

Lead: summary of epidemiologic evidence

Updated November 22, 2007

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Overall summary: Epidemiological evidence of associations between lead and adverse pregnancy outcomes and child health and development

Outcome	Maternal low-level lead exposure	Paternal occupational lead exposure	Childhood lead exposure
Spontaneous abortion	High-level exposure – L Low-level exposure – L	L	
Stillbirth	I	I	
Preterm birth	L	I	
Small for gestational age	L	I	
Neural tube birth defects	I	I	
Cardiac birth defects	I	I	
Orofacial clefts	I	I	
Other birth defects	I	I	
Postnatal growth in stature	I		L
Cognitive function: age 0-2	L		L
Cognitive function: age ≥ 3	L		S
Psychomotor function: age 0-2			I
Psychomotor function: ≥ 3	I		L
Visual function			I

Auditory function	L		L
Attention deficit	I		L
Aggression, other problem behaviours	I		L
Delayed age at menarche			L
Delayed pubic hair development, females			L
Delayed breast development			I
Dental caries			Deciduous teeth – L Permanent teeth – I
Childhood leukemia	I		I
Neuroblastoma	I	L	

1. Spontaneous abortion

Reviews

Author			
(Anttila and Sallmen 1995)	Literature review, included 6 epidemiologic studies of parental occupational exposure to lead or mixed metal exposures including lead	Limited evidence of an association between spontaneous abortion and paternal occupational lead exposure	Inadequate evidence to assess possible association between spontaneous abortion and maternal occupational lead exposure
(Hertz-Picciotto 2000), USA	Review article, included historical reports and 8 recent epidemiologic studies of lead exposure and spontaneous abortion	High spontaneous abortion rates reported among women with high-level occupational lead exposure during the 19 th and early 20 th centuries	Author concluded there was consistent evidence that high-level maternal lead exposure increases spontaneous abortion risk
Recent epidemiologic studies of low to moderate maternal lead exposure have produced little evidence for an association with spontaneous abortions but a recent well- study did show an association (see Borja-Aburto et al, 1999)	Authors concluded that low to moderate lead exposures comparable to the USA during the 1970s may increase the risk of spontaneous abortion; epidemiologic studies had serious limitations including low statistical power, indirect exposure indices, inadequate or no control of potential confounders		
(Bellinger 2005), USA	Reviewed 2 cohort studies of paternal exposure and the Hertz-Picciotto (2000) review of maternal exposure	The Borja-Aburto study indicates that maternal lead exposures as low as 5–9 µg/dL might be associated with a doubling of spontaneous abortion risk but independent replication of the findings is desirable.	Limited evidence that paternal lead exposures <30 µg/dL are associated with spontaneous abortion

Spontaneous abortion: Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(McMichael and others 1986), Port Pirie, Australia	Case-control	Nested within birth cohort	831 pregnant women, 75% from Port Pirie, 25% from adjacent regions, 23 spontaneous abortions (spontaneous abortions), 11 stillbirths (stillbirths)	Mean maternal and cord BPb levels were 10-11 $\mu\text{g/dL}$ in Port Pirie and 6-11 $\mu\text{g/dL}$ in adjacent region		Maternal age, years resided in Port Pirie, marital status, country of birth, race, blood pressure
Mean maternal BPb, spontaneous abortions vs pregnancies of 20+ wk gestation	11.3 \pm 0.81, SD=3.53, $\mu\text{g/dL}$, n=19 10.8 \pm 0.15, SD=4.86, $\mu\text{g/dL}$, n=557	Mean difference in maternal blood lead, t=0.44, p=.66				
(Lindbohm and others 1991), Finland	Nested case-control	Cohort of men monitored for occupational lead exposure	515 cases of spontaneous abortion, 1024 women with previous live births but no spontaneous abortions	BPb measured 1-6 times/yr among exposed men; estimated paternal lead exposure during spermatogenesis phase about 80 days before conception;	16% of case and 12% of control fathers had BPbs \geq 31 $\mu\text{g/dL}$	Paternal exposure to cadmium and mercury, maternal exposure to organic solvents, mercury, and alcohol, parity, contraception, previous spontaneous abortion
Non-monotonic exposure-risk relation between spontaneous abortions and paternal BPb closest in time to	0.9 (0.5-1.4) 0.8 (0.3-2.3) 3.0 (1.0-8.7)	Spontaneous abortions associated with paternal BPb within a year of spermatogenesis period; odds ratio for BPb \geq 31	3.8 (1.2-12.0)			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
period of spermatogenesis; odds ratios for BPb 20.7-30, 31-38 and ≥ 39 vs < 20.7 $\mu\text{g/dL}$		vs < 20.7 $\mu\text{g/dL}$				
(Hu 1991), Boston	Retrospective cohort	35 female survivors of childhood lead poisoning during 1930-44 (confirmed by medical records in Boston Children's Hospital), 22 women without a history of childhood lead poisoning matched for age, sex, and neighbourhood	11 spontaneous abortions or stillbirths among 51 pregnancies in matched exposed group; 6 sp abor or stillbirths among 48 pregnancies in matched unexposed comparison group	Criteria for lead poisoning were history of pica, lead lines on long bone x-ray, clinical signs and symptoms of lead poisoning but not rickets		Two groups did not differ appreciably with respect to education, smoking, alcohol, medication use
Odds ratio, fetal death (early or late) vs history of childhood lead poisoning	1.92, 0.65-6.07, calc'd from data in paper					
(Kristensen and others 1993), Oslo, Norway	Retrospective cohort	10,992 men in printing industry during 1930-1974 and alive in 1960	Fathered 6251 infants; 387 preterm births (16-36 wk), 39 early preterm birth (16-27 wk), 60 stillbirths (28+ wk), 17 late sp abortions (< 28 wk)	Lead exposure based on job title		Father's occupational status, year of birth, twin birth, maternal age, birth order, sex

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Odds ratio, late spontaneous abortion (<28 wk) and paternal occupational lead exposure, yes vs no	2.4, 0.81-6.9					
(Alexander and others 1996), Trail, British Columbia	Cohort	784 men employed in a lead smelter	2021 self-reported pregnancy outcomes including 12 stillbirths, 30 birth defects, 203 spontaneous abortions	Assessed lead exposure through work history and BPb monitoring results (mean 28, range 7-70 µg/dL);	Categorized BPb levels as low (< 25 µg/dL), medium (25-39 µg/dL) or high (≥ 40 µg/dL)	Paternal age, year of conception, gravidity
Odds ratios, spontaneous abortion, paternal BPb 25-39 and 40+ vs <25 µg/dL	25-39 µg/dL 1.0 (0.6-1.7) ≥40 µg/dL 0.7 (0.4-1.5)					
(Driscoll and others 1998), USA	Retrospective cohort	Women in U.S. Forest Service, age 18-52 yr	788 pregnancies reported by 464 foresters and 1,612 pregnancies by 1,073 non-foresters; self-reported information on exposures and pregnancy outcomes	Potentially exposed to lead from use of lead-based paint to mark trees for cutting		Maternal age, strenuous work activity, smoking, alcohol, herbicide use

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Female foresters had increased risk of spontaneous abortion; risk relative to non-foresters	1.4, 1.1-1.9	Use of lead-based paints associated with spontaneous abortion; respective odds ratios for two different lead-based paints	2.77 (1.11-6.88) 1.81 (1.21-2.70)			
(Borja-Aburto and others 1999), Mexico City	Nested case-control	Cohort of 668 pregnant women recruited during 1 st trimester	35 spontaneous abortions, 60 matched controls	Measured BPb	Mean BPb (and range): cases - 12.0 µg/dL (3.1-29), controls 10.1 µg/dL (1.3-26)	Matching variables included maternal age, date, gestational age when blood sample taken for lead determination, and private/public clinic status; adjusted for history of previous spontaneous abortion; screened several other variables found to not be confounders
Incremental risk of spontaneous abortion per maternal BPb increment of 5 µg/dL	1.8 (1.1-3.1)	Spontaneous abortion, odds ratio per increment in maternal BPb of 1 µg/dl	1.13, 1.01-1.3	Mean blood lead, case vs control mothers	12.0 (range 3.1-29) vs 10.1 (range 1.3-26), F=5.61, p=.02	
Monotonic dose-response-relationship between maternal blood lead and risk	BPb 5-9 10-14 ≥15	OR 2.3 5.4 12.2 p-trend=.03				

Summary: Spontaneous abortion

Maternal high-level lead exposure, limited evidence

A 1995 review found inadequate evidence of an association between self-reported spontaneous abortion and maternal occupational lead exposure (Anttila and Sallmen 1995) but a subsequent review concluded that high-level prenatal occupational lead exposure during the 19th and early 20th centuries likely increased the risk of spontaneous abortion (Hertz-Picciotto 2000). In a retrospective cohort study of 35 female survivors of childhood lead poisoning (confirmed by medical records), there was a statistically non-significant increased risk of spontaneous abortion or stillbirth (RR=1.92, 95% CI 0.65-6.07) (Hu 1991).

Maternal environmental lead exposure, limited evidence

A nested case-control analysis within the Port Pirie birth cohort study revealed no association between spontaneous abortion and maternal blood lead (BPb) (mean maternal blood lead levels, cases vs controls, 11.3 ± 0.81 (SE) vs 10.8 ± 0.15 , $t=0.44$, $p=.66$) (McMichael and others 1986). A cohort study of female foresters reported an association between spontaneous abortion and occupational use of lead-based paints (exposure (yes/no) to 2 brands of lead-based paints, OR=2.77, 95% CI 1.11-6.88; OR=1.81, 95% CI 1.21-2.70); the potential importance of such use as a source of lead exposure is not clear and the study did not include BPb measurements (Driscoll and others 1998). A reviewer found limited evidence for increased risk of spontaneous abortion at prenatal blood lead levels below 30 $\mu\text{g}/\text{dL}$ (Hertz-Picciotto 2000). In particular, a birth cohort study in Mexico City revealed a monotonic dose-response relationship between spontaneous abortion and prenatal blood lead (respective odds ratios for 5-9, 10-14 and ≥ 15 $\mu\text{g}/\text{dL}$ were 2.3, 5.4 and 12.2, $p\text{-trend}=.03$) (Borja-Aburto and others 1999). A reviewer noted that the Borja-Aburto et al study suggests that maternal blood lead levels as low as 5-9 $\mu\text{g}/\text{dL}$ may be associated with a doubling of spontaneous abortion risk but called for independent replication before drawing firm conclusions (Bellinger 2005).

Paternal occupational exposure, limited evidence

A reviewer found limited evidence that paternal blood lead levels below 30 $\mu\text{g}/\text{dL}$ are associated with spontaneous abortion (Bellinger 2005). A cohort study of Finnish men occupationally exposed to lead found an association between spontaneous abortion and preconceptual paternal BPb levels (BPb ≥ 31 vs < 20.7 $\mu\text{g}/\text{dL}$, OR=3.8 (95% CI 1.2-12.0) (Lindbohm and others 1991). A similar study in British Columbia found no association with paternal blood lead levels (paternal blood lead 25-39 or ≥ 40 vs < 25 $\mu\text{g}/\text{dL}$, OR=1.0, 95% CI 0.6-1.7; OR=0.7, 95% CI 0.4-1.5); selection bias is possible as only 38% of workers participated in this study (Alexander and others 1996). A retrospective cohort study of Norwegian men reported an elevated risk of 2nd trimester spontaneous abortion and likely lead exposure based on job titles (OR=2.4, 95% CI 0.8-6.9) (Kristensen and others 1993).

2. Stillbirths

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(McMichael and others 1986), Port Pirie, Australia	Birth cohort	831 pregnant women, 75% from Port Pirie (lead smelter town), 25% from adjacent regions	23 spontaneous abortions (spontaneous abortions), 11 stillbirths (stillbirths)	Mean maternal and cord BPb levels were 10-11 µg/dL in Port Pirie and 6-11 µg/dL in adjacent region		Maternal age, years resided in Port Pirie, marital status, country of birth, race, blood pressure
Mean 2 nd trimester maternal BPb level, stillbirths vs live births	Stillbirths 10.3±0.8 (SE) µg/dL, n=10 SD=2.53 Live births 9.9±0.2, n=481 SD=4.39	t=0.29, p=.77				
(Savitz and others 1989), USA	Case-control	Nested within surveys of national probability samples of live births (with 4-fold over sampling of low birth weight infants) and stillbirths (gestational age ≥ 28 wk or weight ≥ 1000g) in 1980	Numbers of live births and stillbirths for analysis of maternal occupation were respectively 3,668 and 2,096 and for paternal occupation were 5,669 and 3,170	Self-reported information on parental occupational exposures during 12 mos before delivery;	note – more fathers than mothers were employed during the 12 mos before delivery	Race, previous miscarriage; restricted to women who received prenatal care, age < 40 yr, no to medium alcohol consumption, no previous stillbirths
Odds ratio, stillbirths vs parental occupational lead exposure	maternal 1.6, 0.8-3.1 paternal 1.1, 0.9-1.3					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Baghurst and others 1991), Port Pirie, Australia	Cohort	Lead smelter town	9 stillbirths, 23 preterm births, 22 normal births	Measured lead concentrations in the umbilical cord and placental tissues		
Mean maternal BPb ($\mu\text{g/dL}$), gestation wk 14-20, stillbirths vs controls	Stillbirths 8.2, 6.0-11.1, n=9, SD=3.90 Live births 8.7, 7.7-9.9, n=22, SD=2.63 t=0.42, p=.68	Mean lead concentration in placenta body and membranes ($\mu\text{g/g}$ dry tissue, 95% CL), stillbirths vs controls	Placenta body Cases 0.76, 0.44-1.30, n=9 Controls 0.48, 0.38-0.61, n=22	Placenta membranes Cases 2.73, 0.69-10.8, n=6 Controls 0.78, 0.61-1.00, n=22		
(Aschengrau and others 1993), Boston	Case control	Hospital-based	1,039 birth defects, 77 stillbirths, 1,177 controls	Drinking water quality data for supply used at maternal residence during 1 st trimester	Lead levels in drinking water at maternal 1 st trimester residence: 90 th percentile 0.2 $\mu\text{g/L}$, highest level 20 $\mu\text{g/L}$	Race, age, health insurance coverage, previous child with birth defect, alcohol during 1 st trimester, water source
Odds ratio, drinking water lead level 2.5-80 vs <2.5 $\mu\text{g/L}$	2.1, 0.6-7.2					
(Kristensen and others 1993), Oslo, Norway	Retrospective cohort	10,992 men in printing industry during 1930-1974 and alive in 1960	Fathered 6251 infants; 387 preterm births (16-36 wk), 39 early preterm birth (16-27 wk), 60	Lead exposure based on job title		Father's occupational status, year of birth, twin birth, maternal age, birth order, sex

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			stillbirths (28+ wk), 17 late sp abortions (<28 wk)			
Odds ratio, stillbirths, likely occupational lead exposure vs unexposed	2.0, 0.88-4.7					
(Alexander and others 1996), Trail, British Columbia	Retrospective cohort	784 men employed in a lead smelter	2021 self-reported pregnancy outcomes including 12 stillbirths, 30 birth defects, 203 spontaneous abortions	Assessed lead exposure through work history and BPb monitoring	Mean BPb 28 $\mu\text{g/dL}$ (range 7-70)	Year of conception, prior stillbirths/birth defects, gravidity
Relative risk, birth defect or stillbirth vs paternal BPb	<25 $\mu\text{g/dL}$ 1.0 (referent) 25-39 2.9, 0.6-13.3 ≥ 40 2.5, 0.5-11.0	NOTE: mixture of stillbirths and birth defects				
(Irgens and others 1998), Norway	Retrospective cohort	Record-based cohort of persons with occupational lead exposure; perinatal deaths defined as stillbirths 15+ wk gestation plus neonatal deaths during first wk after delivery – 13 among exposed women,	1,886 infants among lead-exposed women, 35,930 infants of lead-exposed men (including 2,128 infants of highly exposed men); about 1.2 million infants of	Lead exposure status inferred from occupational title		Maternal or paternal age and education

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		191 among exposed men	parents in occupations not exposed to lead			
Odds ratio, perinatal mortality, likely vs unlikely parental occupational lead exposure	Maternal All exposures 1.05, 0.59-1.76 high exposure 3.74, 0.62-12.7 low exposure 1.14, 0.19-3.78	Paternal All exposures 0.87, 0.75-1.01 high exposure 1.20, 0.72-1.88 low exposure 0.85, 0.73-0.99				

Summary: Stillbirths

Maternal exposure, inadequate evidence

The Port Pirie birth cohort study found no association between stillbirth and 2nd trimester maternal blood lead levels (cases vs controls, 10.3 ± 0.8 (SE) vs 9.9 ± 0.2 , $t=0.29$, $p=.77$) (McMichael and others 1986). In a subsequent nested case-control study within this cohort, geometric mean placental membrane lead levels were higher among pregnancies ending in stillbirth ($2.73 \mu\text{g/g}$, 95% CI 0.69-10.8, $n=6$) than controls ($0.78 \mu\text{g/g}$, 95% CI 0.61-1.00, $n=22$) but the difference was not statistically significant (Baghurst and others 1991). A large population-based case-control study found a borderline association between stillbirth and self-reported prenatal occupational lead exposure (OR=1.6, 95% CI 0.8-3.1) (Savitz and others 1989). A small case-control study in Boston reported a statistically non-significant association between stillbirth and drinking water lead levels in communities where mothers resided during the 1st trimester (drinking water lead 2.5-80 vs $<2.5 \mu\text{g/L}$, OR=2.1, 95% CI 0.6-7.2) (Aschengrau and others 1993). In a Norwegian retrospective cohort study, there was a statistically non-significant elevated risk of late spontaneous abortion, stillbirths and neonatal deaths among women with likely high-level lead exposure based on job title (OR=3.74, 95% CI 0.62-12.7) (Irgens and others 1998).

Paternal occupational exposure, inadequate evidence

A large U.S. population-based case-control study revealed no association between stillbirth and self-reported paternal occupational lead exposure (OR=1.1, 95% CI 0.9-1.3) (Savitz and others 1989). Among a Norwegian cohort of printers, stillbirths were associated with potential lead exposure based on job title (OR=2.0, 95% CI = 0.88-4.7) (Kristensen and others 1993). A cohort of male lead smelter workers in British Columbia reported statistically non-significant associations between stillbirth and birth defects (12 stillbirths and 30 birth defect cases were combined for analysis) and blood lead levels (25-39 and ≥ 40 vs $<25 \mu\text{g/dL}$, OR=2.9, 95% CI 0.6-13.3; OR=2.5, 95% CI 0.5-11.0) (Alexander and others 1996). The dilution of stillbirths by birth defect cases reduces the usefulness of this study. In a large Norwegian retrospective cohort study, late spontaneous abortion, stillbirths and neonatal deaths combined were not associated with likely paternal high-level lead exposure based on job title (OR=1.20, 95% CI 0.72-1.88) (Irgens and others 1998).

3. Preterm birth

Reviews

Author		
(Andrews and others 1994)	Literature review, included 25 reports of 20 individual epidemiologic studies of lead exposure and pregnancy outcomes	Limited evidence that preterm delivery is associated with maternal lead exposure
(Agency for Toxic Substances and Disease Registry 2007)	Literature review	Noted that some studies found associations between preterm birth and maternal or cord BPb levels

Preterm birth: Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Huel and others 1981), France	Retrospective cohort		110 mother-infant pairs; 9 preterm births		Geometric mean and 95 th percentile hair lead levels in mothers and infants were 8.4/95 and 7.3/95 µg/g	No adjustment for potential confounders
Geometric mean hair lead level, mothers of preterm vs normal infants	15.5 µg/g, n=9 8.1 µg/g, n=63 p<.05					
(McMichael and others 1986), Port Pirie, Australia	Birth cohort	831 pregnant women, 75% from Port Pirie, 25% from adjacent regions	35 infants were preterm by dates and 25 by neonatal examination	Measured maternal and cord BPb levels	Mean BPb levels were 10-11 µg/dL in Port Pirie and 6-11 µg/dL in adjacent region	Age, gravidity, SES, occupation, smoking

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Relative risk of preterm birth vs maternal BPb at delivery (referent was <8 µg/dL)	8-10 µg/dL 2.1, 0.6-7.6 11-13 3.0, 0.8-11.3	≥14 4.4, 1.2-16.8	Odds ratios for preterm birth after excluding stillbirths (paper does not state CIs)	1.0, 2.7, 6.1, 8.7	Preterm birth associated with maternal BPb at delivery; relative risk per µg/dL BPb increment	1.11
(Savitz and others 1989), USA	Case-control	Probability samples of U.S. live births and stillbirths (National Natality Survey and National Fetal Mortality Survey), 1980	7381 healthy live birth controls, 743 preterm births, 468 IUGR births, 3973 stillbirths (28+ wk or birth weight 1000+ g)	Parental occupation/industry and job-exposure matrix used to impute occupational exposures		Child's race, sex, maternal smoking; restricted to maternal age ≥ 20 yr
Preterm birth vs likely parental occupational lead exposure	maternal 2.3, 0.7-7.0	paternal 1.0, 0.6-1.7				
(Factor-Litvak and others 1991), Yugoslavia	Birth cohort	Subjects recruited in a town near a lead smelter, refinery and battery plant and in an unexposed town	1008 mother-infant pairs	Measured maternal BPb at about gestation wk 18	Mean maternal BPb in smelter and comparison town were 0.92 (range 0.14-2.64) and 0.26 (0.08-0.90 µM/L)	Maternal age, ethnicity, prenatal smoking, maternal height, education, parity, infant sex
Linear regression analysis, change in gestation length (d) per unit change in maternal	β=0.1 d, -2.7 to 2.9, n=888	Preterm birth, odds ratio per unit change in maternal 2 nd trimester BPb level	0.99, 0.97-1.01			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
2 nd trimester BPb level (µM/L)		(µM/L)				
(Baghurst and others 1991), Australia	Birth cohort	Smelter town, 749 pregnancies followed from gestation wk 20	9 stillbirths, 23 preterm births, 18 births associated with premature rupture of the amniotic membranes, 22 normal births	Measured lead concentrations in prenatal maternal and cord blood and placental tissues		
Geometric mean maternal BPb, gestation wk 14-20, preterm vs term infants	11.9 (10.2-13.9), n=23, SE=3.7/3.92=0.94 SD=4.51 8.7 (7.7-9.9), n=22 µg/dL, SE=2.2/3.92=0.56, SD=2.63	Preterm birth, lead concentration (µg/g dry tissue) in placental membrane, cases vs controls	Preterm 1.24, 0.91-1.67, n=23 controls 0.78, 0.61-1.00, n=22			
(Bellinger and others 1991a), Boston	Retrospective cohort	Hospital-based, middle-class urban population, 4354 women interviewed within 2 d of delivery, 1979-1981	503 mother-infant pairs		Mean cord BPb 7.0 (range 0.1-35 µg/dL)	Maternal age, marital status, employment, education, race, ponderal index, parity, smoking, alcohol use during pregnancy, coffee consumption in 1 st trimester, hematocrit at delivery, diabetes, caesarian section; also gestation length

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
						in birth weight analyses
Relative risk per 1 $\mu\text{g/dL}$ increment of cord BPb	0.98, 0.93-1.02	Cord BPb ≥ 15 vs < 5 $\mu\text{g/dL}$, calculated from data in report	0.8, 0.3-1.8	Multiple regression analysis, change in gestation length (d) per unit change in cord BPb ($\mu\text{g/dL}$)	$\beta=0.04\pm 0.01$	
(Kristensen and others 1993), Oslo, Norway	Retrospective cohort	10,992 men in printing industry during 1930-1974 and alive in 1960	Fathered 6251 infants; 387 preterm births (16-36 wk), 39 early preterm birth (16-27 wk), 60 stillbirths (28+ wk), 17 late sp abortions (< 28 wk)	Lead exposure based on job title		Father's occupational status, year of birth, twin birth, maternal age, birth order, sex
Odds ratio, preterm birth and paternal occupational lead exposure, yes vs no	0.9 (CI not stated)					
(Irgens and others 1998), Norway	Retrospective cohort	Record-based cohort of persons with occupational lead exposure	1,886 infants among lead-exposed women, 35,930 infants of lead-exposed men (including 2,128 infants of highly exposed men); comparison to	Lead exposure status inferred from occupational title		Maternal age and education

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			about 1.2 million infants of parents in occupations not exposed to lead			
Relative risk, highly exposed vs unexposed parents	Maternal Low exposure 1.10, 0.95-1.26 High exposure 1.93, 1.09-3.28	Paternal Low exposure 0.89, 0.86-0.93 High exposure 0.90, 0.78-1.03				
(Lin and others 1998), New York State	Retrospective cohort	Record-based cohort, men in lead-exposed occupations and control group of bus drivers	747 live births among lead-exposed men and 2,259 in control group	Registry of men monitored for occupational lead exposure	Data for men with BPb levels ≥ 40 $\mu\text{g/dL}$ during 1981-85 and those with levels ≥ 25 $\mu\text{g/dL}$ during 1986-92	Paternal age, maternal education, perinatal complications, prenatal care, maternal history of spontaneous abortion, race, parity, infant sex
Odds ratio, preterm birth, paternal BPb levels ≥ 25 $\mu\text{g/dL}$ for at least 5 yr before conception, yes vs no	3.03, 1.35-6.77					
(Torres-Sanchez and others 1999), Mexico City	Case-cohort		161 preterm births, 459 full-term controls;	Measured cord BPb	Cord BPb quartiles were < 5.1 , 5.1-9, 9.1-14, and ≥ 15 $\mu\text{g/dL}$	Prepregnancy maternal weight, marital status, and prenatal smoking
Odds ratio, preterm birth, cord BPb level vs	Primiparous women 5.1-9	Multiparous women 5.1-9				

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
<5.1 µg/dL	2.72, 1.03-7.19 9.1-14.9 2.82, 1.13-7.02 15+ 2.60, 1.01-6.71	0.48, 0.21-1.08 9.1-14.9 1.12, 0.53-2.36 15+ 0.86, 0.41-1.84				
(Falcon and others 2003), Spain	Birth cohort	Southeast Spain, hospital-based	89 mother-infant pairs, 10 preterm births (≤ 37 wk)	Measured placenta lead level	Mean placenta lead (ng/g) was 113.4 ± 58.0 (SD), range 35.5-304	
Pearson's correlation coefficient, maternal BPb vs gestation length (d)	R=-0.32, p=.002	Mean lead ng/g dry tissue	Preterm birth or premature rupture of membranes, 153.9 ± 71.7 (SD), n=18	Normal deliveries 103.2 ± 49.5 , n=71		
Chen et al 2006 (Chen and others 2006), Taiwan	Retrospective cohort; record linkage to identify live births and stillbirths, 1993-97	Men and women occupationally exposed to lead	738 births of exposed mothers, 967 births of exposed fathers	BPb during pregnancy (mothers) or the 9 wk before conception (fathers)	Mean BPb: mothers - 10.1 µg/dL (max 62.8), fathers - 12.9 µg/dL (max 135)	Parental age, education, parity, infant sex
Preterm birth	Maternal blood Pb <10 10-19 ≥ 20	RR 1.0 1.97, 0.92-3.86 1.86, 0.68-4.28 p-trend=.06			Paternal blood Pb <10 10-19 ≥ 20	RR 1.0 1.17, 0.53-2.32 0.55, 0.19-1.28 p-trend=.30
(Jelliffe-Pawlowski and others 2006), California	Retrospective cohort study	Population-based sample of women monitored for BPb during pregnancy	262 births during 1996-2002	682 BPb measurements among 262 pregnant women	Range of maternal BPb was <1 to 130 µg/dL	Gestation length, race, private/public insurance, parity, maternal age, infant

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		because of potential for occupational or environmental exposure				sex
Multiple regression analysis, change in gestation length (d) (adjusted for gestation length) per unit change in maximum prenatal maternal BPb level ($\mu\text{g/dL}$)	BLL <10 $\mu\text{g/dL}$ $\beta=0.3\pm0.5$ (SE) BLL \geq 10 $\mu\text{g/dL}$ $\beta=-0.3\pm0.1$	Odds ratio, preterm birth, maximum prenatal maternal BPb \geq 10 vs <10 $\mu\text{g/dL}$	3.2, 1.2-7.4	Multiple linear regression analysis, change in gestation length (d) (adjusted for gestation length) per unit change in maximum trimester-specific maternal BPb level ($\mu\text{g/dL}$)	BLL <10 $\mu\text{g/dL}$ 1 st trimester $\beta=0.5\pm0.9$ 2 nd trimester $\beta=-0.1\pm0.9$ 3 rd trimester $\beta=1.2\pm0.8$	BLL \geq 10 $\mu\text{g/dL}$ 1 st trimester $\beta=-1.2\pm1.2$ 2 nd trimester $\beta=-1.0\pm0.3$ 3 rd trimester $\beta=-0.2\pm0.1$
(Berkowitz and others 2006), Idaho, USA	Retrospective cohort	5 towns within 21 sq mi of Bunker Hill Superfund NPL site	Infants born 1973-1974 near lead smelter, comparison group of Idaho births 1970-1981	Mothers may have been exposed to high airborne lead emissions during September 1973 to December 1974 because of inoperative bag house		Infant sex, maternal age, parity, previous preterm birth or pregnancy loss after gestation wk 20
Odds ratio, preterm birth, exposed vs unexposed infants	0.68, 90% CI 0.34-1.35					

Summary: Preterm birth

Maternal exposure, limited evidence

Reviewers found limited epidemiologic evidence for an association between preterm birth and prenatal maternal lead exposure (Andrews and others 1994). Other reviewers noted the available evidence but did not assign a level of evidence (Agency for Toxic Substances and Disease Registry 2007). Most studies of preterm birth and maternal lead exposure indices have found positive associations. In a small nested case-control study in France, preterm birth was associated with maternal hair lead levels (mean level, case vs control mothers, 15.5 vs 8.1 $\mu\text{g/g}$, $p < .05$) (Huel and others 1981). In the Port Pirie birth cohort study, there was a monotonic dose-response relationship between preterm birth and prenatal maternal blood lead levels with a substantially increased risk in the highest exposure category (maternal blood lead ≥ 14 vs < 8 $\mu\text{g/dL}$, $\text{OR} = 4.4$, 95% CI 1.2-16.8) (McMichael and others 1986). A nested case-control study within this cohort found somewhat higher placental membrane lead levels among pregnancies ending in preterm birth (geometric mean lead concentration, cases vs controls, 1.24 $\mu\text{g/g}$ (95% CI 0.91-1.67) vs 0.78 $\mu\text{g/g}$ (95% CI 0.61-1.00) (Baghurst and others 1991). A large U.S. case-control study revealed a statistically non-significant increased risk of preterm birth among women with likely occupational lead exposure inferred from job title and industry ($\text{OR} = 2.3$, 95% CI 0.7-7.0) (Savitz and others 1989). In 2 birth cohort studies, preterm birth was not associated with cord blood lead in Boston (per 1 $\mu\text{g/dL}$ increment, $\text{OR} = 0.98$, 95% CI 0.93-1.02) (Bellinger and others 1991a) or with placental, prenatal maternal blood or cord blood lead levels in the former Yugoslavia (per 2nd trimester maternal blood increment ($\mu\text{M/L}$), $\text{OR} = 0.99$, 95% CI 0.97-1.01) (Factor-Litvak and others 1991). All of these studies adjusted for prenatal maternal smoking and other potential confounders. In a Norwegian retrospective cohort study, preterm birth was related to likely high-level occupational lead exposure based on job title ($\text{OR} = 1.93$, 95% CI 1.09-3.28) (Irgens and others 1998). A case-cohort study in Mexico City reported a non-monotonic dose-response relationship between preterm birth and cord blood lead levels but only among primiparous women (cord blood lead ≥ 15 vs < 5.1 $\mu\text{g/dL}$, $\text{OR} = 2.60$, 95% CI 1.01-6.71) (Torres-Sanchez and others 1999). Gestation length was inversely associated with placental lead concentration in a small Spanish case control study with limited statistical analysis (Pearson's $r = -0.32$, $p = .002$) (Falcon and others 2003). A retrospective cohort study of occupationally exposed persons in Taiwan revealed a dose-response relationship between preterm birth and maternal prenatal blood lead levels (maternal blood lead 10-19 vs < 10 $\mu\text{g/dL}$, $\text{RR} = 1.97$, 95% CI 0.92-3.86; blood lead ≥ 20 vs < 10 $\mu\text{g/dL}$, $\text{RR} = 1.86$, 95% CI 0.68-4.28; p -trend = .06) (Chen and others 2006). In a Californian retrospective cohort study, women with maximum pregnancy blood lead levels of at least 10 $\mu\text{g/dL}$ had a substantially increased risk of preterm birth ($\text{OR} = 3.2$, 95% CI 1.2-7.4, compared to women with lower maximum levels); among women with blood lead levels of at least 10 $\mu\text{g/dL}$, gestation length decreased by an average of 1 day per increment of 1 $\mu\text{g/dL}$ in 2nd trimester maximum maternal blood lead level (Jelliffe-Pawlowski and others 2006). Maternal exposures to airborne lead emissions in Shoshone County, Idaho (during a 15-month period when air emissions were high because of a damaged bag house) was not associated with increased risk of preterm birth ($\text{OR} = 0.68$, 90% CI 0.34-1.35) (Berkowitz and others 2006). Synthesis: There were associations between preterm birth and measured lead body burden levels in 5 of 7 recent cohort or case-control studies; 4 of the 5 positive studies observed dose-response relationships. Thus there is limited but relatively strong evidence of an association between preterm birth and maternal lead exposure.

Paternal occupational exposure, inadequate evidence

Paternal lead exposure inferred from job histories was not associated with preterm birth in studies in the general US population (likely paternal lead exposure, yes vs no, $\text{OR} = 1.0$, 95% CI 0.6-1.7) (Savitz and others 1989), among Norwegian printers (yes vs no, $\text{OR} = 0.9$, CI not stated) (Kristensen and others 1993) and among the general Norwegian population (likely high vs no exposure, $\text{OR} = 0.90$, 95% CI 0.78-1.03) (Irgens and others 1998). In a U.S. retrospective cohort study of occupationally exposed men, there was a moderately strong association between preterm birth and blood lead levels of at least 25 $\mu\text{g/dL}$ for at least 5 years ($\text{OR} = 3.03$, 95% CI 1.35-6.77) (Lin and others 1998). A retrospective cohort study of persons occupationally exposed to lead in Taiwan reported no association between preterm birth and preconceptual blood lead level (≥ 20 vs < 10 $\mu\text{g/dL}$, $\text{OR} = 0.55$, 95% CI 0.19-1.28, $p = .30$) (Chen and others 2006). Synthesis: Among the 2 studies that measured blood lead levels, a U.S. retrospective cohort study found a relatively strong dose-response relationship but a similar study in Taiwan did not. Three weak studies (did not measure body burden lead levels) found no relationship. Thus there is inconsistent and inadequate evidence for an association between preterm birth and paternal occupational lead exposure.

4. Intrauterine growth retardation, small for gestational age

Reviews

Author		
(Andrews and others 1994)	Literature review, included 25 reports of 20 individual epidemiologic studies of lead exposure and pregnancy outcomes	Inadequate evidence that IUGR is associated with maternal lead exposure
(Agency for Toxic Substances and Disease Registry 2007) (p. 330)	Literature review	Inadequate evidence for association between IUGR and maternal occupational lead exposure

Intrauterine growth retardation, small for gestational age: Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Huel and others 1981), France	Retrospective cohort	Residents of small industrial town	110 mother-infant pairs, 10 infants were small for gestation length	Geometric mean and 95 th percentile hair lead levels in mother and infant were 8.4/95 and 7.3/95 µg/g		
GM hair lead level, mothers of IUGR vs normal infants	9.0 vs 8.1 µg/g, p>.05					
(McMichael and others 1986), Port Pirie, Australia	Birth cohort		831 pregnant women, 75% from Port Pirie, 25% from adjacent	Mean maternal and cord BPb levels were 10-11 µg/dL in Port Pirie and 6-		Infant sex and gestational age; maternal

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			regions, 68 infants had IUGR	11 µg/dL in adjacent region		weight for height, smoking, and parity
Mean maternal BPb at delivery, birth weight <2500g vs ≥2500g	10.4±1.1, n=17 SD=4.5 11.2±0.21, n=464 SD=4.5	Birth weight adjusted for gestation length and IUGR not associated with maternal BPb (results stated without supporting data in paper)				
(Savitz and others 1989), USA	Case-control	Probability samples of U.S. live births and stillbirths (National Natality Survey and National Fetal Mortality Survey), 1980	7381 healthy live birth controls, 743 preterm births, 468 IUGR births, 3973 stillbirths (28+ wk or birth weight 1000+ g)	Parental occupation/industry and job-exposure matrix used to impute occupational exposures		Child's race, sex, maternal smoking; restricted to maternal age ≥ 20 yr
IUGR vs likely paternal occupational lead exposure	Paternal 1.2, 0.8-1.8	Only 1 exposed case mother				
(Bellinger and others 1991a), Boston	Birth cohort	Hospital-based, middle-class urban population, 4354 women interviewed within 2 d of delivery, 1979-1981	503 mother-infant pairs		Mean cord BPb 7.0 (range 0.1-35 µg/dL)	Maternal age, marital status, employment, education, race, ponderal index, parity, smoking, alcohol use

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
						during pregnancy, coffee consumption in 1 st trimester, hematocrit at delivery, diabetes, caesarian section; also gestation length in birth weight analyses
Multiple regression analysis, change in birth weight (g) per unit change in cord BPb ($\mu\text{g/dL}$), adj for GL	$\beta=-3.00\pm 2.41$	IUGR relative risk per cord blood increment of 1 $\mu\text{g/dL}$	1.06, 1.00-1.13			
(Factor-Litvak and others 1991), Yugoslavia	Birth cohort	Subjects recruited in a town near a lead smelter, refinery and battery plant and in an unexposed town	1008 mother-infant pairs	Measured maternal BPb at about gestation wk 18	Mean maternal BPb in smelter and comparison town were 0.92 (range 0.14-2.64) and 0.26 (0.08-0.90 $\mu\text{M/L}$)	Maternal age, ethnicity, prenatal smoking, maternal height, education, parity, infant sex, gestation length
Linear regression analysis, change in birth	$\beta=7.3$ g, -70.9 to 85.5, n=888	Linear regression analysis, change in	$\beta=38.6$ g, -26.9 to 104.1			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
weight (g) adjusted for gestation length and other covariates per log increment in maternal 2 nd trimester BPb level ($\mu\text{M/L}$), adj for GL		birth weight (g) adjusted for gestation length and other covariates per log increment in cord BPb level ($\mu\text{M/L}$), adj for GL				
(Loiacono and others 1992), Yugoslavia	Birth cohort	106 pregnant women from a lead smelter and 55 from unexposed comparison town; all were non-smokers	1008 pregnancies	Measured placental cadmium and lead		Ethnicity, maternal age, height, parity, education, gestational age and infant sex
No association between birth weight adjusted for gestation length and placental lead level	Result stated without supporting data					
(Kristensen and others 1993), Oslo, Norway	Retrospective cohort	10,992 men in printing industry during 1930-1974 and alive in 1960	Fathered 6251 infants; 387 preterm births (16-36 wk), 39 early preterm birth (16-27 wk), 60 stillbirths (28+ wk), 17 late sp abortions (<28 wk)	Lead exposure based on job title		Father's occupational status, year of birth, twin birth, maternal age, birth order, sex
Odds ratio, SGA and paternal occupational lead exposure, yes vs no	1.0, 0.75-1.4	Odds ratio, low birth weight (adj for gestational age) and paternal occupational lead exposure, yes vs no	0.9, 0.61-1.2			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Gonzalez-Cossio and others 1997), Mexico City	Birth cohort		272 mother-infant pairs with complete data; anthropometric measurements at birth; gestation length ≥ 37 wk for all infants	Mean lead levels included maternal blood (8.9 $\mu\text{g/dL}$), cord blood (7.1 $\mu\text{g/dL}$), maternal tibia (9.8 $\mu\text{g/g}$), and maternal patella (14 $\mu\text{g/g}$)		Parity, maternal education, gestation length, maternal smoking
β -coefficient, change in birth wt at term per unit change in maternal tibial bone lead ($\mu\text{g/g}$), adj for GL	$\beta = -7.29 \pm 2.45(\text{SE})$ g, $p = .003$	Birth weight at term decrement for a tibial bone lead increment of 10 $\mu\text{g/g}$	-73 g, $p = .003$	β -coefficients, birth wt vs quartile of maternal patellar bone lead (4.47-9.59, 9.60-15.14 and >15.14 vs ≤ 4.46 $\mu\text{g/g}$)	Q2 - $7.57 \pm 61.0(\text{SE})$, $p = .90$ Q3 -50.9 ± 62.0 , $p = .41$	Q4 -155.6 ± 61.2 , $p = .01$
β -coefficient, birth wt vs cord blood lead, >8.5 vs <4.6 $\mu\text{g/g}$	$\beta = -41.8 \pm 64.0(\text{SE})$, $p = .51$	β -coefficient, birth wt vs maternal blood lead, >11.0 vs <5.5 $\mu\text{g/g}$	$\beta = -98.3 \pm 60.0(\text{SE})$, $p = .10$			
(Irgens and others 1998), Norway	Retrospective cohort	Record-based cohort of persons with occupational lead exposure	1,886 infants among lead-exposed women, 35,930 infants of lead-exposed men (including 2,128 infants of highly exposed men); about 1.2 million infants of parents in occupations not exposed to lead	Lead exposure status inferred from occupational title		Maternal age, education, gestation length
Odds ratio, low birth	Maternal					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
weight (adjusted for gestation length), likely vs unlikely parental occupational lead exposure	1.34, 1.12-1.60 paternal 0.91, 0.86-0.96					
(Lin and others 1998), New York State	Retrospective cohort	Record-based cohort, men in lead-exposed occupations and control group of bus drivers	747 live births among lead-exposed men and 2,259 in control group	Registry of men monitored for occupational lead exposure	Data available for men with BPb levels $\geq 40 \mu\text{g/dL}$ during 1981-85 and those with levels $\geq 25 \mu\text{g/dL}$ during 1986-92	Paternal age, maternal education, perinatal complications, prenatal care, maternal history of spontaneous abortion, race, parity, infant sex
Odds ratio, IUGR, paternal BPb levels $\geq 25 \mu\text{g/dL}$ for at least 5 yr before conception, yes vs no	0.82, 0.28-2.37					
(Seidler and others 1999), Germany Not used...	Retrospective cohort	3216 pregnant women, enrolled during gestation wk 15-28, 1987-1988	Physician-reported pregnancy outcome history, 194 SGA infants	Self-reported maternal occupational history; job-exposure matrix to assess exposure to organic solvents, carbon tetrachloride, herbicides, chlorophenols, polychlorinated biphenyls, aromatic amines, lead and lead compounds, mercury	Exposure level based on working hr/d with chemical exposure	Maternal age, smoking, alcohol, BMI, parity

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
				and mercury ¹¹⁵ compounds		
SGA vs maternal occupational lead exposure moderate vs unexposed	2.8, 0.8-9.6 p-trend=.46					
(Odland and others 1999), Russia and Norway	Birth cohort	Hospitals in 6 Russian and 3 Norwegian northern communities	262 mother-infant pairs		Maternal BPb levels in Norway and Russia were 1.2 (range 0.4-3.9 $\mu\text{g/dL}$) and 2.9 (range 0.8-13 $\mu\text{g/dL}$)	Screened several variables; final model included maternal age, BMI, height, serum zinc, urinary creatinine, maternal smoking, country
Multiple regression analysis, change in birth weight (adjusted for gestation length) per maternal BPb increment of 1 $\mu\text{M/L}$	β =-51.6g, -103.1 to -0.1, per $\mu\text{g/dL}$ β =-1068g, -2134 to -2, per $\mu\text{M/L}$					
(Osman and others 2000), Sweden	Birth cohort		106 mother-infant pairs	Measured placental lead and other metal concentrations		Infant sex, parity, gestation length
Multiple regression	β = -9.7 g, -16.9					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
analysis, change in birth weight (adjusted for gestation length) per unit change of cord BPb	to -2.5, per $\mu\text{g/dL}$ $\beta = -2.0 \text{ g}, -3.5 \text{ to } -0.51$, per nM/L					
(Sowers and others 2002), New Jersey, USA	Birth cohort	3 prenatal clinics in Camden, NJ; subjects 42% African-American, 38% Hispanic	705 mother-infant pairs, 62 FGD	Measured maternal BPb during each trimester, at delivery and postpartum	Mean prenatal BPb 1.2 ± 0.03 (SE) $\mu\text{g/dL}$	Ethnicity, dietary calcium, maternal age, smoking, growth, BMI
No association between SGA and maternal blood lead	Result stated without supporting data					
(Odland and others 2004), Arctic and sub-Arctic areas of Norway and Russia	Retrospective cohort	Hospital delivery departments in 6 communities, 1993-1994	262 mother-infant pairs; pregnancy outcome verified from medical records	Measure lead and other metals in maternal blood, serum or urine, cord blood, neonatal urine and placenta	Median placenta lead was $0.09 \mu\text{g/g}$, range $0.03-0.57$; mean maternal BPb was $2.1 \mu\text{g/dL}$, range $0.4-13.5$	Maternal BMI, height, age, smoking, placental or maternal BPb, parity, gestation length, country
Change in birth weight (g) per unit increase in placenta lead ($\mu\text{g/g}$); adj for GL	$\beta = -736 \text{ g}, -1527$ to 55 per $\mu\text{g/g}$	Note that range of placenta lead was $0.03-0.57 \mu\text{g/g}$				
Chen et al 2006 (Chen and others 2006), Taiwan	Retrospective cohort; record linkage to	Men and women occupationally exposed to lead	738 births of exposed mothers, 967 births of exposed fathers	BPb during pregnancy (mothers) or the 9 wk before conception	Mean BPb: mothers - $10.1 \mu\text{g/dL}$ (max	Parental age, education, parity, infant

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	identify live births and stillbirths, 1993-97			(fathers)	62.8), fathers – 12.9 µg/dL (max 135)	sex
SGA, odds ratio by parental BPb level <10, 10-19, ≥20 µg/dL	Maternal 1.0 1.62, 0.91-2.75 2.15, 1.15-3.83 p-trend <.01	Paternal 1.0 0.94, 0.49-1.66 0.94, 0.51-1.62 p-trend=.77				
(Jelliffe-Pawlowski and others 2006), California	Retrospective cohort study	Population-based sample of women monitored for BPb during pregnancy because of potential for occupational or environmental exposure	262 births during 1996-2002	682 BPb measurements among 262 pregnant women	Range of maternal BPb was <1 to 130 µg/dL	Gestation length, race, private/public insurance, parity, maternal age, infant sex
Odds ratio, low birth weight (adjusted for gestation length) or SGA, maximum prenatal maternal BPb ≥10 vs <10 µg/dL	SGA 4.2, 1.3-13.9	Multiple linear regression analysis, change in birth weight (g) (adjusted for gestation length) per unit change in maximum prenatal maternal BPb level (µg/dL)	BLL <10 µg/dL β=26.0±16.0(SE) BLL ≥10 µg/dL β=1.6±3.4	Multiple linear regression analysis, change in birth weight (adjusted for gestation length) per unit change in maximum trimester-specific maternal BPb level (µg/dL)	BLL <10 µg/dL 1 st trimester β=30.8±31.2 g 2 nd trimester β=35.1±28.4 g 3 rd trimester β=-8.2±27.0 g	BLL ≥10 µg/dL 1 st trimester β=25.5±24.0 g 2 nd trimester β=-18.2±13.8 g 3 rd trimester β=1.6±3.0 g
(Berkowitz and others 2006), Idaho, USA	Retrospective cohort	5 towns within 21 sq mi of Bunker Hill	Infants born 1973-1974 near lead	Mothers may have been exposed to high airborne		Infant sex, maternal age,

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		Superfund NPL site	smelter, comparison group of Idaho births 1970-1981	lead emissions during September 1973 to December 1974 because of inoperative bag house		parity, previous preterm birth or pregnancy loss after gestation wk 20
Odds ratio, SGA, exposed vs unexposed infants	1.92, 90% CI 1.33-2.76	Odds ratio, term low birth weight (<2500g), exposed vs unexposed infants	2.39, 90% CI 1.57-3.64			

Summary: Intrauterine growth retardation, small for gestational age

Maternal exposure, limited evidence

Two reviews found inadequate evidence for an association between FGD and maternal lead exposure (Andrews and others 1994; Agency for Toxic Substances and Disease Registry 2007). In a small retrospective cohort of women from a French industrial town, IUGR was not associated with maternal hair lead levels (mean level, case vs normal infant mothers, 9.0 vs 8.1 µg/g, $p>.05$) (Huel and others 1981). In an Australian birth cohort from a lead smelter town and adjacent region, birth weight adjusted for gestation length and IUGR were not associated with prenatal maternal blood lead levels (result stated without supporting data) (McMichael and others 1986). A cohort study in a Yugoslavian smelter town and comparison town revealed no association between birth weight adjusted for gestation length and placental lead level (result stated without supporting data) (Loiacono and others 1992). This study found no associations between birth weight adjusted for gestation length and cord blood lead (change in weight per log increment of cord blood lead, $\beta=38.6$ g, 95% CI -26.9 to 104.1) or 2nd trimester maternal blood lead (change in weight per log increment of cord blood lead, $\beta=7.3$ g, 95% CI -70.9 to 85.5) (Factor-Litvak and others 1991). A birth cohort study in Boston reported an inverse dose-response relationship between birth weight adjusted for gestation length and cord blood lead levels (per unit increase in cord blood lead concentration (µg/dL), RR=1.06, 95% CI 1.00-1.13) (Bellinger and others 1991a).

Several recent cohort studies have reported associations between FGD and maternal lead exposure indices including: (1) tibial bone lead (change in birth weight adjusted for gestation length per unit increase in bone lead (µg/g), $\beta=-7.29\pm 2.45$ (SE) g, $p=.003$) (Gonzalez-Cossio and others 1997), (2) maternal occupations likely exposed to lead (OR=1.34, 95% CI 1.12-1.60) (Irgens and others 1998), moderate intensity lead exposure vs unexposed (OR=2.8, 95% CI 0.8-9.6; but risk vs exposure intensity p -trend=.46) (Seidler and others 1999), (3) cord blood lead (change in birth weight adjusted for gestation length per unit change in cord blood lead (µg/dL), $\beta=-9.7$ g, 95% CI -16.9 to -2.5) (Osman and others 2000), (4) placental lead concentration (change in birth weight adjusted for gestation length per placenta lead increment (µg/g), $\beta=-736$ g, 95% CI -1527 to 55) (note that the range of placenta lead concentrations was 0.03-0.57 µg/g) (Odland and others 2004), (5) maternal blood lead level (change in birth weight adjusted for gestation length per maternal blood lead increment (µg/dL), $\beta=-51.6$ g, 95% CI -103.1 to -0.1) (Odland and others 1999); blood lead 10-19 or ≥ 20 vs <10 µg/dL, OR=1.62, 95% CI 0.91-2.75; OR=2.15, 95% CI 1.15-3.83, p -trend<.01 (Chen and others 2006); maximum prenatal maternal blood lead ≥ 10 vs <10 µg/dL, OR=4.2, 95% CI 1.3-13.9 (Jelliffe-Pawlowski and others 2006) and (6) maternal

residence in lead-contaminated regions (residence in Shoshone County, Idaho during a 15-month period when air lead emissions were high (SGA, OR=1.92, 90% CI 1.33-2.76; term low birth weight, OR=2.39, 95% CI 1.57-3.64) (Berkowitz and others 2006). The Mexico City cohort mentioned above found no association between birth weight adjusted for gestation length and cord blood lead (change in birth weight, cord blood lead >8.5 vs <4.6 $\mu\text{g/g}$, $\beta=-41.8\pm64.0(\text{SE})$, $p=.51$) and an inverse association of borderline statistical significance with maternal blood lead (change in birth weight, maternal blood lead >11.0 vs <5.5 $\mu\text{g/g}$, $\beta=-98.3\pm60.0(\text{SE})$, $p=.10$) (Gonzalez-Cossio and others 1997). A birth cohort in New Jersey observed no relationship between FGD and prenatal maternal blood lead (stated without supporting data) but mean blood lead levels were very low ($1.2\pm0.03(\text{SE}) \mu\text{g/dL}$) (Sowers and others 2002). In sum, 6 of the 8 cohort studies reported since 1990 and that measured maternal lead body burden found associations with fetal growth deficit including dose-response relationships. Each of these studies adjusted for several potential confounders (e.g., 5 studies adjusted for maternal smoking).

Paternal occupational exposure, inadequate evidence

A case-control and two retrospective cohort studies revealed no association between FGD and paternal employment in jobs likely exposed to lead with odds ratios of 1.2, 95% CI 0.8-1.8 (Savitz and others 1989), 1.0, 95% CI 0.75-1.4 (Kristensen and others 1993) and 0.91, 95% CI 0.86-0.96 (Irgens and others 1998). Two retrospective cohort studies in New York State and Taiwan showed no association between FGD and a history of blood lead levels above 25 $\mu\text{g/dL}$ for at least 5 years before conception (yes vs no, OR=0.82, 95% CI 0.28-2.37) (Lin and others 1998) or preconceptional blood lead level (≥ 20 vs $< 10 \mu\text{g/dL}$, OR=0.94, 95% CI 0.51-1.62, $p\text{-trend}=.77$) (Chen and others 2006).

5. Birth defects

5a. Neural tube defects

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Elwood and Coldman 1981), Canada	Case-control	Mothers resident in 142 communities population 10,000 or greater	468 stillbirths caused by anencephaly, 4129 live birth controls	Measured drinking water levels of lead and other elements in each community		Average family income, population, latitude, longitude, percent of married women employed
Mean drinking water lead levels, case vs control communities	10.3 vs 11.5 $\mu\text{g/L}$ (paper does not state SD or SE)	Multiple logistic regression coefficient, drinking water lead level vs case/control status	-0.007, $p>0.05$			
(Aschengrau and others 1993), Boston	Case-control	Hospital-based	1,039 birth defects, 1,177 controls	Drinking water quality data for water supply used at maternal residence during 1 st trimester	Median lead level in drinking water was undetectable, 90 th percentile = 20 $\mu\text{g/L}$, max = 80 $\mu\text{g/dL}$	Race, age, health insurance coverage, previous child with birth defect, alcohol during 1 st trimester, water source
CNS birth defects, drinking water lead >1	0.8 $p>0.05$					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
vs ≤ 1 $\mu\text{g/L}$						
(Bound and others 1997), England	Ecologic	Births of residents in defined small regions, 1957-81	348 NTDs, 806 matched controls including 531 cardiac defects, 156 GI defects, 205 urinary tract defects	Data from water supply authorities on lead in drinking water 1957-81; tap water survey in 1984-85 (1076 homes)	Assessed proportion of homes in each region with tap water lead levels >10 $\mu\text{g/L}$	Matched for date of LNMP; adjusted for SES
Logistic regression, estimated change in ln odds ratio per unit change in % of homes in region with tap water lead >10 $\mu\text{g/L}$; not adj for SES	Anencephaly 1.175 \pm 0.46(SE) Spina bifida 0.960 \pm 0.397 All NTDs 0.901 \pm 0.318	Estimated change in ln odds ratio per unit change in % of homes in region with tap water lead >10 $\mu\text{g/L}$; adj for SES	Anencephaly 1.069 \pm 0.552(SE) Spina bifida 0.747 \pm 0.467 All NTDs 0.647 \pm 0.368			
(Croen and others 1997), California	Two case-control studies	Population-based, 1989-1991	1) 507 live born or stillborn neural tube birth defect (NTD) cases, 517 live birth controls, (2) 201 live born or stillborn conotruncal heart birth defect cases, 439 oral cleft defect cases, 455 live birth controls	Mother-reported periconceptual residential history; assessed maternal residential proximity to 764 hazardous waste disposal sites incl 105 National Priority List (NPL) sites; categorized chemicals and potential for human exposure at nearby residences	Various combinations of maternal race/ethnicity, education, alcohol, family income, periconceptual vitamin supplement use, neighbourhood educational attainment, employment status, infant sex	
OR, NTDs, maternal residence <1 mi from a	2.0, 0.9-4.1					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
NPL site containing lead						
(Irgens and others 1998), Norway	Retrospective cohort	Paternal occupations at risk of lead exposure (including 2,128 infants of highly exposed men)	1,886 infants among lead-exposed women, 35,930 infants of lead-exposed men; about 1.2 million infants of parents in occupations not exposed to lead	Lead exposure based on job title		Maternal age and education
Neural tube birth defects, relative risk, likely parental occupational lead exposure, yes/no	Maternal 2.9, 1.1-6.4 Paternal 1.0, 0.7-1.4					
(Dawson and others 1999), Galveston, Texas	Birth cohort study	Prenatal clinic; predominantly Hispanic and African-American women, average age 29 (non-NTD) and 24 (NTD)	29 non-NTD and 11 NTD pregnancies	Measured amniotic fluid folate, B12, calcium, lead, and methionine at gestation wk 15-20		
Mean (\pm SE) 2 nd trimester amniotic fluid lead concentration, case vs control mothers	12.0 \pm 0.6(SE) μ M/L, n=11 5.7 \pm 0.1, μ M/L, n=29 p< .001					
(Brender and others	Case-control	Mexican-American	NTD infants (n=184),	Self-reported parental		Household

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
2002), Texas		mothers	healthy control infants (n=225)	occupational exposures from 1 yr before to 3 mos after conception		income
NTD, odds ratio, self-reported paternal periconceptual occupational lead exposure, yes/no	1.3, 0.8-2.3					
(Brender and others 2006), Texas	Case-control	Mexican-American women living in 1 of the 14 Texas counties bordering Mexico	184 NTD cases, 225 healthy live birth controls	Mother-reported periconceptual environmental and occupational exposures	Measured BPb in 103 case and 119 control mothers	
Odds ratio, maternal BPb ≥ 6 vs < 6 $\mu\text{g/dL}$	1.5, 0.6-4.3	Parental occupation potentially exposed to lead	Maternal 0.9, 0.2-4.2 Paternal 1.3, 0.8-2.2	Drinking water lead >10 vs ≤ 10 $\mu\text{g/L}$	0.8, 0.2-2.6	
Residence < 2 miles of point source of airborne lead emissions	0.6, 0.2-1.5					

Summary: Neural tube birth defects

Maternal exposure, inadequate evidence

NTDs were not associated with average municipal drinking water lead levels in communities of maternal residence in a Canadian ecologic study (mean levels in case and control communities were 10.3 and 11.5 $\mu\text{g/L}$) (Elwood and Coldman 1981). A Massachusetts case-control study reported no association between NTDs and drinking water lead levels in the community of maternal residence at delivery (≥ 1 vs < 1 $\mu\text{g/L}$, OR=0.8, $p>.05$); the use of such a low cut-off point greatly reduces the chance of observing an association if it exists (Aschengrau and others 1993). An English ecologic study found a statistically non-significant association between NTDs and tap water lead levels (change in OR per unit change in % of homes in region with tap water lead >10 $\mu\text{g/dL}$, 0.65 ± 0.37) (Bound and others 1997). In a population-based case-control study in California, NTDs were associated with periconceptual maternal residential proximity to NPL sites containing lead (OR=2.0, 95% CI 0.9-4.1) (Croen and others 1997). A Norwegian retrospective cohort study observed an association between NTDs and prenatal maternal occupations likely exposed to airborne inorganic lead (inferred from job titles) (OR=2.9, 95% CI 1.1-6.4) but this study had no information on

blood lead levels (Irgens and others 1998). A very small study in Texas reported higher mean amniotic fluid lead levels among NTD cases (n=11) compared to controls (n=29) (12.0 ± 0.6 vs 5.7 ± 0.1 $\mu\text{M/L}$, $p<.0001$) but did not control for potential confounders (Dawson and others 1999). There was a statistically non-significant elevated risk of NTDs at maternal blood lead levels of at least 6 $\mu\text{g/dL}$ (OR=1.5, 95% CI 0.6-4.3) in a larger Texan case-control study; the OR increased to 3.8 (95% CI 0.8-19.5) when adjusted for breastfeeding (Brender and others 2006). This study found no association with self-reported maternal occupational lead exposure (OR=0.9, 95% CI 0.2-4.2), drinking water lead levels above 10 $\mu\text{g/L}$ (OR=0.8, 95% CI 0.2-2.6) or maternal residence within 2 miles of a point source of airborne lead emissions (OR=0.6, 95% CI 0.2-1.5). Synthesis: Inadequate evidence. Studies to date were generally of low quality (small sample sizes, lack of direct measures of lead body burden, lack of adjustment for potential confounders such as diet/folate intake).

Paternal occupational exposure, inadequate evidence

A Norwegian retrospective cohort study and a Texan case-control study, respectively, found no association between NTDs and paternal occupational lead exposure (inferred from job titles) (OR=1.0, 95% CI 0.7-1.4) (Irgens and others 1998) or self-reported paternal occupational lead exposure (OR=1.3, 95% CI 0.8-2.3) (Brender and others 2002). Synthesis: Inadequate evidence. The 2 available studies revealed no association.

5b. Cardiac defects

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Zierler and others 1988), Massachusetts	Case-control		270 cases cardiac birth defects, 665 live birth controls	Measured lead and 10 other chemicals in drinking water in 204 communities	Median lead was < detection limit (1 µg/L), 90 th percentile = 0.7 µg/L, max = 500 µg/L	Other chemicals in drinking water, drinking water source, maternal education
Logistic regression odds ratio, total cardiac birth defects, ≥1 vs <1 µg/L	1.13, 0.60-2.14					
(Correa-Villasenor and others 1993), Baltimore-Washington Infant Study	Case-control,	Population-based	290 atrial septal defects, 575 ventricular septal defects, 62 pulmonary atresia, 288 endocardial cushion defects, 3572 controls with other birth defects, 1981-89	Parent-reported occupational and other exposures during 6 mos before conception including frequency per week	Most information came from mothers as only 21% of case fathers and 15% of control fathers were interviewed	Maternal age, YOB SES, genetic disorder of infant, family history of cardiac defects, father at interview
Odds ratio, pulmonary atresia, paternal preconception occupational exposure to lead soldering, yes/no	2.3, 1.1-4.9	Odds ratio, pulmonary atresia, paternal preconception occupational exposure to lead soldering, at least 2-3 times/wk vs unexposed, unadjusted	4.1, 1.2-11 p-trend=0.005			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Aschengrau and others 1993), Boston	Case-control	Hospital-based	1,039 birth defects, 1,177 controls	Drinking water quality data for water supply used at maternal residence during 1 st trimester	Median lead level in drinking water was undetectable, 90 th percentile = 20 µg/L, max = 80 µg/dL	Race, age, health insurance coverage, previous child with birth defect, alcohol during 1 st trimester, water source
Cardiac birth defects, drinking water lead >1 vs ≤1 µg/L	2.2, 0.9-5.7					
(Croen and others 1997), California	Two case-control studies	Population-based, 1989-1991	1) 507 live born or stillborn neural tube birth defect (NTD) cases, 517 live birth controls, (2) 201 live born or stillborn conotruncal heart birth defect cases, 439 oral cleft defect cases, 455 live birth controls	Mother-reported periconceptual residential history; assessed maternal residential proximity to 764 hazardous waste disposal sites incl 105 National Priority List (NPL) sites; categorized chemicals and potential for human exposure at nearby residences	Various combinations of maternal race/ethnicity, education, alcohol, family income, periconceptual vitamin supplement use, neighbourhood educational attainment, employment status, infant sex	
OR, conotruncal defects, maternal residence <1 mi from	2.3, 0.8-6.4					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
a NPL site containing lead						
(Vinceti and others 2001), Italy	Ecologic	Northern region with several ceramic tile factories	Assessed birth defects in contaminated and comparison region during period 1982-95	Air emissions of lead from ceramic tile plants; annual air lead emissions decreased from 722 tons in 1979 to 47 tons in 1997	Mean BPb levels in occupationally and non-occupationally exposed adults in study region were 58.1 and 32.3 µg/dL in 1977; mean levels in occupationally exposed female workers were 25.7 µg/dL in 1985 and 19.1 µg/dL in 1993-95	
Cardiac birth defects, relative risk, maternal residence in contaminated vs comparison region	1982-86 2.59, 1.68-3.82 1987-90 1.18, 0.62-2.06	1991-95 0.97, 0.57-1.54				
(Jackson and others 2004), Baltimore, Washington, USA	Case-control	Baltimore-Washington Infant Study	54 cases of total anomalous pulmonary vein return (TAPVR), 522 healthy live birth controls, 1981-89	Parent-reported home exposures and job histories during 6 mos before conception and pregnancy	Parental lead exposure based industrial hygiene assessment, job-exposure matrix, self-reported exposures	No adjustment for potential confounders
Likely maternal lead exposure (occupational or other) during 3 mos before and after	1.57, 0.64-3.47	Likely paternal lead exposure (occupational or other) during 6 mos	1.83, 1.00-3.42			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
conception, unadjusted OR		before conception, unadjusted OR				

Summary: Cardiac birth defects

Maternal exposure, inadequate evidence

A case-control study in Massachusetts found no association between cardiac birth defects and drinking water lead levels in communities of prenatal maternal residence (>1 vs ≤ 1 $\mu\text{g/L}$, OR=1.13, 95% CI 0.60-2.14); 90% of lead concentrations were below 1 $\mu\text{g/L}$ (Zierler and others 1988). Further investigation with about 4-fold more cases revealed a borderline association between cardiac birth defects and lead levels in the water supply serving the maternal residence during the 1st trimester (>1 vs ≤ 1 $\mu\text{g/L}$, OR=2.2, 95% CI 0.9-5.7) (Aschengrau and others 1993). In a lead-polluted region of Italy, an ecologic study reported an elevated risk of cardiac birth defects during 1982-86 (SIR=2.59, 95% CI 1.68-3.82) but not during 1991-95 (SIR=0.97, 95% CI 0.57-1.54); annual air lead emissions in the region decreased by 93% between 1979 and 1997 (Vinceti and others 2001). In the Baltimore-Washington Infant Study, there was a statistically non-significant elevated risk of pulmonary vein defects among infants of women who were likely exposed to lead at home or work during the 3-month periods before and after conception (OR=1.57, 95% CI 0.64-3.47) (Jackson and others 2004). Synthesis: Inadequate evidence. Available studies were weak (no measurement of lead body burden) and provided no convincing evidence of an association.

Paternal occupational exposure, inadequate evidence

Case-control studies within the Baltimore-Washington Infant Study found associations between pulmonary atresia and self-reported paternal exposure to lead soldering at least 2-3 times weekly (OR=4.1, 95% CI 1.2-11, p-trend=.005) (Correa-Villasenor and others 1993) and between total anomalous pulmonary vein return and likely paternal occupational lead exposure (based on industrial hygiene assessment, a job-exposure matrix or self-reports) during the 6 months before conception (OR=1.83, 95% CI 1.00-3.42) (Jackson and others 2004). Synthesis: Inadequate evidence. The one available study found associations with specific cardiac defects but requires confirmation.

5c. Orofacial clefts

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Aschengrau and others 1993), Boston	Case-control	Hospital-based	1,039 birth defects, 1,177 controls	Drinking water quality data for water supply used at maternal residence during 1 st trimester	Median lead level in drinking water was undetectable, 90 th percentile = 20 µg/L, max = 80 µg/dL	Race, age, health insurance coverage, previous child with birth defect, alcohol during 1 st trimester, water source
Ear-facial-neck birth defects, drinking water lead >1 vs ≤1 µg/L	1.7 p>.05					
(Kristensen and others 1993), Norway	Cohort,	10,992 men in printing industry	fathered 6,251 infants	Lead exposure based on job title		Maternal age, year of birth, sex, birth order
Cleft lip, likely paternal occupational lead exposure, yes/no	1.6, 1.0-2.5					
(Irgens and others 1998), Norway	Retrospective cohort	Paternal occupations at risk of lead exposure (including 2,128 infants of highly exposed men)	1,886 infants among lead-exposed women, 35,930 infants of lead-exposed men; about 1.2 million infants of parents in occupations not exposed to lead	Lead exposure based on job title		Maternal age and education

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Isolated cleft palate, relative risk, likely parental occupational lead exposure, yes/no	1.3, 0.9-2.0					
(Lorente and others 2000), Europe	Case-control		100 mothers of infants with oral clefts, 751 mothers of healthy infants, 1989-1992	All subjects were employed during the 1 st trimester; self-reported exposures		Maternal age, SES, study centre, degree of urbanization, country of origin
Isolated cleft palate and cleft lip and palate combined, odds ratio, self-reported maternal occupational lead exposure, yes/no	isolated CP 3.0, 1.1-8.6 cleft lip & palate 1.7, 0.6-4.3					
(Vinceti and others 2001), Italy	Ecologic	Northern region with several ceramic tile factories	Assessed birth defects in contaminated and comparison region during period 1982-95	Air emissions of lead from ceramic tile plants; annual air lead emissions decreased from 722 tons in 1979 to 47 tons in 1997	Mean BPb levels in occupationally and non-occupationally exposed adults in study region were 58.1 and 32.3 µg/dL in 1977; mean levels in occupationally exposed female workers were 25.7 µg/dL in 1985 and 19.1 µg/dL in 1993-95	
Orofacial defects, relative risk, maternal residence in contaminated vs	Oral clefts 1982-86 2.28, 1.16-4.07	1991-95 1.31, 0.42-3.16	Cleft lip 1982-86 2.43, 1.13-4.62	1991-95 0.80, 0.13-2.65		

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
comparison region	1987-90 2.04, 0.75-4.53		1987-90 1.64, 0.42-4.45			

Summary: Orofacial clefts

Maternal exposure, inadequate evidence

A case-control study in Massachusetts found a statistically non-significant elevated risk of facial/neck birth defects among infants of women living in communities with drinking water lead levels above 1 µg/L (OR=1.7, $p > .05$) (Aschengrau and others 1993). A European case-control study reported an association between isolated cleft palate and self-reported maternal 1st trimester occupational lead exposure (OR=3.0, 95% CI 1.1-8.6) and a statistically non-significant risk of cleft lip and cleft palate (OR=1.7, 95% CI 0.6-4.3) (Lorente and others 2000). An ecologic study of a region of Italy polluted by air emissions from ceramic tile plants showed that the risk of oral cleft defects was elevated during 1982-1986 (SIR=2.28, 95% CI 1.16-4.07) but decreased in recent years (1991-1995) after lead emissions declined substantially (SIR=1.31, 95% CI 0.42-3.16) (Vinceti and others 2001). Synthesis: Inadequate evidence. The 3 available studies provide some evidence of an association but did not measure lead body burden and had limited or no adjustment for potential confounders..

Paternal occupational exposure, inadequate evidence

Retrospective Norwegian cohort studies found borderline associations between paternal occupational lead exposure inferred from job titles and cleft lip (OR=1.6, 95% CI 1.0-2.5) (Kristensen and others 1993) and cleft palate (OR=1.3, 95% CI 0.9-2.0) (Irgens and others 1998). Synthesis: Inadequate evidence. The 2 available reports both came from Norway, did not measure lead body burden and the men were likely occupationally exposed to other toxicants (e.g., solvent exposure among printers).

5d. Other birth defects

Original studies

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Aschengrau and others 1993), Boston	Case-control	Hospital-based	1,039 birth defects, 1,177 controls	Drinking water quality data for water supply used at maternal residence during 1 st trimester	Median lead level in drinking water was undetectable, 90 th percentile = 20 µg/L, max = 80 µg/dL	Race, age, health insurance coverage, previous child with birth defect, alcohol during 1 st trimester, water source
Genital birth defects, drinking water lead >1 vs ≤1 µg/L	0.9 p>0.05					
(Wulff and others 1996), Ronnskar Sweden	Birth cohort	Births of women living near copper smelter and an unexposed comparison regions	120 birth defects among 2,724 births near copper smelter; 582 birth defects among 15,191 births in comparison region	Known high environmental levels of lead, arsenic, cadmium, mercury	Exposure index was residential proximity to copper smelter	
Chromosomal abnormalities, relative risk, smelter vs comparison region	2.6, 0.9-6.7					
(Irgens and others 2000), Norway	Retrospective cohort	1.2 million births in Norway, 1970-1993	Birth record information on birth defects diagnosed with first postnatal week	Birth record information on paternal occupation		Maternal age

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Club foot, odds ratio, paternal occupation as printer, yes/ no (18 exposed case fathers)	1.6, 0.9-2.9	Syndactyly, odds ratio, paternal occupation as printer, yes/ no (22 exposed case fathers)	1.4, 0.9-2.1			

Summary: Other birth defects

Maternal exposure, inadequate evidence

A case-control study in Massachusetts found a statistically non-significant elevated risk of genital tract birth defects among infants of women living in communities with drinking water lead levels above 1 µg/L (OR=0.9, p>.05) (Aschengrau and others 1993). A retrospective cohort study in Sweden revealed an increased risk of chromosomal abnormalities among infants of women living near a copper smelter with known airborne emissions of lead, arsenic and other metals/metalloids (RR=2.6, 95% CI 0.9-6.7) (Wulff and others 1996).

Paternal exposure, inadequate evidence

A Norwegian retrospective cohort study reported associations of borderline statistical significance between paternal occupation in printing and club foot (OR=1.6, 95% CI 0.9-2.9) and syndactyly (OR=1.4, 95% CI 0.9-2.1) (Irgens and others 2000).

6. Postnatal growth in height

Reference	Design	Sampling frame	Outcome	Exposure	Covariates
(Schwartz and others 1986), USA	Cross-sectional	NHANES II, 2,695 children age 6 mos to 7 yr	Measured growth parameters	BPb range 4-35 µg/dL	Screened multiple variables and age, race, sex, and several nutritional covariates
Multiple regression, change in height per unit change in current BPb (µg/dL); no evidence of a threshold	$\beta = -0.119 \pm 0.0005$ cm, $p < .0001$				
(Shukla and others 1989), Cincinnati	Birth cohort	260 inner city African-American mother-infant pairs	Measured growth parameters quarterly to age 15 mos	Median maternal BPb 7.7 µg/dL, mean infant BPb levels at 3 and 15 months were 5.3 and 15 µg/dL	Screened and adjusted as necessary for birth length, gestation length, postnatal complications, prenatal smoking, maternal age, infant iron status, hemoglobin, total iron-binding capacity, sex, SES, developmental stimulation, maternal race and height
Difference between expected and observed height at age 15 mos per unit change in postnatal BPb from age 3 to 15 mos (µg/dL); among subgroup with prenatal maternal BPb >7.7 µg/dL	regression slope $b = -.015$, $p = .013$				
(Shukla and others 1991), Cincinnati	Birth cohort	235 children	Measured growth of children quarterly to age 33 mos	Mean BPb levels at 18 and 33 mos were 17 (range 2.9-63 µg/dL) and 16 (range 2.9-44	Prenatal smoking, race, HOME score, maternal height, total iron-binding capacity, SES, sex, stature at 18 mos

Reference	Design	Sampling frame	Outcome	Exposure	Covariates
				μg/dL)	
Change in stature at age 33 mos per unit change in average postnatal BPb (μg/dL); adj for sex, race, iron-binding capacity, maternal smoking, height, length at age 18 mos	Avg BPb 3-15 mos β=5.60±2.22 cm, p=.01 Avg BPb 18-33 mos β=-0.13±0.57, p=.83	Avg BPb 3-15 mos X avg BPb 18-33 mos β=-1.81±0.80, p=.025			
(Greene and Ernhart 1991), Cleveland	Birth cohort	185 inner city, low-income infants at baseline; 50% of mothers alcoholic; recruited 1980-81	Measured weight, stature, and head circumference at birth and at 5 follow-up examinations to age 58 mos	Mean maternal, cord blood, and infant BPb levels at ages 6, 24, 36, and 58 mos were 6.5±1.9, 6.0±2.1, 10±3.3, 17±6.5, 17±5.9, and 16±6.6 μg/dL;	Race, sex, parity, gestation length, timing of first prenatal visit, maternal age, prenatal smoking, alcohol, marijuana use, prepreg wt, ht, head circumference, paternal size, parental education
Multiple regression, standardized height at age 58 mos (% of 1 SD) vs average maternal and cord BPb	β=-0.26±3.37(SE) cm, p=.94	Multiple regression, standardized height at age 58 mos (% of 1 SD) vs postnatal BPb, adj for body length at birth	BPb at age 6 mos β=-3.91±2.07, p=.06	BPb at age 58 mos β=1.62±1.40, p=.25	
(Vivoli and others 1993), Trento, Italy	Cross-sectional	418 children age 11-13 yr	Measured height, weight	Mean BPb levels in boys and girls were 8.5 and 7.0 μg/dL (range 1.5-17.5 μg/dL)	Parent's height, menarche date; SES was not a confounder
Multiple regression, change in height at age 11-13 per	Boys β=-	Girls β=-13.2±4.11,			

Reference	Design	Sampling frame	Outcome	Exposure	Covariates
unit change in log current BPb	27.4±11.49(SE), p=.02	p=.002			
(Kim and others 1995), Chelsea and Somerville, Massachusetts	Cohort	58 children, followed from age 6- 8 yr to 18-21 yr, Caucasian population	Measured weight and height at baseline and after follow-up	Mean dentin lead level at age 6-8 yr was 14.9 µg/g; mean tibial and patellar bone lead levels at age 18-21 yr were 1.2 and 5.0 µg/g)	Age, sex, race, birth weight, SES, baseline BMI, age increase, age at baseline
Multiple regression, change in height at age 6-8 yr per unit change in log ₁₀ dentin lead level	β=-0.9±1.1 cm	Multiple regression, change in height between age 6-8 and 18-21 yr per unit change in log ₁₀ dentin lead level	β=-2.8±2.5 cm		
(Kafourou and others 1997), Greece	Cross-sectional	522 children age 6-9 yr, residents of two industrialized towns and one control town since birth	Measured height, head, chest circumference	Mean BPb was 12±8.7 (range 1.3-51 µg/dL)	Sex, father's height, father's occupational status (skilled vs unskilled), age, hemoglobin, town
Multiple regression, change in height per unit change in current BPb µg/dL	β=- 0.086±.037(SE) cm, p=.02	Inverse association between BPb and height (height deficit for a BPb increment of 10 µg/dL)	0.9, 0.1-1.2		
(Ballew and others 1999), USA	Cross-sectional	(NHANES III), 4,391 children age 1- 7 yr with complete data	Measured stature, head circumference, weight, BMI	Mean BPb 3.7±0.17 µg/dL	Age, sex, race/ethnicity, household income, previous anemia, current anemia, iron deficiency, dietary vitamin C and iron, calcium supplements

Reference	Design	Sampling frame	Outcome	Exposure	Covariates
Multiple regression, change in height at age 1-7 per unit change in current BPb	$\beta=-0.157\pm.032$ cm, $p<.0001$				
(Selevan and others 2003), NHANES III, USA	Cross-sectional	2,186 African-American, Mexican-American, non-Hispanic white girls age 8-18 yr	Assessed age at menarche and Tanner stage for pubic hair and breast development	GM BPb < 3 $\mu\text{g}/\text{dL}$ in all 3 ethnic groups	Age, age squared, race, ethnicity, family income, anemia at examination, dietary vit C, iron, calcium
Multiple regression, difference in height BPb ≥ 3 vs < 1.0 $\mu\text{g}/\text{dL}$	Regression slope $r=-0.51$, $p<.001$				

Summary: Postnatal growth in height

Maternal exposure, inadequate evidence

In the Cleveland birth cohort, height at age 58 months was not associated with average maternal and cord blood lead levels (change in height (% of 1 SD) per unit change in average maternal and cord blood lead level ($\mu\text{g}/\text{dL}$), $\beta=-0.26\pm 3.37(\text{SE})$, $p=.94$) (Greene and Ernhart 1991).

Childhood exposure, limited evidence

In the Cincinnati birth cohort, there was an inverse dose-response relationship between infant blood lead at age 3 months and growth in stature from age 3 to 15 months (regression slope $b=-0.015$ cm per $\mu\text{g}/\text{dL}$, $p=.013$) (Shukla and others 1989). Further follow-up revealed an inverse association between stature at age 33 months and the interaction between average blood lead from age 3 to 15 months times that for age 18 to 33 months ($\beta=-1.81\pm 0.80$ cm, $p=.025$) (Shukla and others 1991). In the Cleveland birth cohort, standardized height at age 58 months was inversely associated with blood lead at age 6 months (change in height (% of 1 SD) per unit change in blood lead ($\mu\text{g}/\text{dL}$), $\beta=-3.91\pm 2.07$, $p=.06$) but not with current blood lead ($\beta=1.62\pm 1.40$, $p=.25$) (Greene and Ernhart 1991). Three large cross-sectional studies based on NHANES II and III found inverse dose-response relationships between children's height and current blood lead levels extending below 10 $\mu\text{g}/\text{dL}$ with no evidence of a threshold. Among children age 1-7, height inversely associated with current blood lead levels in NHANES II (change in height per unit change in current blood lead ($\mu\text{g}/\text{dL}$), $\beta=-0.12\pm 0.0005$ cm, $p<.0001$) (Schwartz and others 1986). Similarly, height was inversely associated with current blood lead level among all children in NHANES III (boys and girls age 1-7, $\beta=-0.157\pm 0.032$ cm, $p<.0001$) (Ballew and others 1999) and among the subset of girls age 8-18 (difference in height, current blood lead ≥ 3 vs < 1.0 $\mu\text{g}/\text{dL}$, regression slope $r=-0.51$ cm, $p<.001$) (Selevan and others 2003). A small birth cohort study in Massachusetts revealed no association between height at age 6-8 and log tooth dentin lead levels ($\beta=-0.9\pm 1.1(\text{SE})$, $p>.05$) (Kim and others 1995). A cross-sectional study of Italian children age 11-13 revealed an inverse association between height and log current blood lead levels (boys, $\beta=-27.4\pm 11.5(\text{SE})$ cm, $p=.02$) (Vivoli and others 1993). Similarly, a cross-sectional study of Greek children age 6-9 reported an inverse association between height and current blood lead ($\mu\text{g}/\text{dL}$) ($\beta=-0.086\pm 0.037(\text{SE})$ cm, $p=.02$) (Kafourou and others 1997).

7. Neuropsychological function

7a. Cognitive deficits

Meta-analyses and reviews

Reference			
(Needleman and Gatsonis 1990)	Meta-analysis, 12 studies, 1972-1987; analyzed subgroups of 7 studies using BPb and 5 studies using dentin lead; estimated average effect using weighted partial correlation coefficients	Inadequate control of SES and familial factors, over control of lead exposure covariates, inclusion of subjects with clinical lead poisoning, lack of data needed for regression analyses	Ranges of mean blood and dentin lead levels were 13-30 $\mu\text{g}/\text{dL}$ and < 5.5 to 13 $\mu\text{g}/\text{g}$; 8 studies measured IQ using WISC-R while 2 used the Stanford-Binet and 1 study each used the British Ability and the McCarthy Scales
Full-scale IQ inversely associated with BPb; partial $r=-0.15$ (-0.2, -0.1)	Full-scale IQ inversely associated with dentin lead; partial $r=-0.08$ (-0.13, -0.03)		
(Thacker and others 1992)	Literature review of studies published before mid-1989; selected 5 birth cohort studies with follow-up to age 2-5 yr (published 1979-1988); did not estimate average effect because of methodologic differences	Inadequate study design, especially inadequate elimination of bias and confounding	Ranges of mean and peak postnatal BPb levels in 5 studies were 4.8-24 and 5.0-85 $\mu\text{g}/\text{dL}$; assessed cognitive function using Bayley's MDI up to age 2 yr and the McCarthy, Stanford-Binet, and Wechsler Preschool and Primary Scale of Intelligence (WPPSI) scales for older children
MDI scores at ages 6-24 mos were inversely associated with maternal or cord BPb levels in adjusted analyses for 3/5 studies	Limited evidence for small IQ deficits at BPb levels <25 $\mu\text{g}/\text{dL}$	Full-scale IQ scores at ages 36-58 mos were inversely associated with postnatal BPb levels in adjusted analyses for 2 studies	

Reference			
(Schwartz 1993), Boston, USA	Reanalysis of selected epidemiologic studies of childhood neuropsychological function and lead; used non-parametric smoothing to detect threshold or non-linearity's in neurotoxic effects of lead	The inverse dose-response relationship between McCarthy score and BPb reported by Bellinger et al (1991) had no threshold down to 1 µg/dL	The inverse association between IQ and dentin lead reported by Needleman et al (1979) was insensitive to the exclusion of outliers or the inclusion of covariates and to the use of robust estimation techniques; the association occurred across the range of dentin lead levels
(Schwartz 1994)	Meta-analysis, 3 longitudinal and 4 cross-sectional studies of full-scale IQ in school-age children (1981-1993); outcome chosen because it is much more stable and predictive of future outcomes than developmental measures among preschoolers; weighted effect estimates by inverse of variance	Studies that did not measure BPb and full-scale IQ among school-age children	BPb measured once in cross-sectional studies; BPb at age 24 mos for 1 longitudinal study and average BPb from birth to age 3 yr in the other 2 longitudinal studies; range of mean BPb levels was 6.5-23 µg/dL
A BPb increment from 10 to 20 µg/dL was associated with an average full-scale IQ deficit of 2.57±0.41 points (range in 7 studies was 1.3-5.8 points)	Analysis of residuals of full-scale IQ and BPb provided no evidence of a threshold		
(Pocock and others 1994)	Meta-analysis of studies of full-scale IQ among children age 5 yr or older; included 5 longitudinal and 14 cross-sectional studies of BPb and 7 cross-sectional studies of tooth lead; used regression coefficients to estimate IQ change for a doubling of BPb from 10 to 20 µg/dL or tooth lead from 5 to 10 µg/g	Pre-1979 studies, studies with <100 children, studies using hair lead or circumpolar lead	Longitudinal studies – most included prenatal maternal BPb, cord BPb, and repeated measures of child BPb; range of mean BPb levels at age 2 yr was 6.8-21 µg/dL; 4/5 used WISC and 1 used WPPSI to measure IQ; children age 5-10 yr at IQ measurement

Reference			
Inverse associations between IQ and BPb at age about 2 yr – overall estimated IQ decrement for a BPb increment from 10 to 20 µg/dL was 1.85 points (0.85-2.85)	IQ weakly associated with average postnatal BPb levels and not associated with cord blood or antenatal maternal BPb levels	Cross-sectional studies of BPb – range of mean BPb was 7.4-24 µg/dL; most used WISC-R, two used British Ability Scale or WPPSI	Heterogeneous results but the 2 largest studies that controlled for potential confounders observed the strongest inverse associations between IQ and BPb
Overall estimated IQ decrement for a BPb increment from 10 to 20 µg/dL was 2.53 points (1.73-3.33)	Cross-sectional studies of whole tooth or dentin lead – range of mean tooth lead was 5.1-13 µg/g	Inverse association between IQ and tooth lead in all 7 studies but statistically significant in only 2 studies	Overall estimated IQ decrement for a tooth lead increment from 5 to 10 µg/g was 1.03 points (0.50-1.56)
(Banks and others 1997)	Literature review, 11 cross-sectional and 6 longitudinal studies of blood or tooth lead and IQ and other neuropsychological outcomes (1979-1995)	Cross-sectional studies	Small decrements in IQ, school performance, and attention associated with BPb level across the range 10-40 µg/dL
Longitudinal studies	Quite consistent in showing inverse associations between early cognitive development and prenatal lead exposure; some evidence that postnatal lead exposure is also important		
(Lidsky and Schneider 2003), Philadelphia	Review of literature on effects of lead on cognitive development of children	The long half-life of lead in brain (about 2 yr) can cause neurotoxicity after BPb levels have declined	There is solid evidence for adverse effects of lead on behavioural and cognitive development of children at BPb levels below 10 µg/dL
The ability of lead to substitute for calcium and zinc contributes to many of its toxic effects	Neurotoxic effects of lead include apoptosis, excitotoxicity, modulation of neurotransmitter storage/release and second messengers and direct toxic effects on mitochondria, cerebrovascular endothelial cells, astroglia and oligodendroglia		

Reference			
(Bellinger 2004), Boston, USA	Review of epidemiologic studies of health effects of lead exposure	No threshold below which lead has no adverse developmental effects has been demonstrated	Recent studies show significant inverse associations between IQ and BPb below 10 µg/dL; data consistent with steeper slope below 10 µg/dL
(Koller and others 2004), UK	Review of epidemiologic studies of childhood cognitive function and low-level lead exposure	Concluded that there is no safe level of lead exposure	Concluded that lead accounts for only 1-4% of variance in cognitive ability whereas social and parenting factors account for at least 40%
(Lanphear and others 2005), USA	Pooled analysis; assessed full-scale IQ score; 1,333 children, participated in 7 international population-based longitudinal studies, followed from birth or infancy until age 5-10 years	Median peak BPb was 18 µg/dL (at age 2.5 yr); median BPb was 9.7 µg/dL at age 5-7; 5 th and 95 th BPb percentiles were 2.4 and 30 µg/dL	
Change in IQ for a change in BPb from 5 th to 95 th percentile Early childhood BPb β=-2.04, -3.27 to -0.81 Peak BPb β=-2.85, -4.10 to -1.60	Lifetime avg BPb β=-3.04, -4.33 to -1.75 Current BPb β=-2.70, -3.74 to -1.66	Change in IQ for given changes in current BPb, log-linear model	2.4-10 µg/dL β=-3.9, -2.4 to -5.3 10-20 µg/dL β=-1.9, -2.6 to -1.2
20-30 µg/dL β=-1.1, -1.5 to -0.7 2.4-30 µg/dL β=-6.9, -4.2 to -9.4			

7b. Cognitive function, age 0-2

Original studies published since 1998

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Shen and others 1998), Shanghai	Birth cohort		133 infants; followed infants at ages 3, 6, and 12 mos; measured BPb and BSID at each visit	Categorized cord BPb as high (10.7-17.5 $\mu\text{g/dL}$) or low (2.1-7.4 $\mu\text{g/dL}$)		Assessed several potential confounders and adjusted for father's occupational class and mother's education
Mean MDI scores vs cord BPb level	Age 6 mos <10 $\mu\text{g/dL}$ 88.3	≥ 10 $\mu\text{g/dL}$ 82.0 F=4.78, p=.03		Age 12 mos <10 $\mu\text{g/dL}$ 100.3	≥ 10 $\mu\text{g/dL}$ 95.1 F=5.00, p=.03	
(Mendelsohn and others 1998), Bellevue Hospital Center, New York City	Cross-sectional	African-American and Hispanic children screened for BPb at pediatric clinic during 1993-1995; levels consistently <25 $\mu\text{g/dL}$	68 children age 1-3 yr, BSID	Capillary BPb, range 10-24.9 $\mu\text{g/dL}$		Child age, sex, immigrant status, iron deficiency, cognitive stimulation, maternal age, verbal IQ, education, Latino ethnicity, public assistance status, parity
Multiple regression, change in MDI at age 1-3 yr, current capillary BPb ≥ 10 vs <10 $\mu\text{g/dL}$	$\beta = -6.2, -10.8$ to -1.7	PDI vs current capillary BPb (continuous var)	Pearson's r = -0.15, p=.22			
(Factor-Litvak and others 1999), Kosovo	Birth cohort	Lead smelter and comparison town	Examined 463 infants at age 6 mos; Bayley Scales at age 6, 12, 18, and 24 mos	Smelter town: enrolled infants in 3 strata - <15, 15-20, >20 $\mu\text{g/dL}$	Mean cord BPb levels in the smelter and comparison towns were 22 vs 5.4 $\mu\text{g/dL}$	Maternal education and IQ, ethnicity, and HOME score

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Multiple regression, change in MDI per unit change in log ₁₀ current BPb	Age 2 yr β =-5.3, -10.1 to -0.5					
(Stewart and others 2000), Oswego Newborn and Infant Development Project, New York State	Birth cohort	141 neonates of women exposed to Lake Ontario fish and 152 neonates of unexposed women	Neonatal Behavioral Assessment Scale (NBAS) on postnatal days 1 and 2	Maternal fish consumption; measured cord BPb and other contaminants	50 th and 75 th percentiles cord BPb = 1.7 and 2.0 μ g/dL	HOME scores, parental education, SES, paternal age, prepregnancy weight, prenatal weight gain, stress, smoking, ETS, caffeine, prenatal vitamin and prescription drug use, child sex, birth weight, head circumference
Change in % poor NBAS scores (at least 1 SD below mean) per tertile change in cord BPb	β =-0.028, p=.69					
(Darvill and others 2000), Oswego Newborn and Infant Development Project, New York State	Birth cohort	See Stewart et al 2000 above; offspring of women consuming Lake Ontario fish;	Examined 230 infants at 6 mos and 216 at 12 mos using the Fagan Test of Infant Intelligence (a test of preference for a novel stimulus –		Median contaminant levels were cord blood total PCBs (0.5 μ g/L) and lead (2.0 μ g/dL), breast milk total PCBs (153 ng/g lipid) and maternal hair mercury (0.5 μ g/g)	HOME score, parental ages, maternal education, height, weight, prepregnancy weight, weight gain during pregnancy, nutrition scale, herbal tea, caffeine, vitamin and non-prescription drug use, stress before

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			the latter implies intact short term memory)			pregnancy, smoking, prenatal child sex, parity, birth weight
Fagan test scores vs cord BPb levels	Age 6 mos Pearson's r=-0.40, p=.54	Age 12 mos Pearson's r=-0.10, p=.15				
(Gomaa and others 2002), Mexico City	Longitudinal cohort,		197 mother-infant pairs; BSID-II (Spanish Version) at age 24 mos	Measured umbilical cord BPb and maternal cortical (tibial) and trabecular (patellar) bone lead within 4 wk of delivery		Maternal IQ, age, child sex, parental education, marital status, breast-feeding duration, child hospitalization status
Multiple regression coefficient, change in Bayley MDI at age 24 mos vs ln cord blood and 4 th vs 1 st quartiles of maternal patellar bone lead levels	Cord BPb β =-4.48±2.04(SE), p=.03	Maternal bone lead β =-6.48±2.79, p=.02				
(Emory and others 2003), Atlanta, Georgia	Birth cohort	79 African-American infants	Fagan Test of Infant Intelligence (FTII) at age 7 mos	Measured maternal and cord BPb levels	All maternal BPb levels <5 µg/dL (mean 0.7 µg/dL, range 0.05-3.3)	All children were from low-income African American households
Mean maternal BPb, 15 th vs 85 th percentile FTII subgroups	15 th percentile FTII 0.94±0.26(SD)	85 th percentile FTII 0.44±0.15 µg/dL, n=12				

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	µg/dL, n=12	t=5.77, p<.001				
(Tellez-Rojo and others 2006), Mexico City	Birth cohort	Mexico City, recruited during 1994-95 and 1997-99 at maternity hospitals serving low and middle income populations, term births, birth wt at least 2 kg	294 children, BSID at ages 1 and 2	Children restricted to those with BPb <10 µg/dL at ages 1 and 2 yr	BPb levels: cord – mean 5.49±3.43(SD), 12 mos 4.66±2.87, 24 mos 5.78±4.10	Birth weight, sex, age at exam, maternal IQ, cohort
Longitudinal model, change in MDI at age 1 and 2 yr per unit change in ln BPb at stated age	BPb age 1 yr β=-1.14, -3.4 to 1.11	BPb age 2 yr β=-4.70, -6.97 to -2.44	Change in MDI at age 1 or 2 yr per unit change in ln current BPb	Age 1 yr β=-0.15, p=.57	Age 2 yr β=-1.04, p<.01	
(Hu and others 2006), Mexico City	Birth cohort	Recruited during 1997-99 during prenatal visits at 3 clinics in Mexico City	146 mother-infant pairs; BSID at age 24 mos		Maternal blood and plasma lead at GW 12, 24 and 34; cord and infant blood at age 24 mos; used log _e blood lead in all statistical analyses; mean maternal blood lead (1 st T=7.07 µg/dL, 2 nd T=6.08 µg/dL, 3 rd T=6.86 µg/dL); mean infant blood lead (cord=6.20, 12 mos=5.22, 24 mos=4.79 µg/dL)	Blood lead at other times (prenatal, current), sex, height for age Z-score, current wt, mat IQ, mat age
Change in MDI per SD	1 st trimester	2 nd trimester BPb	3 rd trimester BPb	Current BPb	Change in MDI per	1 st trimester BPb

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
increment of natural log blood lead ($\mu\text{g/dL}$), adj for blood lead in other trimesters or current blood lead	BPb $\beta=-3.54$, $p=.03$	$\beta=0.80$, $p=.65$	$\beta=1.18$, $p=.44$	$\beta=-0.01$, $p=.62$	natural log blood lead ($\mu\text{g/dL}$)	$\beta=-6.39$, $p=.04$
Change in MDI per SD increment of natural log plasma lead ($\mu\text{g/L}$), adj for plasma lead in other trimesters or current plasma lead	1 st trimester BPb $\beta=-2.40$, $p=.19$	2 nd trimester BPb $\beta=-1.29$, $p=.56$	3 rd trimester BPb $\beta=1.42$, $p=.46$	Current BPb $\beta=-0.01$, $p=.80$	Change in MDI per natural log plasma lead ($\mu\text{g/L}$)	1 st trimester BPb $\beta=-6.94$, $p=.04$

Summary: Cognitive function, age 0-2

Reviews

A review noted that 3 of the 5 birth cohort studies reported by mid-1989 observed inverse associations between Bayley's Mental Development Index (MDI) scores at age 6-24 months and maternal or cord blood lead levels in analyses adjusted for potential confounders (Thacker and others 1992).

Original studies published since 1998

Maternal exposure, limited evidence

In a small birth cohort in Shanghai, MDI scores were reduced among infants with elevated cord blood lead levels (≥ 10 vs < 10 $\mu\text{g/dL}$, mean MDI scores at age 6 months, 82.0 vs 88.3, $F=4.78$, $p=.03$; mean MDI scores at age 12 months, 95.1 vs 100.3, $F=5.00$, $p=.03$) (Shen and others 1998). In the Oswego birth cohort study (consumers of Lake Ontario sports-caught fish), Neonatal Behavioral Assessment Scale (NBAS) scores on postnatal days 1 or 2 were not associated with cord blood lead levels ($\beta=-0.03$, $p=.69$) (Stewart and others 2000). This study also reported no correlation between Fagan intelligence test scores at ages 6 and 12 months and cord blood lead levels (age 6 months, Pearson's $r=-0.40$, $p=.54$; age 12 months, $r=-0.10$, $p=.15$) (Darvill and others 2000). In a Mexico City birth cohort, Bayley MDI scores at age 24 months were inversely associated with natural log cord blood lead ($\beta=-4.48 \pm 2.04(\text{SE})$, $p=.03$) and maternal patellar bone lead levels (4th vs 1st quartile, $\beta=-6.48 \pm 2.79$, $p=.02$) (Gomaa and others 2002). After adjustment for other prenatal and postnatal lead concentrations, the only statistically significant lead exposure predictor of Bayley MDI at age 2 in the Mexico City birth cohort was 1st trimester maternal blood lead (change in Bayley MDI per SD increment of natural log blood lead, $\beta=-3.54$, $p=.03$); there was also a statistically non-significant inverse relation between MDI and maternal 1st trimester plasma lead concentration ($\beta=-2.40$, $p=.19$) (Hu and others 2006). A small birth cohort study in Atlanta reported that relatively low Fagan intelligence scores at age 7 months were associated with higher prenatal maternal blood lead levels (all were below 5 $\mu\text{g/dL}$) (difference in mean maternal blood lead, 15th vs 85th percentile Fagan scores, $0.94 \pm 0.26(\text{SD})$ vs 0.44 ± 0.15 $\mu\text{g/dL}$, $t=5.77$, $p<.001$) (Emory and others 2003).

Postnatal exposure, limited evidence

A birth cohort study in a Kosovo smelter and comparison town found an inverse dose-response relationship between MDI at age 2 years and current blood lead levels (MDI vs log current blood lead, $\beta=-5.3$, 95% CI -10.1 to -0.5) (Factor-Litvak and others 1999). A small cross-sectional study in New York City found an inverse association between Bayley MDI scores among children age 12-36 months and current blood lead levels ($\beta=-6.2$, 95% CI -10.8 to -1.7) (Mendelsohn and others 1998). In a single trimester analytic model, the Mexico City birth cohort found an inverse association between Bayley MDI scores at age 2 years and current blood lead ($\beta=-1.04$, $p<.01$) (Tellez-Rojo and others 2006). However, in a multi-trimester model, with adjustment for prenatal maternal blood lead concentrations in each trimester, Bayley MDI at age 2 was not associated with current blood lead level ($\beta=-0.01$, $p=.62$) (Hu and others 2006).

7c. Cognitive function, age 3 or older

Original studies published since 1998

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Tong and others 1998), Port Pirie, Australia	Birth cohort	Mother-infant pairs recruited in lead smelter town and surrounding region, 1979-82	375 children followed from birth to age 11-13; conducted Bayley Scales at age 2 yr, McCarthy Scales of Children's Abilities at age 4 yr, and WISC-R at ages 7 and 11-13 yr	Mean BPb at birth, ages 6, 15, and 24 mos, ages 3, 4, 5, 6, 7, and 11-13 yr were 8.5, 14.5, 21, 21, 19, 15, 14, 13, 12, and 7.9 µg/dL	Lifetime mean BPb was 14 (range 5.0-32 µg/dL)	Sex, birth weight, birth order, breastfeeding, maternal IQ, maternal age at subject's birth, SES, HOME score, parental smoking, parents living together
Change in full-scale IQ scores vs BPb decline between age 7 and 11-13 yr	BPb decline <2.3 µg/dL -5.4, -3.8 to -7.0 2.3-4.9 µg/dL -5.0, -3.2 to -6.8	>4.9 µg/dL -3.8, -2.3 to -5.3 p-trend=.45	BPb decrements vs changes in full-scale IQ scores between age 7 and 11-13 yr	r=0.12, p=.09		
(Walkowiak and others 1998), 3 cities in Germany	Cross-sectional	Recruited during 1991 in 3 cities in former East Germany; lead sources included smelters, other industry and lead pipes	384 children age 5-7 yr; Simple Reaction Time and Continuous Performance Test		Geometric mean BPb 4.3 (range 1.4-17 µg/dL)	Various combinations of variables including age, birth weight, number of siblings, height, nationality, education, sex, prenatal maternal smoking, duration of breastfeeding
Multiple linear regression coefficient, WISC vocabulary plus block design test score	slope b=-1.17, p<.10					

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
vs log BPb						
(Factor-Litvak and others 1999), Kosovo	Birth cohort	Lead smelter and comparison town	McCarthy Scales at age 4 yr (n=331) and Wechsler Intelligence Scales at age 7 yr (n=301)	Enrolled infants in 3 cord BPb strata - <15, 15-20, and >20 µg/dL	Mean cord BPb levels in the smelter and comparison towns were 22 vs 5.4 µg/dL	Maternal education and IQ, ethnicity, and HOME score
Multiple regression, change in McCarthy GCI per unit change in log ₁₀ current BPb	Age 4 yr β=-9.4, -14.2 to -4.6	Multiple regression, change in Wechsler full-scale IQ per unit change in log ₁₀ current BPb	Age 7 yr β=-9.0, -12.4 to -5.5	Strongest associations were those between cognitive fcn at a given age and current BPb		
(Tong and others 2000), Port Pirie, Australia	Birth cohort	Mother-infant pairs recruited in lead smelter town and surrounding region, 1979-82	375 children followed from birth to age 11-13; conducted WISC-R at ages 7 and 11-13 yr	Mean BPb at birth, ages 6, 15, and 24 mos, ages 3, 4, 5, 6, 7, and 11-13 yr were 8.5, 14.5, 21, 21, 19, 15, 14, 13, 12, and 7.9 µg/dL	Lifetime mean BPb was 14 (range 5.0-32 µg/dL)	Sex, birth weight, birth order, breastfeeding, maternal IQ, maternal age at subject's birth, SES, HOME score, parental smoking, parents living together
Regression coefficient, full-scale IQ at age 11-13 vs log lifetime average blood lead level	Girls β=-7.4, -1.7 to -13.1	Boys β=-2.6, -8.0 to 2.9				
(Lanphear and others 2000), NHANES III, USA,	Cross-sectional		4,853 children age 6-16 yr; Arithmetic and Reading subtests of the		Geometric mean BPb 1.9±0.1 µg/dL; 2.1% had	Sex, race/ethnicity, poverty index ratio, parental education, and

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			Wide Range Achievement Test-Revised (WRAT) and the Block Design and Digit Span subtests of WISC-R		levels ≥ 10 $\mu\text{g/dL}$	serum ferritin and cotinine; prenatal/postnatal tobacco smoke, low birth weight, and admission to neonatal intensive care units were not confounders
Change in test score per unit change in current BPb, total group	Arithmetic $\beta=-0.70\pm0.17$ reading $\beta=-0.99\pm0.19$	block design $\beta=-0.10\pm0.04$ digit span $\beta=-0.05\pm0.02$	Change in test score per unit change in current BPb, children with BPb <5 $\mu\text{g/dL}$	Arithmetic $\beta=-1.06\pm0.48$ reading $\beta=-1.66\pm0.36$	block design $\beta=-0.05\pm0.07$ digit span $\beta=-0.09\pm0.07$	
(Wasserman and others 2000a), Yugoslavia	Birth cohort	Examined 442 children with at least one IQ measurement at ages 3, 4, 5, or 7 yr	McCarthy Scales of Children's Abilities at ages 3 and 4 yr, Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) at age 5 and WISC-III at age 7	Average BPb from age 2 to 7 yr was 17.4 $\mu\text{g/dL}$; prenatal blood lead estimated as log average maternal blood lead in 2 nd T and at delivery	Evaluated change in BPb over time; postnatal blood lead categorized as early (age 0-2) and later (age 2 to age at testing)	HOME score, ethnicity, maternal age, education, IQ, and parity, infant sex, birth weight, assessment age, postnatal BPb increment of at least 50% from birth to age 2 yr or from age 2 yr to age at follow-up, prenatal maternal BPb
Change in full-scale IQ at age 3-7 per log increment in prenatal maternal BPb, adjusted for at least 50% increased BPb during childhood and other var.s	Prenatal BPb $\beta=-6.05\pm1.35$, $p<.001$	Change in full-scale IQ at age 3-7 for children with a postnatal increase of at least 50% in BPb (compared to prenatal), adjusted for prenatal BPb and	Persistent postnatal BPb increase of at least 50% $\beta=-2.71\pm1.12$, $p<.05$			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		other var.s				
(Schnaas and others 2000), Mexico City	Birth cohort	Recruited 502 pregnant women at GW 12; 436 normal pregnancies	112 children age 5 yr; measured GCI using McCarthy scales every 6 mos from age 3 to 5 yr	Measured maternal blood lead at GW 12, 20, 28 and 36, delivery and infant blood lead at birth, age 6 mos and every 6 mos until age 54 mos	Assessed mean BPb levels at age 6-18, 24-36 and 42-54 mos were 10.1, 9.7 and 8.4 µg/dL	Maternal IQ, sex, Apgar score at 5 min, birth weight, birth order, maternal education, family SES
Change in GCI at age 48 mos per ln increment of average BPb level at ages 24, 30 and 36 mos	-5.8 pts, p=.02	GCI scores at various ages not associated with maternal (prenatal or at delivery) or cord BPb levels	Result stated without supporting data			
(Calderon and others 2001), Mexico,	Cross-sectional		Children age 6-9 yr (41 living near smelter, 39 from unexposed area but with lower SES); WISC-RM (revised version for Mexico)		Geometric mean BPb levels in the exposed and comparison regions were 8.9±0.03 and 9.7±0.02 µg/dL	Sex, age, SES, parental education, transferrin saturation, height by age index
Full-scale IQ vs BPb (partial correlation coefficient for IQ vs BPb)	-0.18, p=0.13					
(Canfield and others 2003a), Rochester,	Cohort	276 children enrolled at age 5-7 mos in	Conducted Stanford-Binet Intelligence Scale	Mean levels at ages 6, 12 and	Lifetime avg, peak and current	Child's sex, birth weight, iron status

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
New York		dust-control efficacy study, 1994-95	at ages 3 (n=151) and 5 yr (n=154); tested vocabulary, spatial pattern analysis, quantitative ability, memory	60 mos were 3.4, 9.7 and 6.0 $\mu\text{g}/\text{dL}$	BPb levels at age 5 were: 7.4, 11.1 and 5.8 $\mu\text{g}/\text{dL}$	(serum transferrin saturation at ages 3 and 5 yr), maternal IQ, education, race, prenatal smoking, household income, HOME score
Change in IQ at ages 3 or 5 yr per unit change in BPb, all children	lifetime $\beta=-0.46\pm 0.15$, $p=.004$ peak $\beta=-0.23\pm 0.09$, $p=.01$ concurrent $\beta=-0.46\pm 0.14$, $p=.002$ 6-24 mos $\beta=-0.43\pm 0.17$, $p=.02$	Change in IQ at ages 3 or 5 yr per unit change in BPb, subgroup with peak BPb <10 $\mu\text{g}/\text{dL}$	lifetime $\beta=-1.37\pm 0.60$, $p=.03$ peak $\beta=-1.40\pm 0.48$, $p=.005$ concurrent $\beta=-1.58\pm 0.46$, $p=.001$ 6-24 mos $\beta=-0.75\pm 0.51$, $p=.15$	IQ deficit per 10 $\mu\text{g}/\text{dL}$ increment of average lifetime BPb	All children $\beta=-4.6$, -7.6 to -1.5 Children with peak BPb <10 $\mu\text{g}/\text{dL}$ $\beta=-14$, -26 to -1.7	
(Bellinger and Needleman 2003), Boston, USA	Cohort		48 children age 10 yr whose BPb from birth to age 10 yr never exceeded 10 $\mu\text{g}/\text{dL}$	BPb measured at birth and at ages 6, 12, 18, 24, 57 and 120 months		
Change in IQ at age 10 per unit change in peak BPb since birth	peak BPb since birth <10 $\mu\text{g}/\text{dL}$ $\beta=-1.56$, $p=.03$	peak ≥ 10 $\mu\text{g}/\text{dL}$ $\beta=-0.58$				
(Wasserman and others 2003), Kosovo	Birth cohort,	Mother-infant pairs in lead smelter and	244 children reexamined at age 12	Measured tibial bone lead at	Assessed \log_{10} avg BPb levels	Ethnicity, birth order, birth weight, sex,

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		comparison town	yr, WISC-III at ages 10 and 12 yr	ages 11-13 yr	from birth to age 12	HOME score, maternal age, education, IQ
Change in full-scale IQ at age 10-12 per unit change in blood or bone lead levels	<p>Avg \log_{10} serial BPb $\beta=-5.02\pm 2.36$</p> <p>\log_{10} bone Pb $\beta=-8.00\pm 2.29$</p> <p>Current BPb $\beta=-4.48\pm 2.15$</p>	Change in full-scale IQ at age 10-12 per unit change in blood or bone lead levels in a model with both blood and bone Pb	<p>\log_{10} bone Pb $\beta=-11.16\pm 3.83$</p> <p>Avg \log_{10} serial BPb $\beta=3.97\pm 3.85$</p>			
(Chiodo and others 2004), Detroit	Birth cohort		237 African American inner-city children followed to age 7-8 yr; WISC-III and several other neuropsychological tests		Mean current BPb was 5.4 ± 3.3 (SD) $\mu\text{g/dL}$	Maternal SES, education, vocabulary score, parity, number of children age < 18 yr, HOME score, sex, family environment score
Change in full-scale IQ at age 7-8 per unit change in current BPb	$\beta=-0.20$, $p<.01$ (SE or CI not stated)	Full-scale IQ at age 7-8 yr vs current BPb level when dichotomized at various BPb levels	<p>BPb $3+<3$ $\beta=-0.18$, $p<.01$</p> <p>BPb $5+<5$ $\beta=-0.14$, $p<.05$</p>	<p>BPb $7.5+<7.5$ $\beta=-0.12$, $p<.1$</p> <p>BPb $10+<10$ $\beta=-0.10$, $p<.1$</p>	Scatter plot showed inverse linear trend across range 1-25 $\mu\text{g/dL}$	
(Ris and others 2004), Cincinnati	Birth cohort	Excluded mothers known to be diabetic, alcoholic, or addicted to drugs and those with neurologic disorders, psychoses	195 children, recruited during 1979-1985, followed to age 15-17 yr, 92% African-American; standardized	Measured prenatal maternal and childhood BPb levels – quarterly until		Maternal IQ, SES, avg HOME score, adolescent marijuana use, obstetrical complications, sex, age at assessment,

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		or mental retardation	neuropsychological tests	age 5 yr, again at age 5.5, 6 and 6.5 yr		education of primary caregiver
Change in learning/IQ score at age 15-17 per unit change in BPb	Prenatal BPb $\beta=-0.075\pm 0.054$, $p=.17$	Avg postnatal BPb $\beta=-0.034\pm 0.029$, $p=.25$	BPb age 6-7 yr $\beta=-0.119\pm 0.051$, $p=0.02$			
(Lanphear and others 2005), USA	Pooled analysis; assessed full-scale IQ score	1,333 children, participated in 7 international population-based longitudinal studies, followed from birth or infancy until age 5-10 years		Median peak BPb was 18 $\mu\text{g/dL}$ (at age 2.5 yr); median BPb was 9.7 $\mu\text{g/dL}$ at age 5-7	5 th and 95 th BPb percentiles were 2.4 and 30 $\mu\text{g/dL}$	
Change in IQ for a change in BPb from 5 th to 95 th percentile (Early childhood BPb $\beta=-2.04, -3.27$ to -0.81 Peak BPb $\beta=-2.85, -4.10$ to -1.60	Lifetime avg BPb $\beta=-3.04, -4.33$ to -1.75 Current BPb $\beta=-2.70, -3.74$ to -1.66	Change in IQ for given changes in current BPb, log-linear model	2.4-10 $\mu\text{g/dL}$ $\beta=-3.9, -2.4$ to -5.3 10-20 $\mu\text{g/dL}$ $\beta=-1.9, -2.6$ to -1.2	20-30 $\mu\text{g/dL}$ $\beta=-1.1, -1.5$ to -0.7 2.4-30 $\mu\text{g/dL}$ $\beta=-6.9, -4.2$ to -9.4	
(Yolton and others 2005), USA	Cross-sectional	4399 children age 6-16	Conducted Arithmetic and Reading subtests of the Wide Range Achievement Test-Revised (WRAT) and the Block Design and	Measured blood lead, serum cotinine and ferritin	Geometric mean BPb 1.9 ± 0.1 $\mu\text{g/dL}$; 2.1% had levels ≥ 10 $\mu\text{g/dL}$	Sex, race/ethnicity, poverty index ratio, parental education, marital status, child's serum ferritin and cotinine

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			Digit Span subtests of WISC-III			
Test score vs blood lead (ng/L)	Math $\beta=-0.57\pm0.17$, $p<.005$	Reading $\beta=-0.80\pm0.21$, $p<.001$	Block design $\beta=-0.08\pm0.03$, $p<.05$	Digit span $\beta=-0.03\pm0.02$, $p>.05$		
(Chen and others 2005), Baltimore, Cincinnati, Newark, Philadelphia	Randomized trial	BSID at baseline, Wechsler preschool IQ at age 3, WISC at age 5	780 children age 12-33 mos with BPb 20-44 $\mu\text{g/dL}$; tested succimer treatment vs placebo	Measured BPb at intervals before and after each treatment	Up to 24 BPb measurements per child	Clinic centre, race, sex, language, parental education and employment, single parent, age at BPb test, caregiver IQ
Change in MDI at age 12-33 mos per 10 $\mu\text{g/dL}$ increment in BPb at age 2 yr	$\beta=-2.9$, -4.7 to -1.0	Change in IQ at age 7 per 10 $\mu\text{g/dL}$ BPb increment	BPb age 2 $\beta=-1.1$, -2.9 to 0.7 BPb age 5 $\beta=-2.9$, -4.8 to -1.1	BPb age 7 $\beta=-5.4$, -7.8 to -2.9 Peak BPb $\beta=-0.7$, -2.1 to 0.7	Average BPb $\beta=-3.3$, -5.4 to -1.1	
(Schnaas and others 2006), Mexico City	Cohort	Recruited at clinic during 1987-1992, followed to 2002	150 children age 6-10; Wechsler Intelligence Scale for Children-Revised, Spanish version	Measured BPb at various ages	GM BPb: pregnancy 8.0 $\mu\text{g/dL}$ (range, 1-33); age 1-5 yr 9.8 $\mu\text{g/dL}$ (2.8-36.4); age 6-10 yr 6.2 $\mu\text{g/dL}$ (2.2-18.6)	
IQ at age 6-10 vs ln BPb, adjusted for BPb at other time points	3 rd trimester BPb $\beta=-3.90$, -6.45	BPb age 1-5 y $\beta=0.10$, -3.88 to 4.06	BPb age 6-10 y $\beta=0.17$, -1.41 to 1.76		The dose-response BPb-IQ function was	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
	to -1.36				log-linear, strongest effects on IQ within the first few $\mu\text{g/dL}$	

Summary: Cognitive function, age 3 or older

Reviews

Several meta-analyses and literature reviews covering studies published before 1996 provided limited evidence that relatively low-level postnatal lead exposure, as indicated by blood or dentin lead levels, caused cognitive deficits in school-age children (Banks and others 1997; Needleman and Gatsonis 1990; Pocock and others 1994; Schwartz 1994; Thacker and others 1992). The estimated average full-scale IQ deficit from a blood lead increment from 10 to 20 $\mu\text{g/dL}$ was 2-3 points (Pocock and others 1994; Schwartz 1994). In a reanalysis of two birth cohort studies (Bellinger and others 1991b; Needleman and others 1979), there were inverse dose-response relationships in non-parametric smoothing models between Bayley MDI scores and blood lead levels and between WISC full-scale IQ scores and dentin lead levels across the observed ranges with no apparent thresholds (Schwartz 1993). Schwartz also noted that these associations were insensitive to exclusion of outliers, inclusion of covariates and robust estimation techniques (Schwartz 1993). Recent assessments have concluded that there is now good evidence for adverse effects of lead on behavioural and cognitive development of children at blood lead levels below 10 $\mu\text{g/dL}$ (Bellinger 2004; Koller and others 2004; Lidsky and Schneider 2003). Bellinger also noted that: (i) no threshold below which lead has no adverse developmental effects has been demonstrated, i.e., no apparent safe level of lead exposure; (ii) there appears to be a steeper slope for the inverse association between IQ and blood lead below 10 $\mu\text{g/dL}$ compared to higher levels (Bellinger 2004). Most impressively, a pooled analysis of 7 international population-based longitudinal studies, that followed a total of 1333 children from birth or infancy until age 5-10 years revealed inverse associations between full-scale IQ and postnatal lead exposure indices including early childhood levels ($\beta=-2.04, -3.27$ to -0.81), peak blood lead ($\beta=-2.85, -4.10$ to -1.60), lifetime average blood lead ($\beta=-3.04, -4.33$ to -1.75) and current blood lead ($\beta=-2.70, -3.74$ to -1.66) (Lanphear and others 2005). A recent review concluded that the best fit for the relationship between childhood cognitive scores and blood lead concentrations is inverse log-linear (using the natural log of blood lead concentration) (Rothenberg and Rothenberg 2005).

Original studies published since 1998

Low-level prenatal exposure, limited evidence

In the Yugoslavia/Kosovo birth cohort, full-scale IQ at age 3-7 was inversely associated with log average maternal blood lead during 2nd trimester and at delivery, adjusted for postnatal blood lead increases of at least 50% ($\beta=-6.05\pm 1.35, p<.001$) (Wasserman and others 2000a). In a Cincinnati birth cohort comprised mainly of African-American children, there was a statistically non-significant inverse relationship between IQ at age 15-17 and prenatal maternal blood lead ($\beta=-0.075\pm 0.054, p=.17$) (Ris and others 2004). In the Mexico City birth cohort study, IQ at age 6-10 was inversely associated with 3rd trimester maternal blood lead (per natural log blood lead increment, $\beta=-3.90, -6.45$ to -1.36) but not with postnatal blood lead at age 1-5 ($\beta=0.10, -3.88$ to 4.06) or 6-10 ($\beta=0.17, -1.41$ to 1.76), in analyses that adjusted for blood lead levels at other time periods (Schnaas and others 2006).

Low-level childhood exposure, sufficient evidence

In the Port Pirie cohort, full-scale IQ at age 11-13 was inversely associated with log lifetime average blood lead level in girls ($\beta=-7.4$, -1.7 to -13.1) but not significantly so in boys ($\beta=-2.6$, -8.0 to 2.9) (Tong and others 2000). The (Tong and others 1996; Tong and others 1998) Yugoslavia/Kosovo birth cohort reported inverse associations between McCarthy GCI at age 7 and log blood lead at age 4 ($\beta=-9.4$, -14.2 to -4.6) and age 7 ($\beta=-9.0$, -12.4 to -5.5) (Factor-Litvak and others 1999) and between WISC-III full-scale IQ at age 10-12 and log average lifetime blood lead ($\beta=-5.02\pm 2.36$) or log current blood lead ($\beta=-4.48\pm 2.15$) (Wasserman and others 2003). This study also showed an inverse association between full-scale IQ at age 3-7 and postnatal blood lead increases of at least 50%, adjusted for average maternal blood lead during 2nd trimester and at delivery ($\beta=-2.71\pm 1.12$, $p<.05$) (Wasserman and others 2000a). When both tibial bone lead at age 11-13 and average lifetime blood lead were included in the same model, full-scale IQ was inversely associated with log tibial bone lead ($\beta=-11.16\pm 3.83$) but not with log lifetime blood lead ($\beta=3.97\pm 3.85$) (Wasserman and others 2003). In a small Mexico City birth cohort, McCarthy GCI scores at age 4 were inversely associated with natural log average blood lead level based on measurements at ages 24, 30 and 36 months (change in GCI score per natural log increment of average blood lead from age 24 to 36 months, $\beta=-5.8$ points, $p=.02$) (Schnaas and others 2000). In the Rochester birth cohort, full-scale IQ at age 3-5 was inversely associated with various blood lead indices including lifetime average (change in IQ per unit change in blood lead ($\mu\text{g/dL}$), $\beta=-0.46\pm 0.15$, $p=.004$), peak ($\beta=-0.23\pm 0.09$, $p=.01$), current ($\beta=-0.46\pm 0.14$, $p=.002$) and average at age 6-24 months ($\beta=-0.43\pm 0.17$, $p=.02$) (Canfield and others 2003a). The reduction in full-scale IQ per unit change in blood lead was greater among children with blood lead levels below 10 $\mu\text{g/dL}$ (per unit change in current blood lead ($\mu\text{g/dL}$), $\beta=-1.58\pm 0.46$, $p=.001$). Among children in a Boston birth cohort whose blood lead level since birth never exceeded 10 $\mu\text{g/dL}$, there was an inverse association between full-scale IQ at age 10 and blood lead level at age 2 (per 10 $\mu\text{g/dL}$ increment, $\beta=-1.56$, $p=.03$) (Bellinger and Needleman 2003). Among a Detroit African-American birth cohort, full-scale IQ at age 7-8 was inversely associated with current blood lead ($\beta=-0.20$, $p<.01$) (Chiodo and others 2004). In a Cincinnati birth cohort comprised mainly of African-American children, there was an inverse relationship between IQ at age 15-17 and blood lead at age 6-7 ($\beta=-0.12\pm 0.05$, $p=0.02$) (Ris and others 2004). Follow-up of participants in a randomized trial of succimer vs placebo for blood lead levels of 20-44 $\mu\text{g/dL}$ at age 12-33 months revealed an inverse association between full-scale IQ at age 7 and blood lead at age 2 (per 10 $\mu\text{g/dL}$ blood lead increment, $\beta=-5.4$, 95% CI .78 to -2.9) (Chen and others 2005). (Factor-Litvak and others 1999; Wasserman and others 2000a; Wasserman and others 2003; Bellinger and Needleman 2003) The Port Pirie cohort reported a weak correlation between changes in full-scale IQ and blood lead decrements between age 7 and 11-13 ($r=0.12$, $p=.09$) (Tong and others 1998).

In a pooled analysis of 7 longitudinal cohort studies (involving 1,333 children), there were inverse dose-response relationships between IQ and early-childhood, peak, lifetime average and current blood lead levels (Lanphear and others 2005). Over the blood lead range 2.4-30 $\mu\text{g/dL}$, the average adjusted IQ decrement estimated using a log-linear model was 6.9 points (95% CI 4.2-9.4). Even among children with current blood lead levels below 10 $\mu\text{g/dL}$, there was an inverse association with full-scale IQ ($\beta=-3.9$, 95% CI -2.4 to -5.3). In sum, recent birth cohort studies and a pooled analysis have demonstrated significant inverse associations between full-scale IQ among children age 3 or older and relatively low-level childhood blood lead levels (current, previous or lifetime average). Findings included dose-response relationships and independence from several potential confounders. A notable exception was the Mexico City birth cohort study in which IQ at age 6-10 was inversely associated with 3rd trimester maternal blood lead (see above) but not with blood lead at age 1-5 (per natural log blood lead increment, $\beta=0.10$, -3.88 to 4.06) or 6-10 ($\beta=0.17$, -1.41 to 1.76), in analyses that adjusted for blood lead levels at other time periods (Schnaas and others 2006).

In a German cross-sectional study, there was an inverse association of borderline statistical significance between WISC vocabulary plus block design test scores and current blood lead ($b=-1.17$, $p<.10$) (Walkowiak and others 1998). A large cross-sectional study, based on almost 5000 children age 6-16 in NHANES III, found inverse associations between scores on 4 subscales of the Wide Range Achievement Test-Revised and WISC-R and current blood lead level, independent of several potential confounders, including arithmetic ($\beta=-0.70\pm 0.17$), reading ($\beta=-0.99\pm 0.19$), block design ($\beta=-0.10\pm 0.04$) and digit span ($\beta=-0.05\pm 0.02$)

(Lanphear and others 2000). Further analysis of children enrolled in NHANES III confirmed inverse dose-response relationships between arithmetic, reading and block design scores in analyses adjusted for several potential confounders including serum cotinine (Yolton and others 2005). A small cross-sectional study of children age 6-9 living near a lead smelter or unexposed comparison region revealed a statistically non-significant inverse relationship between full-scaled IQ and current blood lead (partial correlation coefficient -0.18, $p=.13$) (Calderon and others 2001).

7d. Psychomotor function

Original studies published since 1998

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Counter and others 1998), Ecuador	Cross-sectional	77 low SES children age 4-15 yr, resided in 2 Andean villages with lead recycling and glazing activities	Finger tapping and other tests	Mean BPb levels in boys and girls were 52 and 40 $\mu\text{g/dL}$ (range 6.6-119 $\mu\text{g/dL}$)	No adjustment for potential confounders	
Mean BPb, children with abnormal vs normal finger tapping scores	62.3 \pm 25.4(SD) vs 39.9 \pm 23.8 p=0.004					
(Walkowiak and others 1998), 3 cities in Germany	Cross-sectional	Recruited during 1991 in 3 cities in former East Germany; lead sources included smelters, other industry and lead pipes	384 children age 5-7 yr; Simple Reaction Time and Continuous Performance Test		Geometric mean BPb 4.3 (range 1.4-17 $\mu\text{g/dL}$)	Various combinations of variables including age, birth weight, number of siblings, height, nationality, education, sex, prenatal maternal smoking, duration of breastfeeding
Multiple linear regression coefficient, test score vs log BPb	Maximum Finger Tapping Test score slope b=-0.38, p>.05	Simple Reaction Time slope b=0.04, p>.05				
(Wasserman and others 2000b), Kosovo	Birth cohort	283 children examined at age 54 mos	Modified Bruininks Oseretsky Test of Motor Proficiency,	Mean BPb levels at birth and at age 4 yr were 22 and 40	Maternal age, parental education,	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			Beery Test of Visual Motor Integration (VMI)	$\mu\text{g/dL}$ in smelter town and 5.4 and 9.6 $\mu\text{g/dL}$ in comparison town	birth order, HOME scores, maternal IQ, birth weight	
Change in fine motor score per unit change in average lifetime BPb (log base 10)	Fine motor $\beta=-2.06\pm 0.68$	Gross motor $\beta=0.36\pm 0.80$				
(Ris and others 2004), Cincinnati	Birth cohort	195 children, recruited during 1979-1985, followed to age 15-17 yr, 92% African-American	Standardized neuropsychological tests in 1997-99; fine motor function assessed by Grooved Pegboard Test and Finger Tapping Test	Measured prenatal maternal and childhood BPb levels – quarterly until age 5 yr, again at age 5.5, 6 and 6.5 yr	Maternal IQ, SES, avg HOME score, adolescent marijuana use, sex	
Multiple regression, change in fine motor score at age 15-17 per unit change in BPb	Prenatal BPb $\beta=-.017\pm .020$, $p=.42$	BPb age 6 $\beta=-.046\pm .016$, $p=.004$	Avg postnatal BPb $\beta=-.016\pm .013$, $p=.21$			
(Tellez-Rojo and others 2006), Mexico City	Birth cohort	Mexico City, recruited during 1994-95 and 1997-99 at maternity hospitals serving low and middle income populations, term births, birth wt at least 2 kg	294 children, BSID at ages 1 and 2	Children restricted to those with BPb $<10 \mu\text{g/dL}$ at ages 1 and 2 yr BPb levels: cord – mean $5.49\pm 3.43(\text{SD})$, 12 mos 4.66 ± 2.87 , 24 mos 5.78 ± 4.10	Birth weight, sex, age at exam, maternal IQ, cohort	
Longitudinal model, change in PDI at age 1	BPb age 1 yr $\beta=-0.42$, -2.31	Change in PDI at age 1 or age 2 per unit	Age 1 yr $\beta=-0.01$, $p=.98$			

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
and 2 yr per unit change in ln BPb at stated age	to 1.46 BPb age 2 yr $\beta=-5.44, -7.35$ to -3.54	change in current BPb	Age 2 yr $\beta=-1.18, p<.01$			

Summary: Psychomotor function, original studies published since 1998

Age 0-2

Childhood exposure, inadequate evidence

(Cooney and others 1989a; Cooney and others 1989b; Ernhart and others 1988; Wigg and others 1988) In a Mexico City birth cohort, PDI scores were inversely associated with natural log current blood lead at age 2 ($\beta = -1.18, p < .01$) but not at age 1 ($\beta = -0.01, p = .98$) (Tellez-Rojo and others 2006).

Age 3 or older

Maternal exposure, inadequate evidence

In the Cincinnati birth cohort study, fine motor function scores at age 15-17 were inversely associated with blood lead at age 6 ($\beta = -0.046 \pm 0.016$) but not with prenatal ($\beta = -0.017 \pm 0.020$) or average childhood levels (-0.016 ± 0.013) (Ris and others 2004).

Childhood exposure, limited evidence

In the Yugoslavia/Kosovo birth cohort, fine motor function scores at age 54 months were inversely associated with log average childhood blood lead levels ($\beta = -2.06 \pm 0.68$) (Wasserman and others 2000b). A small cross-sectional study of children age 4-15 in Andean villages with lead recycling and glazing activities revealed higher mean blood levels among those with abnormal finger tapping scores (mean blood lead, abnormal vs normal, 62.3 ± 25.4 (SD) vs 39.9 ± 23.8 , $p = .004$) (Counter and others 1998). In a German cross-sectional study, there was no association between maximum finger tapping test scores and current blood lead ($b = -0.38, p > .05$) (Walkowiak and others 1998).

7e. Sensory function

Reviews

Author		
(Schwartz 1993), Boston, USA	Reanalysis of selected epidemiologic studies of childhood neuropsychological function and lead; used non-parametric smoothing to detect threshold or non-linearities in neurotoxic effects of lead	The association between hearing threshold and BPb reported by Schwartz and Otto (1991) had no threshold down to the lowest observed concentrations
(Otto and Fox 1993), USA	Review of literature on auditory and visual function and lead exposure	Epidemiologic and toxicologic evidence show that increased hearing thresholds and latencies of brainstem auditory evoked potentials are associated with low or moderate lead exposure

Sensory function, original studies published since 1998

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Altmann and others 1998), 3 cities in Germany	Cross-sectional		384 children age 5-7; measured visual evoked potentials		Geometric mean BPb 4.25 (range 1.4-17 µg/dL)	Area, age, birth weight, head circumference, weight, quality of fixation, visual acuity
Visual-evoked potential latencies (VEP) vs log current blood lead	N75 $\beta=0.086\pm0.059(\text{SE})$, $p=.14$	P100 $\beta=-0.094\pm0.058$, $p=.11$	N150 $\beta=-0.108\pm0.059$, $p=.07$			
VEP interpeak amplitudes vs log current blood lead	N150-P100 $\beta=-0.081\pm0.059$, $p=.09$	P100-N75 $\beta=-0.174\pm0.059$, $p=.002$	N150-N75 $\beta=-0.156\pm0.058$, $p=.004$			
(Osman and others 1999), Katowice industrial region, Poland	Cross-sectional	Children from 3 towns in industrial region with blood	155 children age 4-14 yr; conducted audiometric and	Median BPb 1-3 yr before study 12.2 µg/dL (range	Age, sex, Apgar score, ear and throat abnormalities,	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
		lead measured 1-3 years before recruitment	brainstem auditory evoked potential measurements	2.3-38.9)	frequent colds, mumps, gentamycin use, environmental noise, prenatal maternal smoking, family income	
Multiple regression, change in hearing threshold (dB) per unit change in current BPb; right ear results shown (similar findings for left ear)	500 Hz b=0.054 dB, 0.035-0.074 1000 Hz b=0.044 dB, 0.026-0.062 2000 Hz 0.048 dB, 0.029-0.066	4000 Hz 0.060 dB, 0.039-0.081 6000 Hz 0.068 dB, 0.044-0.092 8000 Hz 0.072 dB, 0.050-0.094	Among children with BPb levels below 10 µg/dL there were still significant associations between hearing thresholds at various frequencies and BPb levels	Change in average audio-evoked potential latencies of waves I, II and III, blood lead ≥10 vs <10 µg/dL	0.1 ms	
Change in brainstem audio-evoked wave I latency per unit change in BPb	$\beta=0.057$, 95% CI 0.016-0.098					
(Rothenberg and others 2000), Mexico City	Birth cohort	133 children followed to age 5 yr	Brainstem auditory evoked responses	Mean prenatal maternal, cord, 18-month, and 60-month BPb levels, respectively, were 8.1, 8.7, 10.8, and 8.0 µg/dL; used natural log BPb level in analytical models	Sex, head circumference and age at testing	

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Linear multiple regression, I-V latency (msec) vs ln BPb	Prenatal BPb $\beta=-0.044, -0.097$ to $0.009, p=.11$ BPb age 1 $\beta=-0.063, -0.123$ to $-0.003, p=.04$	BPb age 4 $\beta=-0.084, -0.161$ to $-0.007, p=.03$	Linear multiple regression, III-V latency (msec) vs ln BPb	Prenatal BPb $\beta=-0.051, -0.100$ to $-0.002, p=.04$ BPb age 1 $\beta=-0.031, -0.089$ to $0.026, p=.28$	BPb age 4 $\beta=-0.076, -0.149$ to $-0.003, p=.04$	
(Zou and others 2003), China	Cross-sectional	114 children age 1-6 yr	Brainstem auditory evoked potential responses	Range of BPb levels was 3.2-38.0 $\mu\text{g/dL}$, median 9.0 $\mu\text{g/dL}$	Age, sex	
Partial correlation coefficient, auditory-evoked potential latencies vs BPb	I $\beta=0.365$ ms, $p<.001$	III $\beta=0.179$ ms, $p=.06$	V $\beta=0.247$ ms, $p=.009$	I-III $\beta=-0.051$ ms, $p=.59$	III-V $\beta=0.128$ ms, $p=.18$	
I-V $\beta=0.020$ ms, $p=.84$	Similar results for left ear	Average auditory-evoked potential peak latencies, children with BPb <10 vs ≥ 10 $\mu\text{g/dL}$	I 1.68 vs 1.72 ms, $p=.04$	III 3.88 vs 3.95 ms, $p=.11$	V 5.69 vs 5.82 ms, $p=.02$	

Summary: Sensory function

Visual function: Original studies since 1998

Childhood exposure, inadequate evidence

In a German cross-sectional study, there were statistically non-significant associations between visual-evoked potential latencies and log current blood lead level among children age 5-7 (N75 latency, $\beta=0.086\pm 0.059$ (SE), $p=.14$; P100 latency, $\beta=-0.094\pm 0.058$, $p=.11$; N150 latency, $\beta=-0.108\pm 0.059$, $p=.07$) (Altmann and others 1998).

Auditory function: Reviews

Reviewers concluded that epidemiologic and toxicologic evidence support a relationship between increased hearing thresholds and low or moderate lead exposure (Otto and Fox 1993; Schwartz 1993). Findings included monotonic dose-response relationships extending to blood lead levels below 10 µg/dL with no evidence of a threshold (Schwartz 1993).

Auditory function: Original studies since 1998

Maternal exposure, limited evidence

In a Mexico City birth cohort, there was a statistically non-significant dose-response relationship between I-V and III-V latencies at age 5 and natural log maternal 2nd trimester blood lead levels over the range 8-31µg/dL (β =-0.044, -0.097 to 0.009, p =.11) (Rothenberg and others 2000).

Childhood exposure, limited evidence

In a Polish cross-sectional study, hearing thresholds at age 4-14 were associated with current blood lead levels (e.g., at 500 Hz, slope of hearing threshold vs blood lead (µg/dL), b =0.054 dB, 95% CI 0.035-0.074) (Osman and others 1999). This study also reported an association between brainstem audio-evoked potential wave I latency and current blood lead (β =0.057, 95% CI 0.016-0.098). The Mexico City cohort found *inverse* (i.e., apparently favourable) associations between I-V latencies at age 5 years and natural log blood lead levels at ages 1 (β =-0.063, -0.123 to -0.003, p =.04) and 4 years (β =-0.084, -0.161 to -0.007, p =.03); there were similar associations for III-V latencies (Rothenberg and others 2000). The authors speculated that these results might be explained by reduced auditory brainstem pathway length caused by lead exposure (similar to the known inverse association between head circumference and lead exposure). In a cross-sectional study of Chinese children age 1-6 years, auditory evoked-potential peak latencies were associated with current blood lead over the range 3-38 µg/dL (partial correlation coefficient, latency vs current blood lead, wave I, β =0.365 ms, p <.001; III, β =0.179 ms, p =.06; V, β =0.247 ms, p =.009) (Zou and others 2003). This study found no association between interpeak latencies and current blood lead levels (I-III, β =-0.051 ms, p =.59; III-V, β =0.128 ms, p =.18; I-V, β =0.020 ms, p =.84).

7f. Attention deficit and related problem behaviours

Original studies published since 1998

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Mendelsohn and others 1998), Bellevue Hospital, New York	Cross-sectional	BPb screening program, 72 children age 12-36 mos (Latino or African-American) recruited 1993-95	Behavior Rating Scale of the Bayley Scales of Infant Development; scores analyzed as percentiles, i.e., lower scores indicated more problem behaviours	Capillary BPb <25 µg/dL; categorized capillary BPb levels as <10 and 10-24.9 µg/dL	Assessed and adjusted as necessary for age, sex, country of origin, iron deficiency, mother's age, marital status, education, parity, verbal IQ, depression score, cognitive stimulation in home, ethnicity, SES	Adjusted as necessary for age, sex, country of origin, iron deficiency, mother's age, marital status, education, parity, verbal IQ, depression score, cognitive stimulation in home, ethnicity, SES
Regression coefficient, total problem behaviour score percentile (lower value = more problem behaviours) vs current BPb ≥10 (yes/no)	$\beta=-17.3$, $p=.02$	Multiple regression, total favourable behaviour score vs current blood lead (µg/dL, continuous variable)	$\beta=-1.1$, $p=.08$			
(Wasserman and others 1998), former Yugoslavia	Birth cohort	379 children from a lead industry town and a comparison town follow to age 3 yr; recruitment began in 1985	Mothers completed Child Behavior Checklist at age 3 yr	Measured prenatal maternal, cord and infant BPb levels	Town, child sex, ethnicity, maternal education, HOME score, residence type	Town, child sex, ethnicity, maternal education, HOME score, residence type

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Aggressive behaviour at age 3 yr vs natural log BPb at stated age	Cord BPb $\beta=1.25\pm0.85$, $p=.15$	BPb 6 mos $\beta=2.11\pm1.00$, $p=.04$	BPb 36 mos $\beta=1.85\pm1.08$, $p=.09$			
(Stokes and others 1998), Silver Valley, Idaho	Retrospective cohort	Persons who lived at age 9 mos to 9 yr near lead smelter during 1974-75 when airborne lead emissions were high; comparison group of 287 age-sex matched persons in low exposure region	281 persons age 19-29 yr; measured Simple Reaction Time, an indicator of attention	Mean BPb level among smelter town children at baseline in 1974 was 50 $\mu\text{g}/\text{dL}$	Current mean BPb and current tibial bone lead levels in exposed and comparison groups were 2.9 and 1.6 $\mu\text{g}/\text{dL}$ and 4.6 and 0.6 $\mu\text{g}/\text{g}$	Sex, education
No association between Simple Reaction Time test scores and tibial bone lead levels	Result stated without supporting data					
(Walkowiak and others 1998), 3 cities in Germany	Cross-sectional	Recruited during 1991 in 3 cities in former East Germany; lead sources included smelters, other industry and lead pipes	384 children age 5-7 yr; Simple Reaction Time and Continuous Performance Test		Geometric mean BPb 4.3 (range 1.4-17 $\mu\text{g}/\text{dL}$)	Various combinations of variables including age, birth weight, number of siblings, height, nationality, education, sex, prenatal maternal smoking, duration of breastfeeding
Multiple linear regression coefficient,	Continuous Performance Test	Simple Reaction Time				

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
test score vs log BPb	false negatives slope $b=0.23$, $p<.05$	slope $b=0.04$, $p>.05$				
(Burns and others 1999), Port Pirie, Australia	Birth cohort	Lead smelter town, 322 children age 11-13 yr	Assessed emotional and behavioural problems using mother-completed Child Behavior Checklist	Measured BPb at birth, ages 6, 15, and 24 mos, age 3, 4, 5, 6, 7, and 11-13 yr; lifetime geometric mean levels for girls and boys were 13.9 and 14.3 $\mu\text{g/dL}$	Parental smoking habits, parental education, birth weight, duration of breastfeeding, HOME score, maternal IQ	Parental smoking habits, parental education, birth weight, duration of breastfeeding, HOME score, maternal IQ
Odds ratio, mother-rated problem behaviours per lifetime mean BPb increase from 10 to 30 $\mu\text{g/dL}$	Girls 2.8, 1.0-6.8	Boys 3.2, 1.4-6.6				
(Factor-Litvak and others 1999), Kosovo	Birth cohort	301 children from a smelter and comparison town followed to age 7.5 yr	the Child Behavior Checklist at age 3 yr	Mean BPb levels at birth and age 4 yr were 22 and 40 $\mu\text{g/dL}$ in the smelter town and 5.4 and 9.6 $\mu\text{g/dL}$ in the comparison town; assessed current and avg lifetime BPb levels	Maternal education and IQ, ethnicity, and HOME score	Maternal education and IQ, ethnicity, and HOME score

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
Multiple regression, increase in aggressive behaviour score at age 3 per log increase in current BPb level	$\beta=1.85, -0.27$ to 3.97					
(Wasserman and others 2001), former Yugoslavia	Birth cohort	191 children in town without lead industry	Children with at least one mother-reported behaviour rating at age 4-5 yr		Mean BPb levels at birth and at age 4 yr were 5.4 and 9.6 $\mu\text{g}/\text{dL}$; computed \log_{10} of the avg BPb based on semi-annual measurements from birth to age 4-5 yr	Age, maternal smoking, education, child sex, ethnicity, birth weight, acceptance
Multiple regression, change in problem behaviour score at age 4-5 yr per log increment in avg BPb since birth	Total problem behaviours $\beta=0.24\pm 0.18(\text{SE})$, $p>.05$	Aggression $\beta=0.08\pm 0.14$, $p>.05$	Inattention $\beta=0.06\pm 0.14$, $p>.05$	Delinquency $\beta=0.32\pm 0.15$, $p<.05$		
(Dietrich and others 2001), Cincinnati	Birth cohort	Reexamined 186 youth at age 15-17 yr (92% African-American)	Self-Report of Delinquent Behavior, Parental Report of Predelinquent and Delinquent Behavior	Mean 1 st trimester maternal BPb 8.9 $\mu\text{g}/\text{dL}$; measured subjects' BPb frequently until age 6 yr; 35% had at least one	Assessed several potential confounders and adjusted as necessary; routinely HOME score, parental IQ, SES	Assessed several potential confounders and adjusted as necessary; routinely HOME score, parental IQ, SES

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
				BPb above 25 $\mu\text{g/dL}$ by age 5 yr; mean BPb at age 15-17 yr was 2.8 $\mu\text{g/dL}$		
Change in parent-reported problem behaviour score per unit increase in BPb	Prenatal maternal BPb $\beta=0.194\pm0.089(\text{SE})$, $p=.03$	BPb age 6 yr $\beta=0.131\pm0.072$, $p=.07$	Avg postnatal BPb $\beta=0.090\pm0.056$, $p=.11$			
(Calderon and others 2001), Mexico,	Cross-sectional	Children <1.5 km from smelter emitting arsenic and lead and comparison group 7 km from smelter and upwind	41 exposed children age 6-9 yr, 39 unexposed children; conducted WISC-RM (revised version for Mexico)		Geometric mean BPb levels in the exposed and comparison regions were 8.9 ± 0.03 and 9.7 ± 0.02 $\mu\text{g/dL}$	Sex, age, SES, parental education, transferrin saturation, height by age index
Partial correlation coefficient, score on "sequential" (a factor based on WISC-RM subscales related to attention) vs log current BPb	$r=-0.30$, $p=.01$					
(Needleman and others 2002), Boston, USA	Case-control	African-American sub-study: 158 cases and 51 controls, white sub-study: 36 cases, 95 controls; mean age 16 yr	Cases defined as arrested and court-adjudicated as delinquents, controls had no history of arrests and low self-reported delinquency	Measured tibial bone lead levels using x-ray fluorescence		Race, parental education and occupation, two parents in home, number of children in home, neighbourhood

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			scores			crime rate
Odds ratio, delinquency, tibial bone lead ≥ 25 vs < 25 $\mu\text{g/g}$	Total group 3.7, 1.3-10.5	White youth 3.8, 1.1-13.3 African-American youth 2.2, 0.5-10.0				
(Canfield and others 2003b), Rochester, New York	Cohort	Recruited as infants in 5 hospitals in Rochester, NY	170 children age 48-54 mos; conducted Shape School test of ability to conduct progressively more complex tasks that require attention switching and inhibition (associated with frontal lobe function); examiners rated and categorized attentiveness as focused, settled or active inattention	Mean BPb < 10 $\mu\text{g/dL}$ at all ages tested; used BPb level at age 48 mos in analytic models	Mean BPb 6.49 $\mu\text{g/dL}$, range 1.7-20.8	Age, sex, gestation length, maternal IQ, education, HOME score, race, colour or shape knowledge for practice phase
Regression coefficient and SE, attentiveness score vs current BPb	Control phase $\beta = -0.017 \pm 0.012(\text{SE})$, $p > .05$	Inhibit phase $\beta = -0.016 \pm 0.013$, $p > .05$				
(Chiodo and others 2004), Detroit	Birth cohort	237 African American inner-city children followed to age 7-8 yr	WISC-III and several other tests		Mean current BPb was $5.4 \pm 3.3(\text{SD})$ $\mu\text{g/dL}$ (range 1-25)	As necessary for number of children age < 18 , Peabody Picture Vocabulary Test score, prenatal smoking, alcohol, cocaine, life stress, HOME score,

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
						caregiver disruption, parity, examiner, caregiver's age, conflict tactics, child education, sex, FES
Change in Barkley-DuPaul ADHD scores per unit change in current BPb ($\mu\text{g/dL}$)	ADHD score $\beta=0.16, p<.05$ Impulsivity $\beta=0.10, p>.05$ Inattention $\beta=0.18, p<.05$	Change in Child Behaviour Checklist scores per unit change in current BPb ($\mu\text{g/dL}$)	Attention $\beta=0.15, p<.05$ Total problem behaviour score $\beta=-0.12, p>.05$	Change in Barkley Direct Observation scores per unit change in current BPb	Off task $\beta=0.14, p<.05$ Fidgeting $\beta=0.07, p>.05$	
Sustained attention score (number correct on visual Continuous Performance Test) among children age 7-8 yr inversely associated with current BPb	$\beta=-0.14, p<0.001$	Working memory score (Seashore rhythm score) among children age 7-8 yr inversely associated with current BPb	$\beta=-0.15, p<0.05$	Executive function score (percent errors on Wisconsin card sorting test) among children age 7-8 yr associated with current BPb	$\beta=0.30, p<0.05$	
(Ris and others 2004), Cincinnati	Birth cohort	recruited during 1979-1985, 92% African-American	195 children followed to age 15-17 yr; standardized tests of executive function, attention, memory, achievement, vocabulary,		Measured prenatal maternal and childhood BPb levels – quarterly until age 5 yr, again at age 5.5, 6 and 6.5	Excluded mothers with diabetes, alcoholism, to drug addiction, neurologic disorders, psychoses or

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
			visuoconstruction skills and fine-motor coordination; principle components analysis revealed 5 factors – memory, learning/IQ, attention, visuoconstruction and fine motor coordination		yr	mental retardation; adjusted for maternal IQ, SES, avg HOME score, adolescent marijuana use, birth weight, sex
Continuous Performance Test attention factor score vs BPb	Prenatal BPb $\beta=-0.156\pm0.06(\text{SE})$, $p=.001$	Avg childhood BPb $\beta=-0.113\pm0.040$, $p=.005$	Current BPb $\beta=-0.119\pm0.051$, $p=.02$			

Summary: Attention deficit and related problem behaviours, original studies published since 1998

Attention deficit

Maternal exposure, inadequate evidence

The Cincinnati birth cohort found inverse associations between Continuous Performance Test attention factor scores and prenatal blood lead ($\beta=-0.156\pm0.06(\text{SE})$, $p=.001$) (Ris and others 2004).

Childhood exposure, limited evidence

A retrospective cohort of persons age 19-29 who had lived near a lead smelter as children revealed no association between Simple Reaction Time test scores (an indicator of attentiveness) and current tibial bone lead levels (result stated without supporting data) (Stokes and others 1998). In a German cross-sectional study, false negatives on the Continuous Performance Test (CPT) was associated with log current blood lead levels (multiple regression slope $b=0.23$, $p<.05$); there was no association between reaction time on the Simple Reaction Time (SRT) test and current blood lead ($b=0.04$, $p>.05$) (Walkowiak and others 1998). A cross-sectional study of children age 1-3 in New York City revealed an inverse association between Bayley favourable behaviour scores and current blood lead (blood lead ≥ 10 vs <10 $\mu\text{g/dL}$, $\beta=-17.3$, $p=.02$) (Mendelsohn and others 1998). In the comparison group from a town with no smelter, the Kosovo study reported no association between mother-reported inattention at age 4-5 and log average blood lead since birth ($\beta=0.06\pm0.14$) (Wasserman and others 2001). A small cross-sectional study of children age 6-9 living within 1.5 km of a smelter in Mexico and an unexposed comparison group revealed an inverse association between sequential, a factor based on WISC-RM subscales related to attention, and log current blood lead level (partial $r=-0.30$, $p=.01$) (Calderon and others 2001). Among children age 48-54 months in a Rochester cohort, observer-rated attentiveness scores were not associated with blood lead levels at age 48 months (Canfield and others 2003b). A Detroit birth cohort study reported associations between Barley-DuPaul attention score deficits among children age 7-8 and current blood lead (ADHD score, $\beta=0.16$, $p<.05$; impulsivity, $\beta=0.10$, $p>.05$; inattention, $\beta=0.18$, $p<.05$) (Chiodo and others 2004). This study also reported

associations between current blood lead and Child Behaviour Checklist inattention ($\beta=0.15$, $p<.05$) and Barkely Direct Observation off-task score ($\beta=0.14$, $p<.05$). The Cincinnati birth cohort found inverse associations between Continuous Performance Test attention factor scores and average childhood blood lead ($\beta=-0.113\pm 0.040$, $p=.005$) and current blood lead ($\beta=-0.119\pm 0.051$, $p=.02$) (Ris and others 2004).

Aggression, other problem behaviours

Maternal exposure, inadequate evidence

The Yugoslavia/Kosovo birth cohort study reported a statistically non-significant association between mother-reported aggressive behaviour at age 3 and natural log cord blood lead ($\beta=2.11\pm 1.00$, $p=.04$) (Wasserman and others 1998). In the Cincinnati birth cohort, parent-reported problem behaviours at age 15-17 were associated with maternal blood lead $\beta=0.194\pm 0.089$ (SE), $p=.03$) (Dietrich and others 2001).

Childhood exposure, limited evidence

The Yugoslavia/Kosovo birth cohort study reported an association between mother-reported aggressive behaviour at age 3 and natural log blood lead at age 6 months ($\beta=2.11\pm 1.00$, $p=.04$); there were statistically non-significant relationships between such behaviour and natural log current blood lead level ($\beta=1.85\pm 1.08$, $p=.09$) (Wasserman and others 1998). This study also reported a statistically non-significant association between aggressive behaviour at age 7-8 and log current blood lead level ($\beta=1.85$, 95% CI -0.27 to 3.97) (Factor-Litvak and others 1999). In the comparison group from a town with no smelter, the Kosovo study reported no association between log average blood lead since birth and mother-reported problem behaviours at age 4-5 (total problem behaviours, $\beta=0.24\pm 0.18$ (SE), $p>.05$; aggression, $\beta=0.08\pm 0.14$, $p>.05$); there was, however, an association between mother-reported delinquency and log average lifetime blood lead level ($\beta=0.32\pm 0.15$, $p<.05$) (Wasserman and others 2001). In the Port Pirie cohort, mother-rated problem behaviours at age 11-13 were associated with lifetime average blood lead level (for a blood lead increment from 10 to 20 $\mu\text{g}/\text{dL}$, girls, OR=2.8, 95% CI 1.0-6.8; boys, OR=3.2, 95% CI 1.4-6.6) (Burns and others 1999). In the Cincinnati birth cohort, parent-reported problem behaviours at age 15-17 were associated with blood lead at age 6 ($\beta=0.131\pm 0.072$, $p=.07$) and non-significantly with lifetime average blood lead ($\beta=0.090\pm 0.056$, $p=.11$) (Dietrich and others 2001). A case-control study in Boston observed an association between court-adjudicated delinquency and current tibial bone lead levels, independent of race and other potential confounders (tibial lead ≥ 25 vs < 25 $\mu\text{g}/\text{g}$, OR=3.7, 95% CI 1.3-10.5) (Needleman and others 2002).

8. Pubertal reproductive system development

Reference/Outcome	Design/Stratum	Sampling frame/Association	Subjects	Exposure assessment	Exposure levels	Covariates
(Wu and others 2003), USA	Cross-sectional	1,706 girls age 8-16 yr in NHANES III	Self-reported attainment of menarche and physician-rated Tanner Stage 2 pubic hair and breast development	BPb range 0.7-22 µg/dL		Race/ethnicity, age, family size, urban residence, poverty income ratio, body mass index
Likelihood of having attained pubertal markers, current BPb ≥ 5 vs < 5 µg/dL	At least Tanner stage 2 pubic hair devmt 0.27, 0.08-0.93	At least Tanner stage 2 breast devmt 1.20, 0.51-2.85	Menarche 0.19, 0.08-0.43			
(Selevan and others 2003), NHANES III, USA	Cross-sectional	2,186 girls age 8-18 yr	Assessed age at menarche and Tanner stage for pubic hair and breast development	GM BPb < 3 µg/dL in all 3 ethnic groups		Age, age squared, height, BMI, family income, ever smoked 100 cigarettes, dietary iron, vitamin C and calcium, anemia
Odds ratio, likelihood of reaching a successive stage of breast development per BPb increment from 1 to 3 µg/dL	Non-Hispanic Whites 0.82, 0.47-1.42	African-American 0.64, 0.41-0.97 Mexican-American 0.76, 0.63-0.91	Odds ratio, likelihood of reaching a successive stage of pubic hair development per BPb increment from 1 to 3 µg/dL	Non-Hispanic Whites 0.75, 0.37-1.51	African-American 0.62, 0.41-0.96	Mexican-American 0.70, 0.54-0.91
Odds ratio, likelihood of reaching menarche, BPb 3 vs 1 µg/dL (limited to girls age 8-16)	Non-Hispanic Whites 0.74, 0.55-1.002	African-American 0.78, 0.63-0.98	Mexican-American 0.90, 0.73-1.11			

Summary: Pubertal reproductive system development, original studies published since 1998

Age at menarche

Childhood exposure, limited evidence

A large cross-sectional study of age 8-16 girls based on NHANES III found associations between delayed onset of menarche and current blood lead among non-Hispanic white girls (likelihood of reaching menarche, blood lead ≥ 3 vs < 1 $\mu\text{g}/\text{dL}$, OR=0.74, 95% CI 0.55-1.002) and African-American girls (OR=0.78, 95% CI 0.63-0.98) but not among Mexican-American girls OR=0.90, 95% CI 0.73-1.11) (Selevan and others 2003). These estimates were based on current blood lead levels over the range 0.7-22 $\mu\text{g}/\text{dL}$ and were adjusted for age, family size, urban residence, poverty and body mass index. An independent analysis of NHANES III data found an inverse association between likelihood of having attained menarche and current blood lead levels among girls of all ethnicities/races combined (OR=0.19, 95% CI 0.08-0.43) (Wu and others 2003).

Age at female pubic hair development

Childhood exposure, limited evidence

A large cross-sectional study of age 8-16 girls based on NHANES III found associations between delayed pubic hair development and current blood lead level among African-American girls (likelihood of reaching a successive stage of pubic hair development, blood lead ≥ 3 vs < 1 $\mu\text{g}/\text{dL}$, OR=0.64, 95% CI 0.41-0.97) and Mexican-American girls (OR=0.76, 95% CI 0.63-0.91) but not among non-Hispanic white girls (OR=0.82, 95% CI 0.47-1.42) (Selevan and others 2003). An independent analysis of NHANES III data found an inverse association between likelihood of having attained at least Tanner stage 2 pubic hair development and current blood lead levels among girls of all ethnicities/races combined (OR=0.27, 95% CI 0.08-0.93) (Wu and others 2003).

Age at breast development

Childhood exposure, inadequate evidence

A large cross-sectional study of age 8-16 girls based on NHANES III found associations between delayed breast development and current blood lead level among African-American girls (likelihood of reaching a successive stage of breast development, blood lead ≥ 3 vs < 1 $\mu\text{g}/\text{dL}$, OR=0.62, 95% CI 0.41-0.96) and Mexican-American girls (OR=0.70, 95% CI 0.54-0.91) but not among non-Hispanic white girls (OR=0.75, 95% CI 0.37-1.51) (Selevan and others 2003). An independent analysis of NHANES III data found no association between likelihood of at least Tanner stage 2 breast development and current blood lead levels among girls of all ethnicities/races combined (OR=1.20, 95% CI 0.51-2.85) (Wu and others 2003).

9. Dental caries

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
(Moss and others 1999), USA	Cross-sectional	24,901 persons age 2 years and older in NHANES III	Assessed dental decay and repair	Measured BPb	Age, race, poverty income ratio, cigarette smoke exposure, sex, region, household head education, dietary carbohydrate and calcium, days since last dental visit, usual frequency of dental care
Odds ratio of dental caries at age 5-17, referent = BPb \leq 2.3 μ g/dL	2.3-4.1 μ g/dL 1.36, 1.01-1.83 >4.1 μ g/dL 1.66, 1.12-2.48				
(Campbell and others 2000), Rochester, New York	Cohort	248 children age 6-12 yr, mainly African-American and Hispanic	Linked dental caries database and BPb level database	Mean BPb at ages 18-37 mos was 10.7 (range 0-45 μ g/dL)	Screened several potential confounders; age, school grade, and number of tooth surfaces at risk
Odds ratio, deciduous teeth caries, BPb \geq 10 vs <10 μ g/dL	1.77, 0.97-3.24	Odds ratio, permanent teeth caries, BPb \geq 10 vs <10 μ g/dL	0.95, 0.43-2.09		
(Gemmel and others 2002), Boston and rural Maine	Randomized trial	543 children age 6-10 yr; residents of Boston/Cambridge urban area or Farmington rural area	Dental caries	Mean BPb levels in urban and rural areas were 2.9 \pm 2.0 μ g/dL (range up to 13 μ g/dL) and 1.7 \pm 1.0 μ g/dL (range up to 7 μ g/dL)	Age, sex, family income, maternal education, maternal smoking, frequency tooth brushing, use of medium/hard bristles, gum chewing habits
Regression coefficient, number of carious surfaces	Boston/Cambridge β =0.28 \pm 0.09, p=.002	Regression coefficient, number of carious surfaces of permanent teeth vs log	Boston/Cambridge β =0.02 \pm 0.07, p=.8		

Reference	Design	Sampling frame	Subjects	Exposure	Covariates
of deciduous teeth vs log current BPb ($\mu\text{g/dL}$)	Farmington $\beta=-0.15\pm0.09$, $p=.1$	current BPb ($\mu\text{g/dL}$)	Farmington $\beta=-0.10\pm0.10$, $p=.3$		

Summary: Dental caries, original studies published since 1998

Childhood exposure, limited evidence

A large cross-sectional study based on NHANES III found a dose-response relationship between dental caries of primary or permanent teeth and current relatively low blood lead levels, independent of potential confounders (blood lead >4.1 vs ≤ 2.3 $\mu\text{g/dL}$, OR=1.66, 95% CI 1.12-2.48) (Moss and others 1999). A small cohort study found an association between current blood lead levels and deciduous tooth caries at age 6-12 (≥ 10 vs <10 $\mu\text{g/dL}$, OR=1.77, 95% CI 0.97-3.24) but not permanent tooth caries (OR=0.95, 95% CI 0.43-2.09) (Campbell and others 2000). Among children age 6-10 enrolled in a randomized trial in urban Boston/Cambridge and rural Maine, the number of carious surfaces of deciduous teeth was associated with log current blood lead levels in the urban region ($\beta=0.28\pm0.09$ (SE), $p=.002$) but not the rural region ($\beta=-0.15\pm0.09$, $p=.1$); there was no association with number of carious surfaces of permanent teeth in either region (Gemmel and others 2002).

10. Childhood cancer

Reference	Design	Sampling frame	Outcome	Exposure	Covariates
(Kerr and others 2000), New York State	Case-control	Population-based age <15 yr	183 neuroblastoma cases, 372 controls	Self-reported parental occupations and work-related exposures during pregnancy	Child's age, parental age, education
Odds ratio, self-reported parental occupational lead exposure, yes vs no	Maternal 4.7, 1.3-18.2 Paternal 2.4, 1.2-4.8				
(De Roos and others 2001), USA, Canada	Case-control	139 hospitals, 1992-1994	538 cases neuroblastoma age <19 yr, 538 controls matched for date of birth	Self-reported parental occupational exposures during 2 yr before child's birth; expert assessment of likely exposures	Child's age, maternal race, age, education
Odds ratio, likely occupational exposure to solder	Paternal 2.6, 0.9-7.1	Only 1 case mother exposed to solder or other metals			
(Infante-Rivard and others 2001), Montreal	Case-control	Population-based, age <10 yr, 1980-93	491 acute lymphatic leukemia cases, 491 matched controls	Child's residential history, parent-reported drinking water source, municipal water quality data, 1970-1993, 1995-1996 tap water survey (227 homes)	Matched for age, sex, region; adjusted for maternal age, education
Odds ratio, avg drinking water lead >10 vs ≤10 µg/L	prenatal 1.22, 0.54-2.76 postnatal 0.81, 0.43-1.51	Odds ratio, cumulative drinking water lead exposure >95 th vs ≤95 th percentile (µg.day.L ⁻¹)	prenatal 0.86, 0.44-1.68 postnatal 0.82, 0.44-1.53		

Reference	Design	Sampling frame	Outcome	Exposure	Covariates

Summary: Childhood cancer, original studies published since 1998

Leukemia

Parental or childhood exposure, inadequate evidence

A large population-based case-control study in Quebec found no association between childhood ALL and prenatal drinking water lead levels (>10 vs ≤10 µg/L, OR=1.22, 95% CI 0.54-2.76) or cumulative prenatal lead exposure from drinking water (>95th vs ≤95th percentile of µg.d.L, OR=0.86, 95% CI 0.44-1.68) (Infante-Rivard and others 2001). There was also no association with childhood drinking water lead levels exceeding 10 µg/L (OR=0.81, 95% CI 0.43-1.51) or cumulative childhood lead exposure from drinking water (OR=0.82, 95% CI 0.44-1.53). An ecologic study in Nevada reported no increased leukemia in areas where drinking water arsenic levels were 10-25 (SIR=0.61, 95% CI 0.12-1.79) or 35-90 µg/L (SIR=0.86, 95% CI 0.37-1.70) (Moore and others 2002).

Neuroblastoma

Maternal occupational exposure, inadequate evidence

One case-control study reported an association between childhood neuroblastomas and self-reported maternal prenatal occupational lead exposure (OR=4.7, 95% CI 1.3-18.2); the association was somewhat attenuated when exposure was defined as self-reported plus expert-rated potential for such exposure (OR=3.5, 95% CI 0.7-22.6) (Kerr and others 2000).

Paternal occupational exposure, limited evidence

Associations between childhood neuroblastomas and self-reported paternal occupational lead exposure were observed in case-control studies in New York State (OR=2.4, 95% CI 1.2-4.8) (Kerr and others 2000) and the USA/Canada (OR=2.6, 95% CI 0.9-7.1) (De Roos and others 2001). The association in the New York study persisted when exposure was defined as self-reported plus expert-rated potential for such exposure (OR=2.2, 95% CI 0.9-5.4) (Kerr and others 2000).

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