

Cadmium: summary of epidemiologic evidence

December 29, 2004

1. Overall summary

This section summarizes epidemiologic evidence cited in the tables below and will be updated as new evidence becomes available. I would appreciate feedback on any errors or omissions.

Health effect	Level of evidence ^a	Comments
Late fetal deaths (stillbirths)	(Inadequate)	A case-control study of late fetal deaths (stillbirths) in Massachusetts found no association with drinking water cadmium levels in communities of maternal residence (Aschengrau et al 1993). A Swedish ecologic study found no overall increased risk of late fetal deaths among women living in municipalities with above average environmental cadmium levels; however, in the municipality with the highest cadmium concentration, the relative risk of stillbirths was significantly elevated (Landgren 1996).
Birth defects: total	(Inadequate)	A small retrospective cohort study in an industrial town in France found no association between birth defects and infant or maternal hair cadmium levels (Huel et al 1981). A case-control study in Massachusetts found no association between total birth defects and drinking water cadmium levels in communities of maternal residence (Aschengrau et al 1993). A Swedish ecologic study found no increased risk of total birth defects among infants of women living in a smelter town (Wulff et al 1996b).
Birth defects: specific types	(Inadequate)	CNS A large case-control study in Canada found no association between anencephaly and drinking water cadmium levels in communities of maternal residence (Elwood and Coldman 1981).
	(Inadequate)	Cardiac A case-control study in Massachusetts found no association between CNS birth defects and drinking water cadmium levels in communities of maternal residence (Aschengrau et al 1993). A Swedish ecologic study found no increased risk of cardiac birth defects among infants of women living in a smelter town; this study had limited statistical power (Wulff et al 1996b). A large case-control study of cardiac birth defects (the Baltimore-Washington Infant Study) found an association between atrial septal defect with Down syndrome and self-reported paternal occupation as a welder (note: welders may be exposed to cadmium, zinc, beryllium, iron, mercury, lead and other toxicants) (Wilson et al 1998). Orofacial A case-control study in Massachusetts found no association between orofacial birth defects and drinking water cadmium levels in communities of maternal residence (Aschengrau et al 1993).
	(Inadequate)	Genital A case-control study in Massachusetts found no association between genital birth defects and drinking water cadmium levels in communities of maternal residence (Aschengrau et al 1993). A Swedish ecologic study

		<p>found no increased risk of cryptorchidism among infants of women living in a smelter town; this study had very limited statistical power (Wulff et al 1996b).</p> <p>Note A literature review noted that high-dose prenatal cadmium exposure causes skeletal birth defects in experimental animals (Agency for Toxic Substances and Disease Registry 1999).</p>
Gestation length	(Inadequate)	<p>A small retrospective cohort study in an industrial town in France found no association between preterm birth and infant or maternal hair cadmium levels (Huel et al 1981). A birth cohort study in a lead smelter town in the former Yugoslavia found no association between gestation length and placental cadmium among non-smoking women (Loicono et al 1992). A small cross-sectional study in a cadmium-polluted river basin in Japan found an inverse association between gestation length and maternal urinary cadmium levels (Nishijo et al 2002). A small cross-sectional study in a cadmium-polluted region in China found a borderline <i>inverse</i> association between preterm birth and placental cadmium levels (Nishijo et al 2002).</p>
Birth weight adjusted for gestation length	(Inadequate)	<p>A small retrospective cohort study in an industrial town in France found an inverse association between small for gestational age infants and infant but not maternal hair cadmium levels; this study did not adjust for prenatal maternal smoking (Huel et al 1981). Among infants of smokers, but not non-smokers, birth weight adjusted for gestation length and other potential confounders was inversely associated with maternal whole blood cadmium levels and positively associated with cord red blood cell zinc levels (Kuhnert et al 1987). A birth cohort study in a lead smelter town in the former Yugoslavia found no association between birth weight adjusted for gestation length and placental cadmium among non-smoking women (Loicono et al 1992). A literature review concluded that there is limited evidence for an association between reduced birth weight and cadmium exposure in humans (Jarup et al 1998). A birth cohort study in Norway and Russia found an inverse association between birth weight adjusted for gestation length and maternal blood cadmium levels (Odland et al 1999). A literature review noted that high-dose prenatal cadmium exposure causes reduced intrauterine growth rates in experimental animals (Agency for Toxic Substances and Disease Registry 1999). A small cross-sectional study in a cadmium-polluted river basin in Japan found no association between birth weight and maternal urinary cadmium levels (Nishijo et al 2002). A small cross-sectional study in Norway and Russia found a borderline inverse association between birth weight and placental and maternal blood cadmium levels (Odland et al 2004).</p>
Birth height	(Inadequate)	<p>A small cross-sectional study in a cadmium-polluted region in China found an inverse association between birth height and placental cadmium levels (Nishijo et al 2002).</p>
Neonatal asphyxia	(Inadequate)	<p>A small cross-sectional study in a cadmium-polluted region in China found no association between neonatal asphyxia (Apgar score ≤ 7) and placental cadmium levels (Nishijo et al 2002).</p>
Kidney function:	(Limited)	<p>A cross-sectional study of children age 12-15 years in the Czech Republic found no associations between urinary</p>

urinary protein excretion		protein levels and blood cadmium levels (Bernard et al 1995). A cross-sectional study of children age 6-14 years in Belgium, Germany and Poland showed that those living in regions polluted with cadmium and/or lead had increased urinary levels of Clara cell protein, β 2-microglobulin, 6-keto-prostaglandin F _{1a} , brush border antigens, N-acetyl- β -D-glucosaminidase (NAG), prostaglandin E ₂ , epidermal growth factor and laminin fragments; this study did not assess the relationships between urinary protein and cadmium levels (Price et al 1999). A cross-sectional study of children age 17 years in Belgium found no association between urinary protein levels (cystatin-C, β 2-microglobulin) and blood cadmium levels (Staessen et al 2001). In a cross-sectional study of children age 6-17 years living near a zinc smelter in Pennsylvania, urinary NAG, alanine aminopeptidase and albumin were not associated with urinary cadmium (Noonan et al 2002). A cross-sectional study of children age 8-12 years living near nonferrous smelters in France found an association between urinary NAG and blood cadmium levels (Burbure et al 2003). A literature review concluded that urinary cadmium levels as low as 2-3 μ g/g creatinine are associated with renal tubular damage in the general population and in occupationally exposed persons (Jarup et al 1998).
Cancer: children	(Inadequate)	A Swedish birth cohort study found an increased cancer risk among children born near a smelter known to emit cadmium and other toxicants (Wulff et al 1996a). In a case-control study of acute lymphoblastic leukemia in Montreal, there were no associations with prenatal or postnatal exposure to detectable cadmium levels ($\geq 1\mu$ g/L) in community drinking water supplies or tap water samples; there were also no associations with cumulative prenatal or postnatal cadmium exposure (Infante-Rivard et al 2001).
Cancer: adults	Sufficient	Based on epidemiologic studies of adult cancers and toxicologic evidence, an expert panel concluded that there was sufficient evidence that inhaled cadmium and cadmium compounds are carcinogenic in humans (International Agency for Research on Cancer 1993). A literature review noted that the tumour suppressor gene p53 is inhibited by cadmium, disrupting control of DNA repair, cell proliferation, differentiation and survival of cells with DNA damage (Meplan et al 1999). Other reviewers concluded that there is inadequate evidence that inhaled cadmium can cause human cancers and limited evidence that ingested cadmium causes prostatic hyperplasias and adenomas, testicular tumours and leukemia in experimental animals (Agency for Toxic Substances and Disease Registry 1999). Literature reviews concluded that inhaled cadmium is a probable or known cause of lung cancer in humans and causes tumours at several sites and by various routes in rodents including lung, prostate, testes, adrenals, injection sites and hematopoietic system (Jarup et al 1998, Waalkes 2000). The latter review concluded that there is inadequate epidemiologic evidence for associations between cadmium exposure and cancers of the prostate, liver, kidney or stomach.
Sexual maturation	(Inadequate)	A cross-sectional study of Belgian males age 17 years from a rural control area and regions polluted by a lead smelter and two waste incinerators in Belgium found no association between testicular volume or sexual maturation stage and blood cadmium levels (Staessen et al 2001).
Semen quality	(Inadequate)	A case-control study in the Netherlands found no association between semen quality indices and self-reported welding

		fume exposure or urinary cadmium levels (Tielemans et al 1999a). A cross-sectional study of Croatian men found no association between semen quality indices and blood cadmium levels (Telisman et al 2000). A literature review concluded that high-dose postnatal cadmium exposure causes testicular atrophy in experimental animals (Agency for Toxic Substances and Disease Registry 1999).
Fertility	(Inadequate)	A cohort study in Belgium found a slightly <i>increased</i> birth rate among men working in a cadmium smelter; there were no associations between likelihood of a live birth and cadmium exposure time period or individual urinary cadmium levels (Gennart et al 1992). A retrospective cohort study in Italy found an inverse association between likelihood of conception and paternal preconceptional occupational exposure to welding fumes (note: welders may be exposed to cadmium, zinc, beryllium, iron, mercury, lead and other toxicants) (Spinelli et al 1997). A cross-sectional study of couples seeking <i>in vitro</i> fertilization in the Netherlands showed that the <i>in vitro</i> fertilization rate was not associated with male partner occupational exposure as a welder (Tielemans et al 1999b). A cohort study in Finland found a borderline favourable association between likelihood of conception and male partner occupational exposure to cadmium inferred from work history (Sallmen et al 2000).
Neurotoxicity	Inadequate	A small cross-sectional study of children age 5-16 years in Maryland found inverse associations between full-scale IQ and fine motor function scores and current hair cadmium levels; gross motor, reading, spelling and math scores were not associated with current hair cadmium levels (Thatcher et al 1982). A literature review concluded that there is inadequate evidence for associations between childhood neurotoxic effects and cadmium exposure (Agency for Toxic Substances and Disease Registry 1999).
Immune function	(Inadequate)	A cross-sectional study of children age 5-14 years in Germany found dose-response relationships between low blood IgG levels (but not IgM, IgA or IgE) and negative skin-prick reaction to 12 common antigens and current urinary cadmium levels (Ritz et al 1998). A literature review concluded that prenatal cadmium exposure causes immune system abnormalities in experimental animals (Agency for Toxic Substances and Disease Registry 1999).
Thyroid function	(Inadequate)	A cross-sectional study of children age 7-10 years in Germany found no association between serum FT ₃ levels and blood cadmium levels (Osius et al 1999).
Genotoxicity	Children (Inadequate)	A Swedish birth cohort study found a 2.6-fold increased risk of chromosomal abnormalities (increase was of borderline statistical significance) among infants of women living in a smelter town with significant cadmium, lead, arsenic, copper and sulphur dioxide pollution (Wulff et al 1996b).
	Adults (Limited)	A literature review concluded that there is limited and mixed evidence for an association between chromosome abnormalities in adults and cadmium exposure (Agency for Toxic Substances and Disease Registry 1999).
	Experimental	Other reviews concluded that cadmium is weakly mutagenic (Waalkes 2000) and, at low concentrations, interferes

	systems Sufficient	with nucleotide and base excision DNA repair (Hartwig et al 2002). A recent experimental study found that cadmium at micromolar concentrations markedly increased yeast mutation rates and specifically inhibited one type of DNA repair, i.e., mismatch repair (Jin et al 2003).
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^a Sufficient evidence = based on peer-reviewed reports of expert groups or authoritative reviews that concluded that a causal relationship existed; limited evidence = relationships for which several epidemiologic studies, including at least one case-control or cohort study, showed fairly consistent associations and evidence of exposure-risk relationships after control for potential confounders; inadequate evidence = relationships for which epidemiologic studies were limited in number and quality (e.g., small studies, ecologic studies, limited control of potential confounders), had inconsistent results, or showed little or no evidence of exposure-risk relationships. Levels in parentheses are the author's interpretation of available evidence; other levels are based on expert group reviews.

2. Developmental effects

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
(Elwood and Coldman 1981), Canada	Case-control study, 468 stillbirths caused by anencephaly, 4129 live birth controls, mothers resident in 142 communities population 10,000 or greater	Measured drinking water calcium, magnesium, copper, zinc, nickel, lead, selenium, mercury, chromium, silver, cobalt, cadmium and molybdenum levels for each community	No significant associations between anencephaly and drinking water level of cadmium or any other element tested; avg water cadmium level, cases vs controls	9.0 vs 9.0 µg/L, p>0.05		Average family income, population, latitude, longitude, percent of married women employed
(Huel et al. 1981), small industrial town, France	110 mother-infant pairs; assessed birth weight	GM, 5 th and 95 th percentile hair cadmium levels for mothers were 0.4, 0.04 and 4.1 µg/g and for neonates were 0.5, 0.06 and 6.9 µg/g	Inverse association between small for gestational age and infant but not maternal hair cadmium; GM hair cadmium, SGA vs normal infants	infant hair 1.0 vs 0.5 µg/g, p<0.05 maternal hair 0.7 vs 0.4 µg/g, p>0.05	+	Sex, gestation length, mother's weight
			Preterm birth not associated with infant or maternal hair cadmium; GM hair cadmium, SGA vs normal infants	infant hair 0.5 vs 0.5 µg/g, p>0.05 maternal hair 0.5 vs 0.4 µg/g, p>0.05		As above
			Birth defects not associated with infant or maternal hair cadmium; GM hair cadmium, SGA vs normal infants	infant hair 0.6 vs 0.5 µg/g, p>0.05 maternal hair 0.7 vs 0.4 µg/g, p>0.05		As above
(Kuhnert et al.	202 women (125 non-	Measured maternal blood	Among infants of smokers,	mat blood Cd	+	Gestation length,

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
1987), Cleveland, Ohio	smokers, 77 smokers); assessed relation of zinc and cadmium to birth weight (note: zinc reduces cadmium toxicity to some degree)	cadmium, placental cadmium and zinc and maternal, cord plasma and red cell zinc and maternal plasma thiocyanate (the latter was used to assess maternal smoking status); report does not state cadmium concentrations	but not non-smokers, birth weight adjusted for gestation length was inversely associated with maternal whole blood cadmium and positively associated with cord red blood cell zinc levels	F[8,192]=7.1, p<0.001 cord RBC zinc F[9,191]=4.2, p<0.001		maternal age, parity, gravidity, race, red cell count, plasma thiocyanate (to control for maternal smoking)
			No association between birth weight adjusted for gestation length and cadmium exposure indices in infants of non-smokers			As above
(Loiacono et al. 1992), the former Yugoslavia	Birth cohort study, 1008 pregnant women from a lead smelter and comparison town; assessed birth weight	Measured placental cadmium and maternal and cord blood lead	No association between gestation length and placental cadmium; gestation length increase per ng cadmium per g placental tissue	0.04 d (CI -0.04 to 0.1)		Ethnicity, maternal age, height, parity, education, gestation length and infant sex
			No association between birth weight adjusted for gestation length and placental cadmium; birth weight change per ng cadmium per g placental tissue	0.7 g (CI -1.7 to 3.0)		As above
(Aschengrau et al. 1993), Massachusetts	Hospital-based case control study, 1,039 birth defects, 77 stillbirths, 1,177 controls	Quality of drinking water source used at maternal residence during 1 st trimester; median, 90 th percentile and highest levels for cadmium were undetectable, 0.2 and 1.2 µg/L	Stillbirths not associated with drinking water cadmium level (odds ratio for ≥ 0.4 vs < 0.4 µg/L)	1.2 (p>0.05)		Race, age, health insurance coverage, previous child with birth defect, alcohol during 1 st trimester, water source

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
			Total, CNS, orofacial, cardiac and genital birth defects not associated with drinking water cadmium levels (respective crude odds ratios for ≥ 0.4 vs < 0.4 $\mu\text{g/L}$)	0.9, 1.6, 1.0, 1.6, 0.8		As above
(Wulff et al. 1996b), Ronnskar copper smelter, Sweden	Ecologic study; linked 2,724 births in population living near smelter and 15,191 births in comparison region to congenital malformation registers	High environmental levels of cadmium, arsenic, lead, mercury	No statistically significant increases of birth defects in smelter region (but limited statistical power – e.g., only 2 CNS defects observed in smelter region); relative risk, smelter vs comparison region	heart defects 1.7 (0.6-4.4) cryptorchidism 1.0 (0.5-2.2)		
(Landgren 1996), Sweden	Ecologic study, 38,718 births in 19 municipalities in one county; linked birth, congenital malformation, cardiology, cytogenetic and cancer registries	Measured contaminants in vegetation (lead, selenium, arsenic, cadmium, mercury) and ambient air (sulphur dioxide, nitrogen oxides, hydrocarbons); municipalities categorized as above or below mean contaminant level; mean ground arsenic level 93 $\mu\text{g/g}$ (range 14-323)	Stillbirths not associated with residence in municipalities with above average environmental cadmium levels			Year of birth, maternal age, parity
			In the municipality with the highest cadmium concentration, the relative risk of stillbirths was significantly elevated	2.2 (CI 1.1-4.5)		
(Jarup et al. 1998), Sweden	Literature review		There is limited evidence for an association between reduced birth weight and			

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
			cadmium in humans			
(Wilson et al. 1998), Baltimore-Washington Infant Study	Case-control study, 1585 cases of heart birth defects, 3572 healthy live birth controls	Self-reported information on various exposures	Atrial septal defect with Down syndrome associated with paternal welding (odds ratio)	1.7 (p < 0.05)		Adjusted as necessary for family history of congenital heart disease, maternal diabetes, age, smoking, alcohol, ionizing radiation exposure, race, SES
(Odland et al. 1999), Russia and Norway	262 mother-infant pairs from hospitals in each of three Russian and three Norwegian communities	Median maternal and cord blood cadmium levels, respectively, were 0.2 (range 0.06-4.0 µg/L) and 0.06 (range 0.06-4.3 µg/L)	Inverse association between birth weight and maternal blood cadmium levels in multivariate linear regression analysis (result stated without supporting data)	p<0.05		Gestation length, maternal age and BMI
(Agency for Toxic Substances and Disease Registry, 1999), USA	Literature review		Animals – high-dose prenatal exposure caused fewer litters, IUGR, skeletal birth defects			
(Salpietro et al. 2002), [citation ordered]	45 healthy non-smoking pregnant women	Measured maternal and cord blood cadmium levels at delivery	Birth weight inversely associated with maternal and cord blood cadmium concentrations			
(Nishijo et al. 2002), Japan	Cross-sectional study, 57 mother-infant pairs, 1999; assessed birth weight	Women lived in cadmium-contaminated river basin; measured cadmium levels in maternal urine and colostrum	Birth weight not associated with maternal urinary cadmium; partial regression coefficient	-0.015, p>0.05		Maternal age, gestation length

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
		milk				
			Gestation length inversely associated with maternal urinary cadmium; partial regression coefficient	-0.34, p<0.05	+	Maternal age
(Zhang et al. 2004), China	Cross-sectional study, 44 mother-infant pairs, 2002-2003; assessed birth weight	Soil irrigated with cadmium-contaminated water; measured cadmium in maternal and cord blood and placenta; ranges – maternal blood 0.8-25.2 µg/L, cord blood 0.0-1.5 µg/L, placenta 0.1-4.0 µg/g dry weight	Borderline <i>inverse</i> association between preterm delivery and placental cadmium level; odds ratio, >0.145 vs ≤0.145 µg/g (calculated from data in Table 2 in paper); preterm delivery not associated with maternal or cord blood cadmium (data not shown here)	0.13 (0.01-1.01)	(+)	
			Neonatal asphyxia (Apgar score ≤7) not associated with maternal or cord blood or placental cadmium level; odds ratio for placental cadmium >0.145 vs ≤0.145 µg/g (calculated from data in Table 3 in paper)	1.0 (0.2-4.4)		
			Inverse association between birth height and cord blood but not maternal blood or placental cadmium level; partial regression coefficient (avg height difference, infants with cord blood cadmium >0.4 vs ≤0.4 µg/L)	-2.2cm, p=0.03	+	Maternal age, height, weight, gestation length

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
(Odland et al. 2004), arctic and sub-arctic areas of Norway and Russia	Cross-sectional study, 50 mother-infant pairs from hospital delivery departments in 6 communities, recruited during 1993-1994; pregnancy outcome verified from medical records	Measure cadmium, copper, iron (as ferritin), nickel, lead, selenium and zinc in maternal blood, serum or urine, cord blood, neonatal urine and placenta; placental cadmium range 0.01-0.20 µg/g	Borderline inverse association between birth weight and placental and maternal blood cadmium levels; change in birth weight (g) per µg cadmium per g of placental tissue	1694 (-2038, 5426)		Country, gestation length

^a + means that a statistically significant association or dose-response relationship was demonstrated

Developmental effects: summary

Late fetal deaths (stillbirths)

A case-control study of late fetal deaths (stillbirths) in Massachusetts found no association with drinking water cadmium levels in communities of maternal residence (Aschengrau et al 1993). A Swedish ecologic study found no overall increased risk of late fetal deaths among women living in municipalities with above average environmental cadmium levels; however, in the municipality with the highest cadmium concentration, the relative risk of stillbirths was significantly elevated (Landgren 1996).

Birth defects

A large case-control study in Canada found no association between anencephaly and drinking water cadmium levels in communities of maternal residence (Elwood and Coldman 1981). A small retrospective cohort study in an industrial town in France found no association between birth defects and infant or maternal hair cadmium levels (Huel et al 1981). A case-control study in Massachusetts found no association between total, CNS, orofacial, cardiac or genital birth defects and drinking water cadmium levels in communities of maternal residence (Aschengrau et al 1993). A Swedish ecologic study found no increased risk of total birth defects among infants of women living in a smelter town; this study had very limited statistical power, e.g., there were only 2 CNS birth defects among exposed women (Wulff et al 1996b). A large case-control study of cardiac birth defects (the Baltimore-Washington Infant Study) found an association between atrial septal defect with Down syndrome and self-reported paternal occupation as a welder (note: welders may be exposed to cadmium, zinc, beryllium, iron, mercury, lead and other toxicants) (Wilson et al 1998). A literature review noted that high-dose prenatal cadmium exposure causes skeletal birth defects in experimental animals (Agency for Toxic Substances and Disease Registry 1999).

Gestation length

A small retrospective cohort study in an industrial town in France found no association between preterm birth and infant or maternal hair cadmium levels (Huel et al 1981). A birth cohort study in a lead smelter town in the former Yugoslavia found no association between gestation length and placental cadmium among

non-smoking women (Loicono et al 1992). A small cross-sectional study in a cadmium-polluted river basin in Japan found an inverse association between gestation length and maternal urinary cadmium levels (Nishijo et al 2002). A small cross-sectional study in a cadmium-polluted region in China found a borderline *inverse* association between preterm birth and placental cadmium levels (Nishijo et al 2002).

Birth weight adjusted for gestation length

A small retrospective cohort study in an industrial town in France found an inverse association between small for gestational age infants and infant but not maternal hair cadmium levels; this study did not adjust for prenatal maternal smoking (Huel et al 1981). Among infants of smokers, but not non-smokers, birth weight adjusted for gestation length and other potential confounders was inversely associated with maternal whole blood cadmium levels and positively associated with cord red blood cell zinc levels (Kuhnert et al 1987). A birth cohort study in a lead smelter town in the former Yugoslavia found no association between birth weight adjusted for gestation length and placental cadmium among non-smoking women (Loicono et al 1992). A literature review concluded that there is limited evidence for an association between reduced birth weight and cadmium exposure in humans (Jarup et al 1998). A birth cohort study in Norway and Russia found an inverse association between birth weight adjusted for gestation length and maternal blood cadmium levels (Odland et al 1999). A literature review noted that high-dose prenatal cadmium exposure causes reduced intrauterine growth rates in experimental animals (Agency for Toxic Substances and Disease Registry 1999). A small cross-sectional study in a cadmium-polluted river basin in Japan found no association between birth weight and maternal urinary cadmium levels (Nishijo et al 2002). A small cross-sectional study in Norway and Russia found a borderline inverse association between birth weight and placental and maternal blood cadmium levels (Odland et al 2004).

Birth height

A small cross-sectional study in a cadmium-polluted region in China found an inverse association between birth height and placental cadmium levels (Nishijo et al 2002).

Neonatal asphyxia

A small cross-sectional study in a cadmium-polluted region in China found no association between neonatal asphyxia (Apgar score ≤ 7) and placental cadmium levels (Nishijo et al 2002).

3. Kidney function

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
(Bernard et al. 1995), Czech Republic	Cross-sectional study, 141 children from 2 schools near a lead smelter and 51 from a rural, age 12-15 yr; measured urinary β 2-microglobulin, Clara cell protein, retinol-binding protein, albumin, N-acetylglucosaminidase (NAG)	Mean blood cadmium levels in 3 schools were 5-7 (range 1-23 ng/dL)	No associations between urinary protein levels and blood cadmium levels (result stated without supporting data)			Adjusted for age, sex, blood lead, and zinc protoporphyrin
(Jarup et al. 1998), Sweden	Literature review		Urinary cadmium levels as low as 2-3 μ g/g creatinine are associated with renal tubular damage in the general population and in occupationally exposed persons	+		
(Price et al. 1999), Belgium, Germany and Poland	Cross-sectional study of 304 children age 6-14 yr in regions polluted with cadmium and/or lead and comparison regions	Measured urinary levels of cadmium (mean 0.2-0.4 μ g/g creatinine in control areas and 0.2-0.8 μ g/g creatinine in exposed areas), lead (mean 3.9-7.2 μ g/g creatinine in control areas and 5.2-25 μ g/g creatinine in exposed areas) and several proteins	Residence in exposed regions associated with urinary levels of Clara cell protein, β 2-microglobulin, 6-keto-prostaglandin F _{1a} , brush border antigens, NAG, prostaglandin E ₂ , epidermal growth factor and laminin fragments (result stated without supporting data; did not assess relationship between urinary proteins and urinary cadmium)			
(Staessen et al. 2001), Antwerp,	Cross-sectional study, 200 adolescents age 17 yr from a rural control area and regions polluted by	Measured blood (GM 0.3-0.4 μ g/L) and urinary cadmium and lead, serum	No association between urinary protein levels (cystatin-C, β 2-			Sex and smoking

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
Belgium	a lead smelter and two waste incinerators; measured serum and urinary biomarkers of renal function	PCBs and dioxin-like compounds and urinary VOC metabolites	microglobulin) among youth age 17 yr and blood cadmium (result stated without supporting data)			
(Noonan et al. 2002), Pennsylvania	Cross-sectional study, 159 children age 6-17 yr living in a zinc smelter and a comparison community; assessed renal function	Measured urinary cadmium (GM 0.075 µg/g creatinine), N-acetyl-β-D-glucosaminidase (NAG), alanine aminopeptidase (AAP), albumin and β2-microglobulin; note - urinary cadmium levels did not differ between smelter and comparison communities	Urinary NAG, AAP and albumin among children age 6-17 yr not associated with current urinary cadmium; Spearman correlation coefficients	NAG 0.09 (-0.07, 0.24) AAP 0.15 (0.00-0.30) albumin 0.03 (-0.12, 0.19) β2-microglobulin -0.01 (-0.20, 0.19)		Age, sex, urinary creatinine
(de Burbure et al. 2003), France	Cross-sectional study, 400 children age 8-12 yr, living near two nonferrous smelters and age/sex-matched comparison group from unpolluted neighbouring regions; assessed renal function by measuring urinary proteins (total, albumin, transferrin, β2-microglobulin, retinol-binding protein, brush border antigen, NAG)	Measured blood cadmium (mean 0.5 µg/L in all 4 sex/region subgroups) and urinary mercury, blood lead (mean 2.7-4.2 µg/dL in 4 sex/region subgroups) and urinary mercury (0.9-1.2 µg/g creatinine)	Urinary NAG associated with blood cadmium; partial correlation coefficient, log NAG vs log blood cadmium	0.25, p=0.0002		Body mass index, urinary creatinine

Kidney function: summary*Urinary protein excretion*

A cross-sectional study of children age 12-15 years in the Czech Republic found no associations between urinary protein levels and blood cadmium levels (Bernard et al 1995). A cross-sectional study of children age 6-14 years in Belgium, Germany and Poland showed that those living in regions polluted with cadmium and/or lead had increased urinary levels of Clara cell protein, β 2-microglobulin, 6-keto-prostaglandin $F_{1\alpha}$, brush border antigens, N-acetyl- β -D-glucosaminidase (NAG), prostaglandin E_2 , epidermal growth factor and laminin fragments; this study did not assess the relationships between urinary protein and cadmium levels (Price et al 1999). A cross-sectional study of children age 17 years in Belgium found no association between urinary protein levels (cystatin-C, β 2-microglobulin) and blood cadmium levels (Staessen et al 2001). In a cross-sectional study of children age 6-17 years living near a zinc smelter in Pennsylvania, urinary NAG, alanine aminopeptidase and albumin were not associated with urinary cadmium (Noonan et al 2002). A cross-sectional study of children age 8-12 years living near nonferrous smelters in France found an association between urinary NAG and blood cadmium levels (Burbure et al 2003). A literature review concluded that urinary cadmium levels as low as 2-3 μ g/g creatinine are associated with renal tubular damage in the general population and in occupationally exposed persons (Jarup et al 1998).

4. Cancer Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
(International Agency for Research on Cancer 1993)	Expert panel review of epidemiologic and toxicologic literature		Cadmium and cadmium compounds are carcinogenic to humans (Group 1)			
(Wulff et al. 1996a), Ronnskar smelter, Sweden	Birth cohort study; assessed cancer incidence among children born in smelter region during 1961-90; cases identified from national cancer registry (age < 16 yr)	Smelter region exposed to airborne cadmium, lead, arsenic, copper and sulphur dioxide; assessed parental occupational exposure in smelter	Observed 13 childhood cancer cases in the smelter region vs. 6.7 expected from national rates; only one case father was occupationally exposed	2.0 (CI 0.9-3.0)		
(Jarup et al. 1998), Sweden	Literature review		Inhaled cadmium should be considered a probable human carcinogen (adult lung cancer)	+		
(Meplan et al. 1999), France	Review of literature on role of metals in p53 function	p53 controls the proliferation, survival, DNA repair, and differentiation of cells with DNA damage	p53 depends on zinc ions and is impaired by cadmium which readily substitutes for zinc in a several transcription factors			
(Agency for Toxic Substances and Disease Registry, 1999), USA	Literature review		Adult humans – inadequate evidence for association with cancer			
			Animals – limited evidence that ingested cadmium causes prostatic hyperplasias and adenomas, testicular tumours, leukemia			

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
(Waalkes 2000)	Review of literature on cadmium carcinogenesis		Occupational exposure by inhalation increases lung cancer risk			
			Inadequate epidemiologic evidence for association with prostate, liver, kidney, stomach cancers			
			Causes tumours at several sites and by various routes in rodents including lung, prostate, testes, adrenals, injection sites and hematopoietic system			
(Infante-Rivard et al. 2001), Montreal	Population-based case-control study, 491 acute lymphoblastic leukemia cases, 491 matched controls, age < 10 yr, 1980-1993	Child's residential history from conception to present, parent-reported drinking water source, water quality data for arsenic, cadmium, chromium, lead, zinc, nitrate, 1970-1993, 1995-1996 tap water survey (227 homes)	ALL not associated with prenatal or postnatal exposure to drinking water containing detectable cadmium levels (odds ratio, >1 vs ≤1 µg/L)	prenatal 1.4 (0.5-4.0) postnatal 1.9 (0.6-5.8)		Matched for age, sex, region; adjusted for maternal age, education
			ALL not associated with prenatal or postnatal cumulative drinking water cadmium exposure (odds ratio, >95 th vs ≤95 th percentile of µg.day.L ⁻¹)	prenatal 1.1 (0.6-2.2) postnatal 1.1 (0.6-2.0)		As above

Cancer: summary*Children*

A Swedish birth cohort study found an increased cancer risk among children born near a smelter known to emit cadmium and other toxicants (Wulff et al 1996a). In a case-control study of acute lymphoblastic leukemia in Montreal, there were no associations with prenatal or postnatal exposure to detectable cadmium levels ($\geq 1\mu\text{g/L}$) in community drinking water supplies or tap water samples; there were also no associations with cumulative prenatal or postnatal cadmium exposure (Infante-Rivard et al 2001).

Adults

Based on epidemiologic studies of adult cancers and toxicologic evidence, an expert panel concluded that there was sufficient evidence that inhaled cadmium and cadmium compounds are carcinogenic in humans (International Agency for Research on Cancer 1993). A literature review noted that the tumour suppressor gene p53 is inhibited by cadmium, disrupting control of DNA repair, cell proliferation, differentiation and survival of cells with DNA damage (Meplan et al 1999). Other reviewers concluded that there is inadequate evidence that inhaled cadmium can cause human cancers and limited evidence that ingested cadmium causes prostatic hyperplasias and adenomas, testicular tumours and leukemia in experimental animals (Agency for Toxic Substances and Disease Registry 1999). Literature reviews concluded that inhaled cadmium is a probable or known cause of lung cancer in humans and causes tumours at several sites and by various routes in rodents including lung, prostate, testes, adrenals, injection sites and hematopoietic system (Jarup et al 1998, Waalkes 2000). The latter review concluded that there is inadequate epidemiologic evidence for associations between cadmium exposure and cancers of the prostate, liver, kidney or stomach.

5. Reproductive effects

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
(Gennart et al. 1992), Belgium	Cohort study, 74 lead battery plant workers, 83 cadmium smelter workers, 70 alkaline battery plant workers exposed to airborne manganese dust (median 180 µg/m ³ for respirable dust), 138 unexposed workers (polyethylene plant, battery container producing plant, smelter maintenance workers); self-reported reproductive history	Measured blood lead (mean 46, range 24-75 µg/dL in exposed men), blood manganese (mean 0.8 µg/dL in exposed men), urinary cadmium (mean 6.9, range 2.1-24 µg/g creatinine in exposed men), urinary manganese (mean 0.8 µg/g creatinine)	Birth rate slightly increased among cadmium smelter workers (relative risk of live birth, post- vs pre-exposure periods)	1.2 (CI 1.0-1.5)		Age
			Likelihood of a live birth not reduced during cadmium exposure period (odds ratio, post- vs pre-employment period)	1.0 (CI 0.8-1.3)		
			Likelihood of a live birth not increased during years when urinary cadmium below group median level	1.0 (CI 0.8-1.4)		
(Spinelli et al. 1997), Italy	Retrospective cohort study, 622 women who delivered liveborn infants in 4 hospitals during early 1993; self-reported time to pregnancy	Mother-reported parental occupational exposures	Likelihood of conception inversely associated with paternal preconceptional occupational exposure to welding fumes (fecundability ratio, exposed vs unexposed)	0.8 (0.6-1.0)		Maternal age, parity, intercourse frequency, smoking, alcohol, coffee, tea
(Tielemans et al. 1999b), The	Cross-sectional study (letter to editor), 836 couples seeking <i>in vitro</i>	Self-reported exposures to pesticides, organic solvents,	<i>In vitro</i> fertilization rate not associated with male			Female age, indication for <i>in</i>

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
Netherlands	fertilization treatment; assessed <i>in vitro</i> fertilization success (number of oocytes fertilized)	metal dust or fumes, welding fumes	partner exposure to welding fumes			<i>in vitro</i> fertilization, previous birth, female education
(Tielemans et al. 1999a), The Netherlands	Case-control study, based on infertility clinics; 3 case definitions: (A) 692 with sperm concentration < 20x10 ⁶ /ml or < 50% motile or < 14% normal morphology, (B) sperm concentration < 5x10 ⁶ /ml or < 10% motile or < 5% normal morphology, (C) azoospermia (no sperm)	Self-reported occupational history, job-exposure matrix; urine from 69 cases and 20 controls tested for nickel, chromium, cadmium and manganese	Poor semen quality (case group A) not associated with self-reported welding fume exposure (33 exposed cases)	1.1 (CI 0.5-2.3)		Female partner's age, education, clinic
			No association between semen quality and urinary cadmium (mean urinary cadmium levels in cases and controls); also no associations with urinary manganese, chromium or nickel	0.16 vs 0.19 µg/g creatinine (p = 0.42)		
(Agency for Toxic Substances and Disease Registry, 1999), USA	Literature review		Animals – high-dose postnatal exposure caused testicular atrophy			
(Telisman et al. 2000), Croatia	Cross-sectional study, 98 men occupationally exposed to lead, 51 unexposed men, age 20-45 yr; assessed self-reported health status, semen quality, serum hormones	Measured blood lead, cadmium, ALAD activity, erythrocyte protoporphyrin (EP), serum zinc, copper; also measured seminal fluid lead	Blood cadmium not associated with semen quality indices (Spearman's rank correlation coefficients,	% abnormal sperm R _s =0.09, p>0.05	+	Lead, zinc, copper, ALAD, EP, smoking, alcohol, age, lead exposure

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
		and cadmium in a subgroup of 118 men	blood cadmium vs semen quality index)	total sperm count $R_s = -0.07$, $p > 0.05$ % motile sperm $R_s = -0.12$, $p > 0.05$		duration
(Sallmen et al. 2000), Finland	Cohort study, 769 wives of men occupationally exposed to lead and other metals; assessed time to pregnancy	Detailed work history	Borderline association between <i>increased</i> fertility and occupational exposure to cadmium inferred from work history; likelihood of conception	1.5 (0.9-2.2)		Paternal occupational lead exposure
(Staessen et al. 2001), Belgium	Cross-sectional study, 200 adolescents age 17 yr from a rural control area and regions polluted by a lead smelter and two waste incinerators; physicians measured testicular volume and staged sexual maturation	Measured blood cadmium and lead, serum PCBs and dioxin-like compounds and urinary VOC metabolites	No association between testicular volume or sexual maturation stage and blood cadmium levels			

Reproductive effects: summary

Sexual maturation

A cross-sectional study of Belgian males age 17 years from a rural control area and regions polluted by a lead smelter and two waste incinerators in Belgium found no association between testicular volume or sexual maturation stage and blood cadmium levels (Staessen et al 2001).

Fertility

A cohort study in Belgium found a slightly *increased* birth rate among men working in a cadmium smelter; there were no associations between likelihood of a live birth and cadmium exposure time period or individual urinary cadmium levels (Gennart et al 1992). A retrospective cohort study in Italy found an inverse

association between likelihood of conception and paternal preconceptual occupational exposure to welding fumes (note: welders may be exposed to cadmium, zinc, beryllium, iron, mercury, lead and other toxicants) (Spinelli et al 1997). A cross-sectional study of couples seeking *in vitro* fertilization in the Netherlands showed that the *in vitro* fertilization rate was not associated with male partner occupational exposure as a welder (Tielemans et al 1999b). A cohort study in Finland found a borderline favourable association between likelihood of conception and male partner occupational exposure to cadmium inferred from work history (Sallmen et al 2000).

Semen quality

A case-control study in the Netherlands found no association between semen quality indices and self-reported welding fume exposure or urinary cadmium levels (Tielemans et al 1999a). A literature review concluded that high-dose postnatal cadmium exposure causes testicular atrophy in experimental animals (Agency for Toxic Substances and Disease Registry 1999). A cross-sectional study of Croatian men found no association between semen quality indices and blood cadmium levels (Telisman et al 2000).

6. Other health effects

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
(Thatcher et al. 1982), Maryland	Cross-sectional study, 149 children age 5-16 yr in rural schools; conducted Wechsler Intelligence Scale for Children, revised (WISC-R) for children age 6-16 yr, Wechsler Pre-school and Primary Scale of Intelligence (WIPPSI) for children age 5 yr, Wide Range Achievement Test (WRAT – includes reading, spelling and math subscales) and tests of fine and gross motor function (Purdue Pegboard test, Stott, Moyes and Henderson Test of Motor Impairment)	Measured hair cadmium (mean 1.7, range 0-8.9 µg/g) and lead (mean 7.5, range 0-178 µg/g) content	Full-scale IQ among children age 5-16 yr inversely associated with current hair cadmium level; partial R	-0.28, p=0.001	+	Age, sex, race, SES
			WRAT reading, spelling and math scores among children age 5-16 yr not associated with current hair cadmium; respective partial Rs	-0.13, -0.12, -0.15 p>0.05 for each		As above
			Fine motor function score (preferred hand) among children age 5-16 yr inversely associated with current hair cadmium; partial R	-0.20, p=0.05	+	As above
			Gross motor function score among children age 5-16 yr not associated with current hair cadmium; partial R	-0.02, p>0.05		As above

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
(Wulff et al. 1996b), Sweden	Birth cohort study; linked 2,724 births in population living near copper smelter and 15,191 births in comparison region to congenital malformation registers	High environmental levels of cadmium, arsenic, lead, mercury	Borderline increased risk of chromosomal abnormalities; note – incidence in comparison group was lower than expected	2.6 (CI 0.9-6.7)		
(Ritz et al. 1998), Germany	Cross-sectional study, 842 children age 5-14 yr, from two industrially polluted regions (chemical production, mining, smelting) and a comparison agricultural region; assessed immune function (blood immunoglobulin levels, immediate hypersensitivity reactions to skin-prick challenges with 12 common aeroallergens)	Measured urinary (GM 0.15, range 0.01-6.2 µg/g creatinine) and blood (GM 0.2, range 0.1-7.2 µg/L) cadmium	Borderline dose-response relationship between blood IgG concentrations in lowest quartile and urinary cadmium levels; odds ratios, urinary Cd 0.11-0.23, 0.24-0.43 and ≥0.44 vs <0.11 µg/g creatinine	1.3 (0.9-1.9) 1.6 (1.0-2.6) 1.9 (0.9-4.0) p-trend=0.08	(+)	Age, sex, region, season, environmental tobacco smoke in home, urinary arsenic, lead and mercury
			No associations between IgM, IgA or IgE levels and urinary cadmium			As above
			Dose-response relationship between negative skin prick responses to all 12 common allergens and urinary cadmium; odds ratios, urinary Cd 0.11-0.23 and ≥0.24 vs <0.11 µg/g creatinine	1.5 (1.0-2.3) 1.7 (1.0-2.7)	+	Blood IgG and IgE levels, age, body mass index, sex, region, season
(Osius et al. 1999), Germany	Cross-sectional study, 671 children age 7-10 yr (complete data for 320 children); from region potentially exposed to PCBs, lead, cadmium and mercury from a toxic waste incinerator and two	Measured blood PCBs, cadmium (GM 0.2, range ND-1.8 µg/L) and lead and 24-hr urinary mercury and serum	Serum FT ₃ level among children age 7-10 yr not associated with current blood cadmium; β-coefficient, blood	β=0.001, p=0.996		Sex, age, environmental tobacco smoke, fish consumption, blood lead, 24-hr urinary

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
	comparison regions; assessed thyroid function	TSH, FT ₄ and FT ₃	cadmium >0.34 vs <0.15 µg/L; no data presented for TSH or FT ₄			mercury
(Agency for Toxic Substances and Disease Registry, 1999), USA	Literature review	Animals – high-dose prenatal exposure causes cognitive, behavioural and neurophysiologic abnormalities	Children – inadequate evidence for association with neurotoxic effects			
			Adult humans – limited and mixed evidence for association between chromosome abnormalities and cadmium exposure			
			Animals – high-dose prenatal exposure causes immune system abnormalities			
(Waalkes 2000)	Review of literature on cadmium carcinogenesis		Cadmium is weakly mutagenic; it competes with zinc at sites on enzymes and other proteins			
(Hartwig et al. 2002)	Review of literature on interference with DNA repair and cell cycle control processes by cadmium and other metals		Cadmium, nickel, cobalt and arsenic interfere with nucleotide and base excision repair at low concentrations			
(Jin et al. 2003), USA	Experimental study, effect of cadmium on yeast mutation rates and DNA repair	At very low concentrations (µM),	Cadmium specifically inhibited one type of DNA			

Reference, location	Design	Exposure	Results	Association ^a	DR ^a	Covariates
	systems	cadmium markedly increased yeast mutation rates	repair, i.e., mismatch repair			

Other health effects: summary

Neurotoxicity

A small cross-sectional study of children age 5-16 years in Maryland found inverse associations between full-scale IQ and fine motor function scores and current hair cadmium levels; gross motor, reading, spelling and math scores were not associated with current hair cadmium levels (Thatcher et al 1982). A literature review concluded that there is inadequate evidence for associations between childhood neurotoxic effects and cadmium exposure (Agency for Toxic Substances and Disease Registry 1999).

Immune function

A cross-sectional study of children age 5-14 years in Germany found dose-response relationships between low blood IgG levels (but not IgM, IgA or IgE) and negative skin-prick reaction to 12 common antigens and current urinary cadmium levels (Ritz et al 1998). A literature review concluded that prenatal cadmium exposure causes immune system abnormalities in experimental animals (Agency for Toxic Substances and Disease Registry 1999).

Thyroid function

A cross-sectional study of children age 7-10 years in Germany found no association between serum FT₃ levels and blood cadmium levels (Osius et al 1999).

Genotoxicity

A Swedish birth cohort study found a 2.6-fold increased risk of chromosomal abnormalities (increase was of borderline statistical significance) among infants of women living in a smelter town with significant cadmium, lead, arsenic, copper and sulphur dioxide pollution (Wulff et al 1996b). A literature review concluded that there is limited and mixed evidence for an association between chromosome abnormalities in adults and cadmium exposure (Agency for Toxic Substances and Disease Registry 1999). Other reviews concluded that cadmium is weakly mutagenic (Waalkes 2000) and, at low concentrations, interferes with nucleotide and base excision DNA repair (Hartwig et al 2002). A recent experimental study found that cadmium at micromolar concentrations markedly increased yeast mutation rates and specifically inhibited one type of DNA repair, i.e., mismatch repair (Jin et al 2003).

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