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

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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.

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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

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						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.

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						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

Study Description	Population	Age (yr) Mean (S.D)	Blood Pb (µg/dl) Mean (S.D.)	Outcome Measured	Statistical Modeling; Covariates	Findings	Observed Effect
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.

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	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.

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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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