 3.60); p trend=0.38 OR (95% CI) of sperm motility<50% by blood Pb: <25th percentile reference 25-50th percentile OR=1.04(0.43, 2.53) 50-75th percentile OR=1.95(0.70, 5.46) >75th percentile OR=1.66(0.64, 4.29) ; p trend=0.16 OR (95% CI) sperm morph.<4% normal by blood Pb: <25th percentile reference 25-50th percentile OR=0.88(0.32, 2.44) 50-75th percentile OR=2.58(0.86, 7.73) >75th percentile OR=1.16(0.37, 3.60) ; p trend=0.51 Molybdenum was negatively associated with several sperm parameters *Note*: the CI was listed incorrectly for the following: Incorrect -25-50th percentile OR=0.89(1.57, 2.89)	Blood Pb was associated with a greater OR for below-reference sperm concentration; not motility or morphology.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Pers com by email on 9/7/2011 from John Meeker: correct: 25-50th percentile OR=0.89(0.27, 2.89)	
Cross-sectional and Case-control Mendiola (2011) Spain *Also listed for endocrine*	Men attending infertility centers of the Instituto Bernabeu in Murcia and Alicante; 30 mend (case) with oligo-astheno-teratozoospermia and 30 (control) normospermic men; Years=2005-2007	33.5 (3.8)	Whole blood Control=9.7 (2.3) Case=9.8 (2.3) Blood plasma Control=2.9 (0.25) Case=2.9 (0.23) Seminal plasma Control=2.9 (0.34) Case=3.0 (0.30)	Seminal volume, sperm count, motility, morphology, seminal plasma, blood plasma, and whole blood Pb, Cd, Hg, plasma FSH, LH, T	Mann-Whitney U test, Multiple linear regression, Spearman rank correlation Age, BMI, number of cigarettes per day	Cross sectional - Multivariate analysis for ln sperm parameters by ln blood Pb- β(95%CI): Sperm concentration (10^6/ml) β=-0.02(-1.7,1.6) % immotile sperm β=0.05 (-0.32,0.43) % Normal sperm β=-0.31 (-1.5, 0.89) Cross sectional - Multivariate analysis for ln sperm parameters by ln plasma Pb- β(95%CI): Sperm concentration (10^6/ml) β=0.08(-4.1,5.2) % immotile sperm β=-0.49 (-1.8,0.62) % Normal sperm β=-0.08 (-3.5,3.4) Cross sectional - Multivariate analysis for ln sperm parameters by ln seminal Pb- β(95%CI): Sperm concentration (10^6/ml) β=-1.0(-3.1,2.3) **% immotile sperm β=1.5(0.37,1.9); p<0.05** % Normal sperm β=-0.54 (-3.1,2.0) Immotile sperm also related to Cd Case-Control - Mean Pb concentrations in seminal plasma, whole blood, and blood plasma in men with sperm-related abnormalities (case) and normospermic men: Seminal plasma – case = 3.0 (0.30) Seminal plasma – normal = 2.9 (0.34) Blood plasma – case = 2.9 (0.20) Blood plasma – normal = 2.9 (0.25) Whole blood – case = 9.8 (2.3) Whole blood – normal = 9.7 (2.3)	Sperm motility, concentration, morphology did not differ by blood Pb; motility was negatively related to seminal Pb concentrations; not sperm concentration or morphology.
Cross-sectional Naha (2007) Bangalore, India *Population overlap with Naha (2006)*	Male paint factory workers (Pb exposed n=20 >10 years and n=30 7-10 years exposure) and non-occupationally exposed desk job workers (referent n=50) in Bangalore; Years not stated	Range 31-45	Referent=10 (2.3) Exposed 7-10 years=50 (3.5) >10 years=68 (2.5) Semen Pb Referent=2.99 (0.76) Exposed >10 years=15.9(2) 7-10 years=25.3 (2.3)	Sperm count (density mil./ml), motility, viability, morphology, DNA hyploidy, seminal fluid indicators (volume, etc.) plasma LH, FSH, T	ANOVA, t test, Scheffe's F test Adjustments not described.	Mean (SD) of selected sperm values by Pb group: Count (million/ml) referent =137 (39) **Count 7-10 year-Pb =75.3 (19); p<0.001** Abnormal morph (%) referent =34 (3.9) **Ab. morph (%) 7-10 year-Pb =45 (3.22); p<0.001** Motility (%) referent =79 (8.5) **Motility (%) 7-10 year-Pb =30.9 (3.5) ; p<0.001** Seminal volume (ml) referent =4.65 (0.73) **Seminal vol. 7-10 year-Pb =2.61 (0.52); p<0.001** DNA hyploidy (%) referent =7.8(2.3) **DNA hyploidy 7-10 year-Pb =15.9 (3.5); p<0.001** The same sperm parameters were significantly different for the >10 year exposure group relative to referents and the 7-10 year group. **Pb exposure in both the 7-10 and >10 year duration exposed group was also associated with significantly (p<0.001) decreases in sperm ATPase,**	Occupational exposure (with higher blood Pb ≥50µg/dL and seminal Pb≥16µg/dL) was associated with decreased sperm count, motility, seminal volume, and increased abnormal morphology, DNA hyploidy, and other

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						seminal plasma total protein, seminal plasma cholesterol, and increase in liquefaction time, seminal plasma fructose, and amino acids. FSH, LH, and T did not differ between occupationally Pb-exposed and office workers. **Blood Pb and seminal Pb were significantly higher in the 7-10 year Pb group than the controls (p<0.001) and the >10 year-Pb group (p<0.001) than both the controls and the 7-10 year Pb group.**	sperm changes.
Cross-sectional Naha (2005) Kolkata, India *Population overlap with Naha (2006)*	80 (Pb-exposed n=50 >10 years and n=30 7-10 years exposure) male workers in battery factory and 40 non-occupationally exposed referents in Kolkata; Years not stated	Not reported	Values presented graphically, for n=10 of each group in Figure 4 from Naha et al. (2005); estimates presented below Referent=7 (2) Exposed 7-10 years=14 (2) >10 years=28 (5)	Sperm count, density, motility, viability, morphology, and seminal volume	ANOVA, t test, Scheffe's F test Adjustments not described.	Mean (SD) of selected sperm values by Pb group: Count (million) referent =391 (13) **Count 7-10 year-Pb =178 (10); p<0.001** Density (million/ml) referent =137(7.2) **Density 7-10 year-Pb =75(2.4); p<0.001** Motility (%) referent =79 (2.2) **Motility (%) 7-10 year-Pb =60(1.05); p<0.001** Abnormal morph (%) referent =34 (1.1) **Ab. morph (%) 7-10 year-Pb =44.5 (0.57); p<0.001** Seminal volume (ml) referent =4.65 (0.16) **Seminal vol. 7-10 year-Pb =2.61 (0.10); p<0.001** The same sperm parameters were significantly different for the >10 year exposure group relative to referents and the 7-10 year group. **Pb in both the 7-10 and >10 year duration exposed group was also associated with statistically significantly (p<0.001) increases in liquefaction time, and head, mid piece, and tail abnormality**. **Blood Pb and seminal Pb were significantly higher in the 7-10 year Pb group than the controls (p<0.001) and the >10 year-Pb group (p<0.001) than both the controls and the 7-10 year Pb group.**	Occupational exposure (with higher blood Pb >14µg/dL and seminal >11µg/dL estimated from graph) was associated with decreased sperm count density, motility, seminal volume, increased abnormal morphology, and other sperm changes.
Cross-sectional Naha (2006) Kolkata, India *Population overlap with Naha (2005) and Naha (2007)*	80 Pb-exposed workers from paint and battery plants (longer exposed n=50 >10 years and shorter exposed n=30 7-10 years exposure) in Kolkata and 50 non-occupationally Pb exposed referents and; Years not stated	Range 31-45	Blood: Referent=13.6(2.5) Exposed 7-10 years=48.3(5) >10 years=77.2 (1.3) Semen: Referent=3.99(1.4) Exposed 7-10 years=10.9(0.8) >10 years=18.3(2.1)	Sperm count (10^6/ml), protein, RNA, DNA, DNA hyploidy, morphology, viability, motility, viability, morphology, and seminal volume	ANOVA, t test, Scheffe's F test Adjustments not described.	Mean (SD) of selected sperm values by Pb group: Count (million/ml) referent =137(39) **Count 7-10 year-Pb =75(15); p<0.001** Protein (µg/mg) referent =27(4.9) **Protein 7-10 year-Pb =15(3); p<0.001** RNA (µg/mg) referent =19(4.4) **RNA (µg/mg)7-10 year-Pb =7(1.4); p<0.001** DNA (ng/mg) referent =72(9) **DNA (ng/mg)7-10 year-Pb =30(8.3); p<0.001** DNA hyploidy (%) referent =11.8(7.2) **DNA hyploidy (%) 7-10 year-Pb =18(1.5); p<0.001** The same sperm parameters were significantly different (p<0.001) for the >10 year Pb-exposure group relative to referents and 7-10 yr-Pb-group.	Occupational exposure (with higher blood Pb ≥48µg/dL and seminal Pb≥11µg/dL) was associated with decreased sperm count density, motility, seminal volume, increased

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Abnormalities (gross morphological, head, mid piece, and tail) of spermatozoa, membrane lipid peroxidation, seminal plasma DHAA, SM%, and fructose were higher in both Pb-exposed groups relative to referents (p<0.001). **Sperm viability by staining and by HOST, seminal plasma total ascorbate, sperm ATPase activity, sperm motility, FP%, and sperm velocity were decreased in both Pb- exposed groups relative to referents (p<0.001).** **Blood Pb and seminal Pb were significantly higher in the 7-10 year Pb group than the controls (p<0.001) and the >10 year-Pb group (p<0.001) than both the controls and the 7-10 year Pb group.**	abnormal morphology, and other sperm changes.
Cross-sectional Noack-Fuller (1993) Location not stated; authors work in Germany	22 male volunteers without Pb occupational exposure; Years not stated	Range 21-50	Exposure determined by seminal Pb: Semen= 0.98 (0.65) Sem.Plasma= 0.77 (0.56) ** lack of blood Pb data limits utility	Sperm density, sperm count, motility, morphology, motion activity (velocity, linearity), semen and seminal plasma Pb, Cd, Se, Zn	Spearman rank correlation Adjustments not described.	Authors state no significant correlations were found between semen parameters and semen or seminal plasma levels of Pb.	Seminal and sperm Pb were not correlated to semen parameters.
Case report Pleban (1983) Location not stated	Male patients undergoing infertility studies; Years not stated	Not reported	Not reported Exposure determined by seminal fluid Pb (µg/dL): Range= 0.2-2.3 ** lack of blood Pb data limits utility	Seminal plasma /spermatozoa levels of trace metals (Cd, Cu, Fe, Se)	Observational study. Statistical methods not utilized. * lack of study and statistical information limits utility	Seminal plasma Pb Range 0.2-2.3 µg/dL Spermatozoa Pb: Range 0.97-6.19 µg/g	Study did not evaluate fertility or sperm parameters.
Cross-sectional Plechaty (1977) Location not stated; authors work in Farmington, Connecticut	21 male medical students and technicians without Pb occupational exposure; Years not stated	26 (5)	Blood Pb =13.1 (3.5) Seminal Pb=5.9(2.7)	Sperm count, sperm density, seminal protein	Statistical methods not reported Adjustments not described. * unknown if authors tested for correlation between blood Pb and sperm parameters. Lack of study and statistical details limits utility	Authors state no significant correlations between blood Pb and seminal Pb or between seminal Pb and sperm counts.	Seminal Pb was not correlated to sperm counts.
Cross-sectional Robins (1997) East London, South Africa	382 male Pb battery workers in East London (97 with semen sample); Year=1994	Participants in reproductive portion of study=38 Non-participants=43	Blood=53 (11.2) Range=22-110 Semen = 9.6(10.6) Range=1.0-87	Sperm count, density, motility, morphology	Multivariate regression analysis Age, alcohol, smoking, pretest sexual abstinence	Sperm density (mil/ml) by blood Pb: Pb 28-39µg/dL = 65.6(50.7) Pb 40-59µg/dL = 70.9(60.5) Pb 60-93µg/dL = 79.1 (63.4); p trend=0.09 Sperm count (mil) by blood Pb: Pb 28-39µg/dL = 166.5 (156.2)	Sperm count, density, and motility were not associated with blood or semen Pb

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Pb 40-59µg/dL = 162.6(190.5) Pb 60-93µg/dL = 216.6(214); p trend=0.39 Sperm motility (%motile) by blood Pb: Pb 28-39µg/dL = 62.4(13.4) Pb 40-59µg/dL = 60.7(17.2) Pb 60-93µg/dL = 60.4(19.5); p trend=0.21 Sperm morphology (% normal) by blood Pb: Pb 28-39µg/dL = 5.8(3.9) Pb 40-59µg/dL = 4.9(4.7) Pb 60-93µg/dL = 2.6(2.7); p trend=0.16 P trend was also not significant for cumulative blood Pb (years x µg/dL), ZPP, and semen Pb for the above endpoints. Total duration (years exposure) was also not significant, except for morphology. **Sperm morphology (% normal) by duration (years):** 0.5-6.4 years = 5.5(5.4) 6.5-9.9 years = 4.6(4.4) 10-13.9 years = 4.1(3.9) **14-32 years =3.4 (3.4); p trend=0.04** Dichotomized motility, density, and sperm count were also not significant by current blood Pb, except normal morphology <5% by cum. blood Pb. **Sperm morphology (<5% normal) by years x µg/dL:** 26-373 = 61.9 374-539 = 68.2 540-807 = 69.6 **808-2,618 = 80.6; p trend=0.01** Multiple linear regression models for all endpoints were not significant (and not reported) except for logistic model for dichotomized probability of less than 5% sperm with normal morphology and current blood Pb (p=0.06)	levels. Percent of normal sperm was reduced in several analyses for Pb exposure at borderline significance (p=0.06).
Cross-sectional Saaranen (1987) Kuopio Finland	109 men admitted to a fertility clinic (high Pb) of Kuopio University Central Hospital and 79 referents (n=51 with wives that had conceived and n=28 that had not within 6 month period); Years not stated	Pb = 32.3(4.4) Referent = 30.1 (4.9)	Exposure determined by seminal fluid Pb (µg/dL): Fertile =0.17 (0.1) Infertile =0.36 (0.32) ** lack of blood Pb data limits utility	Sperm density, motility, morphology	Pearson correlation analysis Adjustments not described.	Sperm density (millions/ml) by seminal fluid Pb: Pb<0.2µg/dL = 72.9 (130.3) Pb>0.2µg/dL = 83.4 (124.2) Sperm morphology (% normal) by seminal fluid Pb: Pb<0.2µg/dL = 42.1 (22.5) Pb>0.2µg/dL = 38.9 (21.6) Sperm motility (%) by seminal fluid Pb: Pb<0.2µg/dL = 43.9 (18.9) Pb>0.2µg/dL = 40.0 (23.7) **Seminal fluid Pb was positively correlated to Mg (r=0.296; p<0.004) and Zn (r=0.342; p<0.001)** Detection limit for Pb was 0.02µg/dL.	Sperm parameters did not differ between individuals with and without measureable seminal Pb (above/ below 0.2µg/dL); blood Pb not reported.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Slivkova (2009) Location not stated, authors work in Slovakia and Poland	47 men at infertility center; Years not stated	Mean not reported Range=22-48	Exposure determined by seminal Pb (mg/kg): Pb=1.49 (0.4)mg/kg Range 0.09-2.65 mg/kg ** lack of blood Pb data limits utility	Pathological spermatozoa, Semen Pb, Cd, Fe, Ni, Cu, Zn	Student's t test, ANOVA, correlation using PC software GraphPad version 3.01 (details of test statistics not reported)	Author's state "middle negative correlation between Pb and flagellum ball (r=-0.39)" Author's state correlation was not detected between semen levels of elements and pathological changes in spermatozoa.	Analysis for pathological sperm and seminal Pb appear to have been correlated for flagellum ball; additional details unclear.
Cross-sectional Telisman (2000) Zagreb, Croatia *Also listed for endocrine*	149 male industrial workers in Zagreb (high Pb n=98 workers with occupational exposure; and referent n=51); Years=1987-1989	Pb=30 (5) Referent=31(5)	High Pb=38.7(12.5) Referent=10.9 (3) Median seminal Pb: High Pb=1.53 Referent=0.86	Sperm count, density, motility, viability, morphology, seminal fluid indicators (volume, pH, etc), plasma LH, FSH, PRL, T, E_2, seminal Pb, Cd	Mann-Whitney U test, Pearson correlations, regression analysis, Spearman rank correlation, stepwise multiple regression Authors state adjustments made in regression analysis but specific adjustments not described.	Significant Spearman correlation coefficient for sperm parameters and other measures to blood Pb: **Sperm count =-0.177; p≤0.05** **Progressively motile sperm count =-0.179; p≤0.05** **Head/pathologic sperm(%) =0.209; p≤0.01** **Seminal Zn = -0.222; p≤0.01** **Acid phosphatase = -0.202; p≤0.01** **Citric acid =-0.217; p≤0.01** Blood Pb was not significant to semen volume, sperm density, % motile sperm, progressively motile sperm %, viable sperm, pathologic sperm %LDH-C_4, and fructose. **Other measures of exposure such as ALAD, EP, and exposure duration were related to sperm density, count, motile sperm count, progressively motile sperm% and count, and viability (p<0.05).** **Similar analysis of subset (n=118) with seminal Pb measurements was also significant by blood Pb for head/pathologic sperm, acid phosphatase, and citric acid (p<0.05**), but not sperm count **Seminal Pb was significantly correlated to count and % of progressively motile sperm (p<0.05)** Relationship between Pb and sperm count dichotomized by blood Pb with group I <10µg/dL: Group I to II; p>0.05 (~15µg/dL from Figure 4) **Group I to III; p=0.03 (~25µg/dL from Figure 4)** **Group I to IV; p=0.011 (~35µg/dL from Figure 4)** **Group I to V; p>0.05 (~45µg/dL from Figure 4)** **Group I to VI; p=0.016 (~55µg/dL from Figure 4)** **Log Pb and sperm count r=-0.184; p=0.025** **Pb and sperm count r=-0.166; p=0.043** Relationship between Pb, ALAD, and sperm density: **Log Pb and sperm density r=-0.194; p=0.018** **Pb and ALAD r=-0.814; p<0.0001** **Authors state that in stepwise regression adjusted**	Blood Pb levels were associated with decreased sperm count, decreased sperm density, increased abnormal head morphology, ALAD, and other parameters.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						for potential confounders, log Pb was a significant predictor of sperm density, counts of total and progressively motile sperm, abnormal sperm head morphology, seminal Zn, acid phosphatase, and citric acid.	
Cross-sectional Telisman (2007) Zagreb, Croatia *Also listed for endocrine*	240 Croatian men without occupational Pb exposure at infertility clinic or artificial insemination donors; Years = 2002-2005	Range 19-52 Median 31.9	Median 4.9 Range 1.1-14.9	Sperm count, density, motility, viability, morphology, seminal fluid indicators (volume, pH, etc.), plasma LH, FSH, PRL, T, E_2, seminal Pb, Cd, Cu, Se, Zn, ALAD, EP	Multiple regression analysis, Spearman rank correlation, Mann-Whitney U test Age, smoking, alcohol, blood Cd, serum Cu, Zn, Se	Multiple regression association for log blood Pb: Immature sperm β=0.13,B=0.47(SE=0.26);p<0.07 **Pathologic sp. β=0.31,B=12.6(SE=3.3);p<0.0002** **Wide sperm β=0.32,B=11.9(SE=2.7);p<0.0001** **Round sperm β=0.16,B=6.75;p<0.03** Log Pb was not significantly associated with semen volume sperm concentration, count, viability, motility, or other measures	Blood Pb was associated with increased % pathologic sperm, wide sperm, round sperm; not sperm count, viability, motility, or other measures
Cross-sectional Viskum (1999) Netherlands	19 Danish Pb battery workers undergoing treatment to lower blood Pb; Years= 1985-1989	Range 22 to 41	First phase: Initial median=42 Final median=35 Second phase: Initial median=27.5 Final median=19.9	Sperm concentration, motility, penetration	Linear regression analyses Adjustments not described. Authors state smoking, alcohol consumption, age, and length of employment were not significantly related to any sperm parameters	Regression coefficients (β_{joint}) for blood Pb (µmol/L) where p indicates probability of the data given null hypothesis of no association with blood Pb following treatment for high Pb levels: Log concentration; p=0.06 **Motile sperm (%) β=-10.6; p=0.001** **Motile sperm at 24 hour (%) β=-11.1; p<0.001** **Penetration (cm) β=-1.5; p<0.001** **Normal morphology (%) β=1.2; p=0.005**	Treatment-related decrease in blood Pb was associated with improvements in number of motile sperm & penetration.
Cross-sectional Wildt (1983) Sweden	62 male Pb battery workers; Years=in 1978 and 1979	Range 18-61	High Pb- >50µg/dL at least once in prior 6 months (n=31) Mean = 45µg/dL Lower Pb - <50µg/dL in prior 6 months (n=31) Mean=22µg/dL	Sperm count, motility, viability, Mg, morphology, chromatin stability, LDH-X or LDH-C4, Zn, fructose, acid phosphatase	Mann-Whitney rank sum test Adjustments not described.	Authors state sperm chromatin stability was significantly lower in the high Pb group. Authors state no differences between groups for all semen variables other than for sperm chromatin stability and secretory function of the accessory genital glands.	Sperm and seminal values did not differ between Pb workers above and below 50µg/dL.
Cross-sectional Xu (2003) Location not stated, authors from China	56 male subjects (location and characteristics not stated); Years not stated	34.5 (4.4)	Exposure determined by seminal plasma Pb geometric mean (95%CI) 0.78 (0.4, 1.31) ** lack of blood Pb data limits utility	Sperm count, viability, density, motility, morphology, semen volume, seminal plasma Pb, Cd, Se	Linear correlation analysis, additional details not described Adjustments not described.	Linear correlation coefficient for 8-OHdG, sperm parameters and seminal plasma Pb: 8-OHdG r=0.28; p<0.05 Semen volume r=0.17; p>0.05 Sperm density r=-0.21; p>0.05 Sperm number r=-0.08; p>0.05 Sperm motility r=-0.01; p>0.05 Sperm viability r=-0.07; p>0.05 Sperm morphological defects r=0.14; p>0.05	Seminal Pb levels were not correlated with sperm parameters except for a positive correlation with 8-OHdG.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Xu (1993) Singapore, China	221 men (without occupational exposure to heavy metals) screened for infertility at the Andrology Clinic at the Singapore General Hospital; Years=1990-1992	34.8	Blood = 7.72 (3.13) µg/dL Seminal plasma = 1.27 (0.29) µg/dL	Sperm density, motility, viability, morphology, semen volume, blood and semen levels of Cd, Se, Zn	ANOVA, Correlation coefficient (r), other methods not described Adjustments not described.	Linear correlation coefficient between Pb and sperm density separated by sperm status: Blood Pb - normospermic = -0.093 Blood Pb - oligozoospermic = -0.092 Seminal plasma Pb - normospermic = -0.05 Seminal plasma Pb - oligozoospermic = 0.26 Linear correlation coefficient between Pb and: Sperm density = 0.02 Sperm motility = 0.02 Sperm morphology = -0.08 Semen volume = -0.07 Sperm viability = 0.11.	Pb levels in blood and seminal plasma were not significantly correlated to sperm parameters in men screened for infertility
Case-control Anis (2007) Cairo, Egypt	34 men with erectile dysfunction (case) and 15 controls at Cairo University Hospital; Years not stated	Case = 46.8(10) Control=45.3(8)	Case = 34.76 (38) Control = 3.14 (3.17) Case >25µg/dL = 16 Case<25µg/dL = 18 Blood measured when tissue sampled	Penil cavernous tissue Pb deposition, reactive oxygen species, antioxidants	Student's t test Adjustments not described.	Blood Pb levels Men with erectile dysfunction = 34.76(38) **Control – potent men = 3.14 (3); p=0.0026** Cavernous tissue Pb – erectile dysfunction men Blood Pb>25µg/dL–tissue Pb = 90(66)µg/g **Blood Pb<25µg/dL–tissue Pb = 4(4)µg/g; p<0.0001** Authors also report individuals with higher blood Pb have higher serum ROS and lower levels of serum antioxidants, except vitamin C.	Blood Pb and penile cavernous tissue Pb was higher in men with erectile dysfunction.
Repro: Fertility / Time to Conception							
Case-control and Cross-sectional Al-Saleh (2008a) Riyadh, Saudi Arabia	619 women undergoing IVF at the King Faisal Specialist Hospital; not achieving pregnancy (case n=321); controls achieved pregnancy (n=203); Not achieving fertilization (case n=63); controls produced fertilized eggs (n=556); Years= 2002-2003	31.76 (5.12) Range=19-50	Blood Overall = 3.34 (2.24) Case = 4.11(3.7) Fert.Control = 3.3(2) Follicular fluid Overall = 0.68 (1.82) Case = 0.55(0.6) Fer.Control=0.7 (1.9) Measured when other data collected	Fertilization rate in vitro (%fertilized eggs to number of eggs), blood Cd, Hg, follicular Pb	Chi-squares, Student's t test, Fisher's exact test, binary logistic regression, multiple linear regression, Cox and Snell R-squared analysis, Pearson correlation test, Spearman rank Women's age, husband's age, BMI, age when menstruation started, days of menstrual cycle, duration living in current province, duration living in former province, current province, former province, women's education, husband's education, women's working status, total family income, husband's smoking status, and drinking caffeine, blood and follicular CD, Hg, cotinine	Pb level by fertilization outcome: Blood-Control- with fertilized eggs = 3.26 (2.01) Blood-**Case-no fertilization = 4.11 (3.68); p=0.03** Follicular-Control- with fertilized eggs = 0.7(1.9) Follicular-Case-no fertilization = 0.55(0.59);p=0.4 Odds ratio (OR and 95% CI) for pregnancy outcome by Pb level: Blood Pb β=-0.60; p=0.18; OR = 0.55(0.23,1.31) Follicular Pb β=0.31; p=0.13; OR = 1.36(0.91,2.02) Odds ratio (OR and 95% CI) for fertilization outcome by Pb level: Blood Pb β=-1.22; p=0.06; OR = 0.30(0.08,1.03) Follicular Pb β=0.37; p=0.33; OR = 1.45(0.69,3.02) **Odds ratio (OR and 95% CI) for fertilization model by Pb level for backward elimination procedure:** **Blood Pb β=-0.07; p=0.05; OR = 0.38(0.14,0.99)** Follicular Cd level was positively related to fertilization outcome	Maternal blood Pb levels were associated with decreased OR of fertilization rate, not pregnancy.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Retrospective Apostoli (2000) Northern Italy	251 men working in Pb-related factory in Northern Italy; 119 referent-men working in non-Pb industry; subset of Asclepios project; Years=1977-1996	Pb -exposed: Maternal=28.3 Paternal=31.6 Referent: Maternal=27.3 Paternal=30.3	Mean not reported. Blood Pb determined for Pb workers by records closest to beginning TTP. Exposure not measured for referents	Time to pregnancy, fecundability (odds of conception over a given time)	Kaplan Meier survival analysis of last pregnancy, Chi-square test, cox proportional hazard model Paternal age	Cox proportional risk ratio(RR) (95% CI) on time to pregnancy and age in exposed subjects with only one child: Blood Pb ≤19 µg/dL RR=1 – reference Blood Pb20-39 µg/dL RR=0.91(0.5,1.68); p=0.77 Blood Pb 30-39 µg/dL RR=1.13(0.57,2.24);p=0.73 **Blood Pb ≥40µg/dL RR=0.26(0.09,0.74);p=0.012** Authors state survival analysis of cumulative proportion of unfecund months (limited to subjects with one child to produce more homogeneous contrast of groups) by exposure level (0-19, 20-29, 30-39, ≥40µg/dL) indicates a **delay to conceive in the ≥40µg/dL group; p<0.05.** **Fecundability ratio of all Pb-exposed to referent: = 1.53; p<0.01** (authors state statistically shorter TTP associated with the Pb exposure **p<0.05**). Authors state statistically longer TTP associated with the highest exposure level (≥40µg/dL).	Male workers occupationally exposed to Pb with blood Pb ≥40µg/dL had a statistically significantly longer time to pregnancy and altered fecundability ratio; lower doses were associated with decrease in time to pregnancy.
Cross-sectional Benoff (2003a) Rochester, New York *Also for fertility*	96 men selected from couples undergoing IVF at North Shore University Hospital; Years=1995-1996	Not reported	No blood Pb data Exposure determined by Pb in semen Seminal Pb =39.5 (28.3)µg/dL ** lack of blood Pb data limits utility	Sperm count, concentration, motility, acrosome reaction, morphological assessment , seminal Pb, Cd, Zn, plasma FSH, LH, T	Spearman correlation, receiver operating characteristic (ROC) analysis Adjustments not described. Effect of alcohol consumption, smoking, and age examined separately.	Spearman correlation between seminal plasma Pb: **Fertilization rate in IVF r=-0.447; p<0.0001** Authors suggest 42.3 µg/dL semen Pb level as a threshold for 'normal' fertilization rate of ≥63%.	Semen Pb levels were associated with decreases in fertilization rate in IVF; blood Pb not reported.
Cross-sectional Benoff (2003b) Rochester, New York *Also for fertility*	15 semen donors in an artificial insemination program at University of Rochester Medical Center; Years= 1998-2000	Range 19-39	No blood Pb data Exposure determined by Pb in semen Range – seminal plasma: <10 to >150µg/dL ** lack of blood Pb data limits utility	Sperm count, concentration, motility, acrosome reaction, morphological assessment	Spearman correlation Adjustments not described. Effect of alcohol consumption, smoking, and age examined separately.	Spearman correlation between seminal plasma Pb: **Fertilization rate in IVF r=-0.942; p<0.0001** Spearman correlation between decrease in seminal plasma Pb over time and increase in fertilization rate in IVF over time: **r=-0.9432; p<0.005**	Semen Pb levels were associated with decreases in fertilization rate in IVF; blood Pb not reported.
Prospective (Bloom *et al.* 2010) San Francisco, California *Population overlaps with (Bloom et al.*	15 female IVF patients and 15 male partners recruited at a fertility clinic at the University of California at San Francisco; Years 2007-2008	Female patients: median=36, range=28-44 Male partners: median=38, range=31-48	Female patients: 0.82 (0.32) median=0.77 Male partners: 1.50 (0.80) median=1.32	Number of oocytes collected, number of mature oocytes (oocytes in metaphase-II (MII) arrest), oocyte	Spearman rank correlation coefficients, Wilcoxon rank-sum test, Kruskall-Wallis test, multivariable log-binomial logistic regression. Also, directed acyclic graphs (DAGs), single metal models (SMM), multiple metal models (MMM) and generalized estimating	Probability of oocyte maturation: **Using SMM for female blood Pb, 46% decrease for each 1 µg/dL increase in Pb; RR=0.54(0.311, 0.93);p=0.027** Using the MMM for all blood levels of all metals, 75% decrease for each 1 µg/dL increase in Pb; RR=0.25 (0.03, 2.50), p=0.240 Probability of oocyte fertilization:	Maternal blood Pb levels were associated with decreased oocyte maturation

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
2011b)	Race/ethnicity, Women: Asian =27.6% Men: Asian=14.7%			fertilization (number of zygotes formed); levels of Hg, Cd, and Pb in fasting (women) or non-fasting (men) whole blood and urine.	equations (GEE). Age, cigarette-smoking, race/ethnicity, and creatinine concentration (only in models where urine Cd used as a predictor).	**Asian race/ethnicity was a positive predictor using SMM for female blood Pb (RR=1.46, p=0.001) or MMM for all metals (RR=1.29, p=0.035)** **Using SMM for male blood Pb, 13% increase for each 1 µg/dL increase in Pb; RR=1.13 (1.01, 1.27), p=0.039** **Cigarette-smoking was a positive predictor of oocyte fertilization in SMM for male [blood] Pb (RR-1.38, p=0.0003) as well as in the MMM (RR=1.60, p=0.001).** No correlation between blood Pb and Hg or Cd (creatinine-corrected). Authors also stated that **Asian race/ethnicity of male partners was a positive predictor of oocyte fertilization in SMM for Pb (RR=1.38, p=0.0003) and in the MMM (RR=1.60, p=0.001)**	
Prospective (Bloom *et al.* 2011b) San Francisco, California *Population overlaps with (Bloom et al. 2010)*	54 female IVF patients and 36 male partners recruited at a fertility clinic at the University of California at San Francisco; Years 2007-2008 Race/ethnicity, Women: Asian =29.6% Men: Asian=14.7%	Female patients: median=36, range=28-44 Male partners: median=38, range=31-48	Female patients: 0.83 (0.32) Median= 0.81 Male partners: 1.50 (0.80) Median=1.32	Total mobile count of sperm (TMC), number of embryos, embryo cell number (ECN), embryo fragmentation score (EFS); levels of Hg, Cd, and Pb in fasting (women) or non-fasting (men) whole blood and urine.	Spearman rank correlation coefficients, Wilcoxon rank-sum test, Kruskall-Wallis test, multivariable ordinal log-binomial logistic regression. Also, directed acyclic graphs (DAGs) and generalized estimating equations (GEE). Age, cigarette-smoking, race/ethnicity	In women (n=24), **75% decrease in adjusted odds ratio (95% CI) for an increased ECN per µg/dL increase in blood Pb concentrations; 0.25(0.07, 0.86), p=0.028** No statistically significant predictors of EFS in women. In men (n=15), **42% decrease in the adjusted odd ratio for an increased ECN per µg/dL increase in blood Pb concentrations; 0.58(0.37, 0.91), p=0.018** **Positive association with EFS for blood Pb; adjusted OR (95% CI)=1.47(1.11, 1.94), p=0.007** Authors also report that **Hg levels were negatively associated with EFS for blood Hg in men; adjusted odd ratio(95% CI)=0.85(0.72, 1.00), p=0.044.**	Maternal and Paternal blood Pb were associated with decreased embryo cell number. Also, Paternal blood Pb was associated with an increase in embryo cell fragmentation.
Prospective (Bloom *et al.* 2011a) New York	80 non-pregnant women followed for pregnancy for up to 12 months after stopping contraception; Years 1996-1997	25-35	No positive pregnancy test: 15.54(1.57) Min-Max=6.00-34.00 Positive pregnancy test: 15.44 (1.23) Min-Max=8.00-30.00	Blood levels of As, Cd, Pb, Ni, Mg, Se, Zn; time to pregnancy (TTP)	Cox proportional-hazards regression model for discrete-time data Age, parity, groupings of PCB congeners (estrogenic, anti-estrogenic, and other), serum lipids, frequency of intercourse during fertile window, cigarette use, and alcohol use.	No difference in blood Pb levels between women who became pregnancy and women who did not achieve pregnancy. Authors also reported: Blood levels of the remaining metals did not affect TTP.	Blood Pb levels in women were not related to TTP

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Retrospective Bonde (1997) Denmark	1349 male battery plant employees and 9596 reference employees; Years=employed 1964-1992	Not reported	Workers=35.9 (13) Exposure determined by occupation and by biological monitoring program for Pb workers.	Live born children as measure of fertility	Logistic regression Age, calendar year, paternal parity, children born in previous 5 years	Odds ratio (95% CI) for birth rate by years at risk from exposure to Pb compared to years not at risk: OR=0.997 (0.88, 1.13) to plant reference OR=0.983 (0.87, 1.11) to external reference Odds ratio (95% CI) for reduced fertility by blood Pb with reference group of prior exposure: Years-not at risk Adj.OR = 1 (reference) 1-20µg/dL Pb = 0.77 (0.35, 1.67) 21-40µg/dL Pb =0.92 (0.64, 1.33) >40µg/dL Pb = 1.21 (0.83, 1.76)	Paternal occupational Pb exposure was not associated with birth rate or odds of reduced fertility.
Case-control Cross-sectional Chang (2006) Kaohsiung, Taiwan *Also listed for endocrine*	64 women recruited at an infertility clinic (case); and 83 control women from postpartum clinic in Kaohsiung; Years=1999-2001	Maternal Case = 31.2 (3) Control=32.6(4)	Maternal Case = 3.55 (1.39) Control = 2.78 (2) Paternal Case = 4.79 (1.5) Control = 3.23 (2.3) Pb measured in cases when other data collected; measured in controls 1-2 years after pregnancy	Infertility, Serum FSH, LH, E_2, P_4	t test, multivariate logistic regression analysis Age, BMI, smoking, western medicine use, herbal medicine use, irregular menstruation	Odds ratio (95% CI) for infertility comparing blood Pb above and below 2µg/dL: **OR=2.94 (1.18, 7.34); p=0.021**	Blood Pb levels >2µg/dL were associated with increased OR for infertility.
Retrospective Coste (1991) France	354 male battery workers (229 classified as Pb-exposed, 125 as non-Pb –exposed); Years= 1977 to 1982	36.5 (9)	Pb-exposed workers dichotomized by blood Pb, but #s and means not reported (<40µg/dL, 40-60µg/dL, >60µg/dL) Blood Pb not taken in jobs classified as not exposed	Birth of children as measure of fertility	Chi square test, multiple logistic regression Alcohol, smoking, working conditions (heat, sulfuric acid exposure), age, education, French origin, number of children	Odds ratio (95% CI) for infertility (non-occurrence of live births during observed year) for workers: Non-exposed job = 1 (reference) <40µg/dL Pb = 0.94 (0.70, 1.26) 40-60µg/dL Pb =1.20 (0.91, 1.59) >60µg/dL Pb =0.79 (0.55, 1.13)	Fertility did not differ between workers classified as Pb-exposed and not exposed.
Cross-sectional De Rosa (2003) Location not stated, authors work in Naples Italy *Also listed for sperm and endocrine*	85 men working at a tollgate (exposed) and 85 reference men recruited from clerks, drivers, students and doctors; Year 2000-2002	Range 23-62 Exposed = 38.6 Referent= 39.6	Exposed=20(SE=0.6) Referent=7.4(SE=0.5)	Time to pregnancy (TTP), sperm parameters, serum FSH, LH, T, air levels of CO, NO, SO, Pb, Zn, Met-, Sulp-, and Carboxy-haemaglobin	Linear regression, t test, chi-square, Pearson correlation Adjustments not described.	Pb and time to pregnancy (months) levels by exposure group (SE): Blood Pb – referent = 7.4 (0.5) **Blood Pb – exposed = 20.1 (0.6); p<0.0001** TTP (mo) – referents = 8.1 (0.4) **TTP (mo)-exposed = 15(1.6); p<0.0001** Methaemaglobin, sulphaemaglobin, Zn-protoporphyrin, and air levels of NO, SO, CO, and Pb were all significantly higher in the study group.	Time to pregnancy was significantly increased in exposed men (20µg/dL blood Pb) relative to referents with lower blood Pb.
Cross-sectional Gennart (1992b) Belgium	365 male workers exposed to Pb and Cd (n=83 in Cd smelter; n=74 Pb battery factory;	Referent=42 (11) Cd=52(11) Pb=40(8.6) Mn=33(7.2)	Referent=10.4 (3.3) Cd= 18.6 (5.8) Pb= 46.3 (11.2) Mn= 9.9 (4.1)	Live births as measure of fertility	Cochran and Mantel-Haenszel statistics, logistic regression Adjustments not described	Odds ratio (95% CI) for probability of live birth by occupational Pb exposure: **OR=0.65 (0.43, 0.98**) relative to referent group **OR=0.43 (0.25, 0.73) r**elative to pre-Pb occupational exposure	Occupational exposure to Pb was associated with decrease in OR for live

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
	n=70 in alkaline battery plant) and 138 in unexposed population; Years= 1988-1989						birth relative to pre Pb-exposure or referent population.
Retrospective case-control Gracia (2005) United States	650 infertile men and 698 fertile controls from university-based infertility and prenatal clinics	Case=34.1(0.4) Control=33.5 (0.5) Range=20-55	Exposure determined by occupation ** lack of blood Pb data limits utility	Infertility	Bivariate, stratified, and multivariable analyses Work-related stress, shift work, m metal fumes, radiation, video display, electromagnetic fields, age of female, race, education, clinical site, excess heat, marijuana, alcohol, cigarettes, caffeinated beverages	Odds ratio (95% CI) for prevalence of self-reported Pb exposure between cases and controls: Case = 5.03 Control = 5.28: OR=0.95 (0.6,1.6); p=0.85	Self-reported Pb exposure did not differ between fertile and infertile men.
Case-control Jockenhovel (1990) Germany	172 infertile men (case) attending fertility clinic and 18 men (control) that had fathered a child within 15 months; Years=1987-1988	Not reported	Exposure determined by seminal fluid Pb (µg/dL): Infertile =1.18(0.06) Fertile=0.56(0.05) ** lack of blood Pb data limits utility	Sperm concentration, motility, morphology, seminal Cu	Student's t test Adjustments not described. Note: infertile men were sampled in 1987 and fertile men were sampled in 1988 during a time when the use of leadfree gasoline increased from 28% to almost 50%.	Mean seminal Pb concentrations by fertility group: Fertile=0.56(0.05) µg/dL **Infertile =1.18(0.06) µg/dL; p<0.006**	Mean seminal Pb was higher in infertile men than fertile men; blood Pb not reported.
Retrospective cross-sectional Joffe (2003) Belgium, England, Finland, Italy	1,104 men having fathered a child, 638 occupationally Pb-exposed, external referent-men working in industries without Pb exposure (n=236); internal referent-men working in companies with Pb, but timing of pregnancy indicates Pb exposure did not occur prior to pregnancy (n=230), Asclepios Project; Years= 1995-1998	Father=30 (5) Mother=27 (5)	Pb-exposed workers: Belgium 31.7µg/dL England 37.2µg/dL Finland 29.3µg/dL Italy 29.2µg/dL **Lack of Pb data for referents limits utility	Time to pregnancy	Cox proportional hazard models Country, mothers age, smoking, parity	Time to Pregnancy Hazard ratio (HR) (95% CI) Pb to external referent: **Blood Pb <20 µg/dL HR=1.56 (1.17, 2.07)** **Blood Pb 20-29 µg/dL HR=1.32 (1.05, 1.67)** Blood Pb 30-39 µg/dL HR=1.22 (0.96, 1.54) **Blood Pb ≥40 µg/dL HR=1.30 (1.03, 1.63**) HR (95% CI) Pb to internal referent: Blood Pb <20 µg/dL HR=1.12 (0.84, 1.49) Blood Pb 20-29 µg/dL HR=0.96 (0.77, 1.19) Blood Pb 30-39 µg/dL HR=0.88 (0.70, 1.10) Blood Pb ≥40 µg/dL HR=0.93 (0.76, 1.15) HR (95% CI) duration exposure to external referent: **0-4 Years HR=1.24 (1.00, 1.54)** **5-9 Years HR=1.24 (1.01, 1.54)** 10-14 Years HR=1.06 (0.82, 1.36) **15+ Years HR=1.76 (1.30, 2.37)** HR (95% CI) duration exposure to internal referent: 0-4 Years HR=0.92 (0.76, 1.12) 5-9 Years HR=0.92 (0.75, 1.13) 10-14 Years HR=0.78 (0.62, 1.01) 15+ Years HR=1.31 (0.96, 1.77)	Male workers occupationally exposed to Pb did not differ in time to pregnancy relative to internal referents. The external referents had greater time to pregnancy by some analyses.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						HR (95% CI) cumulative Pb exposure (µg/dL x years) to external referent: **<120 HR=1.28 (1.00, 1.65)** **120-220 HR=1.33 (1.05, 1.70)** 220-420 HR=0.97 (0.76, 1.24) **420+ HR=1.43 (1.13, 1.81)** HR (95% CI) cumulative Pb exposure (µg/dL x years) to internal referent: <120 HR=0.94 (0.73, 1.18) 120-220 HR=0.97 (0.78, 1.22) **220-420 HR=0.71(0.56, 0.89)** 420+ HR=1.04 (0.83, 1.31) Authors state no detectable effect of Pb at levels in the study on male fertility.	
Case-control Kiziler (2007) Istanbul, Turkey	50 men examined for infertility (case) and 45 normal volunteers (control) with approximate equal numbers of smokers and non-smokers at Istanbul University; Year not stated	Not reported	Blood Pb: Control=23.2(5.6) Infertile =36.8(12.3) Seminal plasma Pb: Control=26.3(5.2) Infertile =38.2(11.4)	Sperm concentration; motility; sperm ROS; morphology; seminal and sperm: MDA, GSH carbonyls, and GST; blood Cd; seminal plasma Cd, Pb	ANOVA, Tukey's Range test, Mann-Whitney U test, Pearson correlation Adjustments not described.	Blood Pb: Control=23.2(5.6) Control-non-smoker=19.6(4.5) Control-smoker=26.5(4);**p<0.001 to control non-smoker** Infertile =36.8(12.3);p<0.001 to control Infertile-non-smoker=26.5(5.1);**p<0.001 to control** Infertile-smoker=46.3(9);**p<0.001 to infertile non-smoker** **Seminal Pb, Sperm and seminal MDA, carbonyls, and sperm ROS** were also different from controls in the same pattern as blood Pb: control smokers> control nonsmokers infertile>controls infertile non-smokers>control non-smokers infertile smokers>infertile non-smokers **Sperm and seminal GSH and GST** were also different from controls in the opposite pattern as blood and seminal Pb control smokers< control nonsmokers infertile<controls infertile non-smokers<control non-smokers infertile smokers<infertile non-smokers **Sperm Concentration** ($x10^6$/ml): Control=63.1(23.9) Control-non-smoker=62.8(20.7) Control-smoker=63.3(27.1) Infertile =21.1(12.1);**p<0.001 to control** Infertile-non-smoker=17.0(10);**p<0.001 to control** Infertile-smoker=25.5(13);**p<0.001 to infertile non-smoker**	Mean blood Pb and seminal Pb were higher in infertile men than fertile men. Sperm concentration, motility morphology and other parameters were lower in the infertile men; however, blood and seminal Pb were not correlated to sperm parameters.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Sperm morphology and sperm motility was also different from controls in the same pattern (infertile<controls; infertile non-smokers<control non-smokers; infertile smokers<infertile non-smokers) Pearson correlation between seminal Pb in smokers of the infertile group: **Spermatozoa ROS r=0.422; p<0.05** Cd was correlated to ROS, GSH and GST. Authors state no other correlation between Pb and other parameters.	
Cross-sectional Lin (1996) New York	4256 male Pb workers (high Pb) reporting to New York State Heavy Metals Registry and 5148 (referent) random sample of male bus drivers in New York; Years=1981-1992	Range 20-55	Workers = 37.2 (11) dichotomized blood Pb % of workers: 20-34µg/dL=50.4% 35-49µg/dL=39.1% ≥50µg/dL=10.4% Lack of blood Pb for non-exposed referents	Fertility determined from birth certificates	Standardized fertility rate (SFR) = live births per Pb worker / live births per referent worker during study period. Logistic regression Age, race, education, and residence Note: reporting level pre 1985 was ≥40µg/dL and ≥25µg/dL after 1985	Standardized fertility rate (95% CI) Pb workers: **20-30 years of age SFR=0.86 (0.78-0.95)** 31-40 years of age SFR=0.91 (0.78-1.05) 41-50 years of age SFR=0.88 (0.64-1.34) 51-60 years of age SFR=3.00 (0.60-8.77) **Total for Pb-workers SFR = 0.88 (0.81- 0.95)** Standardized fertility rate (95% CI) Pb workers exposed to Pb for > 5 years: **20-30 years of age SFR=0.50 (0.31-0.76)** **31-40 years of age SFR=0.28 (0.14-0.50)** 41-50 years of age SFR=1.00 (0.37-2.18) **Total for Pb-workers SFR = 0.43(0.31-0.59)** Percent fertility ratio of Pb workers to bus drivers by blood Pb levels: Blood Pb 20-34µg/dL =0.9 (0.7-1.0) Blood Pb 35-49µg/dL =0.9 (0.8-1.0) Blood Pb ≥50µg/dL = 1.1 (0.8-1.5) Percent fertility ratio of Pb workers to bus drivers by duration of time reported with elevated Pb: ≤1 year =1.0 (0.8-1.2) 1-5 years=1.0 (0.9-1.3) **>5 years = 0.3 (0.2-0.5)** Adjusted relative risk of Pb workers with >5 years of Pb exposure compared to Pb workers with shorter duration of Pb exposure **RR=0.38 (0.23-0.61)**	Pb workers exposed for ≥5 years had reduced fertility rate relative to referent population of bus drivers or Pb workers with shorter duration exposure.
Cross-sectional Saaranen (1987) Kuopio Finland	109 men admitted to a fertility clinic (high Pb) of Kuopio University Central Hospital and 79 referents (n=51 with wives that had conceived and n=28 that had not within	Pb = 32.3(4.4) Referent = 30.1 (4.9)	Exposure determined by seminal fluid Pb (µg/dL): Fertile =0.17 (0.1) Infertile =0.36 (0.32) ** lack of blood Pb data limits utility	Sperm density, motility, morphology	Pearson correlation analysis Adjustments not described.	Pb concentration in seminal fluid of fertile and infertile men: Fertile (n=39) Pb = 0.17 (0.1) µg/dL **Infertile (n=79) Pb = 0.36 (0.32) µg/dL; p<0.001**	Seminal Pb levels were higher in infertile men admitted to a fertility clinic.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
	6 month period); Years not stated						
Retrospective Sallmen (1995) Finland *Same population as Taskinen (1988) Lindbohm (1992)*	121 women from previous study of spontaneous abortion among 2688 women biologically monitored for Pb at the Finnish Institute of Occupational Health; Years=1973-1983	Not reported	Exposure was based on self-reported exposure, work descriptions and biological measurements. 36% of subjects were not monitored during the time to pregnancy in question ** lack of blood Pb data limits utility	Fecundability (odds of conception over a given time, incidence density ratio (IDR) of clinically recognized pregnancies	Proportional regression analysis Exposure to carcinogens (Cd, Cr, Ni), age, parity, older age at menarche, low frequency of intercourse vaginitis, use of coffee, use of alcohol	Incidence density ratio (IDR) of clinically recognized pregnancies by blood Pb (95% CI) Not exposed IDR = 1.00 - reference <10 µg/dL IDR= 0.93 (0.56, -1.57) 10-19µg/dL RR=0.84 (0.48, -1.45) ≥20µg/dL RR=0.80 (0.42, -1.54)	Maternal blood Pb levels (estimated by occupation or measured) were not associated with odds of conception.
Retrospective Sallmen (2000a) Finland *Same population as Sallmen (2000b)*	Men monitored for Pb exposure by Finnish Institute of Occupational Health; n=502 men having fathered a child, all occupationally exposed to Pb; Years= 1973-1983	Not reported	Not reported	Fecundability density ratio (FDR)	Proportional hazard regression Adjustments depended on analyses and included: previous abortion, maternal age, coffee consumption, regularity of menstrual cycle, year of pregnancy, and parental exposure to organic solvents	Fecundability density ratio (FDR) by paternal Pb: 0-8 µg/dL blood Pb FDR= 1.0 – reference 10-19µg/dL blood Pb FDR=0.92 (0.73-1.16) 21-29µg/dL blood Pb FDR=0.89 (0.66-1.20) **31-37µg/dL blood Pb FDR=0.58 (0.33-0.96)** 39µg/dL blood Pb FDR=0.83 (0.50-1.32) Fecundability density ratio (FDR) by paternal Pb, restricted to pregnancies that end in birth: 10-19µg/dL blood Pb FDR=0.87 (0.67-1.14) 21-29µg/dL blood Pb FDR=0.93 (0.65-1.33) **31≥µg/dL blood Pb FDR= 0.57 (0.34-0.91)**	Fecundability (odds of conception over a given time) was decreased in men with occupational exposure to Pb and blood Pb level ≥31µg/dL.
Retrospective Sallmen (2000b) Finland *Same population as Sallmen (2000a)*	4146 married men biologically monitored for Pb from the Finnish Central Population Register; Years=1973-1983	Not reported	Mean not reported	Infertility defined as non-occurrence of pregnancy or a delay in the first marital pregnancy.	Binomial regression analysis Age of both spouses at marriage, length of marriage, previous marriage, marriage before July 1973	Relative risk of infertility (95% CI) by blood Pb for individuals with probable Pb exposure: 0-8 µg/dL RR= 1.0 – reference **10-19µg/dL RR=1.27 (1.08-1.51)** **21-29µg/dL RR=1.35 (1.12-1.63)** **31-39µg/dL RR=1.37 (1.08-1.72)** **41-50µg/dL RR=1.50 (1.08-2.02)** **52≥µg/dL RR=1.90 (1.30-2.59)** Success Ratio for pregnancy (95% CI) by blood Pb for individuals with probable Pb exposure: 0-8µg/dL SR = 1.0 – reference **10-19 µg/dL SR =0.86 (0.77-0.97)** **21-29 µg/dL SR = 0.80 (0.70-0.91)** **31-39 µg/dL SR=0.84 (0.70-1.00)** **41-50 µg/dL SR = 0.79 (0.61-1.01)** **52 µg/dL SR = 0.63 (0.44-0.87)** Authors also report separate analyses split by occupation and state fertility was only reduced in Pb battery workers, not foundry/Pb smelting workers. In analyses split by wife's age (<20, 20-25,	Paternal exposure to Pb increased the risk of infertility among men with blood Pb levels ≥10 µg/dL relative to men with blood Pb levels <10µg/dL.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						≥26 years of age), the association was strongest in workers with older wives (≥26 years of age).	
Retrospective Selevan (1984) Location not stated *Also listed for abortion*	376 male Pb battery plant workers; referent group were Pb workers with blood Pb level <25µg/dL or prior to employment in Pb industry; Years =employed in Pb factory in 1977	Age at time of interview-not during study Paternal =45.6 (8.3) Maternal =42.9 (8.2)	Blood Pb from company records: Unexposed-before employment or blood Pb<25µg/dL Low=25-40µg/dL Med=41-60µg/dL High >60µg/dL	Fetal loss, fertility compared to standardized fertility ratios (SFR), and length of time between births	Chi-square analysis, Logistic regression, Cox regression/survival analysis applied to time interval between live births Adjustments depended on outcome including maternal age, prior fetal loss, exclude habitual aborting families, parity, calendar time	Standardized fertility ratio Blood Pb <25µg/dL SFR = 103 Blood Pb 25-40µg/dL SFR=73 Blood Pb 41-60µg/dL SFR=84 Blood Pb >60 µg/dL SFR=68; p-trend=0.11 Risk ratio of survival time between live births: Blood Pb 25-40µg/dL RR=1.08 (0.74, 1.36) Blood Pb 41-60µg/dL RR=1.031 (0.74, 1.44) Blood Pb >60µg/dL RR=0.82 (0.54, 1.26) Authors state that the SFR was consistently less in all the Pb exposed groups than the pre-employment or blood Pb <25µg/dL group.	Paternal blood Pb was not associated with standardized fertility ratio or time between births compared to referent population <25µg/dL.
Cross-sectional Shiau (2004) Taiwan	280 pregnancies (153 without Pb exposure and 127 with Pb exposure) in which father worked at Pb battery plant in Taiwan (133 couples); Years = 1994-1998	Not reported	Annual means 32-41µg/dL	Time to pregnancy (TTP), Fecundability ratio (FR) = the odds of a conception among exposed /odds among not exposed over a given time interval	Multiple regression analysis, cox discrete proportional hazard models Maternal age, pregnancy sequence, paternal and maternal Pb exposure at beginning of calendar year when TTP started	Couples with at least one pregnancy before and after occupational exposure to Pb (n=41) **TTP difference=-1.37 + 0.15; r^2=0.62; p<0.0001.** Fecundability ratio (FR) (95% CI) by concurrent paternal Pb level: Non-exposed FR = 1.00 reference Blood Pb <20 FR = 0.90 (0.61-1.34) Blood Pb 20-29 FR = 0.72(0.46-1.11) **Blood Pb 30-39 FR = 0.52 (0.35-0.77)** **Blood Pb ≥ 40 FR = 0.40 (0.27-0.59)** Fecundability ratio (FR) (95% CI) by parental Pb level at start of calendar year when TTP started: Non-exposed FR = 1.00 reference Blood Pb <20 FR = 0.91 (0.61-1.35) Blood Pb 20-29 FR = 0.71(0.46-1.09) **Blood Pb 30-39 FR = 0.5 (0.34-0.74); p<0.05** **Blood Pb ≥ 40 FR = 0.38 (0.26-0.56); p<0.001** Authors state that the magnitude of prolongation is 0.15 cycles (months increase in TTP) for each 1µg/dL blood Pb beginning at 10µg/dL. Authors state wives of men with higher blood Pb generally took more cycles to become pregnant and cumulative distribution of TTP by blood Pb categories in men was shifted to right (i.e., increased number of cycles) with increased blood Pb; however statistics are not presented for the analysis of the entire population.	Time to pregnancy was increased in male Pb battery workers. Odds of conception were statistically reduced in male Pb battery workers at blood Pb levels ≥30µg/dL.
Cross-sectional Silberstein (2006) Providence, RI	9 women undergoing IVF at Women & Infant's Hospital in	Not reported	Blood not reported, plasma Pb level of 6 samples taken ranged <1 to 7 µg/kg.	Follicular fluid Pb, pregnancy	Mann-Whitney U test	44 follicles from 9 women were used for Pb concentration determination (estimated from data presented in Figure 1 from published manuscript): Follicular Pb-pregnant women (n=17)= 1.7	Follicular Pb levels were significantly higher in non-

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
	Providence; Years not stated		Follicular fluid: Range 0-21.2µg/kg Median-estimated from Fig 1. Graph: Pregnant= 1.7 Non-preg.=2.25			Follicular Pb-non-pregnant women (n=27)=2.25; p=0.00059	pregnant women undergoing IVF compared to pregnant patients.
Case-control Umeyama (1986) Japan	69 infertile men (case-failed to achieve pregnancy for at least 2 years) and 22 fertile men (control-men who had fathered a child in last 2 years).	Control=32.5(3) Case=33.4 (4)	Exposure determined by seminal fluid Pb (converted from mg/dL to µg/dL): Fertile =25.5 Infertile =24.3 ** lack of blood Pb data limits utility	Seminal levels of trace metals (Cd, Ca, Cr, Mg, Sr, Zn, Cu , Mn, Molybdenum, Sn)	Student's t test Adjustments not described.	Seminal Pb level in: Control group = 25.5 (0.0123)mg/dL Case group = 24.3 (0.0179)mg/dL Cd and Al levels were elevated in semen samples from infertile men.	Seminal Pb did not differ between men that fathered a child in last 2 years and men that had failed to do so; blood Pb not reported.
Repro: Spontaneous Abortion							
Retrospective Alexander (1996a) Trail, British Columbia *Same population as Schumacher (1998)* *Also listed for stillbirth and malformations*	929 male employees of the Cominco smelter Years=employed as of 1992-1993	≤35 =23% 36-45 = 46% ≥46 =31%	28.4 (11.8) Blood Pb monitoring data used for exposure	Incidence of spontaneous abortion, stillbirths and birth defects	Odds ratio reported, statistical methods not described. Adjustment listed for total number of pregnancies, prior stillbirths and birth defects	Odds ratio (95% CI) for spontaneous abortion by paternal blood Pb level one year prior to index: Low (<25µg/dL) (reference) Medium (25-39µg/dL) OR=1.0(0.6,1.7) High (≥40µg/dL) OR=0.7(0.4,1.5)	Paternal blood Pb levels were not associated with spontaneous abortion.
Retrospective Al-Hakkak (1986) Iraq	22 male workers at a Pb battery plant (high Pb) and 22 referents (scientific research council employees); Years not stated	High Pb =40.1 (7.6) Referent =39.5 (7.1)	Not sampled Exposure determined by occupation ** lack of blood Pb data limits utility	Spontaneous abortion; chromosome aberrations	t test, Chi-square Adjustments not described.	Percent spontaneous abortion Referent males = 3.40 or 5/76 pregnancies **Male Pb workers = 19.83 or 23/116; p<0.05** Rate of spontaneous abortion Referent males = 0.30(0.52) per family **Male Pb workers = 1.04 (1.15) per family; p<0.01**	Occupational exposure to Pb in male workers was associated with spontaneous abortion.
Nested case-control ecological Aschengrau (1989) Boston, USA	Women with spontaneous abortion ≤27 weeks of gestation (case n=286 and 5 matched controls; n=1391) at Brigham and Women's Hospital; Years= 1976-1978	Not reported	Not sampled Water samples were taken from city/towns of residence ** lack of blood Pb data limits utility	Spontaneous abortion	Logistic regression Other metals, water source, maternal age, education level, history of prior spontaneous abortion	Odds ratio (95% CI) for spontaneous abortion in relation to water sample Pb level = 0.8 (0.5-1.4).	Drinking water levels of Pb was not associated with spontaneous abortion.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Retrospective Beckman (1982) Sweden *Also listed for stillbirth and congenital malformations*	764 male workers at a copper smelter in Sweden; Years = married workers employed in 1978	Not reported	Exposure determined by occupation. Non-exposed pregnancies are pregnancies before father worked at smelter. Exposed pregnancies took place following employment. ** lack of blood Pb data limits utility	Spontaneous abortion, stillbirth, congenital malformations	Chi-square Adjustments depend on endpoint and included: maternal age, paternal age, pregnancy order Note: Column headings in table 7 appear to be switched and data from table 5 and 6 support conclusions in Beckman et al., 1982 and summary in this table	Rate of spontaneous abortion among smelter workers: Non-exposed pregnancy = 7.0% **Exposed pregnancy = 10.8%; p<0.05** Rate of fetal death (spontaneous abortion + stillbirth) among smelter workers: Non-exposed pregnancy = 8.2% **Exposed pregnancy = 13.6%; p<0.01**	Occupational exposure to Pb in male workers was associated with spontaneous abortion and fetal death.
Prospective nested case-control study Borja-Aburto (1999) Mexico City, Mexico *Population may overlap with Hernandez-Avila (2002) and others*	Pregnant women in hospitals in Mexico City, ≤12 weeks gestation at enrollment. Cases (spontaneous abortion, n=35) were matched to 2 controls where possible (n=60); Years=1994-1996	Mean = 28 yr	Cases = 12.03 µg/dL Controls=10.09 µg/dL Maternal blood Pb was taken prior to 12 weeks of gestation.	Incidence of spontaneous abortion	ANOVA, forward step-wise conditional logistic regression models Medical conditions, reproductive characteristics, age, education, smoking, coffee or alcohol consumption, calcium supplements, use of hair dye, video display exposure, unusual physical activity.	Unadjusted OR for spontaneous abortion compared to maternal blood Pb levels during the first 12 weeks of gestation (***p*=0.03 for trend**): < 5 µg/dL = referent 5 – 9 µg/dL = 2.3 (CI not reported) 10 – 14 µg/dL = 5.4 ≥ 15 µg/dL = 12.2 OR treating blood Pb as a continuous variable after multivariate adjustment for increase in blood Pb of: **1µg/dL – OR = 1.13 (1.01, 1.3)** **5 µg/dL – OR = 1.8 (1.1, 3.1)**	Maternal blood Pb levels during the first 12 weeks of gestation were associated with spontaneous abortion.
Retrospective Driscoll (1998) United States	6080 women employees of the Forest Service Years=surveyed about the 10-year period from January 1986 to January 1996	18-52 at time of survey	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Self-reported miscarriage and birth defects	Regression modeling using the generalized estimation equation (GEE) Maternal age at pregnancy, self-reported strenuous work, smoking, and alcohol use	Relationship between work exposures including (Pb-paint) and miscarriages in forest service employees OR (95% CI): **Paint-southern coatings bound. 4.33 (2.02,9.27)** **Paint-nelson boundary 2.03 (1.24,3.33)** **Paint-nelson 1.78 (1.21,2.61)** Paint-southern coatings 1.60 (0.96, 2.64) Paint-Niles 1.46 (0.92, 2.29) **Herbicide use 1.98 (1.10, 3.52)** Birth defects were not related to work exposures.	Occupational exposure of female workers to Pb-based paint was associated with spontaneous abortions.
Retrospective case-control Faikoglu (2006) Istanbul, Turkey	20 patients with spontaneous abortion (case) and 20 normal births (control) in Semiha Sakir Hospital; Years not stated	Not reported	Overall mean = 20.3 Case= 18.8 Control= 22.1 SD not reported Timing of blood samples not reported	Spontaneous abortion	Statistical methods not reported. Adjustments not described.	Authors state there was no correlation between Pb exposure (blood Pb levels) and spontaneous abortion.	Maternal blood Pb was not associated with spontaneous abortion.
Cross-sectional Retrospective Gundacker (2010) Vienna, Austria Also listed for	53 pregnant women recruited at General Hospital in Vienna; Year=2005	30 Range 16-42	Median Maternal = 2.5 Cord = 1.3 Range Maternal = 1.04-8.4	Recall of previous miscarriage, Birth weight, birth length,	Chi-square test, Fisher's exact test, Cochran and Mantel-Haenszel statistics, categorical regression analysis	Authors state that women who miscarried in the past had higher Placental Pb levels: Women without previous miscarriage = 27µg/kg Women - previous miscarriage=39µg/kg; p=0.039	Placental Pb was higher in women with previous miscarriage;

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
birth weight			Cord = 0.02-6.52 Placenta=1.07-7.54 Meconium=0.2-10 Placenta and meconium in µg/kg	head circumference, placental Pb, meconium Pb	Maternal height, gestational length, placental Pb, meconium Pb, maternal education		association to blood Pb not reported.
Retrospective Kristensen (1993) Oslo, Norway *Also listed for stillbirth and other endpoints*	6,251 births to male members of printers' unions in Oslo, Norway; Years= between 1930 and 1974 (n=17 late abortion)	Not reported	Not reported Exposure by paternal job category ** lack of blood Pb data limits utility	Low birth weight, late abortions, stillbirths, preterm births	Logistic regression Gestational age, birth order, sex, prior stillbirth, twin birth, parental consanguinity	Late abortion OR for paternal occupational Pb exposure compared to "other" exposures: OR (95% CI) =2.4 (0.81, 6.9)	Paternal exposure to Pb by occupation was not associated with late abortion.
Retrospective Lamadrid-Figueroa (2007) Mexico City, Mexico	207 Healthy pregnant women, ≤14 weeks gestation at enrollment, with at least one previous pregnancy, and attending the Mexican Institute of Social Security in Mexico City; Years= 2 cohorts: 1997-1999 and 2001-4	Mean = 27.8	Blood = 6.24 (33) Plasma = 0.014 (0.13) Plasma/blood ratio = 0.22 (0.14)% Maternal blood and plasma Pb were measured during the first trimester.	History of spontaneous abortion	Poisson regression models Age, schooling	IRR for history of abortion compared to plasma/ blood ratio tertiles during a current pregnancy: 2nd tertile =1.161 (*p*=0.612) **3rd tertile = 1.903 (*p*=0.015**) IRR for history of abortion compared to different biomarkers of Pb exposure: Plasma Pb = 1.12 (*p* = 0.22) Blood Pb = 0.93 (*p* = 0.56) **Plasma/blood PB ratio = 1.18 (p = 0.02)** Patella Pb = 1.15 (*p* = 0.39) Tibia Pb = 1.07 (*p* = 0.56)	Maternal plasma/whole blood Pb ratio during the first trimester was significantly associated with history of spontaneous abortion, whereas blood Pb and plasma Pb were not.
Retrospective Laudanski (1991) Suwalki Poland *Also listed for stillbirths*	136 women from areas with high levels of Pb in the soil compared to 269 women from nearby villages with normal levels of Pb in the soil; [Years not stated]	Age Range = 17 – 75 yrs.	Exposed = 6.75 (6.53) Referent = 6.2 (3.36) [question of units as blood Pb is reported both as 6.7ug/l and 675ug/dL which is 10x instead of 1/10x] ** lack of blood Pb difference between populations limit utility	Incidence of spontaneous abortion (miscarriage), stillbirths, and preterm labor, maternal blood pressure, blood Cd	Chi-squared, one- and two-tailed *t* tests Adjustments not described.	Pregnancies resulting in spontaneous abortions by pregnancy order: Exposed group 1st pregnancy 8.8% Exposed group 2nd pregnancy 2.2% Referent group 1st pregnancy 17% Referent group 2nd pregnancy 1.1% Maternal blood Pb levels: Exposed group 6.75 (6.53) µg/dL Referent group 6.21 (3.36) µg/dL; p=0.38 **Exposed group had significantly fewer women with 3> pregnancies (39% vs. 52% of pregnancies; p<0.01) and >3 pregnancies that were delivered at full term (35% vs. 44%; p<0.05).** Exposed population had higher blood levels of cadmium (p=0.03).	Incidence of spontaneous abortion and blood Pb levels did not differ between residents of two towns that differ in soil Pb levels.
Retrospective nested case-control Lindbohm (1991b) Lindbohm (1991a	Men with occupational exposure to Pb and wives aged 18 – 40. Women with	Mean age of the women = 28.73 years	Paternal blood levels: <20.7 µg/dL 74% cases 76% controls 20.7-28.98 µg/dL	Incidence of spontaneous abortion	Logistic regression model Adjustments differ by endpoint including paternal exposure to cadmium and mercury,	OR of spontaneous abortion for paternal blood Pb within 1 year of spermatogenesis: ≤20.7 µg/dL (reference) 20.7-28.98 µg/dL OR =0.7 (0.3, 1.9) **≥31.05 µg/d OR = 3.8 (1.2, 12)**	Paternal blood Pb levels (>31µg/dL) measured within 1 year of

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
) Lindbohm (1992) Finland	spontaneous abortion were cases (n=213) and matched to n=300 controls; Years= 1973-1983		17% cases 17% controls 31.05-37.26µg/dL 4% cases 3% controls ≥ 39.33µg/dL 5% cases 4% controls		maternal exposure to organic solvents and mercury, use of alcohol, parity, contraception, previous spontaneous abortion, index of missing information, age, socioeconomic status	OR of spontaneous abortion for paternal blood Pb level measured at any time or classified: ≤20.7 µg/dL (reference) 20.7-28.98 µg/dL OR =1.0 (0.6, 1.7) 31.05-37.26µg/d OR = 1.3 (0.5, 3.4) ≥ 39.33µg/dL OR = 1.6 (0.6, 4.0) OR of spontaneous abortion for paternal blood Pb level measured at any time or classified for both high and low Pb: OR =0.9 (0.8, 1.0)	spermato-genesis were associated with spontaneous abortion.
Prospective McMichael (1986) Port Pirie, South Australia *Also listed for pre-term birth and other endpoints*	774 pregnant women from the Port Pirie birth cohort study of a Pb smelting community (exposed) or surrounding towns (referents); Years= 1979-1982	Age range = 14 – 36 yr.	Maternal blood (SE) at 14-20 weeks Exposed:10.6 (0.17) Referent:7.6 (0.19) Maternal blood (SE) measured at delivery Exposed: 11.2 (0.21) Referent:7.5 (0.25)	Pregnancy outcome including incidence of spontaneous abortion, and other measures	Multiple logistic regression Adjustments not described. Effect of age, years lived in Port Pirie, marital status, country of birth, race, blood pressure examined separately.	Mean maternal blood Pb levels during mid-pregnancy (14-20 weeks)of Port Pirie residents: Spontaneous abortions 11.3 (SE=0.81)µg/dL Other pregnancies 10.8 (SE=0.15) µg/dL Authors report maternal blood Pb, age, years lived in Port Pirie, marital status, country of birth, race, blood pressure were not associated with the risk of spontaneous abortion.	Maternal blood Pb levels were not associated with spontaneous abortion.
Retrospective Murphy (1990) Kosovo, Yugoslavia *Also listed for stillbirths* *Same population as Factor-Litvak (1991),(1999) Loiacono (1992), Lamb (2008)*	639 women recruited at mid-pregnancy: 304 lived in an area with high environmental exposure to Pb (exposed group) and 335 lived in an area with low Pb exposure (referents);Years=1985-1986	Exposed = 21.7 (3.9) years Referent = 22.1 (3.4) years	Geometric Mean: Exposed = 15.9µg/dL Referent = 5.1µg/dL (SD not reported) Maternal blood Pb at recruitment (after recall of pregnancy outcomes) ** lack of temporality of blood Pb data limits utility	Incidence of spontaneous abortion and stillbirths	Maximum likelihood logistic regression analysis Parental age at first pregnancy, parental education, ethnic group, smoking	Effect of living in the Pb-exposed (Titova Mitrovica a Pb smelter town) and referent (Pristina) areas on the OR of the first pregnancy resulting in spontaneous abortion OR (95%CI): OR = 1.1 (0.9, 1.4)	Current maternal blood Pb levels were not associated with spontaneous abortion.
Retrospective Nordstrom (1979b) Sweden *Also listed for weight and malformation* *Population overlaps with Nordstrom (1978a)*	662 female employees at Ronnskar smelter born between 1930-1959.	Not reported	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Incidence of spontaneous abortion and birth weight	Chi-square test for heterogeneity Covariates or adjustments not described	The percent of total pregnancies that ended in spontaneous abortion by employment and residence during pregnancy: Pregnancy before employment or after and residence >10 km from smelter 9.3% Pregnancy during employment or after and residence ≤10 km from smelter 15.1% **p<0.005 for total pregnancies** **p<0.0005 for 3rd or later pregnancies** The percent of total pregnancies that ended in spontaneous abortion by occupation in smelter: Administration and restaurant 13.5% Laboratory 13.7% **Cleaning and/or smelter work 28% (p<0.01)** The father's employment at the smelter increased	Female employees at a smelter had increased frequency of spontaneous abortion.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						the frequency of abortions for 3rd or later pregnancies (**p<0.05**), but not for earlier pregnancies.	
Retrospective Ecological Nordstrom (1978a) Sweden *Population overlaps with Nordstrom (1979b)*	4427 pregnancies in women living in one of 4 areas at different distances from the Ronnskar smelter and born after 1930	Not reported	No blood Pb data Exposure determined by residence * lack of blood Pb data limits utility	Incidence of spontaneous abortion	Chi-square test for heterogeneity Covariates or adjustments not described	The percent of total pregnancies that ended in spontaneous abortion by residence: Area A <10km from smelter 11% Area B ≤10 km from smelter 9.2% Area C 10-30km from smelter 8.2% Area D >30 km from smelter 7.6% **p<0.05 for total pregnancies** **p<0.005 for area A to area D** The percent of first pregnancies that ended in spontaneous abortion by residence: Area A <10km from smelter 10.1% Area B ≤10 km from smelter 6.3% Area C 10-30km from smelter 7.3% Area D >30 km from smelter 5.1% **p<0.025 for area A to other areas**	Women living closer to a smelter had increased frequency of spontaneous abortion.
Cross-sectional Tabacova (1993) Bulgaria	94 pregnant women who were residents of a metal-smelting area; Years not stated	Mean age was between 22.7 and 24.7 yr.	Normal pregnancy 5.2 (0.2) µg/dL Threatened abortion 7.1 (0.7) µg/dL	Pregnancy diagnosis (threatened spontaneous abortion, anemia, toxemia); "threatened" diagnosis is not same as "abortion"	Student's *t* test and Chi squared test No adjustments were made for confounders.	Incidence of blood Pb > 7 µg/dL (% of pregnancies): Normal = 4.5% **Threatened spont. abortion = 41.7% (p < 0.05)** **Anemia = 40% (p<0.05)** **Toxemia (total) = 50% (p<0.05)** **Hospitalized patients = 57.1% (p<0.001)** Women with pregnancy complications were more likely to have had a previous abortion (**p<0.05**) but did not differ by age of mother, number of births, smoking or occupational exposure.	Threatened spontaneous abortion was associated with higher blood Pb levels.
Retrospective Tang (2003) China	57 female battery or capacitor workers (exposed group) compared to 62 women in non-Pb production (referent group); Years not stated	Mean = 32	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Incidence of spontaneous abortion	Fisher's exact test No adjustments were made for confounders.	**Six spontaneous abortions were reported in the exposed group, while none were reported in the referent group (*p* = 0.01)**	Occupational exposure to Pb in female workers was associated with spontaneous abortion.
Retrospective nested case-control Taskinen (1988) Finland Same population as Sallmen(1995)	Women with occupational Pb exposure and blood Pb measurements during 1973-1982 with a pregnancy. Women who had a spontaneous	Age not reported	Maternal blood levels: <10.35 µg/dL 62% cases; 58% refs. 10.35 – 18.63 µg/dL 24% cases 28% controls >20.7 µg/dL 14% cases	Incidence of spontaneous abortion	Univariate and multivariate analysis No adjustments were made for confounders.	Odds ratio (95% CI) of spontaneous abortion by estimated or measured blood Pb level: Univariate Blood Pb <10.35 µg/dL OR = 0.9 (0.47-1.68) Blood Pb 10.35 – 18.63 µg/dL OR = 0.7 (0.3-1.61) Blood Pb >20.7 µg/dL OR = 0.8 (0.23-2.52) Multivariate all Pb levels - OR = 0.69 (0.31-1.54) Odds ratio of spontaneous abortion by measured	Maternal blood Pb levels (estimated by occupation or measured) were not associated with spontaneous

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
	abortion were defined as cases (n=123) and matched to 332 controls.		14% controls Estimated blood Pb measurements from same job match for 51% cases and 55% controls ** lack of individual Pb data limits utility			blood Pb level (n=17 cases, n=32 controls) within one year before or during pregnancy: Blood Pb <10.35 μg/dL (reference) Blood Pb 10.35 – 18.63 μg/dL OR = 0.5 (0.13,1.87) Blood Pb 20.7 – 26.91 μg/dL OR = 0.42 (0.05,3.72) Blood Pb >28.98 μg/dL OR = 1.86 (0.37,9.43)	abortion.
Retrospective Selevan (1984) Location not stated *Also listed for sperm*	376 male Pb battery plant workers; referent group were Pb workers with blood Pb level <25μg/dL or prior to employment in Pb industry; Years =employed in Pb factory in 1977	Age at time of interview-not during study Paternal =45.6 (8.3) Maternal =42.9 (8.2)	Blood Pb from company records: Unexposed-before employment or blood Pb<25μg/dL Low=25-40μg/dL Med=41-60μg/dL High >60μg/dL	Fetal loss, fertility compared to standardized fertility ratios (SFR), and length of time between births	Logistic regression, cox regression/survival analysis applied to time interval between live births Adjustments depended on outcome including maternal age, prior fetal loss, exclude habitual aborting families, parity, calendar time	Odds ratio (95% CI) fetal loss by Pb and split by maternal smoking: Non-smoker Pb 25-40μg/dL OR=1.47 (0.5, 4.32) Non-smoker Pb 41-60μg/dL OR=1.66 (0.66, 4.2) Non-smoker Pb >60μg/dL OR=1.05 (0.28, 4.0) **Smoker Pb 25-40μg/dL OR=6.95 (1.38, 34.93)** Smoker Pb 41-60μg/dL OR=2.05 (0.43,9.85) Smoker Pb >60μg/dL OR=3.72 (0.54, 25.62)	Paternal blood Pb was not associated with fetal loss compared to referent population <25μg/dL.
Prospective Vigeh (2010) Tehran, Iran *Also associated with preterm Vigeh (2011)*	351 pregnant women recruited during first trimester in Tehran; Years= 2006-2008	Spontaneous abortion = 27.3 (4.5) Ongoing pregnancy =25.4 (4.1)	Spontaneous abortion (n=15) = 3.51 (1.42) Ongoing pregnancy (n=336) = 3.83 (1.99) Maternal blood Pb sampled during 1st trimester	Spontaneous abortion	t test, Chi-square test, Fisher's exact test, Pearson correlation coefficient, multiple logistic regression Maternal age, hematocrit, parity, smoking	Odds ratio (95% CI) for spontaneous abortion: Log blood Pb OR=0.33 (0.001-10.1); p=0.53 **Age (per year) OR=1.28 (1.1-1.5); p=0.002** Hematocrit (%) OR=0.97 (0.81-1.2); p=0.79 Parity OR=2.7 (0.12-1.1); p=0.15 Passive smoke OR=0.36 (0.12-1.13); p=0.081	Maternal blood Pb was not associated with spontaneous abortion.
Case-control Yin (2008) Shanxi Province, China	40 women with anembryonic pregnancy (case) and 40 women with full-term babies (control); enrolled at 8-12 weeks of gestation; Years= 2004-2006	Range = 25–35	Maternal plasma Pb: AP group = 5.3 μg/dL (95% CI: 5.2, 5.9) Controls = 4.5 μg/dL (95% CI: 3.7, 5.0) Plasma Pb sampled at miscarriage or at prenatal exam for controls ** lack of blood Pb data limits utility	Anembryonic pregnancy, folate, B_{12}, homocysteine	*t* tests of logarithmically transformed variables No adjustments were made for confounders. Effect of infant alcohol, smoking, education, and vitamin supplementation on pregnancy examined separately.	Concentration of plasma Pb by pregnancy outcome mean (95% CI): anembryonic pregnancy group 5.3 (5.2-5.9 μg/dL) **control group 4.5 (3.7-5.0 μg/dL) ; *p*=0.03**	Maternal plasma Pb was significantly higher in women with anembryonic pregnancies.
Repro: Stillbirth							
Retrospective Alexander (1996a) Trail British Columbia *Same population*	929 male employees of the Cominco smelter Years= employed as of 1992-1993	≤35 =23% 36-45 = 46% ≥46 =31%	28.4 (11.8) blood Pb monitoring data used for exposure	Incidence of spontaneous abortion, stillbirths and birth defects	Odds ratio reported, statistical methods not described. Adjustment listed for total number of pregnancies, prior stillbirths and birth defects	Odds ratio (95% CI) for stillbirths and birth defects by paternal blood Pb level one year prior to index: Low (<25μg/dL) (reference) Medium (25-39μg/dL) OR=2.9(0.6,13.3) High (≥40μg/dL) OR=2.5 (0.5,11)	Paternal blood Pb levels were not associated with stillbirth.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
as Schumacher (1998) *Also listed for abortion*						Separate analysis for birth defects alone not reported	
Case-control Ecological Aschengrau (1993) Boston, USA	Women who delivered at Brigham and Women's Hospital (case n=77 stillbirths and 1177 controls); Years= 1977 to 1980	Not reported	Not sampled Water samples were taken from city/towns of residence ** lack of blood Pb data limits utility	Congenital anomalies, stillbirths, and neonatal deaths	Logistic regression and multiple logistic regression Other metals, water source, maternal age, education level, history of prior spontaneous abortion	Odds ratio (95% CI) for stillbirths in relation to water sample Pb level = 2.1 (0.6-7.2)	Drinking water levels of Pb were not associated with stillbirth.
Nested case-control Baghurst (1991) Port Pirie, South Australia *Also listed for preterm* *Subpopulation of McMichael (1986)*	Subset of Port Pirie birth cohort study of Pb smelting community; 749 pregnancies followed beyond 20 weeks; case - n=12 stillbirth; Years= 1979-1982	Not reported	Maternal blood at delivery Stillbirth 8.2 μg/dL Normal 8.7 μg/dL	Pb levels for incidence of stillbirths, preterm births	ANOVA and Person correlation analyses Adjustments not described.	Mean placental body Pb μg/g by birth outcome: Stillbirth (n=6-9) 0.76 μg/g Normal (n=22) 0.48 μg/g Mean placental membrane Pb μg/g by outcome: Stillbirth (n=6-9) 2.73 μg/g Normal (n=22) 0.78 μg/g Stillbirth placental Pb relative to normal (p=0.10) Comparison to blood Pb not reported.	Placental Pb levels were not different between normal and stillbirths; comparison to blood Pb not reported.
Retrospective Beckman (1982) Sweden *Also listed for abortion and congenital malformations*	764 workers at a copper smelter in Sweden; Years = married workers employed in 1978	Not reported	Exposure determined by occupation. Non-exposed pregnancies are pregnancies before father worked at smelter. Exposed pregnancies took place following employment. ** lack of blood Pb data limits utility	Stillbirth, spontaneous abortion, congenital malformations	Chi-square Adjustments depend on endpoint and included maternal age, paternal age, pregnancy order Note: Column headings in table 7 appear to be switched and data from table 5 and 6 support conclusions in Beckman et al., 1982 and summary in this table	Rate of stillbirths among smelter workers: Non-exposed pregnancy = 1.2% Exposed pregnancy = 2.8%; p>0.05 Rate of fetal death (spontaneous abortion + stillbirth) among smelter workers: Non-exposed pregnancy = 8.2% Exposed pregnancy = 13.6%; p<0.01	Occupational exposure to Pb in male workers was not associated with stillbirth, although it was associated with increase rate of fetal death.
Cross sectional Irgens (1998) Norway *Also listed for preterm birth*	Births in Norway with possible parental occupational Pb exposure (exposed n=1,803 maternal; n=35,930 paternal); Years= 1970-1993	Not reported	Not reported Exposure by parental job category	Perinatal death (not just stillbirths, included deaths from >15 weeks gestation to 1 week after birth), preterm births, serious birth defects, low birth weight,	Logistic regression Maternal age, education, gestational age	Prevalence of low birth weight with parental occupational Pb exposure compared to reference: Maternal exposure: All Pb exposure levels OR=1.05 (0.59,1.76) High Pb OR=3.74 (0.62,12.72) Low Pb OR=1.14 (0.19,3.78) Paternal exposure: All Pb exposure levels OR=0.87 (0.75,1.01) High Pb OR=1.20 (0.72,1.88) Low Pb OR=0.85 (0.73,0.99)	Maternal or paternal occupational Pb exposure was not associated with perinatal death.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Retrospective Kristensen (1993) Oslo, Norway *Also listed for preterm birth and other endpoints*	6,251 births to male members of printers' unions in Oslo, Norway (n=60 stillbirths); Years= 1930 and 1974	Not reported	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Low birth weight, late abortions, stillbirths, preterm births	Logistic regression Birth weight, year of birth	Stillbirth OR for paternal occupational Pb exposure compared to "other" exposures: OR (95% CI) =2.0 (0.88, 4.7) Late abortions OR for paternal occupational Pb exposure compared to "other" exposures: OR (95% CI) =2.4 (0.81, 6.9)	Fathers exposure to Pb by occupation was not associated with stillbirth.
Retrospective Laudanski (1991) Suwalki Poland *Also listed for abortion*	136 women from areas with high levels of Pb in the soil compared to 269 women from nearby villages with normal levels of Pb in the soil; [Years not stated]	Age Range = 17 – 75 yrs.	Exposed = 6.75 (6.53) Referent = 6.21 (3.36) [question of units as blood Pb is reported both as 6.7ug/l and 675ug/dL which is 10x instead of 1/10x] ** lack of blood Pb difference limit utility	Incidence of stillbirths, spontaneous abortion, preterm labor, and maternal blood pressure, blood Cd	Chi-squared, one- and two-tailed *t* tests Adjustments not described.	Pregnancies resulting in stillbirths by pregnancy order: Exposed group 1st pregnancy 2.2% Exposed group 2nd pregnancy 0 Referent group 1st pregnancy 4.8% Referent group 2nd pregnancy 0.3% Exposed population had higher blood levels of cadmium (p=0.03).	Incidence of stillbirth and blood Pb levels did not differ between residents of two towns that differ in soil Pb levels.
Prospective McMichael (1986) Port Pirie, South Australia *Also listed for other endpoints*	740 pregnant women from the Port Pirie birth cohort study of a Pb smelting community (exposed) or surrounding towns (referents); Years= 1979-1982	Age range = 14 – 36 yr.	Maternal blood (SE) at 14-20 weeks Exposed:10.6 (0.17) Referent:7.6 (0.19) Maternal blood (SE) measured at delivery Exposed: 11.2 (0.21) Referent:7.5 (0.25)	Pregnancy outcome including stillbirths (late term fetal deaths) and other outcomes	Multiple logistic regression Adjustments not described. Effect of infant sex, gestational age, maternal relative weight, smoking, and prior parity on birth weight examined separately.	The proportion of stillbirths: Port Pirie 17.5 per 1000 live births Referent 5.8 per 1000 live births South Australia average 8.0 per 1000 live births Mean maternal blood Pb levels (14-20 weeks) Stillbirths 10.3 (SE=0.8)µg/dL Other pregnancies 9.9 (SE=0.2) µg/dL Mean maternal blood Pb at delivery: Stillbirths 7.2 (SE=0.9); p<0.05 diff. from live Live births 10.4 (SE=0.2)	Maternal blood Pb during pregnancy was not significantly associated with stillbirths; maternal blood Pb at delivery was lower in stillbirths.
Retrospective Murphy (1990) Kosovo, Yugoslavia *Also listed for abortion* *Same population as Factor-Litvak (1991), (1999), Loiacono (1992), Lamb (2008)*	639 women recruited at mid-pregnancy; 304 lived in an area with environmental Pb (exposed) and 335 lived in an area without significant Pb (referents); Years= 1985-1986	Exposed = 21.7 (3.9) years Referent = 22.1 (3.4) years	Geometric Mean: Exposed = 15.9µg/dL Referent = 5.1µg/dL Maternal blood Pb at recruitment (after recall of pregnancy outcomes) ** lack temporality of blood Pb data limits utility	Incidence of stillbirths and spontaneous abortion from obstetric histories	Maximum likelihood logistic regression analysis Parental age at first pregnancy, parental education, ethnic group, smoking	Effect of living in the Pb-exposed (Titova Mitrovica a Pb smelter town) and referent (Pristina) areas on the OR of the first pregnancy resulting in stillbirth OR (95%CI): OR = 1.0 (0.6, 1.5)	Current maternal blood Pb levels were not associated with stillbirth.
Retrospective Case-control Savitz (1989) *Also listed for preterm*	National Natality and Fetal Mortality survey in US (case n=2096 mothers n=3170 fathers); Years= 1980	Not reported	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Incidence of stillbirths, preterm deliveries, and small-for gestational age	Multiple logistic regression Stratified analysis, child's race, maternal smoking	Odds ratio (95% CI) for stillbirths by parental employment with Pb exposure: Maternal exposure OR = 1.6 (0.8, 3.1) Paternal exposure OR=1.1 (0.9, 1.3)	Parental Pb exposure by occupation was not associated with stillbirth.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Repro: Fetal Growth & Lower Birth Weight							
Cross-sectional Al-Saleh (2008b) Saudi Arabia	653 infant/mother pairs at King Khalid Hospital, followed from birth to 2 years; Male infants=52%; Year= 2004	Maternal Age: 28.5 (6.0) Gestational age (weeks): 39.72 (1.86)	Cord: 2.21 (1.69) Male: 2.188 (1.686) Female: 2.234 91.699)	head circumference	Multiple linear regression models using backward procedure; ANOVA; student's t-test; Pearson's correlation matrix	**Association of >75th percentile of cord blood Pb and newborn's head circumference: r=-0.16; p=0.042** Predictor variables of head circumference (cm) on newborns with blood Pb levels >75th percentile β (SE): **Log-transformed blood Pb levels: -0.158 (0.718); p=0.036** BMI: 0.347 (0.094); p=0.0 Number of gestational weeks: 0.306 (0.07); 0.0	Cord blood Pb levels were significantly inversely associated with newborn head circumference
Cross-sectional Atabek (2007) Turkey *Also listed for endocrine*	54 infants from presumed high Pb level areas; Years not stated; Male=52%	Not reported	Cord =14.4 (8.9)	Birth weight, length, mid arm circumference, IGF	t-test, Pearson correlation, linear regression models Gestational age, sex, socioeconomic status	Multivariate regression for infant size by cord Pb: **Birth weight β=-0.81; p=0.01** Birth length β=0.41; p=0.05 Mid arm circumference β=0.3; p=0.05	Cord blood Pb was associated with lower birth weight.
Retrospective Bellinger (1991) Boston, USA *Also listed for preterm birth* *Data are reanalysis of Needleman (1984)*	3503 births at Brigham and Women's Hospital; Years= 1979-1981	Mean maternal age = 28 yr.	Cord=7.0 (3.3) µg/dL	birth weight, preterm birth, small for gestational age, intrauterine growth retardation (IUGR)	Multiple linear regression and multiple logistic regression Maternal age at delivery, marital status, mother employed at conception, maternal education, race, maternal ponderal index, parity, smoking status, alcohol and coffee consumption, hematocrit at delivery, maternal diabetes, and delivery by C-section, length of gestation	Adjusted Risk Ratio for indices of fetal growth by cord blood Pb (for each 1µg/dL Pb increase): **Low birth weight (<2500g) RR = 1.05 (1.00, 1.10)** **Intrauterine growth rate RR = 1.06 (1.00, 1.13)** Small for gestational age RR = 1.02 (0.98, 1.05) Multiple regression of birth weight on cord blood Pb (for each 1µg/dL Pb increase): Coefficient = -3.00 (SE=2.41) (*p*=0.21) Mean birth weight by cord blood Pb: <5µg/dL 3320 (SE=16)g 5-9.9µg/dL 3341 (SE=11.5) 10-14.9µg/dL 3319 (SE=22.6) ≥15µg/dL 3241 (SE=50.5) Adjusted risk ratios comparing cord blood < 5 µg/dL with cord blood ≥ 15 µg/dL (approximate from Fig.1. and without 95% CI, although authors report CI includes 1: Low birth weight (<2500g) RR = 2.0 Intrauterine growth rate RR = 2.5 Small for gestational age RR = 1.5 Authors conclude cord blood Pb≥15µg/dL may be associated with moderate increases in risk for decreased fetal growth	Cord blood Pb was marginally associated with low birth weight. Authors conclude cord blood Pb≥15µg/dL may be associated with decreased fetal growth, not <15µg/dL.
Cross-sectional Berkowitz (2006) Idaho *Also listed for*	169, 878 infants born to mothers residing in Idaho; exposed (exposed =	80-85% of mothers were 19-34 throughout	No blood data Exposure from air samples ** lack of blood Pb	Birth weight, small for gestational age (SGA)	Logistic regression analysis Sex, age, whether first born, whether other	Birth weight difference (95% CI) by population: Pre-fire (1970-73) – unexposed = reference Pre-fire (1970-73) – exposed = -7.97 (-38, 22) High Pb (1973-74) – unexposed = reference	Pb emissions associated with damage to a pollution

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
preterm birth	births after a fire resulted in emissions from a Pb smelter plant in 1973; high=Sept 1973 to Dec 1974; post-fire=Jan 1975-Dec 1981), pre-fire from the same area, and unexposed (referent);Male=51-52%	study period	data limits utility		births/terminations occurred after 20 weeks gestation	High Pb (1973-74) – exposed = -72.12 (-121, -23) After fire (1975-81) – unexposed = reference After fire (1975-81) – exposed = -25.81 (-51, -1.03) Odds ratio for low birth weight at term (<or>2500g) Pre-fire (1970-73) – unexposed = reference Pre-fire (1970-73) – exposed = 0.81 (0.55,1.20) High Pb (1973-74) – unexposed = reference High Pb (1973-74) – exposed = 2.39 (1.57,3.64) After fire (1975-81) – unexposed = reference After fire (1975-81) – exposed = 1.28 (0.95,1.74) Odds ratio for small for gestational age Pre-fire (1970-73) – unexposed = reference Pre-fire (1970-73) – exposed = 0.98 (0.73,1.32) High Pb (1973-74) – unexposed = reference High Pb (1973-74) – exposed = 1.92 (1.33,2.76) After fire (1975-81) – unexposed = reference After fire (1975-81) – exposed = 1.32 (1.05,1.67)	control device for a Pb smelter was associated with lower birth weight and increased odds of SGA and low birth weight.
Case-control Bogden (1978) New Jersey, USA	75 mother-infant pairs (n=25 case; low birth weight infants; n=50 matched controls); Newark's Martland Hospital; Year not stated	Not reported	Maternal Case=16.2 (4.5) Control=15.3(5.2) Cord Case=13.8(4.4) Control=13.1(4.3) Maternal sample at delivery	Birth weight	t test; ANOVA, Spearman correlation coefficients Adjustments not described.	Mean blood Pb values by birth outcome: Maternal case (low birth weight)= 16.2 (4.5) Maternal control = 15.3(5.2); p>0.05 Cord case (low birth weight)= 13.8(4.4) Cord control = 13.1(4.3); p>0.05	Maternal and cord Pb did not differ between normal and low birth weight babies.
Prospective Bornschein (1989) Cincinnati, USA *Also listed for preterm*	861 total infants (202 women-infant pairs with complete data) recruited <28 weeks gestation in high-Pb neighborhood; Years= 1980-1985	22.6	7.5 (1.6) Blood sampled 16-28 weeks of gestation	Birth weight, birth length, head circumference, gestational age	Multiple regression analyses Gestational age, alcohol or tobacco use, maternal age, number of prenatal visits, maternal height	Multiple regression models between maternal blood Pb (ln) for complete-data(n=202) cohort: **Birth weight x maternal age -45g; p=0.007** **Birth length -2.5cm; p=0.019** Head Circumference -0; p=0.97 Adjusted relationship between maternal blood Pb (ln) for full (n=861) cohort: **Birth weight r^2=0.45; p<0.0001** **Birth length r=-0.10; p<0.05**	Maternal blood Pb was associated with birth weight and birth length; not head circumference
Cross-sectional Cantonwine (2010b) Mexico City, Mexico *Population may overlap with Hernandez-Avila (2002) and others*	Mother (n=533) - infant (n=390) pairs of women attending one of three hospitals in Mexico City; Years= 1994-1995	Mean age H63w =24.5 (5) H63D=23.9(5.2)	Blood Pb Cord H63w=6.6(3.5) Cord H63D=6.3(4.2) Maternal Tibia µg/g H63w= 10.1 (9.7) H63D=8.7 (9.3) Blood collected at delivery; bone Pb within 1 month	Birth weight	Univariate and bivariate statistics and distribution plots; multiple linear regression Adjustments differ by endpoint including: maternal age, education, infant gender, maternal arm circumference, gestational age, smoking, marital status, parity, maternal hemoglobin, tibia Pb	Regression analysis Pb on birth weight β (95% CI): Cord blood Pb β= -31.1 (-105.4, 43.3)(*p*=0.41) Maternal Pb β= 9.3 (-64.2, 82.9)(*p*=0.80) **Tibia Pb β= -4.4 (-7.9, -0.9)(*p*=0.01)** Adjusted effect of tibia Pb (by quartiles) on birth weight – β (95% CI): 1st quartile (reference); ; p trend 0.06 2nd quartile β= 17.2 (-75.6, 110.1) (*p*=0.72) 3rd quartile β= -19.1 (-112.1, 73.9) (*p*=0.69) **4th quartile β= -95.4 (-189.9,-0.8) (*p*=0.05)** Adjusted effect of *HFE H63D* on birth weight:	Maternal bone Pb was associated with lower birth weight and maternal *HFE H62D* genotype may enhance negative effect of Pb.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Infant *HFE H63D* β=-129.5 (-236,23); p<0.05 Infant *TF P570S* β=34.9 (-68.3, 138); p>0.05 Adjusted effect of *HFE H63D* on birth weight: Infant/maternal both *HFE H63* **β=-176.9 (-319,-35); p<0.05** Not *HFE H63* either Infant or maternal p>0.05	
Cross-sectional Chen (2006) Taiwan *Also listed for preterm birth*	1611 births to parents registered in a Pb surveillance program (n=72 low birth weight; n=135 small for gestational age; Years= 1994-1997	Mean age: maternal = 27.0 (4.3) paternal = 29.8 (4.4) yr.	Mean maternal = 10.1 (10.4) µg/dL Mean paternal = 12.9 (13.8) µg/dL Timing of maternal sample not reported	Preterm births, low birth weight, small for gestational age (SGA)	Simple linear regression models; generalized linear models with binomial distribution and logit link function. Parental age, parental education, parity, and gender of the infant.	Risk ratios (95% CI) for a low birth weight: **Maternal blood Pb (µg/dL) (*p*=0.04 for trend)** <10 = (reference) **10 – 19 = 2.22 (1.06, 4.26)** ≥ 20 = 1.83 (0.67, 4.20) Paternal blood Pb (µg/dL) (*p*=0.08 for trend) <10 = (reference) 10 – 19 = 0.83 (0.43, 1.75) ≥ 20 = 0.42 (0.12, 1.06) Risk ratios (95% CI) small for gestational age (SGA): **Maternal blood Pb (µg/dL) (*p*<0.01 for trend)** <10 = (reference) 10 – 19 = 1.62 (0.91, 2.75) **≥ 20 = 2.15 (1.15, 3.83)** Paternal blood Pb (µg/dL) (*p*=0.77 for trend) <10 = (reference) 10 – 19 = 0.94 (0.49, 1.66) ≥ 20 = 0.94 (0.51, 1.62)	Maternal blood Pb was associated with low birth weight and SGA; whereas, paternal blood Pb was not.
Cross-sectional Clark (1977) Zambia	153 mother-infant pairs; high Pb, n= 122 residents of Pb smelter town; n=31 referent; Year not listed	Not reported	Maternal High Pb = 41.2 (14.4) Referent =14.7 (7.5) Cord High Pb=37 (15.3) Referent = 11.8 (5.6) Timing of maternal sample not reported	Birth weight	Statistical methods not described Adjustments not described.	Authors state there was no significant difference in birth weight between case (residences of a Pb smelter community) and referents.	Birth weight did not differ between two populations that differ in blood Pb.
Prospective cohort Dietrich (1987) Cincinnati, USA *Also listed for preterm birth* *Subset population of Bornschein (1989)*	185 pregnant mothers recruited at prenatal clinic from high Pb area of Cincinnati; Years not stated	Not stated	Maternal 8.3 (3.8) Infant 10 day 4.9 (3.3) 3 month 6.3 (3.8) 6 month 8.1 (5.2) Maternal Pb sampled at first prenatal visit	Birth weight, gestational age, neural effects data	Multiple regression models Adjustments not described for weight data.	Correlation of blood Pb with birth weight: **Maternal Pb r=-.29; p<0.001** **Infant 10-day Pb r=-.14; p<0.05** *Neurological data reported elsewhere*	Maternal and infant blood Pb were associated with lower birth weight
Prospective Ernhart (1986) Cleveland, USA *Same population*	Mother-infant pairs with blood Pb (n=162 cord; n=185 maternal) in	Not reported	Maternal at delivery 6.49(1.88) Cord 5.84 (2.02)	Birth weight, length, head circumference	Multivariate regression Adjustments not described.	Authors report maternal and cord Pb were not statistically significantly related to measures of size including weight (adjusted for gestational age), length, head circumference.	Maternal and cord blood were not associated with

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
as Greene (1991)	Cleveland prospective study; Enrolled Years= 1980-1981						birth weight, length, or head circumference.
Prospective Factor-Litvak (1991) Kosovo, Yugoslavia *Also listed for preterm birth Same population as Murphy (1990), Loiacono (1992), Factor-Litvak (1999), Lamb (2008)*	907 women recruited at mid-pregnancy: 401 lived in an area with high environmental Pb (exposed) and 506 lived in an area with low Pb exposure (referent); Years 1985-1986	[Ages not stated]	At mid-pregnancy: Exposed = 19.0(7.9) Referent = 5.4(2.07) At delivery: Exposed = 23.4(7.7) Referent = 6.8(4.1) Cord blood: Exposed = 22.1(8.5) Referent = 5.6(3.5)	Length of gestation, birth weight	Ordinary least squares regression analysis and maximum likelihood logistic regression analysis. Gestational age, maternal age, ethnic group, cigarette smoking during pregnancy, maternal education, maternal height, parity, and gender of infant.	Regression coefficient (95% CI) relating blood Pb (µmol/L) level to birth weight for combined population (living in the Pb-exposed town of Titova Mitrovica, a Pb smelter town, and referent town of Pristina): Maternal Pb, mid-pregnancy = 73 (-70.9, 85.5) Maternal Pb at delivery = 32.1 (-34.4, 98.5) Cord Pb = 38.6 (-26.9, 104.1)	Maternal blood Pb and cord blood Pb were not associated with birth weight.
Cross-Sectional Gershanik (1974) Louisiana, USA	98 mother-infant pairs delivered at Confederate Memorial Medical Center; Year =1972	Range 11->35	Maternal 10.5(3.8) Cord 9.4 (3.7) Maternal blood sampled at delivery	Birth weight	Statistical methods not described Adjustments not described.	Mean cord blood Pb by birth weight: <1,500g = 7.0 (3.0) 1,500-1,999g = 11.0 (3.7) 2000-2,499g = 10.0 (2.4) 2,500-2,999g =8.6 (3.0) 3,000-3,499g =9.8 (4.3) 3,500-3,999g = 9.9 (3.7) ≥4,000g =11.1 (4.4)	Cord blood Pb was not associated with birth weight.
Cross-sectional Gonzalez-Cossio (1997) Mexico City, Mexico *Population may overlap with Hernandez-Avila (2002) and others*	272 mother-infant pairs of women attending one of three hospitals in Mexico City; Year= 1994	14-18=11% 19-24=43% 25-35=42% ≥36= 3%	Blood Pb Maternal = 8.9 (4.1) Cord = 7.1 (3.5) Maternal bone µg/g Tibia = 9.8 (8.9) Patella=14.2 (13.2) Blood collected at delivery; bone Pb within 1 month	Birth weight	Univariate and bivariate statistics, ordinary least squares multiple regression Maternal height, arm and calf circumference at delivery, smoking, parity, history of poor reproductive outcomes, age, education, site of delivery, infant gender, gestational age.	Regression analysis of maternal tibia Pb on birth weight – regression coefficient (SE): **Continuous Pb = -7.19 (2.45)(p=0.003)** Adjusted effect of tibia Pb (by quartiles) on birth weight – regression coefficient (SE): 1st quartile (reference) 2nd quartile = -7.57 (60.98) (p=0.901) 3rd quartile = -50.86 (62.03) (p=0.413) **4th [15.1µg/g] = -155.55 (61.18) (p=0.012)** Regression analysis of maternal blood Pb on birth weight – regression coefficient (SE): Continuous Pb = -6.2 (5.27)(p=0.241) Adjusted effect of maternal Pb (by quartiles) on birth weight – regression coefficient (SE): 1st quartile (reference) **2nd quartile = -152.21 (58.91) (p=0.010)** 3rd quartile = -534.85 (60.10) (p=0.562) 4th quartile = -98.30 (59.55) (p=0.100)	Maternal bone Pb was associated with lower birth weight. Maternal blood Pb and cord blood Pb were not associated with birth weight.
Cross-sectional Prospective	53 pregnant women recruited at General	30 Range 16-42	Median Maternal = 2.5	Birth weight, birth length,	Chi-square test, Fisher's exact test, Cochran and Mantel-	Factors correlated to birth weight **Maternal blood Pb -0.258; p=0.007**	Maternal Pb was associated

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Gundacker (2010) Vienna, Austria	Hospital in Vienna; Year=2005		Cord = 1.3 Maternal blood at 34-38 weeks gestation.	head circumference, placental Pb, meconium Pb, HG	Haenszel statistics, categorical regression analysis Maternal height, gestational length, placental Pb, meconium Pb, maternal education	**Placental Pb 0.347; p=0.006** Meconium Pb -0.171; p=0.145 Catreg model factors associated with birth weight: **Placental Pb β=0.658 (SE=0.136); p<0.001** **Gestational length β=0.268(SE=0.133); p=0.030** **Maternal blood Pb β=-0.262 (SE=0.131); p=0.058** **Adjusted for gestational length, maternal Hg, Height, education, Plac.Pb, Mec.Pb; p=0.005** Factors correlated to birth length Maternal blood Pb -0.135; p=0.178 Placental Pb 0.221; p=0.095 **Meconium Pb -0.265; p=0.030** Catreg model factors associated with birth length: **Placental Pb β=0.599 (SE=0.154); p<0.001** **Gestational length β=0.406(SE=0.154); p=0.004** **Meconium Pb β=-0.385(0.157); p=0.012** Authors report Pb measures were not correlated to head circumference	with lower birth weight. Placental Pb was associated with higher birth weight and birth length; not head circumference
Cross-sectional Hauser (2008) Chapaevsk, Russia; *Also listed for puberty*	Boys aged 8-9 (n=489); Years=2003-2005 Male=100%	8.41(0.49)	Median (25-75%tile) 3 (2-5) Exposure measured at 8 years of age	Birth weight, height, weight, penile length, puberty onset	Multiple Linear regression Height, weight, BMI, penile length, and gestational age	Adjusted regression coefficient (95% CI) for association of blood Pb (natural log): **Birth weight(kg) -0.084 (-0.15 to -0.02) p =0.01** Gestational age (wks) -0.118 (-.09 to 0.33) p=0.27	Blood Pb in 8-year old boys was negatively related to birth weight.
Cross-sectional Hernandez-Avila (2002) Mexico City, Mexico *Population may overlap with Hernandez-Avila (2002) and others*	223 mother-infant pairs of women attending one of three hospitals in Mexico City; Year= 1994	Mean age = 24.4 years	Blood Pb Maternal = 8.9 (4.1) Cord = 7.1 (3.5) Maternal bone µg/g Tibia = 9.8 (8.9) Patella=14.2 (13.2) Blood collected at delivery; bone Pb within 1 month	Birth length, head circumference	Univariate and bivariate statistics and distribution plots; cumulative odds model. Maternal height, calf circumference, smoking during pregnancy, parity, prior history of poor reproductive outcomes, age, education, hospital of delivery, infant gender and gestational age.	β Coefficients (SE) and OR (95% CI) for birth length: Cord blood Pb β = 0.042 (0.035); OR =1.04 (0.97, 1.12) Patella Pb >24.7 µg/g bone β = 0.210 (0.315); OR =1.23 (0.67, 2.29) Tibia Pb > 16.6 µg/g bone **β = 0.584 (0.299); OR = 1.79 (1.10, 3.22)** β (SE) and OR (95% CI) for head circumference: Cord blood Pb β = -0.035 (0.036); OR =0.97 (0.90, 1.04) Patella Pb >24.7 µg/g bone **β = 0.756 (0.318); OR = 2.13 (1.14, 3.97)** Tibia Pb > 16.6 µg/g bone β = 0.429 (0.299); OR =1.54 (0.86, 2.76)	Maternal bone Pb was associated with lower birth length and head circumference; but not cord blood Pb.
Cross-sectional Huel (1981) France *Also listed for preterm birth*	100 mother-infant pairs in Haguenau Maternity, an area with metallurgical factories ; Year= 1978	25.4 (5.1)	No blood Pb data Exposure from hair samples ** lack of blood Pb data limits utility	Birth weight, gestational age, also Cd	t test, ANOVA, Chi-square test Sex, gestational period, mothers weight	Hair Pb for small for gestational age (SGA) relative to normal births: SGA maternal hair Pb 9.0 ppm; p>0.05 Normal maternal hair Pb 8.1 ppm SGA newborn hair Pb 6.1 ppm Normal newborn hair Pb 6.6 ppm	Hair Pb was not associated with small for gestational age.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Case-control Iranpour (2007) Isfahan, Iran	Mother-infant pairs delivered at Shahid-Beheshti Hospital (case - intrauterine growth restricted [IUGR] births, n=32; normal, n=34); Year = 2005	Case = 27(6) Control = 25(4)	Cord Case=10.7(1.7) Control=11.3(1.9) Maternal Case=12.5(2.0) Control=13.5(2.7) Measured within 12 hours of delivery	Birth weight, head circumference, length	t test, bivariate correlation tested by Spearman coefficient Adjustments not described.	Mean blood Pb values by birth outcome: Maternal case (IUGR) 12.5(2.0) Maternal control 13.5 (2.7); p=0.07 Cord case (IUGR) 1.07 (1.7) Cord control 1.13 (1.9); p=0.2 Correlation between cord Pb and birth weight: IGUR births r=-0.36; p=0.84 Normal r=0.19; p=0.26 Correlation maternal blood Pb and birth weight: IUGR births r=-0.24; p=0.17 Normal r=0.18; p=0.30	Maternal and cord Pb were not associated with birth weight.
Cross-sectional Irgens (1998) Norway *Also listed for preterm birth*	Births in Norway with possible parental occupational Pb exposure (exposed n=1,803 maternal; n=35,930 paternal); Years= 1970-1993	Not reported	Not reported Exposure by parental job category ** lack of blood Pb data limits utility	Low birth weight, stillbirths, preterm births, serious birth defects	Logistic regression Maternal age, education, gestational age	Prevalence of low birth weight with parental occupational Pb exposure compared to reference: Maternal exposure: **All Pb exposure levels OR=1.34 (1.12,1.60)** **High Pb OR=3.47 (1.84,6.12)** **Low Pb OR=1.25 (1.03,1.51)** **Dose-response relationship p<0.005** Paternal exposure: All Pb exposure levels OR=0.91 (0.86,0.96) High Pb OR=0.88 (0.72,1.07) Low Pb OR=0.92 (0.87,0.97)	Maternal occupational Pb exposure was associated with low birth weight. Paternal occupational Pb exposure was negatively associated with low birth weight.
Cross-sectional Janjua (2009) Karachi, Pakistan	540 mother-infant pairs recruited during pregnancy; Year=2005: % male child=54%		Cord blood: Mean =10.8 (0.2) Geometric mean=9.6(1.6)	Birth weight	t test, ANOVA, chi-square, prevalence ratio, multivariable binomial regression	Adjusted Prevalence Ratio (95% CI) for low birth weight (LBW <2500g) by cord blood Pb: Mid upper-arm circumference adjusted: <10µg/dL - reference >10µg/dL Adj.PR = 0.86 (0.61,1.21); p=0.380 Biceps skinfold thickness adjusted: <10µg/dL – reference >10µg/dL Adj.PR = 0.84 (0.59,1.18); p=0.316	Cord blood Pb ≥10g/dL was not associated with low birth weight.
Retrospective cohort Jelliffe-Pawlowski (2006) California, USA *Also listed for preterm birth*	262 mother-infant pairs from California Pb surveillance program; Years= 1996-2002	85% <35	[not stated] Maternal blood sampled during pregnancy	Preterm births, low birth weight, small for gestational age (SGA)	ANOVA, crude and adjusted linear regression models. Preterm birth, maternal age and race, prior parity, infant sex, public or private insurance (as an assessment of poverty).	Linear regression analysis for blood Pb level and birth weight: Blood Pb < 10 µg/dL R^2 = 0.190; Regression coefficient = 26 Blood Pb ≥ 10 µg/dL R^2 = 0.108; Regression coefficient = 1.6; *p*>0.5 Adjusted Odds Ratio for Low Birth Weight: Blood Pb < 10 µg/dL (reference) Blood Pb ≥ 10 µg/dL = 3.6 (0.3, 40.0) Adjusted Odds Ratio for Small for Gestational Age: Blood Pb < 10 µg/dL (reference) **Blood Pb ≥ 10 µg/dL = 4.2 (1.3, 13.9)**	Maternal blood Pb ≥ 10 µg/dL was associated with SGA; however, maternal blood Pb was not associated with low birth weight.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Jones (2010) Memphis, Tennessee *Also listed for preterm birth*	102 mother-infant pairs in Memphis; Year=2006; Male=47%	Mother age range 16-45	Cord = 2.4 (4.3) Geometric mean Cord = 1.3	Gestational age, low birth weight, cord concentration of Mn, Cr, Cu	Spearman correlation, logistic regression	Geometric mean cord Pb (95%CI) by low birth weight (<2500g): <2500g = 1.2 (0.7, 2.2)µg/dL ≥2500g = 1.3 (1.0, 1.5) µg/dL; p>0.1	Cord Pb was not different between infants with low and normal birth weight.
Cross-sectional Kordas (2009) Mexico City, Mexico *Population may overlap with Hernandez-Avila (2002) and others*	474 mother-infant pairs of women attending one of three hospitals in Mexico City; Years= 1994-1995	24.6 (5.1)	Maternal at delivery 8.6(4.2) Tibia Pb=9.9(9.8)	Folate intake, MTHFR genotype, birth weight, birth length, head circumference	Chi-squate test, Univariate and bivariate statistics and distribution plots; multiple regression analyses Maternal age, pre-pregnancy BMI, height, schooling, parity, marital status, smoking, postpartum calf circumference, infant gestational age, sex	Relationship between maternal tibia Pb (continuous), folate, and infant size at birth: **Birth weight- tibia Pb β=-4.8 (SE=1.8); p<0.01** **Birth weight-folate β=0.04 (SE=0.02); p<0.05** Relationship between maternal tibia Pb (categorical), and folate, and infant size at birth: **Birth weight-tibia Pb β=-102.6 (SE=35.7); p<0.01** Birth weight-folate β=34 (SE=38); p>0.05 **Head circ.-tibia Pb β=-0.28 (SE=0.14); p<0.05** **Head circ.-folate β=0.07 (SE=0.15); p>0.05** Authors report maternal or infant MTHFR genotype did not modify effects of Pb on newborn size.	Maternal bone Pb was negatively associated with birth weight and head circumference; folate modified the effect of Pb on birth weight.
Retrospective Kristensen (1993) Oslo, Norway *Also listed for stillbirth and other endpoints*	6,251 births to male members of printers' unions in Oslo, Norway (n=341 children with low birth weight); Years= 1930 to 1974	Not reported	Not reported Exposure by paternal job category ** lack of blood Pb data limits utility	Low birth weight, late abortions, stillbirths, preterm births	Logistic regression Gestational age, birth order, sex, prior stillbirth, twin birth, parental consanguinity	Low birth weight OR for paternal occupational Pb exposure compared to "other" exposures: OR (95% CI) =0.9 (0.61,1.2)	Paternal exposure to Pb by occupation was not associated with birth weight.
Retrospective cohort Lin (1998) New York, USA *Also listed for preterm birth*	3006 births to male workers on the New York State Heavy Metals Registry (exposed n=747); the referent group was a random sample of bus drivers (n=2259); Years= 1981-1992	Age range = 20 – 55 yr.	Exposed = 37.2 (11) µg/dL [Referent not stated]	Birth weight and gestational age	Chi-square tests, crude risk ratios, adjusted risk ratios using an unconditional logistic regression model. Paternal age, race, maternal education, parity, maternal perinatal complications, previous spontaneous abortion history, gender, prenatal care	Relative risk(95% CI) of outcome for all paternal Pb exposure (>25µg/dL): Low birth weight RR=1.00 (0.67,1.50) Small for gestation age RR=0.86 (0.64,1.15) Relative risk(95% CI) of outcome for paternal Pb exposure (>25µg/dL) >5 years: **Low birth weight RR=3.40 (1.39,8.35)** Small for gestation age RR=0.82 (0.28,2.37)	Paternal occupational exposure >25µg/dL for more than 5 years was associated with low birth weight.
Case-control Llanos (2009) Santiago	40 mother-infant pairs in San Juan de Dios Hospital (case n=20 fetal growth restriction-FGR) (n=20 normal); Year not stated	Mothers with normal weight babies =26.2(6) FGR mothers = 27.8 (7)	No blood data Exposure from placenta samples ** lack of blood Pb data limits utility	Fetal growth restriction (FGR), birth weight, height, head circumference, gestational age	Non-parametric Mann-Whitney U-test because data were not normally distributed. Adjustments not described.	Placental concentration of Pb (µg/g dry): Normal 0.04 (0.009) **FGR 0.21 (0.04); p=0.04** FGR placental Cd and As were also higher; p<0.05. Birth characteristics of FGR newborns (% normal): Birth weight – 66%; p=0.00001 Birth height – 89%; p=0.00001 Head circumference – 93%; p=0.008 Gestational age – 96%; p=0.03	Placental Pb was higher in mothers with FGR births.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Prospective Loiacono (1992) *Also listed for gestation length* Kosovo, Yugoslavia *Same population as Murphy (1990), Factor-Litvak (1991, 1999)*	161 women recruited at mid-pregnancy; 106 lived in an area with environmental Pb (exposed) and 55 lived in an area without significant Pb (referents); Years= 1985-1986	Case=26.8 (5) Referent=27(5)	Maternal at delivery Case=21.7 (6.8) Referent=5.2 (1.7) Cord Case=20.3 (7.7) Referent=5.6 (3.9)	Birth weight, gestational age, placental Pb, and placental Cd	Least squares multiple regression Maternal age, ethnic group, cigarette smoking during pregnancy, maternal education, maternal height, parity, maternal blood Pb, and gender of infant.	Regression Coefficient (95% CI) relating placental Pb (per nmol/g) Pb level to birth weight: 0.41g (-1.04, 1.86) Placental Pb: Pb-exposed town of Titova Mitrovica, a Pb smelter town, and referent town of Pristina 69.3 (71.4) nmol/g Referent town of Pristina 21.6 (18.5) nmol/g	Placental Pb was not associated with birth weight.
Prospective McMichael (1986) Port Pirie, South Australia *Also listed for pre-term birth and other endpoints*	721 pregnant women from Port Pirie birth cohort study of a Pb smelting community - Port Pirie (exposed; n=595 with blood Pb) or surrounding towns (referents; n=144 with blood Pb); Years= 1979-1982.	Age range = 14 – 36 yr.	Maternal blood (SE) measured at delivery Exposed: 11.2 (0.21) Referent:7.5 (0.25)	Pregnancy outcome including pre-term delivery, stillbirths (late term fetal deaths) birth weight, IUGR, premature rupture of membranes (PROM), and congenital anomalies	Multiple logistic regression Adjustments not described. Effect of infant sex, gestational age, maternal relative weight, smoking, and prior parity on birth weight examined separately.	Pregnancies with low birth weight (<2500g): Port Pirie 3.9% Referents 1.8% Maternal blood Pb at delivery: Port Pirie <2500g 10.4 (SE=1.1) Port Pirie ≥2500g 11.2 (SE=0.21) Referents <2500g 5.5 (SE=0.1) Referents ≥2500g 7.6 (SE=0.26) Cord blood Pb at delivery: Port Pirie <2500g 9.6 (SE=0.90) Port Pirie ≥2500g 10.0 (SE=0.20) Referents <2500g 9.0 (SE=0.91) Referents ≥2500g 9.1 (SE=0.17) Blood Pb levels were also not associated with crown-heel length, IUGR, PROM, congenital anomalies, or time taken to become pregnant. A significant inverse relationship was reported for maternal blood Pb and head circumference; however this was not observed when analyses were restricted to Port Pirie women.	Maternal and cord blood Pb were not associated with birth weight.
Case-control Min (1996) Maryland, Virginia, and DC USA *Also listed for preterm*	742 births from the Baltimore-Washington Infant Study: (n=220 cases low birth weight), (n=522 controls). Years= 1981-1989	Not stated	No blood Pb data Paternal exposure was estimated from the jobs held during the six months before or during the pregnancy ** lack of individual blood Pb data limits utility	Birth weight, small for gestational age (SGA), preterm birth	Chi-square tests, logistic regression Adjustments differ by endpoint including: race, marital status, maternal/paternal education, maternal/paternal employment, income, maternal height, pregnancy weight gain, smoking, previous pregnancy outcomes	Logistic regression model for low birth weight and intensity of paternal occupational exposure intensity (xTLV) to Pb: No exposure (reference) ≤ 0.1 – OR = 0.70 (0.37, 1.27) > 0.1 to < 0.5 – OR = 1.67 (0.65, 4.30) **≥ 0.5 – OR = 4.72 (1.10, 20.23)** Association between SGA with intensity of paternal occupational exposure intensity (xTLV) to Pb: **≥0.1 – OR = 2.8 (1.1, 7.1)**	Paternal occupational exposure to Pb by job category was associated with low birth weight and SGA.
Cross-sectional Moore (1982) Glasgow, UK *Also listed for preterm birth*	236 mother-infant pairs enrolled in 1977	Range 17-37	Geometric mean Maternal =14.5µg/dL Cord=12.6µg/dL Timing of maternal sample not reported	Birth weight, gestation length	Multiple regression Adjustments not described.	Multiple regression between blood Pb and birth weight: Maternal Pb p>.05 regression coefficient not listed Cord Pb p>.05 regression coefficient not listed	Maternal and cord blood Pb were not associated with birth weight.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Retrospective Needleman (1984) Boston, USA *Also listed for preterm birth and malformations* *Data re-analyzed by Bellinger (1991)*	4354 births at Boston Hospital for women; Years= 1979-1980	Not reported	Not reported	Birth weight, gestational age, malformations	Chi-square test, logistic regression Maternal age, gestation age, birth weight, race	Authors state cord blood Pb was not associated with birth weight or gestation length tested by chi-square test.	Cord blood Pb was not associated with birth weight.
Cross-sectional Neuspiel (1994) New York	581 women giving birth at a public hospital in New York; 18 were cocaine-exposed and 46 were referents; Year=1992	Maternal age Cocaine=30.5 Referent=23.8	Cord blood: Cocaine=4.75 Referent=3.38	Maternal cocaine use, birth weight, head circumference, length	Multiple linear regression Gestational age * Lack of reporting of direct comparison of blood Pb to indicators of fetal growth limit the utility of the study	Multiple linear regression for length (cm) cocaine exposure, Pb and other factors: Cocaine alone β=-2.78; p <0.005 cocaine exposure + cotinine β=-2.84; p<0.005 cocaine exposure + smoking β=-2.90; p<0.005 cocaine exposure **+Pb β=-2.32;p=0.03 cocaine exposure** +Pb, cotinine β=-1.86; p=0.8 cocaine exposure Multiple linear regression for birth weight (g) cocaine exposure, Pb and other factors: Cocaine alone β=-311; p =0.02 cocaine exposure +Pb β=-239;p=0.23 cocaine exposure Multiple linear regression for head circumference (cm) cocaine exposure, Pb and other factors: Cocaine alone β=-1.08; p =0.02 cocaine exposure +Pb β=-0.87;p=0.15 cocaine exposure	Cord blood Pb had an effect on measures of fetal growth (particularly length) and could explain part of the cocaine-related decrease in birth weight, length and head circumference.
Retrospective Nordstrom (1979b) Sweden *Population overlaps with Nordstrom (1978b)* *Also listed for abortion*	662 female employees at Ronnskar smelter and residents of Umea (a referent population); Years=born between 1930-1959	Not reported	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Incidence of spontaneous abortion and birth weight	Chi-square test for heterogeneity Authors state that frequencies of smokers were comparable to the general Swedish population, thus the observed reduced birth weight is not expected to be caused by smoking alone. Other covariates or adjustments not described	The average birth weight by pregnancy order: Referent -1st pregnancy 3372g (532) Referent -2nd pregnancy 3495g (530) Referent -≥3rd pregnancy 3568g (596) Referent -total pregnancy 3460g (554) Employees -1st pregnancy 3375g (541) - p>0.05 Employees -2nd pregnancy 3432g (556) - p>0.05 **Employees -≥3rd pregnancy 3375g (571) - p<0.001** **Employees -total pregnancy 3394g (553) - p<0.01** **Offspring of workers in close proximity to the smelting process had a lower birth weight (p<0.05) relative to offspring of other employees.**	Female employees at a smelter had offspring with lower birth weight.
Retrospective Nordstrom (1978b) Sweden *Population overlaps with Nordstrom (1979b)*	Female employees at Ronnskar smelter during 1975-1976 and women living in one of 4 areas at different distances from the Ronnskar smelter or Umea (a	Not reported	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Birth weight	Chi-square test for heterogeneity Covariates or adjustments not described	Average birth weight by employment or residence: Employees of smelter 3391 (526) Area A <10km from smelter 3395 (528) Area B ≤10 km from smelter 3412 (536) Area C 10-30km from smelter 3495 (544) Area D >30 km from smelter 3470 (580) Referent 3460 (554) **Birth weight of employees and residents of area A**	Women working at smelter or living closer to a smelter had offspring with a lower birth weight.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
	referent population) and born after 1930					**and B were significantly lower than referent or areas C and D (p<0.05-p<0.001).** The difference between birth weight between employees (or residence of A and B) and referents was significant for ≥3rd and later pregnancies (p<0.001) not for 1st or 2nd (p>0.05).	
Cross-sectional Odland (1999) Norway and Russia *Also Odland (2004)* *Also listed for preterm birth*	262 mother-infant pairs from hospital delivery in Russian and Norwegian arctic and subarctic areas; Years= 1993-1994	Russia = 25.0 Norway = 28.2	Median Maternal blood: Russia: 2.9 Norway: 1.24 Cord blood: Russia: 2.07 Norway: 1.04 Timing of maternal sample not reported	Birth weight, birth length, gestational age, blood Cd	Univariate and multivariate linear regression analyses; t test and ANOVA. Maternal BMI, age, smoking, country and gestational age.	Pregnancy outcome by population (mean and SD): **Birth weight Russian 3178 (616)g** **Birth weight Norwegian 3571 (488); p<0.001** **Birth length Russian 51.6 (3.4)cm** **Birth length Norwegian 50.5 (2.2) cm; p=0.003** Median Pb concentrations: **Maternal – Russian = 2.9** **Maternal – Norwegian = 1.24; p<0.001** **Cord – Russian = 2.07** **Cord – Norwegian = 1.04; p<0.001** Multivariate regression analysis of infant birth weight or BMI for combined Russians/Norwegians (change in birth weight or BMI per blood Pb): Birth weight β = -0.5g (per μg/dL) **or -1068g (per μmol/L); *p*<0.05** BMI β = not reported; *p*<0.025	Maternal blood Pb was associated with low birth weight and low BMI.
Cross-sectional Odland (2004) Norway and Russia *Also Odland (1999)*	262 mother-infant pairs from hospital delivery in Russian and Norwegian arctic and subarctic areas; Years= 1993-1994	Russia = 25.0 Norway = 28.2	Median Maternal blood: Russia: 2.9 Norway: 1.24 Total:2.1 Placenta (μg/g): Russia: 2.3 Norway: 1.24 Total 1.89	Birth weight, placental Pb and Cd	Univariate and multivariate linear regression analyses; nonparametric Wilcoxon rank sums test. Maternal BMI, age, smoking, country and gestational age.	Univariate regression analysis of birth weight and placental Pb level: Change (g per unit) = -864 (-1913, 185) (*p*>0.05) Multivariate regression analysis of infant birth weight for combined Russians/Norwegians (change in birth weight per placental Pb): Birth weight β = -736g (per μmol/L); *p*>0.05	Placental Pb was not associated with low birth weight.
Cross-sectional Prospective Osman (2000) Solona, Sweden	106 Swedish women registered at antenatal care units in Solona, Sweden; Years= 1994-1996	Mean age = 31 (4) years.	Mean Placenta = 0.87μg/g Median maternal blood = 1.14μg/dL; sampled week 36 of pregnancy Median cord blood = 1.12μg/dL	Birth weight, birth length, head circumference, placental Pb, and other metals	Mann-Whitney U test; Spearman correlation; multiple regression analyses. Maternal age, smoking habits, number of children, length of gestation. Child's gender, weight, length, head circumference and Apgar points.	Birth weight vs. cord blood Pb level: **β = -2.0 (-3.5, -0.51)** Birth length vs. cord blood Pb level: **β = -0.0088 (-0.016, -0.002)** Birth head circumference vs. cord blood Pb level: **β = -0.0047 (-0.009, -0.0002)** unclear if relationship with maternal blood Pb was examined	Cord blood Pb was associated with lower birth weight, length, and head circumference.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Patel (2009) Nagpur, India *Also listed for preterm*	205 consecutive births at hospital in Nagpur; Year not stated; Male=56%	Maternal age not reported	Total Cord=4.7(12.1) Maternal-cord (n=62) matched samples Maternal = 2.0 (2) Cord =1.6(2.5)	Birth weight, head circumference, gestational age,	Univariate and multivariate linear regression Adjustments not described.	Mean birth weight by cord blood: ≤5µg/dL = 2640 (445) g >5µg/dL = 2617 (408) g Overall mean head circumference = 32.6(1.5) cm Analysis of birth weight and head circumference by blood Pb not reported.	Cord blood Pb does not appear to be related to birth weight; analyses not reported.
Cross-sectional Philion (1997) British Columbia, Canada	9329 births in a smelter city and a referent city in British Columbia; Years=1961-1990	Not reported	No blood Pb data Exposure determined by residence near smelter ** lack of blood Pb data limits utility	Incidence of IUGR	Chi-square tests Adjustments not described.	Odds ratio for IUGR in a smelter city compared with a referent city: OR = 0.83 (0.64, 1.08) p =0.2	Residence in a Pb smelter city was not associated with IGR.
Cross-sectional Rahman (2003) Karachi	73 women delivering over 4 week period at Jinnah Postgraduate Medical Center; Years not stated.	Mothers =25.5 (4.8)	9.91 (4.44) Note reported as mg/dL, but CDC safe level was reported as 10mg/dL, therefore data likely represent µg/dL blood Pb.	Birth weight, length, head circumference, gestation age	Univariate regression and multivariate regression analysis Adjustments not described.	Univariate regression β for blood Pb: Birth weight β=19.12; p=0.146 Head circumference β=0.054; p=0.477 Length β=0.03; p=0.796 Gestational age β=0.291; p=0.375 Pb was removed from the model in the multivariate regression because variables with no significant effect were removed in a step-wise manner.	Maternal blood Pb at delivery was not related to birth weight, length, or head circumference.
Cross-sectional Rajegowda (1972) New York, USA *Also listed for preterm birth*	100 infants randomly selected from births (apparently at Harlem Hospital) to resident mothers of New York City; Years not stated	15 to 37 Median=23	Cord blood 10µg/dL=60% 20µg/dL=34% 30µg/dL=6%	Birth weight and gestational age	Statistical methods not reported Adjustments not described.	Authors state no correlation between cord blood Pb and birth weight	No association between birth weight and cord blood Pb.
Cross-sectional Rhainds (1999) Quebec, Canada	1109 newborns born in hospitals in Quebec; Years= 1993-1995	28 (4.9)	Cord = 1.57	Birth weight, length, gestation length, premature, blood Hg, PCBs, pesticides	Pearson's correlation Adjustments not described.	Mean cord blood Pb by infant weight: <2500g = 1.84µg/dL 2500-2990g = 1.59µg/dL 3000-2490g =1.59µg/dL ≥3500g = 1.53µg/dL Authors state no correlation between blood Pb and birth weight	Cord blood Pb levels were not correlated to birth weight.
Case-control Richter (1999) Prague	50 women-infant pairs with IUGR (case); 43 controls	Case=25.6 (6.1) Control not reported	No blood Pb data ** lack of blood Pb data limits utility	Intrauterine growth retardation (IUGR), placental Pb, Zn	Statistical methods not reported Adjustments not described.	Placental Pb: IUGR births 15.24 (7.85) Controls 11.31 (5.79) ng/g Authors state Pb is significantly higher in the placenta of IUGR births	Placental Pb levels were higher in IUGR births.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Satin (1991) California, USA *Also listed for preterm birth*	723 live births in five cities in California; Year= 1984	26.4 yr.	Cord blood 4.9 µg/dL	Birth weight, preterm birth (<260 days)	One-way ANOVA Ethnicity and sex of infant.	Mean (SE) cord blood Pb by birth weight: ≥2500g 4.9(0.087)µg/dL <2500g 4.8(0.224) µg/dL; p=0.56	Cord blood Pb was not associated with birth weight.
Cross-sectional Seidler (1999) Germany	3216 mother-infant pairs in Western Germany; Years=1987-1988	Mean not reported	Exposure assessed by job-exposure matrix ** lack of blood Pb data limits utility	Small for gestational age (SGA)	Logistic regression analysis Maternal age, smoking, alcohol consumption, BMI, former births	Odds ratio (95% CI) for small for gestational age by categorical Pb exposure (probability x intensity x working hours/day): No Pb exposure OR=1.0 reference Low Pb OR=2.2 (0.2, 24.8) Moderate Pb OR= 1.5 (0.2, 12.8); p-trend =0.71	Probability of maternal occupational exposure was not associated with SGA.
Cross-sectional Prospective Sowers (2002) Camden, New Jersey *Also listed for preterm birth*	705 pregnant women at clinics in Camden; Years not stated	20.5 (SE=0.2)	Maternal blood Pb 12 weeks:1.2 (0.03) 20 weeks:1.08(0.05) 28 weeks:1.10(0.03) Birth:1.32(0.03)	Preterm birth, birth weight, small for gestational age (SGA), low birth weight (LBW)	Univariate analysis, longitudinal regression analyses Age, dietary calcium, race/ethnicity	Authors state no significant association between maternal Pb and low birth weight, or small for gestational age	Maternal blood Pb was not associated with birth weight.
Case-control Srivastava (2001) Lucknow, India	Pregnant women from Lucknow and adjoining areas (case, n=30 women with ultrasound intrauterine growth restriction [IGUR] and n=24 control); Years not stated	Not reported <24 – n=14 24-28- n=19 ≥30 – n=14	Maternal Normal = 10.3(5.7) IUGR = 13.4(8.1) Cord Normal=11.4(5.9) IUGR = 16.0(1.15) Maternal sampled at delivery	Birth weight, Zn levels	t test, ANOVA Adjustments not described. SES, tobacco use, ethnicity, gestational age, age of mother, vegetarian relation to Pb tested separately	Cord blood relation to birth weight: **r=-0.22; p<0.05** Maternal blood Pb at parturition: Normal = 10.3(5.7) **IGUR births = 13.4(8.1); p<0.05** Cord blood Pb: Normal=11.4(5.9) **IGUR births = 16.0(1.15); p<0.05** Mean maternal blood Pb by gestational age: <34 weeks = 4.42 (1.9) **34-37 weeks = 12.89 (7.6); p<0.01** **≥38 weeks = 11.34 (5.7); p<0.005** ANOVA for maternal and cord blood by SES, ethnicity, mother age, tobacco blood Pb at parturition were not statistically different except for effect of SES on maternal Pb.	Maternal and cord blood Pb were associated with lower birth weight and were higher in IGUR births.
Cross-sectional *Ward (1990)* England *Also listed for preterm birth*	79 live births from Merseyside/ Blackpool; Years=1980-1981	Not reported	No blood Pb data ** lack of blood Pb data limits utility	Birth weight, gestational age, head circumference, placental Pb	Statistical methods not described. Adjustments not described.	Correlation between placental Pb and: **Birth weight r=-0.74; p<0.001** **Head circumference r=-0.62;p<0.001**	Placental Pb was negatively correlated with birth weight
Cross-sectional Wibberley (1977) Birmingham, England	126 births at Birmingham Maternal Hospital; Year not stated	Not reported	No blood Pb data ** lack of blood Pb data limits utility	Birth weight	Statistical methods not described Adjustments not described.	Authors state no correlation was found between low birth weight and placental Pb for normal births.	Placental Pb was not associated with birth weight.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Zentner (2006) Santo Amaro, Brazil	55 mother-newborn pairs living within 5 km of Pb smelter admitted to hospital in Santo Amaro; Year=2002	Not reported	Cord blood 3.9μg/dL (	Birth weight, birth length	Multiple linear regression; Pearson correlation coefficients Adjustments not described. Effect of sex, Hb, and per capita income examined separately.	Regression model with blood Pb as dependent variable and birth characteristics: **Birth weight β=-0.275; p=0.048** **Birth length β=-0.460; p=0.003**	Cord blood Pb was associated with low birth weight
Retrospective cohort Zhu (2010) New York *Also listed for preterm birth*	43,288 mother-infant pairs from New York State Heavy Metals Registry with blood Pb≤10μg/dL; Years=2003-2005	15-49	Maternal 2.1 (SD not reported) Sampled before or at birth	Birth weight, preterm birth, small for gestational age	Multiple regression analysis Adjustments differ by endpoint including: timing of Pb test, maternal age, race, Hispanic ethnicity, smoking, drug abuse, in wedlock, participation in financial assistance, parity, infant sex	Association between maternal Pb and birth weight estimate in g (95% CI): 0 (reference) 1 β=-27.4 (-17,-38) 2 β=-38.8 (-24,-53) 3 β=-47.5 (-30,-65) 4 β=-54.8 (-34,-76) 5 β=-61.3 (-38,-84) 6 β=-67.2 (-42,-93) 7 β=-72.5 (-45,-100) 8 β=-77.6 (-48,-107) 9 β=-82.3 (-51,-113) 10 β=-86.7 (-54,-119) Association between maternal Pb and small for gestational age (SGA) OR (95% CI): ≤1.0 (reference) 1.1-2.0 OR=1.07 (0.98,1.17) 2.1-3.0 OR=1.06 (0.98, 1.16) 3.1-9.9 OR=1.07 (0.93, 1.23)	Maternal blood Pb was associated with lower birth weight but not with small for gestational age.
Repro: Preterm Birth / Gestational Age							
Cross-sectional Angell (1982) Kentucky, USA	635 women who delivered babies at Louisville General Hospital; Year not stated	Mean age = 21.1 (4.9) years	Maternal 9.85 (4.4) Child 9.82 (4.8) Cord 9.73 (4.1) Maternal blood at delivery	Preterm delivery, preeclampsia, PROM, meconium staining	Statistical methods not reported. Adjustments not described.	Concentration of Pb in cord blood: Full-term delivery = 9.2 (3.9) μg/dL Preterm delivery = 10.1 (4.5) μg/dL No statistical difference in mean blood Pb concentrations between women with any type of complication and women with no complications.	Maternal, child, and cord blood Pb levels were not associated with preterm delivery.
Prospective nested case-control Baghurst (1991) Port Pirie, South Australia *Also listed for stillbirth* *Subpopulation of McMichael (1986)*	Subset of Port Pirie birth cohort study of Pb smelting community; 749 pregnancies followed beyond 20 weeks; case - n=23 preterm births; Years= 1979-1982	Not reported	Maternal blood at delivery Preterm 11.9 μg/dL Normal 8.7 μg/dL	Pb levels for incidence of stillbirths, preterm births	ANOVA and Person correlation analyses Adjustments not described.	Mean placental body Pb μg/g by birth outcome: Preterm birth (n=23) 0.66 μg/g Normal (n=22) 0.48 μg/g Mean placental membrane Pb μg/g by outcome: Preterm birth (n=23) 1.24 μg/g Normal (n=22) 0.78 μg/g Preterm placental Pb relative to normal (p=0.10) Maternal blood Pb was significantly higher in preterm births than normal births as previously reported in McMichael (1986)	Placental Pb levels were not different between normal and preterm births; relationship between maternal blood Pb and preterm birth reported elsewhere.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Bellinger (1991) Boston, USA *Also listed for birth weight* *Data are reanalysis of Needleman (1984)*	3503 births at Brigham and Women's Hospital; Years= 1979-1981	Mean maternal age = 28 yr.	Cord=7.0 (3.3) µg/dL	Birth weight, preterm birth, small for gestational age, intrauterine growth retardation (IUGR)	Multiple linear regression and multiple logistic regression Maternal age at delivery, marital status, mother employed at conception, maternal education, race, maternal ponderal index, parity, smoking status, alcohol and coffee consumption, hematocrit at delivery, maternal diabetes, and delivery by C-section	Mean length of gestation (weeks) by cord blood Pb: <5µg/dL 39.5 (SE=0.1)g 5-9.9µg/dL 39.8 (SE=0.1) 10-14.9µg/dL 39.9 (SE=0.1) ≥15µg/dL 39.9 (SE=0.1) Multiple regression of length of gestation on cord blood Pb (for each 1µg/dL Pb increase): **Coefficient = 0.4 (SE=0.01) (*p*=0.0002)** Adjusted Risk Ratio for premature birth (<37 weeks) by cord blood Pb (for each 1µg/dL Pb increase): Premature birth RR = 0.98 (0.93, 1.02)	Cord blood Pb was not associated with preterm birth; however cord blood Pb was associated with gestations of a slightly longer duration.
Cross-sectional Berkowitz (2006) Idaho *Also listed for birth weight*	169, 878 infants born to mothers residing in Idaho; exposed (exposed = births after a fire resulted in emissions from a Pb smelter plant in 1973; high=Sept 1973 to Dec 1974; post-fire=Jan 1975-Dec 1981), pre-fire from the same area, and unexposed (referent);Male=51-52%	80-85% of mothers were 19-34 throughout study period	No blood data Exposure from air samples ** lack of blood Pb data limits utility	Birth weight, small for gestational age (SGA)	Logistic regression analysis Sex, age, whether first born, whether other births/terminations occurred after 20 weeks gestation	Odds ratio for preterm infants Pre-fire (1970-73) – unexposed = reference Pre-fire (1970-73) – exposed = 0.93 (0.67,1.28) High Pb (1973-74) – unexposed = reference High Pb (1973-74) – exposed = 0.68 (0.34,1.35) After fire (1975-81) – unexposed = reference After fire (1975-81) – exposed = 1.17 (0.95,1.45)	Pb emissions associated with damage to a pollution control device for a Pb smelter was not associated with preterm birth.
Prospective Bornschein (1989) Cincinnati, USA *Also listed for birth weight* *Also published in Dietrich (1987) and Shukla (1989)*	Cincinnati Pb study; 861 total infants (202 women-infant pairs with full data) recruited <28 weeks gestation in high-Pb neighborhood; Years= 1980-1985	22.6	Maternal=7.5 (1.6) Blood sampled 16-28 weeks of gestation	Birth weight, birth length, head circumference, gestational age	Multiple regression analyses Gestational age, alcohol or tobacco use, maternal age, number of prenatal visits, maternal height	Bivariate, unadjusted correlation between maternal blood Pb (ln) and: Gestation length r=-0.07; p>0.05 Authors state maternal blood Pb was not significantly correlated with duration of gestation.	Maternal blood Pb was not associated with gestational age.
Prospective Cantonwine (2010a) Mexico City, Mexico	327 pregnant women recruited at a hospital in Mexico City, ≤12 weeks gestation at enrollment. Years = 1997-1999	27.1 (5.4)	Maternal blood by trimester 1st =7.2(5.2) 2nd =6.3(4.3) 3rd =6.8(4.5) Maternal plasma 1st =0.17(0.16) 2nd =0.13(0.10) 3rd =0.16(0.26)	Gestational age, Preterm birth	t test, chi-square test, spearman correlation analysis, multiple linear regression analysis Adjustment differ by effect and included maternal age, maternal education, history of adverse birth outcome, infant sex, smoking, parity	Regression models for gestational age and Pb exposure β (95% CI): **1st trimester blood Pb β=-2.76 (-5.2,-0.3); p=0.03** **2nd trimester blood Pb β=-1.8 (-3.4,-0.15); p=0.03** 3rd trimester blood Pb β=-0.47 (-1.8,0.84); p=0.48 1st trimester plasma Pb β=-2.4 (-5,0.21); p=0.07 2nd trimester plasma Pb β=-1.3 (-3,0.29); p=0.11 3rd trimester plasma Pb β=-1.28 (-2.6,0.06); p=0.06 Cord blood β=-0.68 (-2.37, 1); p=0.42	Maternal blood Pb was associated with gestational age.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
			Cord blood=5.9(3.8)			Regression model for gestational age/blood Pb controlling for Pb in other trimesters β (95% CI): 1st trimester blood Pb β=-2.77 (-5.5,-0.02); p=0.05 3rd trimester blood Pb β=.56 (-1.9,-3); p=0.65 Authors state that data support a negative association between fetal exposure to Pb and length of gestation, but is inconclusive for the risk of delivering prematurely. Authors also state negative effects of blood Pb were stronger earlier in pregnancy than later.	
Cross-sectional Chen (2006) Taiwan *Also listed for birth weight*	1611 births to parents registered in a Pb surveillance program (n=74 preterm); Years=1994-1997	Mean age: maternal = 27.0 (4.3) paternal = 29.8 (4.4) yr.	Mean maternal = 10.1 (10.4) µg/dL Mean paternal = 12.9 (13.8) µg/dL Timing of maternal sample not reported	Preterm births, low birth weight, small for gestational age	Simple linear regression models; generalized linear models with binomial distribution and logit link function. Parental age, parental education, parity, and gender of the infant.	Risk ratios (95% CI) for preterm delivery: Maternal blood Pb (µg/dL) (*p*=0.06 for trend) <10 = (reference) 10 – 19 = 1.97 (0.92, 3.86) ≥ 20 = 1.86 (0.68, 4.28) Paternal blood Pb (µg/dL) (*p*=0.30 for trend) <10 = (reference) 10 – 19 = 1.17 (0.53, 2.32) ≥ 20 = 0.55 (0.19, 1.28)	Maternal and paternal blood Pb were not associated with preterm birth.
Prospective cohort Dietrich (1987) Cincinnati, USA *Also listed for birth weight* *Subset population of Bornschein (1989) and Shukla (1989)*	Cincinnati Pb study; 185 pregnant mothers recruited at prenatal clinic from high-Pb neighborhood; Years= 1980-1985	Not stated	Maternal 8.3 (3.8) Infant 10 day 4.9 (3.3) 3 month 6.3 (3.8) 6 month 8.1 (5.2) Maternal Pb sampled at first prenatal visit	Birth weight, gestational age, neural effects data	Multiple regression models Adjustments not described for gestational age data.	Correlation of blood Pb with gestational age: **Maternal Pb r=-.17; p<0.05** Infant 10-day Pb r=-.08; p>0.05 Note: this population is subset of *Bornschein (1989) study which did not find an association between blood Pb and gestational age. And the Dietrich (1987) study was designed to investigate neurological effects, not gestational age.* *Neurological data reported elsewhere*	Maternal blood Pb was associated with gestational age, not infant blood Pb; however results were not significant in full study reported in Bornschein (1989)
Prospective Factor-Litvak (1991) Kosovo, Yugoslavia *Also listed for birth weight* *Same population as Murphy (1990), Loiacono (1992), Factor-Litvak (1999), Lamb (2008)*	907 women recruited at mid-pregnancy: 401 lived in an area with high environmental Pb (exposed) and 506 lived in an area with low Pb exposure (referent); Years= 1985-1986	[Ages not stated]	At mid-pregnancy: Exposed = 19.0(7.9) Referent = 5.4(2.07) At delivery: Exposed = 23.4(7.7) Referent = 6.8(4.1) Cord blood: Exposed = 22.1(8.5) Referent = 5.6(3.5)	Length of gestation, birth weight	Ordinary least squares regression analysis and maximum likelihood logistic regression analysis. Maternal age, ethnic group, cigarette smoking during pregnancy, maternal education, maternal height, parity, and gender of infant.	Regression Coefficient (95% CI) relating blood Pb level to length of gestation: Maternal Pb, mid-pregnancy = 0.1 (-2.7, 2.9) Maternal Pb at delivery = -0.5 (-2.9, 1.9) Cord Pb= -0.4 (-2.7, 1.9) Odds ratio (95% CI) for preterm delivery by blood Pb for combined population (living in the Pb-exposed town of Titova Mitrovica, a Pb smelter town, and referent town of Pristina): OR = 0.99 (per µmol/L) (0.97-1.01)	Maternal blood Pb and cord blood Pb were not associated with length of gestation or preterm birth.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Case-control Fagher (1993) Bialystok, Poland and Lund, Sweden	Women (depending on measurement) from two populations (Lund and Bialystok) delivering by cesarean due to presenting with breech birth (n=30 total; n=17 preterm, case; n=13 control); Year not stated	27(5.4) Swedish and Polish combined	Maternal: Normal: 3.37 (1.88) Preterm birth: 3.16 (1.94) Maternal blood sampled at delivery	Preterm birth, placental Pb, myometrial Pb	Mann-Whitney signed rank test, linear regression analysis Adjustments not described.	**Cross-Sectional: Correlation between maternal blood Pb and gestational age: r=0.61; p<0.01** Case-Control: Pb concentration by preterm or normal birth: Normal – maternal Pb 3.37 (1.88) Normal - myometrium Pb µg/g 0.2(0.1) Normal - placenta Pb µg/g 0.2 (0.2) Preterm – maternal Pb 3.16 (1.94); p=0.59 Preterm - myometrium Pb µg/g 0.2(0.2); p=0.11 Preterm - placenta Pb µg/g 0.3 (0.2);p=0.72	Maternal blood Pb was associated with gestational age.
Cross-sectional Fahim (1976) Missouri, USA;	502 pregnant women; n= 253 from Rolla, Missouri - a city 30-50 miles west of the Pb belt area (exposed); n= 249 from Columbia, Missouri (referents); Year not stated	20-25 years old	Cord Blood: Exposed = 12.0 (SE=0.18) µg/100 g Referents = 11.0 (SE=0.34) µg/100 g Maternal blood sampled at delivery. Means reported by birth outcome. Overall mean not reported.	Incidence of preterm birth, PROM, histopathology of placenta, cord, and membrane	Statistical methods not described Adjustments not described.	Maternal blood Pb Referent full term birth = 13.1 (SE=0.31) **Referent preterm birth = 26.0 (SE=0.84);*p*<0.001** Exposed full term birth = 14.3 (SE=0.16) **Exposed preterm birth= 29.1 (SE=0.54); *p*<0.001** Cord blood Pb: Referent full term birth = 4.3 (SE=0.10) **Referent preterm birth = 9.6 (SE=0.74); *p*<0.001** Exposed full term birth = 4.6 (SE=0.08) **Exposed preterm birth = 17.9 (SE=1.06); *p*<0.001** Maternal and cord Pb levels were higher in PRoM pregnancies (p<0.001). Tissue Pb concentration in placenta or cord did not differ between preterm and full term births.	Maternal and cord blood Pb levels were higher in preterm births than full term births.
Cross-sectional Falcón (2003) Murcia, Spain	81 women who had given birth to healthy singleton babies (n=10 preterm and n= 71 full-term, n=8 PROM); Year not stated	Mean maternal age = 28.1 – 28.8 years.	Placental Pb: 113.4 (58.0) µg/g dry tissue ** lack of blood Pb data limits utility	Preterm birth, premature rupture of membranes (PROM)	Mann-Whitney test; Chi square test; Spearman's coefficient; simple and multiple linear regression Maternal age, cigarettes/day, parity, residual place (urban/rural).	Mean placental Pb ng/g: Normal delivery 103 (50)ng/g **Preterm delivery and PROM 154 (72) ng/g; p=0.004** 1.4 % of the normal births had placental Pb > 120 µg/g dry tissue, while 90% of the preterm births had placenta Pb levels > 120 µg/g dry tissue. Comparison to blood Pb not reported.	Placentas from preterm births and PROMs had higher Pb levels than placentas from normal births; comparison to blood Pb not reported.
Cross-sectional Huel (1981) France *Also listed for birth weight*	100 mother-infant pairs in Haguenau Maternity, an area with metallurgical factories ; Year= 1978	25.4 (5.1)	No blood Pb data Exposure from hair samples ** lack of blood Pb data limits utility	Birth weight, gestational age, also Cd	t test, ANOVA, Chi-square test Sex, gestational period, mothers weight	Hair Pb for preterm births relative to normal births: **Preterm birth maternal hair Pb 15.5 ppm; p<0.05** Normal maternal hair Pb 8.1 ppm **Preterm newborn hair Pb 15.7 ppm; p<0.05** Normal newborn hair Pb 6.6 ppm	Maternal and newborn hair Pb was associated with preterm birth.
Cross sectional Irgens (1998) Norway	Births in Norway with possible parental	Not reported	No blood Pb data Exposure determined by occupation	Low birth weight, stillbirths,	Logistic regression Maternal age, education,	Prevalence of preterm birth with occupational Pb exposure compared to reference for: Maternal exposure:	Maternal occupational Pb exposure was

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Also listed for birth weight	occupational Pb exposure (exposed n=1,803 maternal; n=35,930 paternal); Years=1970-1993		** lack of blood Pb data limits utility	preterm births, serious birth defects	gestational age	All Pb exposure levels OR=1.13 (0.98, 1.29) High Pb OR=1.93 (1.09,3.28) Low Pb OR=1.10 (0.95,1.26) **Dose-response relationship p<0.008** Paternal exposure: All Pb exposure levels OR=0.89 (0.86,0.93) High Pb OR=0.90 (0.78,1.03) Low Pb OR=0.89 (0.86,0.93)	associated with preterm birth. Paternal occupational Pb exposure was negatively associated with preterm birth.
Cross-sectional Jones (2010) Memphis, Tennessee *Also listed for birth weight*	102 mother-infant pairs in Memphis; Year=2006; Male=47%	Mother age range 16-45	Cord = 2.4 (4.3) Geometric mean Cord = 1.3	Gestational age, low birth weight, cord concentration of Mn, Cr, Cu	Spearman correlation, logistic regression	Geometric mean cord Pb (95%CI) by gestational age at delivery: Term = 1.2 (1.0, 1.5)µg/dL Preterm = 1.4 (0.8, 2.6) µg/dL Post-term =1.3 (0.7,2.2)µg/dL ; p>0.1	Cord Pb was not different between term and preterm births.
Retrospective cohort Jelliffe-Pawlowski (2006) California, USA *Also listed for birth weight*	262 mother-infant pairs from California Pb surveillance program; Years= 1996-2002	85% <35	[not stated] Maternal blood sampled during pregnancy	Preterm births, low birth weight, small for gestational age	ANOVA, crude and adjusted linear regression models. Maternal age and race, prior parity, infant sex, public or private insurance (as an assessment of poverty).	Linear regression analysis for blood Pb level and total days of gestation: Blood Pb < 10 µg/dL R^2 = 0.211; Regression coefficient = 0.3 Blood Pb ≥ 10 µg/dL **R^2 = 0.224; Regression coeff. = -0.3; *p*<0.05** Linear regression analysis for max-Pb level in 1st trimester and total days of gestation: Pb<10µg/dL R^2 = 0.264; Regression coef.= 0.5 Pb≥10µg/dL R^2 = 0.217; Reg. coef. = -1.2; *p*>0.05 2nd trimester and total days of gestation: Pb<10µg/dL R^2 = 0.229; Regression coef.= -0.1 **Pb≥10µg/dL R^2 = 0.649; Reg. coef. = -1.0; *p*<0.01** 3rd trimester and total days of gestation: Pb<10µg/dL R^2 = 0.206; Regression coef.= 1.2 **Pb≥10µg/dL R^2 = 0.226; Reg. coef. = -0.2; *p*<0.05** Adjusted Odds Ratio for preterm birth: Blood Pb < 10 µg/dL (reference) **Blood Pb ≥ 10 µg/dL = 3.2 (1.2, 7.4) (*p*<0.5)**	Maternal blood Pb ≥10 µg/dL was associated with preterm birth, particularly for maternal Pb during the 2nd and 3rd trimesters.
Retrospective Kristensen (1993) Oslo, Norway *Also listed for stillbirth and other endpoints*	6,251 births to male members of printers' unions in Oslo, Norway (n=387 preterm births); Years= 1930 and 1974	Not reported	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Low birth weight, late abortions, stillbirths, preterm births	Logistic regression Birth order, sex, twin birth, fathers occupational status, year of birth, maternal age	Preterm birth OR for paternal occupational Pb exposure compared to "other" exposures: OR (95%CI) =2.0 (0.5,8.7)	Fathers exposure to Pb by occupation was not associated with preterm delivery.
Retrospective Laudanski (1991) Suwalki Poland *Also listed for*	136 women from areas with high levels of Pb in the soil compared to 269 women from	Age Range = 17 – 75 yrs.	Current blood Exposed = 6.75 (6.53) Referent = 6.21 (3.36)	Incidence of stillbirths, spontaneous abortion, preterm labor,	Chi-squared, one- and two-tailed *t*-tests Adjustments not described.	Pregnancies resulting in preterm labor by pregnancy order: Exposed group 1st pregnancy 5.4% Exposed group 2nd pregnancy 0.7% Referent group 1st pregnancy 5%	Incidence of preterm labor and current blood Pb levels did not differ

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
abortion	nearby villages with normal levels of Pb in the soil; [Years not stated]		[question of units as blood Pb is reported both as 6.7ug/l and 675ug/dL which is 10x instead of 1/10x] ** lack of blood Pb difference limit utility	and maternal blood pressure, blood Cd		Referent group 2nd pregnancy 0 Exposed population had higher blood levels of cadmium (p=0.03).	between residents of two towns that differ in soil Pb levels.
Prospective Loiacono (1992) Kosovo, Yugoslavia *Also listed for birth weight* *Same population as Murphy (1990), Factor-Litvak (1991, 1999), Lamb (2008)*	161 women recruited at mid-pregnancy; 106 lived in an area with environmental Pb (exposed) and 55 lived in an area without significant Pb (referents); Years= 1985-1986	Expose=26.8(5) Referent=27(5)	Maternal at delivery Exposed=21.7 (6.8) Referent=5.2 (1.7) Cord Exposed =20.3 (7.7) Referent=5.6 (3.9)	Birth weight, gestational age, placental Pb, and placental Cd	Least squares multiple regression Maternal age, ethnic group, cigarette smoking during pregnancy, maternal education, maternal height, parity, maternal blood Pb, and gender of infant.	Regression Coefficient (95% CI) relating placental Pb (per nmol/g) Pb level to length of gestation: 0.05 days (-0.001, 0.10) Placental Pb: Pb-exposed town of Titova Mitrovica, a Pb smelter town, and referent town of Pristina 69.3 (71.4) nmol/g Referent town of Pristina 21.6 (18.5) nmol/g	Placental Pb was not associated with gestation length; potential association with blood Pb reported elsewhere.
Retrospective cohort Lin (1998) New York, USA *Also listed for birth weight*	3006 births to male workers on the New York State Heavy Metals Registry (exposed n=747); the referent group was a random sample of bus drivers (n=2259); Years= 1981-1992	Age range = 20 – 55 yr.	Exposed = 37.2 (11) µg/dL [Referent not stated]	Birth weight and gestational age	Chi-square tests, crude risk ratios, adjusted risk ratios using an unconditional logistic regression model. Paternal age, race, maternal education, parity, maternal perinatal complications, previous spontaneous abortion history, gender, prenatal care	Relative risk(95% CI) of preterm birth for all paternal Pb exposure (>25µg/dL): RR=0.89 (0.64,1.26) Relative risk(95% CI) of preterm birth for paternal Pb exposure (>25µg/dL) >5 years: **RR=3.03 (1.35,6.77)**	Paternal occupational exposure >25µg/dL for more than 5 years was associated with preterm birth.
Prospective McMichael (1986) Port Pirie, South Australia *Also listed for abortion and other endpoints*	730 pregnant women: 557 from the Pb smelting town of Port Pirie (exposed) and 173 from surrounding towns (referent); Years= 1979-1982	Age range = 14 – 36 yr.	Maternal blood (SE) measured at delivery Exposed: 11.2 (0.21) Referent:7.5 (0.25)	Pregnancy outcome including pre-term delivery, stillbirths (late term fetal deaths) birth weight, IUGR, PROM, and congenital abnormalities	Multiple logistic regression techniques Adjustments not described. Effect of age, gravidity, social status, occupation, and smoking were examined separately.	Estimates of relative risk of preterm delivery by blood Pb levels RR(95% CI): ≤ 8 µg/dL (reference) > 8 ≤ 11 µg/dL = 2.1 (0.6, 7.6) >11 ≤ 14 µg/dL = 3.0 (0.8, 11.3) **> 14 µg/dL = 4.4 (1.2, 16.8)** Exclusion of late fetal deaths increased relative risk estimates (2.1 to 2.7; 3.0 to 6.1; 4.4 to 8.7). Age of woman, gravidity, social status, occupation, smoking were not associated with relative risk of preterm delivery. No other pregnancy outcomes were statistically significantly related to blood Pb.	Maternal blood Pb >14µg/dL was associated with increased relative risk of preterm delivery.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Case-control Min (1996) Maryland, Virginia, and DC USA *Also listed for birth weight*	742 births from the Baltimore-Washington Infant Study: (n=220 cases low birth weight or LBW), (n=522 controls). Years= 1981-1989	Not stated	No blood Pb data Paternal exposure was estimated from the jobs held during the six months before or during the pregnancy ** lack of individual blood Pb data limits utility	Preterm birth, birth weight, small for gestational age (SGA)	Chi-square tests, logistic regression Adjustments differ by endpoint and include: race, marital status, maternal education, paternal education, maternal/paternal employment, household income, maternal height, pregnancy weight gain, smoking, previous pregnancy outcomes	Association between preterm SGA cases (LBW) with intensity of paternal occupational exposure intensity (xTLV) to Pb: ≤ 0.1 – OR = 0.24 (0.01, 4.90) **≥0.1 – OR = 2.4 (1.92, 3.11)** Association between preterm normal (non-SGA) cases (LBW) with intensity of paternal occupational exposure intensity (xTLV) to Pb: ≤ 0.1 – OR = 0.69 (0.31, 1.52) ≥0.1 – OR = 2.08 (0.66, 6.52) Statistics for preterm birth were presented as modifier for other analyses such as SGA above, not presented directly.	Paternal Pb exposure was associated with preterm SGA cases not normal births; study did not directly report effect of paternal occupational exposure to Pb by job category on preterm birth.
Cross-sectional Moore (1982) Glasgow, UK *Also listed for birth weight*	236 pregnant women; Year= enrolled in 1977	Range 17-37	Geometric mean Maternal =14.5µg/dL Cord=12.6µg/dL Timing of maternal sample not reported	Birth weight, gestation length	Multiple regression Adjustments not described.	Multiple regression between blood Pb and gestation length: **Maternal Pb regression coefficient -0.056; p<0.01** **Cord Pb regression coefficient -0.047; p<0.05**	Maternal and cord blood Pb were associated with gestational age.
Cross-sectional Needleman (1984) Boston, USA *Also listed for birth weight and malformations* *Data re-analyzed by Bellinger (1991)*	4354 births at Boston Hospital for women; Years= 1979-1980	Not reported	Not reported	Birth weight, gestational age, malformations	Chi-square test, logistic regression Maternal age, gestation age, birth weight, race	Authors state cord blood Pb was not associated with gestation length tested by chi-square test.	Cord blood Pb was not associated with gestational age.
Cross-sectional Odland (1999) Norway and Russia *Also listed for birth weight*	262 mother-infant pairs from hospital delivery in Russian and Norwegian arctic and subarctic areas; Years= 1993-1994	Russia = 25.0 Norway = 28.2	Median Maternal blood: Russia: 2.9 Norway: 1.24 Cord blood: Russia: 2.07 Norway: 1.04 Timing of maternal sample not reported	Birth weight, birth length, gestational age, blood Cd	Univariate and multivariate linear regression analyses; t test and ANOVA. Maternal BMI, age, smoking, country and gestational age.	Pregnancy outcome by population (mean and SD): Gestational age Russian 38.6 (2)wks **Gestational age Norwegian 39.7(1.4)wks; p<0.001** Median Pb concentrations: **Maternal – Russian = 2.9** **Maternal – Norwegian = 1.24; p<0.001** **Cord – Russian = 2.07** **Cord – Norwegian = 1.04; p<0.001** Authors do not present results of multivariate regression analysis for gestational age although results for birth weight are presented for combined Russians/Norwegians. ** lack of analyses by Pb for combined population limits utility	Gestational age differ between two populations with different blood Pb levels.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Patel (2009) Nagpur, India *Also listed for birth weight*	205 consecutive births at hospital in Nagpur; Year not stated; Male=56%	Maternal age not reported	Total Cord=4.7(12.1) Maternal-cord (n=62) matched samples Maternal = 2.0 (2) Cord =1.6(2.5) Maternal blood at birth	Gestational age, birth weight, head circumference	Univariate and multivariate linear regression Adjustments not described.	Univariate regression of mean gestational age by cord blood: ≤5µg/dL = 39.1 (2.0) weeks **>5µg/dL = 38.1 (2.0) weeks; p=0.014** Authors state by multivariate regression – gestational age reduced by a week for every 1µg/dL increase in cord Pb; analysis by maternal blood not reported.	Cord blood Pb was associated with decreased gestational age.
Cross-sectional Rajegowda (1972) New York, USA *Also listed for birth weight*	100 infants randomly selected from births (apparently at Harlem Hospital) to resident mothers of New York City; Years not stated	15 to 37 Median=23	Cord blood 10µg/dL=60% 20µg/dL=34% 30µg/dL=6%	Birth weight and gestational age	Statistical methods not reported Adjustments not described.	Authors state no correlation between cord blood Pb and gestational age.	Cord blood Pb was not associated with gestational age.
Cross-sectional Satin (1991) California, USA *Also listed for birth weight*	723 live births in five cities in California; Year=1984	26.4 yr.	Cord blood 4.9 µg/dL	Birth weight, preterm birth (<260 days)	One-way ANOVA Ethnicity and sex of infant.	Mean (SE) cord blood Pb by gestational length: Normal ≥260 days 4.7 (0.135)µg/dL **Preterm <260 days 6.5 (1.004) µg/dL; p=0.007** A cord blood Pb >5 µg/dL (study median) had a RR (95%CI) for preterm birth of 2.9 (0.9, 9.2).	Cord blood Pb was associated with preterm birth.
Retrospective case-control Savitz (1989) *Also listed for stillbirth*	National Natality and Fetal Mortality survey in US (case n=363 mothers and n=552 fathers); Year=1980	Not reported	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Incidence of stillbirths, preterm deliveries, and small-for gestational age	Multiple logistic regression Stratified analysis, child's race, maternal smoking	Odds ratio (95% CI) for preterm birth by parental employment with Pb exposure: Maternal exposure OR = 2.3 (0.7, 7.0) Paternal exposure OR=1.0 (0.6,1.7)	Parental Pb exposure by occupation was not associated with preterm birth.
Prospective and Cross-sectional Sowers (2002) Camden, New Jersey *Also listed for birth weight*	705 pregnant women at clinics in Camden; Years not stated	20.5 (SE=0.2)	Maternal blood Pb 12 weeks:1.2 (0.03) 20 weeks:1.08(0.05) 28 weeks:1.10(0.03) Birth:1.32(0.03)	Preterm birth, birth weight, small for gestational age (SGA), low birth weight (LBW)	Univariate analysis, longitudinal regression analyses Age, dietary calcium, race/ethnicity	Authors state no significant association between maternal Pb and preterm delivery or small for gestational age	Maternal blood Pb was not associated with preterm birth.
Case-control and Cross-sectional Torres-Sanchez (1999) Mexico City, Mexico *Population may overlap with Borja-Aburto (1999) and others*	459 full-term births (control) compared to 161 preterm births (case) at public hospitals in Mexico City; Year= 1995	Age15-19 Case-17% Control -17% Age20-29 Case-64% Control-64% Age 30-34 Case-14% Control-14%	Overall mean not stated Cord blood (µg/dL) of primiparous women: Case = 9.77(2) Control= 8.24(2.15)	Birth weight, preterm birth, intrauterine growth retardation	Chi-square and Student's *t* test, multivariate logistic regression Adjustments differ by endpoint, including parity, cigarette smoking, prepregnancy weight, and marital status	Case-control Cord blood (µg/dL) of primiparous women: Control= 8.24(2.15) Case = 9.77(2), p=0.051 Cross-sectional OR (95% CI) for preterm birth by cord blood Pb: Primiparous women < 5.1 µg/dL (reference) **5.1 – 9.0 µg/dL = 2.72 (1.03, 7.19)** **9.1 – 14.9 µg/dL = 2.82 (1.13, 7.02)** **> 14.9 µg/dL = 2.60 (1.01, 6.71)**	Cord blood Pb was associated with preterm birth for the 1st pregnancy, but not for later pregnancies.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Multiparous women < 5.1 µg/dL (reference) 5.1 – 9.0 µg/dL = 0.48 (0.21, 1.08) 9.1 – 14.9 µg/dL = 1.12 (0.53, 2.36) > 14.9 µg/dL = 0.86 (0.41, 1.84)	
Prospective Vigeh (2011) Tehran, Iran *Also associated with abortion Vigeh (2010)*	348 pregnant women recruited during first trimester in Tehran; Year= 2006	25	3.8 (2.0) Range 1.0-20.5 Maternal blood Pb sampled during 1st trimester	Preterm birth, gestational age	t test, Chi-square test, Fisher exact test, Pearson's correlation coefficient, logistic regression Maternal age, sex, education, passive smoking, pregnancy weight gain, parity, haematocrit, and type of delivery	Mean blood Pb levels for term and preterm births: Normal (term) 3.72 (2.03) **Preterm 4.52 (1.68); p<0.05** Linear regression between maternal blood Pb and risk of **preterm labor: OR=1.41 (1.08, 1.84**). Correlation between maternal Pb (values <10µg/dL) and **gestational age at delivery r=-0.15; p=0.011**	Maternal blood Pb was associated with preterm birth and gestational age.
Cross-sectional Ward (1987) England *Also listed for birth weight*	100 normal births at Barnsley hospital Year=1980	Not reported	No blood Pb data ** lack of blood Pb data limits utility	Birth weight, gestational age, head circumference, placental Pb	Statistical methods not described. Adjustments not described.	Correlation between placental Pb and: Gestational age p>0.05 Comparison by blood Pb not reported.	Placental Pb was not correlated with gestational age.
Cross-sectional *Ward (1990)* England *Also listed for birth weight*	79 live births from Merseyside/ Blackpool; Years=1980-1981	Not reported	No blood Pb data ** lack of blood Pb data limits utility	Birth weight, gestational age, head circumference, placental Pb	Statistical methods not described. Adjustments not described.	Correlation between placental Pb and: Birth weight r=-0.74; p<0.001 **Gestational age r=-0.56; p<0.001** Head circumference r=-0.62;p<0.001 Comparison by blood Pb not reported.	Placental Pb was correlated with decreased gestational age
Retrospective cohort Zhu (2010) New York *Also listed for birth weight*	43,288 mother-infant pairs from New York State Heavy Metals Registry with blood Pb≤10µg/dL; Years=2003-2005	15-49	Maternal 2.1 (SD not reported) Sampled before or at birth	Preterm birth, birth weight, small for gestational age	Multiple regression analysis Adjustments differ by endpoint including: timing of Pb test, maternal age, race/ ethnicity, smoking, drug abuse, in wedlock, participation in financial assistance, parity, sex	Association between maternal Pb and preterm birth OR (95% CI): ≤1.0 (reference) 1.1-2.0 OR=1.03 (0.93,1.13) 2.1-3.0 OR=1.01 (0.92, 1.10) 3.1-9.9 OR=1.04 (0.89, 1.22)	Maternal blood Pb was not associated with preterm birth.
Repro: Endocrine Effects							
Cross-sectional Abdelouahab (2008) Quebec, Canada	211 people who regularly eat freshwater fish in Quebec; Year=2003; Male=59%	Men = 51.5 Women = 47	By percentile Men: 25th = 2.42 50th = 3.10 75th = 4.20 Women: 25th = 1.23 50th = 1.74 75th = 2.61	Serum TSH, T_3, T_4, organo-chlorines (16 PCB congeners, and 17 OCPs), plasma lipids, blood metals (Hg, Pb, Se)	Multiple regression analyses Adjustments differ by endpoint and included: age, smoking status, Se, plasma lipids, pesticide exposure, corticoid medication, occupational exposure to metals, alcohol consumption, and oestro-progestative hormone intake in women	Multiple regression analyses for blood Pb (β): T_3 men β = 0.12 T_3 women β = 0.15; p<0.1 T_4 men β = -1.93 T_4 women β = -0.36 TSH men β = -0.05 **TSH women β = -0.32; p<0.05** Authors state blood Pb was associated with fish consumption for men (r^2=0.06; p=0.005) not women. T_3 was negatively related to several PCBs in women; T_4 was negatively related to several PCBs in men. TSH was associated with Hg & several PCBs in men.	Blood Pb was negatively associated with TSH in women; not men and T_3, T_4 did not differ in men or women.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Retrospective Alexander (1996b) Trail, British Columbia *Same population as Schumacher (1998)* *Also listed for sperm*	152 male employees (n=119 who donated semen) of the Cominco smelter Years- employed as of 1992-1993; Male=100%	39.7	28.7	Sperm, sperm motility, T, FSH, LH	Least-square means regression model Adjustment listed for age and smoking status	Mean and percentage of FSH, LH, and T that differed from normal values did not differ by blood Pb.	Blood Pb levels were not associated with FSH, LH, or T.
Cross-sectional Assennato (1986) Italy *Also listed for sperm*	39 male employees at a Pb battery plant (high Pb) and 81 workers at a cement plant (referent); Year not stated	Pb=38 (10) Referent=37 (10)	Blood Pb High Pb= 61 (20) Referent= 18 (5) Semen Pb (ppb) High Pb= 79 (36) Referent= 22 (9)	Sperm count, T, PRL, FSH, LH	Pearson correlation, t test, Kolmogorov-Smirnov test, and chi-square test Adjustments not described. Effect of alcohol, cigarette, and coffee consumption, frequency of intercourse, and days of abstinence prior to semen donation examined separately.	Authors state serum FSH, LH, PRL, and T did not differ between Pb battery and cement workers.	Hormone levels did not differ between Pb and cement workers.
Cross-sectional Atabek (2007) Turkey *Also listed for birth weight*	54 infants from presumed high Pb level areas; Years not stated; Male=52%	Not reported	Cord = 14.4 (8.9)	IGF-1, birth weight, length, arm circumference	Linear regression models; Student's t test; Pearson correlation coefficients Gestational age, sex, socioeconomic status	Neonatal IGF-1 by cord blood Pb: <10µg/dL – IGF = 4.13 (4.5)ng/ml ≥10µg/dL – IGF = 4.09 (4.3)ng/ml; p>0.05 Authors report IGF-I was not correlated to cord blood Pb.	Cord blood Pb was not associated with IGF.
Cross-sectional Braunstein (1978) Location not stated *Also listed for sperm*	10 men with chronic high occupational Pb exposure (n=6 judged Pb-poisoned by symptoms; n= 4 exposed without symptoms) and 9 referents; Years not stated	Not reported	Referent= 16.1 (1.7) Poisoned=38.7(3) Exposed=29(5)	FSH, LH, T, E_2, PRL	t test Adjustments not described.	Basal concentrations of testosterone: Referent = 924 (100) ng/dL **Pb-poisoned = 371 (65); p<0.01** **Pb-exposed = 532 (23); p<0.05** Authors state basal concentrations of E_2, LH, FSH, and PRL did not differ between groups. **Authors state GnRH-stimulated LH, clomiphene-stimulated E_2, and hCG-stimulated T were reduced in the Pb-poisoned men**.	Occupational Pb exposure was associated with reduced T and reductions in stimulated levels of T, E_2, and LH.
Case-control Chang (2006) Kaohsiung, Taiwan Also listed for fertility	64 women recruited at an infertility clinic (case); and 83 control women from postpartum clinic in Kaohsiung; Years=1999-2001	Maternal Case = 31.2 (3) Control=32.6(4)	Maternal Case = 3.55 (1.39) Control = 2.78 (2) Paternal Case = 4.79 (1.5) Control = 3.23 (2.3) Pb measured in cases when other data collected; measured in controls 1-2 years after pregnancy	Infertility, Serum FSH, LH, E_2, P_4	t test, multivariate logistic regression analysis Age, BMI, smoking, western medicine use, herbal medicine use, irregular menstruation	Regression model to predict serum estradiol β (SE): Cases/control β = 1.67 (2.22); p=0.481 **Blood Pb (µg/dL) β=1.18 (0.60); p=0.049** **LH (mIU/ml) β=1.15 (0.48); p=0.017** FSH, P4, and age were not significant E_2 predictors Mean serum hormone level by infertility (case/control): LH (mIU/ml)- case = 4.47 (2.75) LH (mIU/ml)-control = 4.38 (2.00); p = 0.813 FSH (mIU/ml)- case = 6.64 (1.88) FSH (mIU/ml)-control = 7.13 (2.05); p = 0.135 E_2 (pg/ml)- case = 30.4 (13.74)	Blood Pb levels was a significant predictor of serum estradiol levels.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						E_2 (pg/ml)-control = 27.5 (12.65); p = 0.181 P_4 (ng/ml)- case = 0.43 (0.20) P_4 (ng/ml)-control = 0.44 (0.19); p = 0.692	
Case reports Cullen (1984) New Haven, Connecticut *Also listed for sperm*	7 men with occupational Pb intoxication referred to Yale Occupational Medicine Clinic; Years not stated	35	73 (19)	Plasma T_4, TBG, T_3, TSH, FSH, LH, PRL, T, free T, urinary cortisol, sperm count, motility, morphology, semen volume	Observational study, comparisons made to reference values. Statistical methods not utilized. * small sample size and observational nature limits utility of study	Authors list the following observations for the 7: FSH was elevated in both azoospermaic men 6 men had subnormal glucocorticoid production 2 men had subnormal T_4 Authors state that T, PRL and other hormonal measures were normal.	Some of the 7 observed men with occupational Pb intoxication had altered FSH, T_4, or glucocorticoids.
Cross-sectional De Rosa (2003) Location not stated, authors work in Naples Italy *Also listed for sperm and fertility*	85 men working at a tollgate (exposed) and 85 reference men recruited from clerks, drivers, students and doctors; Year 2000-2002	Range 23-62 Exposed = 38.6 Referent= 39.6	Exposed=20(SE=0.6) Referent=7.4(SE=0.5)	Time to pregnancy, sperm parameters, serum FSH, LH, T, air levels of CO, NO, SO, Pb, Zn, Met-, Sulp-, and Carboxy-haemaglobin	Linear regression, t test, chi-square, Pearson correlation Adjustments not described.	Pb and hormone levels by exposure group (SE): Blood Pb – referent = 7.4 (0.5) **Blood Pb – exposed = 20.1 (0.6); p<0.0001** FSH (IU/l)-referent =3.2(0.2) **FSH (IU/l)-exposed =4.1(0.3); p<0.05** LH (IU/l)-referent =2.8(0.1) LH (IU/l)-exposed =2.8(0.2); p>0.05 T (µg/L) – referent =4.7(0.2) T (µg/L) – exposed = 4.8(0.2); p>0.05 Methaemaglobin, sulphaemaglobin, Zn-protoporphyrin, and air levels of NO, SO, CO, and Pb were all significantly higher in the study group.	Serum FSH was elevated in exposed men (20µg/dL blood Pb) relative to referents with lower blood Pb; not LH or T.
Cross-sectional Erfurth (2001) Sweden	77 male Pb workers (62 active and 15 retired) and 26 referents without occupational Pb exposure; Years not stated	Median = 43	Median Pb levels Blood Pb-worker=31.1 Referent = 4.1 Plasma Pb-worker=0.13 Referent =0.03 Urine (µg/g creat.) Pb-worker=19.6 Referent =3.9 Bone(µg/g) Pb-worker=25 Referent =2	Serum TSH, T_3, T_4, T, SHBG, cortisol, and GnRH-stimulated FSH, LH, PRL, urinary Pb, finger bone Pb, plasma Pb	Mann-Whitney U, Spearman rank, linear regression analysis age	Basal concentrations of TSH, FSH, LH, PRL, T, cortisol, TSH, T_3, T_4, SHBG did not differ between Pb workers and referents. Median GnRH stimulated TSH, LH, FSH, PRL **FSH - Referents = 162** **FSH - Pb workers =77; p=0.014** LH - Referents = 858 LH - Pb workers =587; p=0.12 TSH - Referents = 336 TSH - Pb workers =335; p>0.2 PRL - Referents =618 PRL - Pb workers =475;>0.2	GnRH-stimulated FSH was decreased in Pb-workers relative to referents with lower blood Pb; not basal T, cortisol, SHBG, T_3, T_4, TSH,LH, PRL, FSH, or stimulated LH, TSH, PRL.
Cross-sectional Gennart (1992a) Belgium	Male Pb battery factory workers (n=98 high Pb) and (n=85 referent) finish workers from same factory, maintenance, and chemical factory; Years not stated	Referent=39 (9) Exposed=38(8)	Referent=20.9(11) Exposed 51(8)	TSH, T_3, T_4, FSH, LH, creatinine and renal measures, Hg, and electro-cardiogram data	Statistical methods not described. Adjustments not described.	TSH, T_3, T_4, FSH, and LH did not differ between occupationally Pb-exposed workers and referent workers.	Hormone levels did not differ between Pb workers and referent workers.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Cross-sectional Gollenberg (2010) US *Same population as Selevan (2003) and Wu (2003)* *Also for puberty*	Girls aged 6-11 in NHANES III (n=705 girls with exposure inhibin B, and LH data); Male=0%	6-11	Median 2.5 (range 0.07-29.4)	Inhibin B, LH, Tanner stage of breast development stage, Tanner pubic-hair stage, urinary Cd, blood iron	Chi-square, ANOVA, logistic regression BMI, race/ethnicity, census region, poverty-income ratio (PIR), age	Effect of blood Pb and urinary Cd on inhibin B: Pb <5μg/dL and low Cd reference Pb <5 / high Cd β=0.17 (-0.15, 0.50);p=0.29 **Pb ≥5 / low Cd β= -0.35 (-0.13, -0.56);p=0.002** **Pb ≥5 / high Cd β= -0.52 (-0.07, -0.97);p=0.02** Effect of blood Pb and blood iron on inhibin B: Pb <1μg/dL and Iron sufficient reference Pb <1 / OK Iron β= -0.11 (0.32, -0.53);p=0.61 **Pb ≥1 / OK Iron β= -0.39 (-0.06, -0.71);p=0.02** **Pb ≥1 / low Iron β= -0.84 (-0.37, -1.31);p=0.008**	Girls with higher blood Pb had lower inhibin B levels; Cd and iron levels affected the relationship between blood Pb and inhibin.
Prospective Gump (2008) Oswego, NY	169 children in Oswego Children's Study; Male=46% ; Years not stated	9.5 years	Range: <1.0 – 6.3 Exposure measured at birth (umbilical cord) and postnatal at 2.6(1.2) years of age Outcome assessed within 2 weeks of 9.5 years of age	Salivary cortisol levels after acute cold stressor	Multiple regression; Specific adjustments not described, but regression listed as adjusted for covariates including demographics (parental height/weight, SES, maternal IQ, HOME score, etc.), indicators of pregnancy health, infant characteristics (head circumference, birth weight, gestational age), cigarette, drug use	Adjusting for covariates, and using a test for linear contrast across Pb quartiles for response to stress: Prenatal Pb not assoc. with initial cortisol (p>0.05) **Prenatal Pb increased cortisol response (p<0.001)** Postnatal Pb not assoc. with initial cortisol(p>0.05) **Postnatal Pb increased cortisol resp. (p<0.005)** Adjusting for covariates, and using regression analyses for Pb as a continuous variable: **Prenatal Pb increased cortisol response at 21 min (p<0.005), 40 min (p<0.01), and 60 min (p<0.05)** **Postnatal Pb increased cortisol response at 21 min (p<0.05), 40 min (p<0.10), and 60 min (p<0.05)** Basal cortisol levels were not associated with Pb.	Cord blood Pb and postnatal blood Pb were associated with increased cortisol response to acute cold stressor.
Cross-sectional Gustafson (1989) Sweden	25 Pb workers (high Pb) in a secondary Pb smelter and 25 age-and sex-matched shift worker referents without occupational Pb exposure; Years not stated; Male=100%	Pb = 36 (10.4) Ref=36.8 (10.5)	Pb-workers=39(0.24) Referents=4.97(0.2)	Plasma LH, FSH, cortisol, PRL, T, Se, and serum TSH, T_3, and T_4, and free T	Wilcoxon matched-pairs signed ranks test, Spearman rank correlation	Mean values (SE) from Pb-workers and referents: Free T (pg/ml)-referents =26.8 (1.67) Free T (pg/ml)-Pb-workers =26.2 (1.72); p=0.8 Total (ng/ml)T-referents =6.2 (0.35) Total (ng/ml)T-Pb-workers = 6.1 (0.42); p=0.6 **FSH (U/L)-referents = 4.5 (0.37)** **FSH (U/L)-Pb-workers =3.6 (0.34); p=0.05** LH (U/L)-referents = 9.0 (0.34) LH (U/L)-Pb workers =8.4 (0.36); p=0.1 PRL (μg/L)-referents =3.5 (0.21) PRL (μg/L)-Pb-workers =3.8 (0.26); p=0.2 Cortisol (nmol/L)-referents = 346(24) Cortisol (nmol/L)-Pb workers = 314 (18); p=0.4 TSH (mU/L)-referents = 1.02 (0.13) TSH (mU/L)-Pb workers =1.23 (0.15); p=0.2 T_3 nmol/L)-referents =2.0 (0.7) T_3 (nmol/L)-Pb-workers =2.1 (2.8); p=0.2 T_4 (nmol/L)-referents =76 (2.9) T_4 (nmol/L)-Pb-workers =84 (2.8); p=0.06 Mean values from workers <40 years of age: **T_4 (nmol/L)-referents =73 (3.0)** **T_4 (nmol/L)-Pb-workers =88 (4.1); p=0.01**	Serum levels of FSH were decreased in Pb-workers relative to referents. Serum levels of LH, FSH, and cortisol were decreased and T_4 was increased in Pb-workers <40 relative to referents; T, PRL, TSH, and T_3 did not differ.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						FSH (U/L)-referents = 4.1 (0.54) **FSH (U/L)-Pb-workers =2.9 (0.28); p=0.03** **LH (U/L)-referents = 8.9 (0.37)** **LH (U/L)-Pb workers = 7.6 (0.32); p=0.04** **Cortisol (nmol/L)-referents = 382 (28)** **Cortisol (nmol/L)-Pb-workers = 295 (23); p=0.04**	
Cross-sectional Hsieh (2009) Taiwan	181 male Pb workers followed from 1991 to end of study; Year not stated	43.2 (8.7)	Not reported	FSH, LH, T, inhibin B	Pearson correlation, chi-square tests, t test, ANOVA, multiple regression analysis Age, smoking, drinking, LH, FSH, and T	Pearson correlation between blood Pb/inhibin B: **Cumulative Pb vs inhibin B = 0.220; p<0.003** **Time-weighted Pb vs inhibin B= 0.231; p<0.008** Association between blood Pb and inhibin B: **Cumulative Pb β = 0.05 (SE=0.02); p=0.017** **Time-weighted Pb β = 1.33 (SE=0.48); p=0.007** Current blood Pb β =0.400 (SE=0.474);p=0.40 FSH, LH, and T were not associated with Pb, but there was a negative relationship between FSH and inhibin B.	Cumulative blood Pb levels (but not current) were associated with increased inhibin B; not LH, FSH, or T.
Case-reports Huseman (1987) Omaha, Nebraska	2 girls in Omaha Nebraska with Pb intoxication; Year not stated; Male=0%	2	Before chelation treatment 92µg/dL 122µg/dL	Serum LH, FSH, T, E_2, PRL, cortisol, free T_4, free T_3, TSH, glucose	Student's t test Adjustments not described. * lack of study and statistical information and small sample size limits utility	Authors state serum release of TSH to 7µg/kg i.v. TRH was reduced in the 2 girls in six of seven challenges; **p<0.05** Basal PRL, FSH, and LH were elevated in patient 1 in five assays. Basal and free T_4 and T_3 and stimulated GH and cortisol response to L-dopa-insulin challenger were all in the normal range.	TSH response to TRH challenge was reduced in two girls with Pb intoxication; PRL, T_3, T_4, cortisol and LH were in normal range.
Case-series Huseman (1992) Omaha, Nebraska	Children with high blood Pb (≥40 µg/dL) examined before (n=12) and after chelation therapy (n=6)	Range 2-5	Range during high Pb= 41-72µg/dL Range during low Pb= 0-30µg/dL	Growth rate, TSH, PRL, IGF-I, GH, PRL, cortisol	Multiple linear regression, Student's t test Adjustments not described.	Growth rate: During high Pb period = 5.8 (SE=1) cm/year During lower Pb period = 11 (SE=2) cm/year Peak GH response to L-dopa insulin test: GH - high Pb period= 25(7)ng/ml GH - lower Pb period = 42(8)ng/ml Peak IGF-1 response to L-dopa insulin test: **IGF - high Pb period=0.4(0.01)µU/ml** **IGF - lower Pb period = 0.98(0.2)µU/ml; p<0.05** Correlation with Pb r=-0.68 N=2 to 12 per hormone sample Authors state basal PRL and TSH, T_3, and T_4, TRH-stimulated PRL and TSH, and cortisol response to insulin-induced hypoglycemia were not affected by blood Pb levels	IGF-1 response L-dopa challenge was reduced in children at high blood Pb levels relative to periods with lower blood Pb; PRL, TSH, T_3, T_4, and cortisol were in normal range.
Cross-sectional Iijima (2007) Tokyo, Japan	Cord blood from 24 pregnant women giving birth at a hospital in Tokyo;	newborns	6.3 (3.4) Reported as ng/g or ng/mL Metals from cord	Serum T_3, T_4, TSH, cord blood Cd, Se	Spearman rank correlation Adjustments not described.	Mean TSH = 2.5 (1.7) µU/ml Mean free T_4 = 2.3 (0.5) ng/dL Spearman Rank Correlation coefficient between cord blood Pb:	Cord blood Pb levels were not correlated to serum levels of

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
	Year=2005; % male of newborns not stated		blood. Thyroid hormones from heel prick 4-6 days postpartum			Free T_4= 0.263; p>0.05 TSH = 0.174; p>0.05 Authors state that TSH was negatively correlated to cord blood Cd levels.	T_3, T_4, or TSH
Cross-sectional Krieg (2007) USA	3385 women 35-60 in NHANES III; Years= 1988-1994	Range 35-60	Mean = 2.8 Geometric mean=2.2	Blood FSH and LH	Regression analyses Age, total bone mineral density, log serum cotinine, alcohol use, currently breastfeeding, hysterectomy, one ovary removed, Norplant use, radiation or chemotherapy, hormone pill use, vaginal cream use, hormone patch use	Slope (SE) for FSH and LH by log blood Pb by status: FSH (IU/L) **Post-menopausal slope= 22.2 (4.3); p=0.0000** Pregnant slope =0.1(0.1); p=0.24 Menstruating slope =2.1(2.1); p=0.33 **Both ovaries removed slope =8.3(2.2); p=0.0054** **Birth control pills slope =-6.3 (1.9); p=0.0015** **Pre-menopausal slope=8.3(2.2); p=0.0006** FH (IU/L) **Post-menopausal slope= 6.2(1.6); p=0.0003** Pregnant slope =-0.8(0.6); p=0.19 Menstruating slope =-0.3(0.8); p=0.75 **Both ovaries removed slope =10.0(4.4); p=0.03** Birth control pills slope =-0.6 (1.1); p=0.56 Pre-menopausal slope=1.7(1.2); p=0.15	Serum FSH was decreased with blood Pb in women taking birth control pills, and increased in other women except pregnant or menstruating. LH was increased with increasing Pb in post-menopausal women and unchanged in others.
Prospective Lamb (2008) Kosovo, Yugoslavia *Same population as Murphy (1990), Factor-Litvak (1991, 1999)* *Also for growth*	309 children assessed at birth, 1, 4, 6.5, and 10 years of age; 161 women recruited at mid-pregnancy; 106 lived in an area with environmental Pb (exposed) and 55 lived in an area without significant Pb (referents); % male not stated; Years not stated	Children assessed at birth, 1, 4, 6.5, and 10 years of age plus or minus 3 months	Median Pb smelter town = 20.2 (7.4) Median referent = 5.6µg/dL (2.0)	maternal free T_4, maternal TSH, child height, weight, BMI	Linear regression analysis Sex, ethnicity, parity, maternal height, maternal education, gestational age at delivery, gestational age at blood sample, HOMES score	Effect of living in the Pb-exposed (Titova Mitrovica a Pb smelter town) and referent (Pristina) areas on the relationship between maternal T_4, TSH and growth: Estimated regression coefficient relating mid-pregnancy free T_4 to child height in referent area: **Birth β=-2.93 (-5.07, -0.80)** **1 year β=-4.83 (-8.07, -1.59)** 4 years β=-4.18 (-9.20, 0.84) 6.5 years β=-5.24 (-10.5, 0.04) **10 years β=-8.18 (-15.5, -0.84)** Estimated regression coefficient relating mid-pregnancy free T_4 to child height in Pb area: Birth β=-0.78 (-4.23, 2.66) 1 year β=0.37 (-5.19, 5.92) 4 years β=0.55 (-6.97, 8.08) 6.5 years β=0.64 (-5.83, 7.10) 10 years β=0.75 (-7.35, 8.85) Regression data for maternal T_4 and BMI and rate of change per month were not significant. Authors report results of post hoc analyses: →maternal T_4 was inversely associated with	Maternal T_4 was inversely associated with TSH but not Pb in low-Pb town. Maternal T_4 was not associated with TSH but was inversely associated with Pb in high Pb town. Maternal T_4 was inversely associated with child height in low Pb town, not high Pb town.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						maternal TSH and this was not related to maternal blood Pb in referent, low Pb town. →maternal T_4 was not associated with maternal TSH, but **maternal T_4 was inversely associated with maternal blood Pb in the high Pb town** →authors suggest Pb altered T_4 - TSH relationship resulted in difference between towns Authors report regression analysis for maternal TSH and childhood height or BMI were not significant.	
Cross-sectional Lopez (2000) Buenos Aires, Argentina	75 male Pb battery workers and 62 referents from Argentinians not exposed to Pb in the workplace; Year not stated	41.1(8.7) Range 21 to 56	Pb-worker=50.9(23) Referent= 19.1(7.1)	Serum T_3, T_4, free T_4, TSH	t test, r-correlation Adjustments not described.	Endocrine values for workers and referent: Referent T_3=138.3(21.2) ng/dL Pb-Workers T_3=134.6(18.2) ng/dL **Referent T_4=6.8(1) µg/dL** **Pb-Workers T_4=8.7(1.5)µg/dL; p<0.001** **Referent free T_4=1.1(0.2) µg/dL** **Pb-Workers free T_4=1.4(0.8) µg/dL; p<0.01** Referent free TSH=1.4(0.6) µIU/ml Pb-Workers free TSH=1.3(0.3) µIU/ml Significant correlation between blood Pb (µg/dL): Pb 8-98 – no correlation T_3, T_4, freeT_4, TSH **Pb 8-50 – correlated T_3, T_4, freeT_4, TSH; p<0.05** **Pb 8-26 – correlated TSH; p<0.05** **Pb 26-50 – correlated T_3, T_4, freeT_4, TSH; p<0.05** **Pb 50-98 – correlated T_3, T_4; p<0.05**	Blood Pb levels were correlated with serum levels of T_3, T_4, or TSH; serum T_4 and free T_4 were higher in male Pb workers than referents.
Cross-sectional Mahmoud (2005) Belgium This study was subset of European study in Bonde (2002) *Also listed for sperm*	68 male workers (high Pb) in a Pb smelter in Hoboken and 91 hospital personnel (referent) in Ghent Belgium; Years = 1996-1997	Workers=37.4 Referents=32.5	Pb workers=30.9 Referents=3.4 Pb levels measured concurrently with other parameters	Sperm concentration (count/semen volume), serum levels of inhibin B, FSH, E_2	Multiple regression analysis, Spearman rank correlations, Wilcoxon test Adjustments depend on endpoint including age, period of abstinence, smoking, FSH, BMI	Median hormone concentrations (95% CI) by Pb: Blood Pb referent (hospital staff) = 3.4 (0.5, 9.0) **Blood Pb -Pb worker = 30.9 (10.2, 59.1); p<0.0001** FSH (IU/L) referent = 4.5 (0.9,16.5) FSH (IU/L) Pb worker = 4.6 (1.5, 34.3); p=0.21 Inhibin B (pg/ml)-referent = 176.8 (38,378) **Inhibin B -Pb worker = 259 (13,608); p<0.0001** E_2 (ng/ml)-referent = 1.9 (1.0,5.4) E_2 (ng/ml)-Pb worker = 1.8 (1.0, 4.0); p=0.20 Authors state the difference in inhibin B remained significant after correction for age and abstinence. Rank correlation by current blood Pb: **Inhibin B- combined pop. r=0.312; p=0.0001** Inhibin B -Pb workers r=0.047; p=0.70 Inhibin B- Hospital workers r=-0.072; p=0.50 FSH- combined population r=0.135; p=0.094 FSH - Pb workers r=0.224; p=0.069 FSH- Hospital workers r=-0.017; p=0.87 Multiple regression for inhibin B by Pb and FSH: **Blood Pb p<0.0001** **FSH p<0.0001**	Inhibin B concentration was significantly positively associated with blood Pb levels in a combined population of Pb workers and hospital staff.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Correlation between serum inhibin B and blood Pb: **Combined population r=0.27; p=0.043** **Smokers r=0.495; p=0.0002** **Non-smokers r=0.201; p=0.0451** **Pb workers r=0.27; p<0.05 controlling for age, FSH, sperm concentration, BMI, and smoking**	
Cross-sectional McGregor (1990, 1991) Location not stated, authors in United Kingdom	90 male Pb workers and 86 age-, SES-matched referents; Years not stated	Pb=31.5(12) Range 16-60 Referent= 41(12) Range 19-60	High Pb=45.9 Range 17-77µg/dL Referent=not reported Range <10-14µg/dL; 2 referents >10µg/dL 84 referent<10µg/dL	Plasma T, FSH, SHBG, LH	t test, multiple regression analyses age	Endocrine values for workers (case) and referent: Referent T=22.7 (8.5) nmol/L Workers T=24.6 (9.5) nmol/L; p=0.17 Referent LH=8.2(1.8) IU/L **Workers LH=6.0(1.8) IU/L; p=0.014** Referent FSH=3.6(1.8) IU/L Workers FSH=3.8(1.5) IU/L; p=0.52 Referent SHBG=33.2(12.8) nmol/L Workers SHBG=34.6(14.5) nmol/L; p=0.53 Age-corrected correlation FSH and Pb in workers: **Blood Pb r=0.298; p=0.004** Tibia Pb r=0.187; p=0.078 Mean (geometric) FSH by blood Pb in workers: <47µg/dL Pb=3.6(1.52) >47µg/dL Pb=4.5(1.63) Correlation between LH and Pb in workers: **Blood Pb r=0.253; p=0.016** Tibia Pb r=-0.009; p=0.936 **Exposure years r=0.338; p=0.002**	Blood Pb was associated with changes in LH and FSH.
Cross-sectional Meeker (2010) Michigan Same population as Meeker (2008)	219 men recruited from infertility clinics; Years not stated	34.2 (5.6)	Median 1.5(IRQ 1, 2) 10th percentile=0.80 25th percentile=1.10 50th percentile=1.50 75th percentile=2.00 95th percentile=4.20	FSH, LH, Inhibin B, T, SHBG, FAI, T/LH, serum As, Cd, Cr, Cu, Mg, Hg, molybdenum, thallium, Se, Zn	Multiple logistic regression Age, smoking, BMI	Regression model for change in serum hormone levels by blood Pb quartiles and covariates regression coefficient (β): FSH <25th percentile reference 25-50th percentile β=0.13(-0.10,0.37) 50-75th percentile β =0.10(-0.15,0.35) >75th percentile β =0.07(-0.42,0.09);p trend=0.19 LH <25th percentile reference 25-50th percentile β =0.004(-0.2, 0.21) 50-75th percentile β =0.13(-0.09,0.35) >75th percentile β =0.08(-0.14,0.29);p trend=0.32 Inhibin B <25th percentile reference 25-50th percentile β =-6.45(-27.2,14.3) 50-75th percentile β =-4.62(-26.6,17.4) >75th percentile β =-7.79(-29,13) ; p trend=0.52 Testosterone <25th percentile reference 25-50th percentile β =28.6(-6.82,64.1) 50-75th percentile β =15.8(-21.8,53.3) **>75th percentile β =39.9(3.32,76)**; p trend=0.07 SHBG <25th percentile reference	Blood Pb was positively associated with serum T; but not in the final adjusted model for other metal exposure and not for FSH, LH, Inhibin B, SHBG, FAI, or T/LH ratio in men at infertility clinic.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						25-50th percentile β =-0.01(-0.16, 0.15) 50-75th percentile β =0.04(-0.12,0.21) >75th percentile β =0.07(-0.10,0.23);p trend=0.34 FAI <25th percentile reference 25-50th percentile β =0.08(-0.04,0.20) 50-75th percentile β =0.03(-0.10,0.17) >75th percentile β =0.08(-0.05,0.21); p trend=0.35 T/LH <25th percentile reference 25-50th percentile β =-0.07(-0.28,0.14) 50-75th percentile β =-0.07(-0.33,0.18) >75th percentile β =-0.11(-0.35,0.14); p trend=0.8 Blood Pb was not associated with any hormone in the final model adjusted for other metal exposure. Molybdenum was negatively associated with T and FAI	
Cross-sectional and Case-control Mendiola (2011) Spain *Also listed for sperm*	Men attending infertility centers of the Instituto Bernabeu in Murcia and Alicante; 30 mend (case) with oligo-astheno-teratozoospermia and 30 (control) normospermic men; Years=2005-2007	33.5 (3.8)	Whole blood Control=9.7 (2.3) Case=9.8 (2.3) Blood plasma Control=2.9 (0.25) Case=2.9 (0.23)	Plasma FSH, LH, T, seminal volume, sperm count, motility, morphology, seminal plasma, blood plasma, and whole blood Pb, Cd, Hg,	Mann-Whitney, Multiple linear regression, Spearman rank correlation Age, BMI, number of cigarettes per day	Cross sectional - Multivariate analysis for hormone parameters by ln blood Pb- β=(95%CI): FSH β=0.04(-0.03,0.03) LH β=0.05 (-0.05,0.07) T β=0.01 (-0.05, 0.02) Lack of significant effect by plasma or seminal Pb Case-Control - Mean Pb concentrations in seminal plasma, whole blood, and blood plasma in men with sperm-related abnormalities (case) and normospermic men: Seminal plasma – case = 3.0 (0.30) Seminal plasma – normal = 2.9 (0.34) Blood plasma – case = 2.9 (0.20) Blood plasma – normal = 2.9 (0.25) Whole blood – case = 9.8 (2.3) Whole blood – normal = 9.7 (2.3)	Plasma levels of FSH, LH and T did not differ by blood Pb in men attending infertility clinic and referents.
Cross-sectional Ng (1991) Location not stated, authors work in China	122 factory workers (high Pb) and 49 referents (referent); Male=100%; Years= 1982 and every 6 months going forward	Pb = 32.6(8.2) Referent =34(13)	Average Pb workers=35.1(12) Referent=8.3(2.8) Current Pb workers=35.2(13) Referent=8.3(2.8) Only one sample per referent	LH, FSH, T, PRL, ALAD	Multiple regression analyses Adjustments differ by endpoint including age and smoking	Mean hormones by Pb-exposure category: T(ng/ml)-referent 7.39(2.21) T-Pb-worker 6.74(2.32); p=0.09 LH (IU/L)-referent 3.24(1.61) LH-Pb-worker 4.59(2.15); p=0.0001 FSH (IU/L)-referent 1.92(1.20) FSH-Pb-worker 2.52(1.72); p=0.01 PRL(mIU/L)-referent 196(125) PRL Pb-worker 191(109); p=0.60 Authors show graphically that LH and FSH were increased in Pb workers with less than 10 years of exposure (**p<0.01**); but unchanged in Pb-worker with more than 10 years exposure relative to referents.	Serum levels of LH and FSH were increased in Pb-workers relative to referents; PRL was not related to Pb. T was decreased in Pb workers with more than 10 years of exposure, but not in other

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Authors show graphically that T was unchanged in Pb workers with less than 10 years of exposure; but T was decreased in Pb-worker with more than 10 years exposure (**p<0.01**) relative to referents. Authors report that LH and FSH appeared to increase over blood Pb from 15 to 40µg/dL.	workers.
Cross-sectional Naha (2007) Bangalore, India *Population overlap with Naha (2006)* *Also listed for sperm*	Male paint factory workers (Pb exposed n=20 >10 years and n=30 7-10 years exposure) and non-occupationally exposed desk job workers (referent n=50) in Bangalore; Years not stated	Range 31-45	Referent=10 (2.3) Exposed >10 years=50 (3.5) 7-10 years=68 (2.5) Semen Pb Referent=2.99 (0.76) Exposed >10 years=15.9(2) 7-10 years=25.3 (2.3)	Serum LH, FSH, T, sperm count (density million/ml), motility, viability, morphology, DNA hyploidy, seminal fluid indicators (volume, etc.)	ANOVA, t test, Scheffe's F test Adjustments not described.	Mean (SD) of LH, FSH, and T by Pb group: LH (µIU/ml) referent = 5.14(2.35) LH (µIU/ml) 7-10 year Pb = 4.27(2.52) LH (µIU/ml) >10 year Pb= 3.9(1.69); p>0.05 FSH (µIU/ml) referent = 2.69(1.22) FSH (µIU/ml) 7-10 year Pb = 2.58(1.94) FSH (µIU/ml) >10 year Pb= 2.16(0.99); p>0.05 T (ng/ml) referent = 5.24(2.40) T (ng/ml) 7-10 year Pb = 4.83(1.21) T(ng/ml) >10 year Pb= 4.59(1.27); p>0.05	Occupational exposure (with higher blood Pb) was not associated changes in serum LH, FSH, or T.
Cross-sectional Robins (1983) New Haven, CT	54 workers and supervisory personnel at a brass foundry and 12 Pb-exposed patients at New Haven hospital; 90% male; Year=1979-1981	White = 39 Black = 38	Range 2-77µg/dL Black = 51.9µg/dL White = 42.2µg/dL	Serum Total T_4, free T_4, T_3, TSH, thyroid binding capacity, zinc protoporphyrin (ZPP)	Linear regression analysis, t test race	Analyses were restricted to male workers due to the small sample size for females. Relation of blood Pb and T_4: **Free T_4; r^2 = 0.085; p=0.048** Mean T_4 Black men = 5.2 **White men = 7.1; p<0.0001** Mean free T_4 Black men = 0.87 **White men = 1.14; p<0.0001** Relation of blood Pb and T_4 by race White-free T_4; r^2 = 0.05; p=0.273 **Black-free T_4; r^2 = 0.21; p=0.03** Authors state similar results were obtained for free T_4, total T_4, or maximum levels.	Serum free T_4 and total T_4 were negatively associated with blood Pb levels in black male Pb workers.
Cross-sectional Rodamilans (1988) Barcelona, Spain	23 male workers in the Pb smelting industry; Years not stated	Range 20-60	Referent =17 (13) Occupational Exposure by years: <1 =66 (22) 1-5 =73 (24) >5 = 76 (11)	Serum, LH, FSH, T, steroid binding globulin (SBG)	Statistical methods not described. Adjustments not described.	Mean serum T (SD) by years Pb exposure: Referent =22.9 (7.6) nmol/L <1 year =24.9 (6.7);p>0.05 1-5 years =23.2 (8); p>0.05 **>5 years =18.6 (4.6); p<0.01 to referent** Mean serum binding globulin (SBG)(SD) by year Pb: Referent =25 (6.7) nmol/L <1 year =26.4 (10);p>0.05 1-5 years =33.6 (11);p>0.05 **>5 years =34 (10.2); p<0.025 to referent** Authors state fee serum T index (T/SBG) decreased (**p<0.05**) in workers with 1-5, or >5 years Pb. **LH was significantly elevated in workers with**	Serum T was reduced and SBG was increased in workers with >5 years of occupational Pb exposure; LH was increased in all Pb-workers relative to referents.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						occupational Pb exposure relative to referents. No difference in FSH by exposure group.	
Cross-sectional Roses (1989) Buenos Aires, Argentina	128 male workers (n=56 Pb workers n=58 classified as not exposed; and 14 as exposed/treated); Years not stated	Range 18-52	Range (µg/dL) Pb-exposed=9 to 86 Unexposed 8 to 28	Serum PRL	Correlation and linear regression Adjustments not described.	Mean serum PRL (ng/ml): Unexposed = 9.9 (7.3) Pb-exposed = 16.3 (10) Correlation between blood Pb and PRL r=0.57; statistics not reported.	Serum PRL did not differ between Pb-workers and referents.
Cross-sectional Schumacher (1998) Trail, British Columbia *Subset of Alexander (1996a)*	151 male employees of the Cominco smelter Year= 1993	40 (7.2)	24.1	Serum TSH, Total T_4, free T_4	Least-squares regression, ANCOVA Age, alcohol consumption	Thyroid function by blood Pb levels: T_4 – no effect; p=0.13 Free T_4 – no effect; p=0.68 TSH – no effect; p=0.54	Serum free T_4, total T_4, and TSH were not associated with blood Pb levels in male Pb workers
Cross-sectional Siegel (1989) New Haven, CT	68 children at New Haven hospital; 52% male; Year=1987	Range 11 months to 7 years	Range 2-77µg/dL	Serum Total T_4, free T_4, ZPP	Linear regression analysis, Pearson correlation Adjustments not described.	Relation of blood Pb and T_4: Free T_4; r^2 = 0.03; p=0.13 Total T_4; r^2 = 0.04; p=0.10	Serum free T_4 and total T_4 were not associated with blood Pb levels in children.
Cross-sectional Singh (2000) Chandigarh, India	58 male gas station workers or mechanics in Chandigarh and 35 referents; Year not stated	Pb=31.7(10.6) Ref=28.8(4.2)	Pb-worker=51.9(9.4) Referent=9.52	Serum TSH, Total T_4, free T_4	Student's t test, multivariate analysis Adjustments not described.	Mean thyroid hormones by Pb exposure: Pb worker T_3 = 1.75(0.47) Referent T_3 = 1.71(0.51) Pb worker T_4 = 9.4(2.9) Referent T_4 = 10.7(4.9) **Pb worker TSH = 2.2(1.4)** **Referent TSH = 1.26(0.86); p≤0.01** Authors report that TSH was not elevated in workers with blood Pb ≤41µg/dL, but it was elevated in workers ≤70µg/dL relative to referents or the workers below 41µg/dL. Authors also state that TSH is elevated in both Pb group exposed for more than 60 months and less than 60 months relative to referents.	Serum TSH was elevated in Pb workers relative to referents; not T_3 or T_4.
Cross-sectional Telisman (2000) Zagreb, Croatia *Also listed for sperm*	146 male industrial workers in Zagreb (high Pb n=98 workers with occupational exposure; and referent n=51); Years=1987-1989	Pb=30 (5) Referent=31(5)	High Pb=38.7(12.5) Referent=10.9 (3) Median seminal Pb: High Pb=1.53 Referent=0.86	Plasma LH, FSH, PRL, T, E_2, seminal Pb, Cd sperm count, density, motility, viability, morphology, seminal fluid	Mann-Whitney U, Pearson correlations, Spearman correlation, regression analysis Authors state adjustments made in regression analysis but specific adjustments not described.	Significant Spearman correlation coefficient for hormones to blood Pb: **Plasma T = 0.188; p≤0.05** **Plasma E_2 = 0.201; p≤0.01** Plasma LH not significant Plasma FSH not significant Plasma PRL not significant	Blood Pb levels were associated with decreased plasma T and E_2, not LH, FSH, PRL.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
				indicators (volume, pH, etc),			
Cross-sectional Telisman (2007) Zagreb, Croatia *Also listed for sperm*	240 Croatian men without occupational Pb exposure at infertility clinic or artificial insemination doners; Years = 2002-2005	Range 19-52 Median 31.9	Median 4.9 Range 1.1-14.9	Plasma LH, FSH, PRL, T, E_2, sperm count, density, motility, viability, morphology, seminal fluid indicators (pH, volume, etc.), seminal Pb, Cd Cd, Cu, Se, Zn, ALAD, EP	Multiple regression analysis, Spearman rank correlation, Mann-Whitney U test Age, smoking, alcohol, blood Cd, serum Cu, Zn, Se	Multiple regression association for log blood Pb: **Prolactin β=-0.18, B=-2.25(SE=0.82); p<0.007** **Testosterone β=0.21, B=5.6(SE=1.9); p<0.003** **E_2 β=0.22, B=0.031(SE=0.009); p<0.0008** Log Pb was not significantly associated with FSH or LH	Blood Pb was associated with increasing serum T and E_2, and decreasing serum PRL; not FSH or LH
Cross-sectional Tomoum (2010) Cairo, Egypt *Also listed for puberty and growth*	41 children living in Pb contaminated areas of Cairo and areas with no obvious Pb pollution; Year = 2007; Male=51%	11.98 (1.13) Range = 10-13	9.46 (3.08) Range=3-15	Serum FSH, LH, E_2 (girls), T (boys), height, weight, puberty /sexual development (Tanner stage pubic hair, testicular size, penile growth in boys; Tanner pubic hair and breast dev. in girls)	Student's t test, Mann-Whitney U test, chi-squared test, Spearman correlation Adjustments not described.	Serum hormone levels by blood Pb above and below 10μg/dL median (IRQ): Male-LH Pb<10→ LH=6.5(5.8) mIU/mL **Male-LH Pb≥10→ LH=0.79(1.0) mIU/mL; p<0.05** Male-FSH Pb<10→ FSH=5.6(7.6) mIU/mL **Male-FSH Pb≥10→ FSH=1.88(1.4) mIU/mL; p<0.05** Female-LH Pb<10→ LH=8.9(6.1) mIU/mL **Female-LH Pb≥10→ LH=1.23(2.5) mIU/mL; p<0.05** Female-FSH Pb<10→ FSH=7.3 (7.9) mIU/mL **Female-FSH Pb≥10→ FSH=3.2(2.6)mIU/mL; p<0.05** Mean (SD) Boys-T Pb<10→ T=4.72 (1.52) ng/mL **Boys-T Pb≥10→ T=1.84(1.04) ng/mL; p<0.05** Girls-Estradiol (E_2) did not differ.	Boys and girls with blood Pb ≥10μg/dL had significantly lower FSH and LH; boys had lower serum T; E_2 did not differ in girls.
Cross-sectional Tuppurainen (1988) Kenya	176 male Pb battery workers; Year =1984	34.1 (8.1)	55.9(23.8)	Serum TSH, T_3, Total T_4, free T_4	Multivariate linear regression, correlation Adjustments not described.	Authors state blood Pb and thyroid hormones are not significant. Thyroid hormones by Pb exposure duration: Free T_4 r^2=0.071; p=0.001 Total T_4 r^2=0.059; p=0.021	Pb exposure duration was associated with decreasing T_4 and free T_4; blood Pb was not related to thyroid hormones.
Cross-sectional Vivoli (1993) Trento, Italy *Also for growth*	418 children 11-13 years of age in Trento; Years not stated; Male=48%	Range:11-13	Male= 8.54 Female=7.01	Height, weight, LH, FSH, T, E_2, DHA-S	Pearson correlation, multiple regression analysis Adjustments differ by sex including: mother's height, father's height, menarche date,	Relationship between LH or FSH and blood Pb was only significant in males >9.9μg/dL: **LH in males r=-0.432; p=0.002** **FSH in males r=-0.360; p=0.013**	Blood Pb in boys 11-13 years of age was negatively associated with LH and FSH in

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (μg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
					T		boys with blood Pb >9.9μg/dL.
Retrospective Zheng (2001) Hangzhou China	82 patients undergoing cerebrospinal fluid evaluations due to disease or injury; Year not stated		Blood Mean = 14.9 (8.31) Range 2.5-40.3	Transthyretin (TTR), T_4, retinal binding protein in blood and in cerebral spinal fluid (CSF)	Linear regression analysis Adjustments not described.	**TTR concentration and Pb in CSF:** **r=-0.29; p<0.05** Pb concentration in CSF and blood: r=0.102; p=0.439 TTR concentration in CSF and blood: r=-0.015; p=0.892 T_4 concentration in CSF and blood: r=0.085; p=0.449	CSF Pb levels were inversely correlated with CSF levels of transthyretin; not blood Pb or TTR or T_4 in patients.
Repro: Congenital Malformations							
Retrospective Alexander (1996a) Trail, British Columbia *Same population as Schumacher (1998)* *Also listed for stillbirth and* abortions	929 male employees of the Cominco smelter Years=employed as of 1992-1993	≤35 =23% 36-45 = 46% ≥46 =31%	28.4 (11.8) Blood Pb monitoring data used for exposure	Incidence of spontaneous abortion, stillbirths and birth defects	Odds ratio reported, statistical methods not described. Adjustment listed for total number of pregnancies, prior stillbirths and birth defects	Odds ratio (95% CI) for stillbirths and birth defects by paternal blood Pb level one year prior to index: Low (<25μg/dL) (reference) Medium (25-39μg/dL) OR=2.9(0.6,13.3) High (≥40μg/dL) OR=2.5 (0.5,11) Separate analysis for birth defects alone not reported	Paternal blood Pb levels were not associated with malformations
Case-control Ecological Aschengrau (1993) Boston, USA	Women who delivered at Brigham and Women's Hospital (case n=77 stillbirths and 1177 controls); Years= 1977 to 1980	Not reported	Not sampled Water samples were taken from city/towns of residence ** lack of blood Pb data limits utility	Congenital anomalies, stillbirths, and neonatal deaths	Logistic regression and multiple logistic regression Other metals, water source, maternal age, education level, history of prior spontaneous abortion	Odds ratio (95% CI) for congenital anomaly in relation to water sample Pb level Cardiovascular Adj.OR= 2.2 (0.9-5.7) Ear, face, neck Adj.OR=1.7 Central nervous system OR=0.8; Adj.not included Gastro-intestinal OR=0.7; Adj.not included Genital OR=0.9; Adj.not included Musculo-skeletal OR=1.0; Adj.not included Integument OR=1.4; Adj.not included	Drinking water levels of Pb were not associated with congenital malformations.
Retrospective Beckman (1982) Sweden *Also listed for abortion, stillbirth*	764 male workers at a copper smelter in Sweden; Years = married workers employed in 1978	Not reported	Exposure determined by occupation. Non-exposed pregnancies are pregnancies before father worked at smelter. Exposed pregnancies took place following employment. ** lack of blood Pb data limits utility	Spontaneous abortion, stillbirth, congenital malformations	Chi-square Adjustments depend on endpoint and included maternal age, paternal age, pregnancy order	Rate of congenital malformations among smelter workers: Non-exposed pregnancy = 3.4% Exposed pregnancy = 4.3%; p>0.05	Occupational exposure to Pb in male workers was not associated with congenital malformations.
Retrospective Ecological case-	364 births with neural tube defects	newborn	Blood not sampled Drinking water by	Neural tube defects	Chi-square test, conditional logistic regression	Matched case-control analyses 1957-1981 Anencephaly	Drinking water levels of Pb

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
control Bound (1997) England	(case) and 3 groups of control births with cardiovascular malformations (n=531), alimentary tract malformations (n=156), and urinary tract malformations (n=205); Years= 1957-1981		district of residence; Pb level determined by proportion of households with high Pb score (>10µg/L drinking water) ** lack of blood Pb data limits utility	(anencephaly or spina bifida and cranium bifidum)	Sex, age and parity of the mother	**Base model + Pb; p = 0.01** Base model + deprivation p = 0.085 Base model + Pb + deprivation p = 0.051 Spina bifida and cranium bifidum **Base model + Pb; p = 0.015** Base model + deprivation p = 0.044 Base model + Pb + deprivation p = 0.110 All neural tube defects **Base model + Pb; p = 0.004** Base model + deprivation p = 0.065 Base model + Pb + deprivation p = 0.079 Yearly prevalence of congenital abnormality Anencephaly + **Year of birth; p = 0.001** **+ District; p = 0.001**; p>0.05 for interaction Spina bifida and cranium bifidum + **Year of birth; p = 0.007** + District p = 0.034; p>0.05 for interaction	were associated with increased risk of neural tube defects.
Case-control Brender (2002) Texas *Same population as Brender (2006)*	184 Mexican-American women with a NTD-affected pregnancy (case) and 225 controls in Texas counties bordering Mexico; Years = 1995-2000	Not reported	Exposure determined by maternal and paternal occupation. ** lack of blood Pb data limits utility	Neural tube defect (NTD), urinary As, Cd, Hg	Crude odd ratios (ORs) and 95% confidence limits (approximate or Fisher's exact), multiple logistic regression Income (paternal exposures), age, education, and BMI (maternal exposures)	Odds ratio (95% CI) for maternal exposure: **Work as cleaner OR=9.5(1.1,82.2)** **Work in health care OR=3.0(1.0,9.0)** **Exposure to glycol ethers OR=∞(1.8, ∞)** Exposure to Pb OR=1.1(0.2,5.8) Exposure to pesticides OR=1.2 (0.3,4.8) **Exposure to solvents OR= ∞ (2.4, ∞)** Odds ratio (95% CI) for paternal exposure: Work in health care OR=1.1(0.3,4.0) Work in transport OR=0.8(0.3,2.2) Work in welding OR =2.5(0.5,14.1) Exposure to glycol ethers OR=0.7(0.4,1.3) Exposure to Pb OR=1.3(0.8,2.3) Exposure to pesticides OR=1.2(0.5,2.8) Exposure to solvents OR= 0.8(0.3,2.2)	Maternal blood Pb and parental occupational exposure by job category were not associated with neural tube defects in Mexican-Americans.
Case-control Brender (2006) Texas *Same population as Brender (2002)*	184 Mexican-American women with a NTD-affected pregnancy (case) and 225 controls in Texas counties bordering Mexico; Years = 1995-2000	Not reported	Blood Pb Case=2.4(1.9) Control=2.5(1.9) Exposure determined approximately 1-year post-conception by blood and urinary specimen; drinking water; and self reported maternal and paternal occupations;	Neural tube defect (NTD), urinary As, Cd, Hg	Mann-Whitney test, Logistic regression Adjustments differ by analyses and include household income and study region	Relation of blood Pb above 95 percentile for Mexican-Americans in NHANES OR (95%CI): <6µg/dL – reference ≥6µg/dL OR=1.5 (0.6, 4.3) Occupational exposure to Pb: Maternal OR = 0.9 (0.2, 4.2) Paternal OR = 1.3 (0.8, 2.2) Pb in drinking water <10µg/L water – reference >10µg/L OR=0.8(0.2, 2.6) Within 2 miles of facility with air emission OR=0.6(0.2, 1.5)	Maternal blood Pb and parental occupational exposure by job category were not associated with neural tube defects in Mexican-Americans; also negative for Pb in drinking

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
			examined for source of exposure to As, Cd, Pb, Hg.				water and residence near Pb air source.
Case-control ecological Croen (1997) California	Mothers of 507 neural tube defect cases and 517 controls; mothers of 201 heart cases and 455 controls	Not reported	No blood Pb data Exposure determined by residence near hazardous waste sites ** lack of blood Pb data limits utility	Neural tube defect, heart cases, cleft	Logistic regression Race/ethnicity, education, family income, preiconceptional vitamin use, neighborhood educational attainment	Crude Odds ratio-OR and (95% CI) for congenital malformation based on residence in census tract containing a hazardous waste site with Pb: Heart defects OR=2.9(0.8,10.0) Neural tube defects OR=1.4(0.5,3.6) Crude Odds ratio-OR and (95% CI) for congenital malformation based on residence within 1 mile of National Priority List site with Pb: Heart defects OR=2.3(0.8,6.4) Neural tube defects OR=2.0(0.9,4.1) Adjusted Odds ratio-OR and (95% CI) for congenital malformation based on residence in census tract containing a hazardous waste sites: Heart defects OR=1.3(0.8,2.1) Neural tube defects OR=0.9(0.7,1.3) Odds ratio-OR and (95% CI) for congenital malformation based on residence within ¼ mile of National Priority List site: Heart defects OR=1.8(0.8,4.2) Neural tube defects OR=1.4(0.8,2.4)	Residence near hazardous waste sites with known Pb was not associated with neural tube defect or heart defects.
Case-control Correa-Villasenor (1993) Maryland, District of Columbia and adjacent counties of northern Virginia	Infants born in hospitals in the Baltimore-Washington DC area; Years 1981-1989	<1 at time of enrollment 1 at time cardiovascular malformations were confirmed	No blood Pb data measured Exposure determined by occupation ** lack of blood Pb data limits utility Paternal occupations of jewelry, welding, lead soldering and paint stripping were thought to be associated with similar chemicals (i.e. lead and chlorinated hydrocarbons).	Cardiac defects in the infant	Logistic regression models, Trend test based on exact procedures. Birth year, socioeconomic index based on maternal education, family income, and head of household occupation (auto body repair, dry cleaning solvents, degreasing solvents, jewelry making lead soldering paint, paint stripping, pesticides, welding, and ionizing radiation), presence of a genetic disorder in the infant, family history of cardiac defects, and presence of father at interview.	Cardiac defect associated with paternal occupation (Trend test): **Pulmonary atresia and lead soldering; p=0.005** Coarctation and paint stripping; p=0.012 Ventricular septal defect (muscular) and paint stripping; p=0.007 Endocardial cushion defect (with and without Down syndrome) and ionizing radiation; p=0.005 and 0.013, respectively Increased odds ratio (95% CI) for: **pulmonary atresia and of endocardial cushion defect with Down syndrome with paternal exposure to lead soldering and welding; 4.7 (1.7, 12.6)** atrial septal defect and of membranous ventricular septal defect and paternal exposure to jewelry making; not significant due to low sample size. Author also reported a greater odds ratio (95% CI) of coarctation and ventricular deptal defect (muscular) and paternal occupation paint stripping with father present at interview; 3.5 (1.5, 8.0) and 3.5 (1.5, 8.5), respectively.	Paternal occupation of lead soldering and welding was associated with certain cardiac defects.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Case-control Dawson (1999) Galveston, Texas	Prenatal patients with neural tube defects (case n=11) and controls (n=29) of the University of Texas Medical Branch at Galveston; Year not stated	22 to 34	No blood Pb data Exposure determined by amniotic fluid levels at 15 to 20 weeks of gestation NTD=248(SE=12) Control=118(SE=2) ** lack of blood Pb data limits utility	Neural tube defects, amniotic fluid Ca, B_{12}, folate, Pb and methionine	Student's t test, Pearson correlation Adjustments not described.	Mean amniotic fluid Pb levels: **NTD-Pb = 248(SE=2)** **Control-Pb =118(SE=2); p≤0.001** Pearson correlation between amniotic Pb and: Folate r=-0.3095; p≤0.06 B_{12} r= -0.3488; p≤0.007 Methionine r=-0.3791; p≤0.02 Ca r=0.3340; p≤0.74	Amniotic fluid levels of Pb were higher in NTD cases than in controls; blood Pb not reported
Case-control ecological Elwood (1981) Canada	468 cases of anencephalus and 4129 control livebirths in Canada; Years=1969-1972	Not reported	No blood Pb data Exposure determined by drinking water ** lack of blood Pb data limits utility	Anencephalus, drinking water Ca, Mg, Cu, Li, Zn, Ni, Pb, Se, Hg, Cr, Ag, Co, Cd, molybdenum	Multiple, logistic regression, Mann-Whitney Adjustments not described.	Coefficient of logistic model and t-statistic of coefficient: Water Pb (ppb) = -0.00732; t-statistic =1.7;p>0.05	Drinking water Pb levels were not associated with anencephalus.
Cross-sectional Irgens (1998) Norway *Also listed for birth weight*	Births in Norway with possible parental occupational Pb exposure (exposed n=1,803 maternal; n=35,930 paternal); Years=1970-1993	Not reported	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Serious birth defects, neural tube defect, low birth weight, stillbirths, preterm births,	Logistic regression Maternal age, education	Prevalence of neural tube defect with occupational Pb exposure compared to reference for: Maternal exposure: **All Pb exposure levels OR=2.87 (1.05, 6.38)** **Low Pb OR=3.00 (1.10, 6.68)** Paternal exposure: All Pb exposure levels OR=0.97 (0.68,1.36) High Pb OR=0.99 (0.17,3.29) Low Pb OR=0.97 (0.67,1.37) Prevalence of serious birth defect with occupational Pb exposure compared to reference for: Maternal exposure: All Pb exposure levels OR=1.25 (0.80, 1.90) **Low Pb OR=1.63 (1.03, 2.46)** Paternal exposure: All Pb exposure levels OR=0.94 (0.82,1.08) High Pb OR=0.74 (0.39,1.29) Low Pb OR=0.95 (0.82,1.09) **Dose-response relationship; p<0.047** Authors also reported lack of statistical significant OR for paternal Pb and isolated cleft palate and cleft lip and Down's syndrome	Maternal occupational Pb exposure was associated with increased risk of neural tube defects. Paternal occupational Pb exposure was not associated with increased odds ratio of birth defects.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Retrospective Kristensen (1993) Oslo, Norway *Also listed for stillbirth and other endpoints*	6,251 births to male members of printers' unions in Oslo, Norway; Years= between 1930 and 1974 (n=17 children with late abortion)	Not reported	Not reported Exposure by paternal job category ** lack of blood Pb data limits utility	Birth defects, low birth weight, late abortions, stillbirths, preterm births	Logistic regression Gestational age, birth order, sex, prior stillbirth, twin birth, parental consanguinity	Standardized morbidity ratio (95% CI) birth defects for boys with paternal occupational Pb exposure compared to "other" exposures: **Cleft lip SMR =4.1 (1.8, 8.1)**	Paternal Pb (by job category) was associated with increased morbidity ration for cleft lip.
Case-control Lorente (2000) Europe	100 mothers of babies with oral clefts (case) and 751 controls who worked during the 1st trimester of pregnancy; Year=1989-1992	Not reported	Not reported Exposure by maternal job category ** lack of blood Pb data limits utility	Oral clefts	Multivariate regression	Odds ratio-OR and (95% CI) for cleft lip with or without cleft palate and maternal exposure to Pb compounds: **OR=4.0(1.3,12.2)**	Maternal Pb (by job category) was associated with increased odds ratio for cleft lip.
Case-control Jackson (2004) Washington, DC, Virginia, and Maryland	54 children with total anomalous pulmonary venous return (case) and 522 controls from the 3140 infants in the Baltimore-Washington Infant Study; Years= recruited 1981-1989	Not reported	Not reported Exposure by paternal job exposure matric, self-report, industrial hygiene assessment ** lack of blood Pb data limits utility	Total anomalous pulmonary venous return (TAPVR)	Fisher's exact test, odds ratio Adjustments not described	Unadjusted odds ratio-OR and (95% CI) for TAPVR and parental Pb during critical period: Any maternal Pb OR=1.57(0.64,3.47); p=0.27 **Any paternal Pb OR=1.83(1.00,3.42); p=0.045** Unadjusted odds ratio-OR and (95% CI) for TAPVR and parental Pb during critical period: Neither parent Pb - reference Mother Pb only OR=0.54(0.01,3.66) Father Pb only OR=1.56(0.81,3.05) **Both parents Pb OR=2.94(1.03,7.60)**	Paternal Pb exposure or exposure of both parents (by job category) was associated with increased odds ratio of total anomalous pulmonary venous return.
Cross-sectional Macdonell (2000) Glasgow, Scotland	Prevalence of births with neural tube defects from 1983-1995 in the Glasgow 93 lead study	Not reported	Blood not sampled Drinking water by postal code of residence; Pb level determined by proportion of households with high Pb score (>10µg/L drinking water) ** lack of blood Pb data limits utility	Prevalence of neural tube defects and Carstairs deprivation category	Pearson correlation Carstairs deprivation category	Prevalence of NTDs for each 1000 live births for areas with "high " water Pb: 1983-95-high water Pb = 2.1 1983-95-other areas = 2.4 1990-95-high water Pb = 0.69 1990-95-other areas = 1.8 Prevalence of NTDs (P-NTD) for each 1000 live births for and proportion of water with Pb>10µg/L by Carstairs deprivation category: Carstaris-1; P-NTD=1.6.1; 0.16%water >10µgPb/L Carstaris-2; P-NTD=2.2; 0.286%water >10µgPb/L Carstaris-3; P-NTD=2.2; 0.21%water >10µgPb/L Carstaris-4; P-NTD=2.2; 0.29%water >10µgPb/L Carstaris-5; P-NTD=2.5; 0.26%water >10µgPb/L Carstaris-6; P-NTD=2.6; 0.17%water >10µgPb/L Carstaris-7; P-NTD=2.8; 0.12%water >10µgPb/L	Drinking water levels of Pb were not correlated with increased risk of neural tube defects

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
Retrospective Needleman (1984) Boston, USA *Also listed for preterm birth, birth weight*	4354 births at Boston Hospital for women; Years= 1979-1980	newborn	Not reported	Birth weight, gestational age, malformations	Chi-square test, logistic regression Maternal age, gestation age, birth weight, race	Logistic regression for relative risk (RR) of minor congenital anomaly by cord Pb: 0.7 µg/dL reference **6.3 µg/dL RR=1.87 (1.44, 2.42)** **15 µg/dL RR=2.39 (1.66, 3.43)** **24 µg/dL RR=2.73 (1.80, 4.16)** Authors state no single characteristic anatomic defect was found associated with cord Pb and Pb was not significantly associated with major or multiple malformations.	Cord blood Pb was associated with increased relative risk of minor congenital anomalies, not major.
Retrospective Nordstrom (1979a) Sweden *Population overlaps with Nordstrom (1978a)*	1291 children born to female employees at Ronnskar smelter; 291 children were born to women working during their pregnancy. This population was compared to 24018 children born in the Skellefteå hospital region. Years=born between 1930-1959.	Not reported	No blood Pb data Exposure determined by occupation ** lack of blood Pb data limits utility	Congenital malformations	Chi-square test for heterogeneity Covariates or adjustments not described	In children of female employees at Ronnskar smelter, congenital malformation rate was higher in cases where mothers worked during pregnancy (5.8%, 17 of 291) versus cases where mothers didn't work during pregnancy (2.2%, 22 of 1000); p<0.005 Congenital malformation rate was higher in children born to mothers employed during pregnancy (5.1%; 13 of 253) versus children born in the hospital region of Skellefteå (2.9%, 694 of 24018); p<0.05	Maternal employment at the smelter during pregnancy was associated with increased rates of congenital malformations in the in utero exposed children.
Retrospective Case-control Sallmen (1992) Finland	27 women with a malformed child (case) and age matched controls (n=57) from wives of men biologically monitored for Pb at the Finnish Institute of Occupational Health; Years=1973-1983	Wives: 18-40 Men: not stated	Exposure was based on self-reported exposure, work descriptions and biological measurements ** lack of comprehensive blood Pb data limits utility	Congenital malformation	Logistic regression Adjusted for one variable at a time due to small sample size including paternal smoking, paternal alcohol, maternal smoking, maternal alcohol, maternal febrile illness, year of discharge	Odds ratio (OR 95% CI)of congenital malformation for paternal Pb exposure: Blood Pb OR=2.4 (0.9,6.5) Pb and paternal smoking **Blood Pb OR=3.2 (1.0, 10.2); p<0.05** Paternal smoking OR=2.8 (0.9, 8.9) Pb and paternal alcohol Blood Pb OR=2.2 (0.8,6.2) Paternal alcohol >5 drinks/wk OR=1.5 (0.6, 4.0) Pb and maternal smoking Blood Pb OR=2.2 (0.8, 6.1) Maternal smoking OR=1.8 (0.6,5.6) Pb and maternal alcohol Blood Pb OR=1.9 (0.6, 6.1) **Maternal alcohol OR=4.5 (1.4, 15.2); p<0.01** Pb and maternal febrile illness Blood Pb OR=2.5 (0.9, 7.4) **Maternal febrile illness OR=2.7 (1.0,7.9)**	Paternal blood Pb (estimated by occupation or measured) was associated with increased relative risk of congenital malformation when considered together with paternal smoking.

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
						Men with 5 highest blood Pb had children with 5 different malformations (congenital heart disease, oral cleft, clubfoot, polydactyly, and malformation of the adrenal gland)	
Cross-sectional ecological Vinceti (2001) Italy	Prevalence of births with major congenital anomalies in Ceramic District (Pb) and control area in northern Italy for three periods: 1982-1986, 1987-1990, 1991-1995 with decreasing Pb exposure	Not reported	Exposure was based on residence in an area in Italy associated with higher Pb exposure due to ceramic industry (Ceramic District) or surrounding control areas ** lack of blood Pb data limits utility	Congenital malformations	Exact mid-P 95% confidence intervals around the relative risk (RR)	Significant relative risk (95% CI) of prevalence of malformations among births in high Pb Ceramic District compared to control area of northern Italy: 1982-86 **All malformations RR=1.48(1.15,1.89)** **Hydrocephalus RR=4.11(1.04,11.18)** **Ear RR=3.65(1.16,8,81)** **Cardiovascular RR=2.59(1.68,3.82)** **Heart RR=2.47(1.57,3.70)** **Musculoskeletal RR=1.60(1.03,2.38)** **Oral clefts RR=2.28(1.16,4.07)** **Cleft lip RR=2.43(1.13,4.62)** **Integument RR=8.22(2.61,19.82)** 1887-1990 no significant effects; All malformations=RR=1.04(0.74,1.42) 1991-1995 **Genital RR=1.94(1.02, 3.38)** **All malformations=RR=1.28(1.00,1.60)** Also tested by not significant for any time period: Nervous system, neural tube defects, eye, respiratory, gastrointestinal, urinary, clubfoot, isolate cleft palate, chromosomes	Residence in Ceramic District in Italy (an area associated with elevated Pb exposure) was associated with increased risk of congenital malformations including cardiovascular, oral clefts, cleft lip, integument, hydrocephalus, ear, and musc-uloskeletal. Elevated risk was only found for 1982-1986, not 1987-1995.
Case-control ecological Zierler (1988) Massachusetts	270 children with congenital heart disease and 685 controls in Massachusetts; Year not stated	Not reported	Exposure was based on self-reported exposure by telephone interview, and public drinking water monitoring ** lack of blood Pb data limits utility	Congenital heart disease, drinking water Pb, As, Cd, Cr, Hg, Se, Fl, Nitrate, Na, Ag, Ba	Multiple logistic regression Maternal education, source of water, other measured water contaminants (As, Cd, Cr, Hg, Se, Fl, Nitrate, Na, Ag, Ba)	Prevalence odds ratio (95%CI) of any congenital heart disease and specific conditions in relation to drinking water higher than minimum detection limit for Pb: Any-Adj.OR=1.13(0.60,2.14) Coarctation of aorta Adj.OR=0.64(0.1,4.1) Patent ductus arteriosus Adj.OR=1.8(0.69,4.6) Cono-trunctal Defect Adj.OR=1.4(0.68,3.0) Ventricular Septal Defect Adj.OR=1.1(0.45,2.8)	Drinking water levels of Pb were not associated with increased risk of congenital heart disease.
Case-control Zeyrek (2009) Sanliurfa, Turkey	74 mother-newborn pairs with NTD (case) and 70 controls in Sanliurfa; Year not stated	Maternal Case=28.8(7) Control=25.8(6)	Cord: Control = 16.5(16) Case =18.2(17.8) Maternal Control =12.5(12.7) Case = 15.5(15) Measured at birth	Neural tube defect (NTD), serum Se, Pb, Zn, Cu, iron, folic acid, vitamin B_{12}	Chi-square, Fisher's exact test, Student's t-test, Mann-Whitney U, Pearson rank correlation Covariates or adjustments not described	Mean serum Pb: Maternal control =12.5(12.7) Maternal case = 15.5(15); p=0.35 Cord control = 16.5(16) Cord case =18.2(17.8); p=0.63 Authors report that maternal and cord Cu were higher and maternal Zn was lower in mother-infant pairs with NTDs	Cord and maternal Pb were not associated with neural tube defects.

Abbreviations: 8-OHdG - 8-hydroxydeoxyguanosin; Adj – adjusted; Ag – silver; ALAD - δ-aminolevulinic acid dehydratase (ALAD); ANCOVA - analysis of covariance; ANOVA - analysis of variance; As – arsenic; B_{12} – vitamin B_{12}; Ba – barium; BMI - body mass index; Ca – calcium; Cd – Cadmium; CI - Confidence interval; CL - confidence limits; CO – carbon monoxide; Cr – chromium; Cu- copper; *p,p'*-DDE - dichlorodiphenyldichloroethylene; DHA-S – dehydroepiandrosterone-sulfate; E_2 – estradiol; EP - erythrocyte protoporphyrin; FAI – free androgen index; Fe – iron; Fl – fluoride; FSH – follicle stimulating hormone; GH – growth hormone; GnRH – gonadotropin-releasing hormone; GSH – reducte glutathione; GST – glutathione S-transferase; Hb – hemoglobin; HCB - hexachlorobenzene; Hg – mercury; HOME - home observation for measurement of the environment; IGF-1 – insulin-like growth factor 1; IUGR – intrauterine growth restriction; IVF – in vitro fertilization; LDH-C4 - lactate dehydrogenase isoenzyme C4, also called LDH-X – lactate dehydrogenase isoenzyme X ; MDA – malondialdehyde; mo - month; Mg – magnesium; Mn – Manganese; Na – sodium; Ni – nickel; NO – nitrogen oxide; NTD – neural tube defect; OCP – organochlorine pesticides; OR - odds ratio; P_4 – progesterone; Pb – lead; PCBs - polychlorinated biphenyls; PRL – prolactin; PROM – premature rupture of membranes; ROS – reactive oxygen species; RR – relative risk; Se – selenium; SBG – steroid binding globulin; SES – socio-economic statue; SHBG – sex hormone-binding globulin; Sn – tin; SO – sulfur oxide; Sr – strontium; T – testosterone; T_3 – triiodothyronine; T_4 – thryoxine; TBG – thyroxine binding globulin; TRH – thryotropin-releasing hormone; TSH – thyroid-stimulating hormone; Zn – zinc; ZPP - zinc protoporphyrin

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