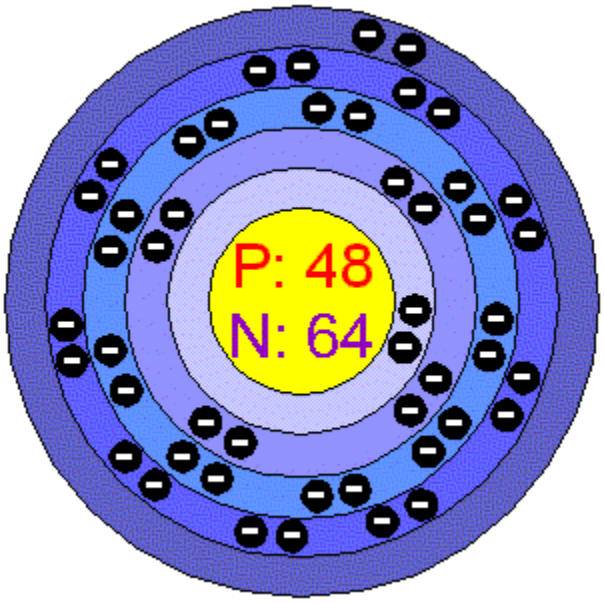
Final Dossier

CADMIUM



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I. Introduction

Nomination

Cadmium was first nominated on May 16, 2000. No name or reason was associated with the nomination. The minutes of the Core Committee meeting of August 1, 2000 indicates that cadmium was considered, but no action was documented. An updated Cadmium dossier was reviewed at the Core Committee meeting held on October 25, 2006 and the Core Committee decided to defer the compound. The dossier was again reviewed at the next Core Committee meeting held on January 31, 2007. Noting possible widespread exposure through use of cadmium/nickel batteries, a good database, and public concern, a full nomination dossier was requested.

The most informative reviews conducted for cadmium include an ATSDR (1999) Toxicological Profile and a WHO/IPCS (1992) Environmental Health Criteria. Because the ATSDR report was more recent, it was the primary document used to develop this dossier. Information was also obtained from REPROTOX, HSDB, and literature searches from PUBMED and TOXNET, which will be discussed in greater detail below.

Production

According to the US Geological Survey, the US produces about 1100 metric tons/year of cadmium and consumes about 1300 metric tons/year. Table 1 comes from the USGS web site. The discrepancy with the 1100–1300 metric ton figure is noted.

Table 1. Cadmium in the US (metric tons)

	2001	**2002**	**2003**	**2004**	**2005**
Production, refinery	680	700	670	550	550
Imports for consumption, metal	107	25	18	38	35
Exports of metal, alloys, scrap	272	168	558	132	200
Shipments from Government stockpile excesses	34	693	80	0	0

According to ATSDR (July 1999), US producers of cadmium in 1997 were Big River Zinc Corporation in Saugett IL and Savage Zinc Inc. in Clarksville TN. International Metals Reclamation Company, a Pennsylvania company, was listed as a recoverer of cadmium from spent nickel-cadmium batteries.

The US Geological Survey reported in 2003 that there are 2 cadmium producers in the US: "Pasminco Ltd. produced primary cadmium as a byproduct of the smelting and refining of zinc concentrates, and the International Metals Reclamation Company Inc. (INMETCO) produced secondary cadmium from scrap, almost entirely from spent nickel-cadmium (NiCd) batteries." http://minerals.usgs.gov/minerals/pubs/commodity/cadmium/cadmimyb03.pdf

According to the USGS, two companies in the United States produced cadmium in 2005. A company in Tennessee (presumably Savage Zinc) produced cadmium metal as a byproduct of smelting and refining zinc, and a company in Pennsylvania (presumably INMETCO) produced cadmium metal from cadmium-containing scrap, mainly from spent nickel-cadmium batteries. Between 2001 and 2005, domestic consumption of cadmium metal declined by about 35% in response to environmental concerns. Cadmium is encountered in batteries (81% of consumption), in pigments (10%), in coatings and plating (7%), in stabilizers for plastics (1.5%), and in

nonferrous alloys and other uses (0.5%). The decrease in cadmium production in the US has been offset by an increase in production in China, where most batteries are manufactured. Some occupational cadmium exposure comes from recycling. Cadmium is recovered from spent NiCd batteries, copper-cadmium alloy scrap, some complex nonferrous alloy scrap, and cadmium-containing dust from electric arc furnaces. In 2005, the U.S. steel industry generated about 700,000 tons of electric arc furnace dust, typically containing 0.003% to 0.07% cadmium. The OSHA PEL (TWA) for cadmium is 0.005 mg/m3.

The following companies were currently cited as major producers of other cadmium compounds: Big River Zinc Corporation, Saugett, Illinois (cadmium oxide); Shepherd Chemical Company, Cincinnati, Ohio (cadmium carbonate); Engelhard Corporation, Cleveland, Ohio (cadmium chloride, cadmium sulfate, and cadmium sulfide/sulfoselenide pigments); and Eagle-Picher Industries, Inc., Milwaukee, Wisconsin (cadmium sulfide-orange cadmium) (SRI 1994). Companies specifically cited as major producers of cadmium sulfide/sulfoselenide pigments include Morton Internationals, Inc., Danvers, Massachusetts; Cerac Incorporated, Milwaukee, Wisconsin; SCM Chemicals, Inc., Baltimore, Maryland; and Warner-Jenkinson Cosmetic Colors, South Plainfield, New Jersey (SRI 1994).

Exposure

According to the July, 1999 ATSDR Toxicological Profile for cadmium:

> Human exposure to cadmium can result from consumption of food, drinking water, or incidental ingestion of soil or dust contaminated with cadmium; from inhalation of cadmium-containing particles from ambient air; from inhalation of cigarette smoke, which contains cadmium taken up by tobacco; or from working in an occupation involving exposure to cadmium fumes and dust. For nonsmokers, ingestion of food is the largest source of cadmium exposures. Most drinking water contains only very low levels of cadmium and is usually not an important route of exposure, although water may leach cadmium from plumbing. Concentrations of cadmium in ambient air are generally less than 5×10^{-6} mg/m3, but concentrations up to 5×10^{-4} mg/m^3 have been detected in air near cadmium-emitting facilities.

The FAO/WHO Expert Committee on Food Additives (JECFA) estimated daily human cadmium intake at 1–4 μg/kg bw/day. An additional 1 μg/kg bw/day might be ingested in water close to sources of cadmium release. And additional 2–4 μg of cadmium is absorbed from smoking a pack of cigarettes.

Public Concern

There is public concern about cadmium exposure subsumed in a more general concern about "toxic metals," usually taken to mean lead, mercury, cadmium, and sometimes chromium. CNN ran a story in 2000 on environmental contamination with cadmium from mine tailings in south-central Colorado. The white-tailed ptarmigan, a member of the grouse family, was found to have elevated renal cadmium levels associated with impaired renal function. A CNN story the following year reported that Dutch officials had seized more than 1.3 million Sony Playstations and accessories due to excessive amounts of cadmium in the console's cables. Under European Union rules, no goods containing more than 0.01 percent cadmium can be imported.

Public concern is focused on the carcinogenicity of cadmium. In 2002, a German web site advocated the banning of nickel-cadmium batteries to prevent widespread cadmium poisoning

from improper disposal (http://www.umweltbundesamt.de/uba-info-presse-e/presse-informationen-e/p3902e.htm). The Children's Health Environmental Coalition (http://www.checnet.org/HealtheHouse/chemicals/chemicals-detail2.asp?Main_ID=369) identifies cadmium as being carcinogenic, a reproductive and developmental toxicant, and an "endocrine disruptor." The web site recommends avoiding products containing cadmium and recommends keeping nickel-cadmium batteries away from children.

Recent news items on CNN and in *USA Today* have reported new interest in "e-cycling." or the recycling of electronic components. In July, the European Union implemented new regulations limiting the disposal of "e-waste." Concern in the US about the 250 million personal computers and 100 million cell phones that are discarded each year in this country has resulted in legislation to keep this material out of landfills. EPA's web site has a section devoted to e-cycling (http://www.epa.gov/ecycling/). An Internet search on the term e-cycling produced 34,200 hits many of which are commercial enterprises that advertise the proper disposal of electronic components. According to the *USA Today* piece, however, much of the e-waste ends up in southeast Asia where environmental regulations are less strict.

II. Overview

ATSDR (1999) summarized the developmental toxicity of cadmium as follows:

> There is very little human data on developmental effects from exposure to cadmium, and the studies that do indicate that maternal cadmium exposure may cause decreased birth weight in humans (Hue1 et al. 1984; Tsvetkova 1970) are of limited use because of weaknesses in the study design and lack of control for confounding factors.
>
> In animals, cadmium has been shown to be a developmental toxin by the inhalation, oral, and parenteral routes (Baranski 1985, 1987; Prigge 1978b). Decreased fetal weight and skeletal malformations are produced by relatively high maternal doses due to placental toxicity, interference with fetal metabolism, and damage to the maternal liver (Holt and Webb 1987). Malformations or skeletal effects reported include sirenomelia (fused lower limbs), amelia (absence of one or more limbs), and delayed ossification of the sternum and ribs (Baranski 1985); dysplasia of facial bones and rear limbs, edema, exenteration, cryptorchism, and palatoschisis (Machemer and Lorke 1981); and sharp angulation of the distal third of the tail (Schroeder and Mitchener 1971). Dosing levels were in the 1-20 mg/kg/day range. The most sensitive indicator of developmental toxicity appears to be impaired neurological development. This observation is supported by later studies that noted brain weights of mice dosed orally with cadmium had significantly decreased brain weights, with high levels of cadmium deposits in the brain (Kostial et al. 1993; Xu et al. 1993b). The lowest exposures shown to cause these effects in animals are 0.02 mg/m^3, 5 hours a day, 5 days a week, by inhalation (Baranski 1985) and 0.04 mg/kg/day, 5 days a week orally (Baranski et al. 1983). These exposures are above the chronic NOAELs calculated for renal effects in humans. However, insufficient information is available on developmental toxicity in humans to determine whether developmental effects of cadmium are of concern at levels of environmental exposure.

ATSDR (1999) summarized the reproductive toxicity of cadmium as follows:

> Evidence is insufficient to determine an association between inhalation exposure to cadmium and reproductive effects in humans. Study results are conflicting, with

some showing no effect on male fertility (Gennart et al. 1992), male hormone levels (Mason 1990), sperm density (Noack-Fuller et al. 1992), or semen quality (Saaranen et al. 1989); others found a reduction in sperm number or viability (Xu et al. 1993a). Animal studies with inhalation exposures have reported increased duration of the estrous cycle (Baranski and Sitarek 1987; Tsvetkova 1970), and increased relative testes weight, but no loss in reproductive success (Kutzman et al. 1986).

No studies were located regarding reproductive effects in men or women after oral exposure to cadmium. A number of animal studies have shown adverse reproductive effects to male and female reproductive capacity from oral cadmium exposure. In male rats and mice, acute oral-exposure near-lethal doses (60-100 mg/kg) can cause testicular atrophy and necrosis (Andersen et al. 1988; Bomhard et al. 1987; Borzelleca et al, 1989), and concomitant decreased fertility (Kotsonis and Klaassen 1978). Lower-dose acute exposures of 25-50 mg!kg did not result in reproductive toxicity in male animals (Andersen et al. 1988; Bomhard et al. 1987; Dixon et al. 1976). A number of intermediate-dosing regimens in the 0.25-5 mg/kg/day range resulted in neither testicular histopathologic lesions nor a decrease in male reproductive success (Bomhard et al. 1987; Dixon et al. 1976; Groten et al. 1990; Kotsonis and Klaassen 1978; Loeser and Lorke 1977a, 1977b; Pleasants et al. 1992; Zenick et al. 1982). Some dosing regimens in the 5-14 mg/kg/day range resulted in necrosis and atrophy of seminiferous tubule epithelium (Cha 1987); increased testes weight (Pleasants et al. 1992, 1993); increased prostatic hyperplasias (Waalkes and Rehm 1992); or significantly increased relative testes weight, decreased sperm count and motility, decreased seminiferous tubular diameter, and seminiferous tubular damage (Saxena et al. 1989). Vitamins A and D3 have been reported to reduce cadmium-related increase in testes weight (Pleasants et al. 1992, 1993).

Higher doses of cadmium are needed to elicit a reproductive toxic response in females than in the males, at least for the effects reported in the literature (Borzelleca et al. 1989). Effects include decreased percentage of fertilized females and percentage of pregnancies (Machemer and Lorke 1981; Sutou et al. 1980) and increased duration of the estrus cycle (Baranski and Sitarek 1987). Reduction in the number of pups born has generally not been seen from female exposures (Petering et al. 1979; Pond and Walker 1975; Sorell and Graziano 1990), but have been observed when both males and females were exposed (Schroeder and Mitchener 1971).

In pregnant albino rats, kidney concentrations of cadmium in the dam exceeded those concentrations found in the liver, while in the pups, renal and liver concentrations were very similar. Body concentrations of cadmium were several orders higher in dams than in the pups (Kostial et al. 1993). Environmental exposures may not be likely to cause reproductive toxicity in exposed humans.

Cadmium and its compounds were evaluated by IARC as carcinogenic to humans (Group 1) in 1997. Several cohorts of exposed workers have been found to have an increase in lung cancer mortality. An increase in prostate cancer has been identified in some cohorts but not in others. Oral administration to rats produced an increase in leukemia and Leydig cell tumors. Inhalation exposure in rats produces lung cancer. According to IRIS (last revised 1992), EPA has classified cadmium as a probable human carcinogen (B1).

The TOXLINE and PUBMED databases were searched to obtain information about cadmium. Using the CAS RN for cadmium (7440-43-9) and terms associated with

developmental and reproductive toxicity (reproductive OR reproduction OR fetus OR fetal OR embryo OR infant OR ovary OR ovarian OR testes OR testicular OR pregnant OR pregnancy), ~5800 references were identified. Many of the references were duplicates and others were of no relevance for a CERHR review. The ATSDR and REPROTOX reviews were used to identify relevant studies published in or prior to 1999. Each individual year from 1999 to 2007 was then searched to identify relevant studies published subsequent to the ATSDR review. Approximately 480 relevant references were identified. Included among the relevant references discussed in this dossier were studies conducted in mammalian species. Because of the large database, less relevant studies such as those conducted in birds, fish, and other aquatic species were not discussed in this dossier. However, those studies are listed in the Endnote database used to download the results of the literature search. Studies available only as abstracts are also not discussed in this dossier. Included in the developmental and reproductive sections are studies addressing genotoxicity in fetal or reproductive tissues or cells.

Because of the large database for cadmium, the literature search summarized in this dossier is limited to search terms associated with reproductive and developmental toxicity. A search for papers on the carcinogenicity of cadmium yielded 5 studies published from 1999 to date. A search for papers on the metabolism of cadmium yielded 1848 papers published from 1999 to date of which 61 were identified as reviews. A search for papers on the toxicokinetics of cadmium yielded 641 papers published from 1999 to date of which 20 were identified as reviews.

A. Developmental Toxicity.

Human

A total of 37 human developmental toxicity studies were identified and 25 of those studies were published from 1999 to date. The effect of cadmium on birthweight was the only endpoint addressed by studies summarized in the ATSDR profile. The more recent studies examined a broader range of topics including possible associations between cadmium and neural tube defects or sudden infant death syndrome; the studies suggested no association. Other more recent studies found possible associations between cadmium and abortion, decreased fetal growth, and autism. Variable findings were reported in studies examining possible links between cadmium and premature delivery. One study reported aromatic DNA adducts in fetuses of women who smoke and attributed the adducts to cadmium-associated impairment of DNA repair. Other studies attempted to determine the role of cadmium in adverse developmental findings in children of smoking mothers. Additional endpoints that were examined included immune system effects, interactions with essential minerals, and placental effects. Human developmental toxicity studies are summarized in Table 2.

Experimental animal

A total of 103 experimental animal developmental toxicity studies were identified and 45 of those studies were published in 1999 or later. Consistent with the studies summarized in the ATSDR profile, the more recent studies reported malformations and neurotoxicity in experimental animals exposed to cadmium during development. The more recent studies examined additional neurological endpoints and reported changes in somatosensory evoked potentials, EEG patterns, neurotransmitter levels, and cocaine sensitivity or dependency; reflex delays; and decreased anxiety. Somewhat variable findings were reported for reproductive function of offspring. Changes in time to

testicular descent or vaginal opening were reported. Other observations in offspring from more recent studies included DNA damage or change in DNA synthesis, gene expression changes, fatty acid changes in brain, effects on mortality or birth weight, changes in thyroid metabolism in brain, alterations in mineral balance, lipid peroxidation, increased apoptosis, and immunotoxicity. Interactions with lead were examined, and synergistic effects were reported for neurotransmitter levels and brain enzymes, while an antagonistic relationship was reported for kidney function. A synergistic effect on malformations was reported with co-exposure to retinoic acid. Other compounds such as antioxidants, essential minerals, and caffeine were found to have an ameliorative effect on cadmium-induced developmental toxicity. Animal developmental toxicity studies are summarized in Table 3.

Table 2. Human Developmental Toxicity Studies

Reference	Findings/Conclusions
In vivo studies	
Akesson, A., M. Berglund, et al. (2002). "Cadmium exposure in pregnancy and lactation in relation to iron status." Am J Public Health **92**(2): 284-7.	"Iron deficiency during pregnancy leads to increased cadmium absorption and body burden. Multiparous women exhibit additional increases with increasing age."
Bonithon-Kopp C, Huel G, Moreau T, Wendling R. Prenatal exposure to lead and cadmium and psychomotor development of the child at 6 years. Neurobehav Toxicol Teratol. 1986 May-Jun;8(3):307-10.	There is a "significant negative relationship between the degree of in utero exposure to cadmium and lead and the child's motor and perceptual abilities. Any effect on memory or verbal skills was not statistically significant."
Brender, J. D., L. Suarez, et al. (2006). "Maternal exposure to arsenic, cadmium, lead, and mercury and neural tube defects in offspring." Environ Res **101**(1): 132-9.	In a case-control study of Mexican-American women living in one of the 14 Texas counties, the authors stated that "Our findings suggest that maternal exposures to arsenic, cadmium, or lead are probably not significant risk factors for NTDs in offspring."
Carrillo-Ponce Mde, L., V. A. Martinez-Ordaz, et al. (2004). "Serum lead, cadmium, and zinc levels in newborns with neural tube defects from a polluted zone in Mexico." Reprod Toxicol **19**(2): 149-54.	"The logistic regression multivariate analysis showed no correlation between NTD and high levels of any of these metals; however, a positive correlation was found to zinc deficiency (OR 5.0, 95% CI 1.07-23.00, p=0.04). These results focus attention to the surrounding nutritional and maternal health factors of major importance in disease etiology."
Durska, G. (2001). "[Levels of lead and cadmium in pregnant women and newborns and evaluation of their impact on child development]." Ann Acad Med Stetin **47**: 49-60.	In a study of mothers and their newborns "A statistically significant correlation was revealed between maternal venous and umbilical cord blood levels of lead ($r = 0.59$, $p = 0.000001$) and cadmium ($r = 0.23$, $p = 0.04$). The levels of both metals seemed to be without effect on the health status and body dimensions measured. Significantly higher levels of cadmium were detected in women who reported a history of abortions."
Falcón, M., P. Vinas, et al. (2003). "Placental cadmium and lipid peroxidation in smoking women related to newborn anthropometric measurements." Arch Environ Contam Toxicol **45**(2): 278-82.	"Our results suggest that the cadmium accumulated in placenta is not the reason for reduced fetal growth in smoking mothers and that placental peroxidation is not enhanced by smoking, although the outcome of pregnancy seems to be negatively influenced by lipid peroxidation."
Frery, N., C. Nessmann, et al. (1993).	"The main finding of this study was the relationship

Reference	Findings/Conclusions
"Environmental exposure to cadmium and human birthweight." Toxicology **79**(2): 109-18.	between a decrease in birthweight and an increase of newborn hair Cd which varied in the presence of placental calcification."
Friel, J. K., H. Longerich, et al. (2005). "Possible altered mineral metabolism in human anencephalic fetuses." Nutr Res **25**(2): 103-9.	In an investigation of trace elements (zinc, copper, manganese, cobalt, nickel, molybdenum, cadmium), in livers, pancreata, sciatic nerves, diaphragms, and kidneys collected at autopsy from 33 anencephalic fetuses and 22 control fetuses, liver concentrations of zinc were higher in anencephalic fetuses.
Galicia-Garcia, V., M. Rojas-Lopez, et al. (1997). "Cadmium levels in maternal, cord and newborn blood in Mexico City." Toxicol Lett **91**(1): 57-61.	"Birthweight was found to be inversely associated ($P < 0.06$) only with cord blood cadmium levels. . . The results of the study suggest that cord blood cadmium holds information about both maternal and newborn cadmium status and also about cadmium effects on birthweight."
Godschalk, R., J. Hogervorst, et al. (2005). "Interaction between cadmium and aromatic DNA adducts in hprt mutagenesis during foetal development." Mutagenesis **20**(3): 181-5.	"Although the Cd/Zn ratio was 2.5-fold higher in the blood of smoking women than in non-smoking women (1.0 +/- 0.2 and 0.4 +/- 0.1, respectively, $P = 0.007$), this difference could not be observed in umbilical cord blood (0.3 +/- 0.1 and 0.3 +/- 0.1, respectively, $P = 0.66$). Similarly, mean DNA adduct levels were increased in the lymphocytes of smoking women compared with non-smoking controls (0.99 +/- 0.31 adducts/10(8) nt and 0.43 +/- 0.12, respectively, $P = 0.009$), but were only marginally higher in the neonates of smokers than in their non-smoking counterparts (0.57 +/- 0.29 and 0.24 +/- 0.09, respectively, $P = 0.38$). . . the number of HPRT-variants per adduct (i.e. the mutagenic efficiency of adducts) correlated positively with the Cd concentrations in cord blood ($r = 0.61$, $P = 0.001$). These data suggest a molecular link between DNA damage, inhibition of DNA repair by Cd and in vivo mutagenesis during foetal development."
Hough, R. L., N. Breward, et al. (2004). "Assessing potential risk of heavy metal exposure from consumption of home-produced vegetables by urban populations." Environ Health Perspect **112**(2): 215-21.	In a study looking at exposure to cadmium and other heavy metals, "The results showed that food grown on 92% of the urban area presented minimal risk to the average person subgroup. However, more vulnerable population subgroups (highly exposed person and the highly exposed infant) were subject to hazard index values greater than unity."
Huel G, Boudene C, Ibrahim MA. Cadmium and lead content of maternal and newborn hair: relationship to parity, birth weight, and hypertension. Arch Environ Health. 1981 Sep-Oct;36(5):221-7.	"Inverse relationships were found (1) between the cadmium content in babies' hair and their birthweight and (2) between the lead content in mothers' hair and the babies' gestational age. Cadmium levels in babies of hypertensive mothers were 3 times as high as in the hypertensive mothers themselves."
Jiang HM. [The clinical significance of multifactor discrimination and analysis of maternal serum Cu, Zn, Cd, Mn contents in the	This case control study of neural-tube defect is in Chinese with an English abstract. The authors concluded that neural tube defect was related to a

Reference	Findings/Conclusions
diagnosis of abnormal fetus] Zhonghua Yu Fang Yi Xue Za Zhi. 1991 Mar;25(2):102-4.	deficiency of maternal serum in Cu, Zn, Mn and to an excess of Cd.
Kuhnert, B. R., P. M. Kuhnert, et al. (1987). "The relationship between cadmium, zinc, and birth weight in pregnant women who smoke." Am J Obstet Gynecol **157**(5): 1247-51.	"The results suggest that increased maternal cadmium and decreased cord vein red blood cell zinc levels in infants of smokers may be significant clinically since increased maternal whole blood cadmium and decreased cord vein red blood cell zinc levels are both significantly related to decreased birth weight."
Kuhnert, P. M., B. R. Kuhnert, et al. (1987). "The effect of smoking on placental and fetal zinc status." Am J Obstet Gynecol **157**(5): 1241-6.	Overall, our data show that a cadmium/zinc interaction does take place in the maternal-fetal-placental unit of pregnant women who smoke and results in less favorable zinc status in the infants.
Kuhnert, B. R., P. M. Kuhnert, et al. (1988). "Associations between placental cadmium and zinc and age and parity in pregnant women who smoke." Obstet Gynecol **71**(1): 67-70.	"These results are consistent with a depletion of body zinc stores with increasing parity and the long half-life of cadmium in the body. The data explain in part the clinical finding that smoking during pregnancy is more harmful in older women."
Kuhnert, B. R., P. M. Kuhnert, et al. (1993). "The relationship between placental cadmium, zinc, and copper." J Am Coll Nutr **12**(1): 31-5.	"These results suggest that Cd-Zn and Cd-Cu interactions occur in the placenta at "normal" levels of Cd exposure and over a very short time period."
Limin Z, Wenzhen P. Zinc, copper, cadmium, vitamin A in tissues of human fetuses with central nervous system malformations. Tianjin Med J 1992;12:751-3	Liver cadmium in anencephalic fetuses was higher (248 ± 56 ppb) than in control fetuses (195 ± 51 ppb).
Lyon, T. D., M. Patriarca, et al. (2002). "Age dependence of potentially toxic elements (Sb, Cd, Pb, Ag) in human liver tissue from paediatric subjects." J Environ Monit **4**(6): 1034-9.	In a odeling m examination of metals in liver samples of infants and children, "Comparison of 95% confidence intervals of the median concentrations of the four elements suggested that there were no differences between the two categories of cause of death, SIDS or those who had died of an identified disease. Cadmium, lead and antimony median concentrations were lower than corresponding values observed in adult populations. . . Cadmium levels were almost negligible in neonates and infants, but increased in older children."
Nishijo, M., H. Nakagawa, et al. (2002). "Effects of maternal exposure to cadmium on pregnancy outcome and breast milk." Occup Environ Med **59**(6): 394-6; discussion 397.	In a study of Japanese mothers it was found that "Maternal exposure to Cd seems to increase early delivery, which leads to a lower birth weight. Also, the Cd is transferred in part to the next generation through breast milk after birth."
Nishijo, M., K. Tawara, et al. (2004). "Relationship between newborn size and mother's blood cadmium levels, Toyama, Japan." Arch Environ Health **59**(1): 22-5.	In a study of Japanese mothers, "A significant inverse correlation was found between infant height and maternal blood Cd. After adjustment for gestational age and maternal weight at 30-32 gestational weeks, the significant inverse relationship between maternal blood Cd and infant height was shown using the multiple regression analysis."
Odland, J. O., E. Nieboer, et al. (1999). "Blood lead and cadmium and birth weight among sub-arctic and arctic populations of Norway and	"The median blood-cadmium concentration for the Russian mothers was 2.2 nmol/L (n = 148) versus 1.8 nmol/L in the Norwegian group (n = 114, p = 0.55).

Reference	Findings/Conclusions
Russia." Acta Obstet Gynecol Scand **78**(10): 852-60.	A weak association was observed between maternal cadmium and amount smoked (r = 0.30, p<0.001); no correlation was found between maternal blood cadmium and birth weight."
Odland, J. O., E. Nieboer, et al. (2004). "Elements in placenta and pregnancy outcome in arctic and subarctic areas." Int J Circumpolar Health **63**(2): 169-87.	"Maternal body mass index (BMI), maternal age, placental lead, or maternal blood lead, and smoking were retained as predictors of birth weight and BMIC in the multivariate odeling."
Osada, H., Y. Watanabe, et al. (2002). "Profile of trace element concentrations in the feto-placental unit in relation to fetal growth." Acta Obstet Gynecol Scand **81**(10): 931-7.	The abstract did not report relationships between decreased prenatal growth and cadmium.
Ostrea, E. M., V. Morales, et al. (2002). "Prevalence of fetal exposure to environmental toxins as determined by meconium analysis." Neurotoxicology **23**(3): 329-39.	"Some maternal and neonatal factors that were significantly associated with the presence of environmental toxins in meconium included multi-gravidity, multiparity, multiple gestation, meconium stained fluid, smoking, gestational age, low birth weight and infant gender. . . The exposure rate (based on meconium analysis) and the median concentration of the pollutants in the positive samples were as follows: cadmium (8.5%; 13.37 microg/ml) . . ."
Palkovicova, L., E. Reichrtova, et al. (2003). "In utero exposure to environmental xenobiotics and allergy development in early childhood." Pediatr Res **53**(6 Pt 2).	"Significant associations between placental lead and cadmium concentrations and frequency of microstructural lesions in the placentas were found. Positivity of eIgE was in the negative correlation with the placental concentrations of cadmium."
Patriarca, M., T. D. Lyon, et al. (1999). "Determination of low concentrations of potentially toxic elements in human liver from newborns and infants." Analyst **124**(9): 1337-43.	In a study measuring concentrations of cadmium and other metals in livers of infants, it was concluded "There was no measurable difference in the concentrations of any of these elements between the SIDS and non-SIDS groups."
Peiker, G., M. Erler, et al. (2000). "[Concentration of heavy metals (Pb, Cd, Hg) in maternal blood]." Z Geburtshilfe Neonatol **204**(5): 187-92.	"At the risk pregnancies (hypertonia during the pregnancy, premature delivery and miscarriage) no increased heavy metal burden was found."
Piasek M, Blanuša M et al. (2001). Placental cadmium and progesterone cncentrations in cigarette smokers. Reprod Toxicol **15**(6):673-681.	"In placentas of smoking women an increase in cadmium, reduced progesterone and a decrease in iron concentrations were found... the results present new evidence that maternal smoking reduces placental progesterone content and support the established association of smoking with placental cadmium."
Piekoszewski, W., E. Forek, et al. (2005). "[Level of cadmium and zinc in placenta of smoking women]." Przegl Lek **62**(10): 1062-6.	"The performed research shown the influence of cigarette smoking of birth weight and cadmium concentration in placenta, however did not proved the hypotheses that accumulation of cadmium and zinc in placenta influence on birth weight."
Ronco, A. M., G. Arguello, et al. (2005). "Metals content in placentas from moderate cigarette	"In this first study performed in our region, we found that moderate smoking mothers deliver neonates with

Reference	Findings/Conclusions
consumers: correlation with newborn birth weight." Biometals **18**(3): 233-41.	decreased birth weight and highly correlated to placental cadmium concentration. Decreased metal nutrient/pollutant ratios, a condition here found in smokers, may indicate a placental dysfunction, contributing to impair birth weight."
Ronco, A. M., F. Garrido, et al. (2006). "Smoking specifically induces metallothionein-2 isoform in human placenta at term." Toxicology **223**(1-2): 46-53.	"In conclusion, MT-2 [metallothionein-2] is the main isoform induced by smoking, suggesting that this isoform could be involved in placental cadmium and zinc retention. This fact, which could contribute to reduce the transference of zinc to the fetus, may be associated to detrimental effects on fetal growth and development."
Salpietro, C. D., S. Gangemi, et al. (2002). "Cadmium concentration in maternal and cord blood and infant birth weight: a study on healthy non-smoking women." J Perinat Med **30**(5): 395-9.	"Since cadmium concentration appeared of the same order of magnitude both in cord and maternal serum, one could speculate that cadmium is transferred easily from the mother to the fetus through the placenta. Finally, we found that birth weight is inversely correlated with maternal and cord blood cadmium concentrations; thus birth weight might be negatively influenced by cadmium levels as a result of the toxic effects of the metal on the placenta."
Sarasua, S. M., R. F. Vogt, et al. (2000). "Serum immunoglobulins and lymphocyte subset distributions in children and adults living in communities assessed for lead and cadmium exposure." J Toxicol Environ Health A **60**(1): 1-15.	In adults urine cadmium levels over 1.5 microg/g were associated with higher levels of IgA and circulating B lymphocytes but no immune system effects were reported in children.
Sikorski, R., Radoma, et al. (1988). "Smoking during pregnancy and the perinatal cadmium burden." J Perinat Med **16**(3): 225-31.	None of the fetoplacental parameters studied was significantly associated with cadmium levels in maternal or cord blood.
Tabacova, S. Little, R.E. et al. (1984). "Complications of pregnancy in relation to maternal lipid peroxides, glutathione, and exposure to metals. Reprod Toxicol **8**(3):217-224	"Maternal exposure to metals (as indicated by blood lead and cadmium) was associated with a decrease in reduced glutathione in blood. Since increased lipid peroxidation has been implicated in other studies as a pathogenetic factor for maternal toxemia, it is suggested that exposure to metals during gestation could enhance the development of pregnancy complications by increasing lipid peroxidation via depletion of reduced glutathione reserves."
Windham, G. C., L. Zhang, et al. (2006). "Autism spectrum disorders in relation to distribution of hazardous air pollutants in the san francisco bay area." Environ Health Perspect **114**(9): 1438-44.	Autism was associated with metals "(AORs for metals: fourth quartile = 1.7 ; 95% CI, 1.0-3.0 ; third quartile = 1.95 ; 95% CI, 1.2-3.1) . The individual compounds that contributed most to these associations included mercury, cadmium, nickel, trichloroethylene, and vinyl chloride. . . Our results suggest a potential association between autism and estimated metal concentrations, and possibly solvents, in ambient air around the birth residence, requiring confirmation and more refined exposure assessment in future studies."

Reference	Findings/Conclusions
	In vitro
Läopez-Ortal, P., V. Souza, et al. (1999). "DNA damage produced by cadmium in a human fetal hepatic cell line." Mutat Res **439**(2): 301-6.	In a human fetal hepatic cell line (WRL-68 cells), "Cd treatment produced DNA single-strand breaks and the damage was greater in acute high dose treated cells. Lipid peroxidation values did not correlate with DNA single-strand breaks."

Table 3. Experimental Animal Developmental Toxicity Studies

Reference	Findings/Conclusions
	In vivo studies
Abraham, R., N. Ringwood, et al. (1984). "Ultrastructural observations on rabbit blastocysts after maternal exposure to cadmium chloride." J Reprod Fertil **70**(1): 323-5.	In blastocysts from rabbits administered cadmium chloride (CdCl2) (0.1 or 1.0%) in drinking water on GD 0 to 5, there were significant changes in the lysosomes (e.g. autophagic vacuoles and residual bodies) of endodermal cells as well as those of the inner cell mass.
Agar, A., P. Yargicoglu, et al. (1996). "Cadmium induced alterations in somatosensory evoked potentials." J Basic Clin Physiol Pharmacol **7**(2): 137-49.	Somatosensory evoked potentials (SEPs) were examined in rats exposed to cadmium during pre- and or postnatal development. **[Findings were difficult to decipher from the abstract.]**
Agar, A., P. Yargicoglu, et al. (1999). "Effect of cadmium-induced lipid peroxidation on EEG spectral components." J Basic Clin Physiol Pharmacol **10**(1): 29-40.	Changes in EEG brain patterns were observed in offspring of rats exposed to cadmium in drinking water during pregnancy.
Agar, A., P. Yargicoglu, et al. (2000). "The effect of pre and postnatal cadmium exposure on somatosensory evoked potentials: relation to lipid peroxidation." Int J Neurosci **101**(1-4): 45-56.	Pre and/or postnatal exposure to cadmium resulted in changes in somatosensory evoked potentials and/or lipid peroxidation in sciatic nerves.
Ahokas, R. A., P. V. J. Dilts, et al. (1980). "Cadmium-induced fetal growth retardation: Protective effect of excess dietary zinc." Am J Obstet Gynecol **136**(2): 216-221.	With prenatal exposure of rats to cadmium, "Cd-induced fetal growth retardation is evidently an indirect rather than a direct effect, resulting from reduced maternal food consumption and metabolism. Since dietary Zn blocks these effects, Cd may be a result of induced Zn deficiency."
Ali, M. M., R. C. Murthy, et al. (1986). "Developmental and longterm neurobehavioral toxicity of low level in-utero cadmium exposure in rats." Neurobehav Toxicol Teratol **8**(5): 463-8.	In a study with exposure of rats to 4.2 and 8.4 micrograms/ml cadmium in drinking water, the authors concluded , ". . .Cd exposure during the critical periods of development might result in developmental and behavioral deficits with longterm implications on adult behavior."
Antonio, M. T., M. J. Benito, et al. (1998). "Gestational administration of cadmium alters the neurotransmitter levels in newborn rat brains." J Appl Toxicol **18**(2): 83-8.	In offspring of rats exposed to 10 mg of cadmium acetate per litre of drinking water throughout pregnancy to parturition or until postnatal day 5, "Cd increased the 5-HT and 5-HIAA contents in all areas of the brain and the DA and DOPAC levels in mesencephalon, but decreased the DA and DOPAC levels in the metencephalon."
Antonio, M. T., I. Corpas, et al. (1999). "Neurochemical changes in newborn rat's	In a study in which rats were exposed to cadmium (10 mg/l) and lead (300 mg/l) during gestation, the

Reference	Findings/Conclusions
brain after gestational cadmium and lead exposure." Toxicol Lett **104**(1-2): 1-9.	study authors concluded, "[These] data suggests that gestational and early lactational exposure to low dose of cadmium and lead could produce alterations in monoaminergic metabolism that can place the exposed animal to a significant risk in adulthood."
Antonio, M. T., N. Lopez, et al. (2002). "Pb and Cd poisoning during development alters cerebellar and striatal function in rats." Toxicology **176**(1-2): 59-66.	In a study in which rats were exposed to 300 mg/l of Pb and 10 mg/l of Cd in drinking water during pregnancy and lactation, the study authors stated "So, it can be concluded that perinatal exposure to lead and cadmium provoke neurochemical alterations in cerebellum and striatum that can be related with the changes in motor activity observed in [] adulthood."
Antonio, M. T., L. Corredor, et al. (2003). "Study of the activity of several brain enzymes like markers of the neurotoxicity induced by perinatal exposure to lead and/or cadmium." Toxicol Lett **143**(3): 331-40.	In a study in whch rats were exposed to lead acetate (300 mg/L) and/or cadmium acetate (10 mg/L) from day 1 of pregnancy to parturition (day 0) or until weaning (day 21), changes in brain enzyme activities in offspring were observed and the study authors stated, "effects produced by the simultaneous administration of lead and cadmium suggests that, in general, both metals exert an additive effect, either competing for the same inhibitory binding sites or increasing cellular damage."
Antonio Garcia, T. and L. Corredor (2004). "Biochemical changes in the kidneys after perinatal intoxication with lead and/or cadmium and their antagonistic effects when coadministered." Ecotoxicol Environ Saf **57**(2): 184-9.	In rats exposed to lead acetate (300 mg/L) and/or cadmium acetate (10 mg/L) in drinking water from day 1 of pregnancy to parturition (day 0) or until weaning (day 21), decreases in offspring renal enzyme activities were observed. Study authors stated ". . . lead and cadmium are able to impair renal function due to biochemical alterations, since ATPases are essential for reabsorption and secretion processes and phosphatases are involved in the differentiation of the proximal tubules. . . simultaneous perinatal administration of both metals seems to protect against the toxicity produced by cadmium or lead separately."
Baranski, B., I. Stetkiewicz, et al. (1982). "Teratogenicity, fetal toxicity and tissue concentration of cadmium administered to female rats during organogenesis." J Appl Toxicol **2**(5): 255-9.	"Cadmium, when administered at a dose of 40 mg Cd per kg per day, was associated with significant maternal toxicity, placental injury and an increased fetal burden of cadmium. At lower dose levels (2-20 mg Cd per kg per day), fetal development was retarded."
Baranski, B., I. Stetkiewicz, et al. (1983). "[Effect of inhalational cadmium poisoning on the prenatal development of rats]." Przegl Lek **40**(6): 479-84.	No abstract available.
Baranski, B., I. Stetkiewicz, et al. (1983). "Effects Of Oral, Subchronic Cadmium	Female rats were gavaged with cadmium at up to 4.0 mg/kg bw/day, 5 days a week for 5 weeks prior to

Reference	Findings/Conclusions
Administration On Fertility, Prenatal And Postnatal Progeny Development In Rats." Archives of Toxicology **54**(4): 297-302.	mating. Subcutaneous edema was increased in the 0.4 mg/kg group. Locomotor activity of female offspring of all cadmium treated rats and of male offspring in the 0.04 and 0.4 mg/kg groups was decreased. There were no effects on percentage of inseminated and pregnant females; numbers of total implantations, corpora lutea, live fetuses, or resorptions; fetal length and body weight; fetal cadmium concentration; placental weight; gross malformations; litter size; viability, lactation, and mortality indices; or body weight gain of offspring during the first 2 months of life.
Baranski, B. (1984). "Behavioral alterations in offspring of female rats repeatedly exposed to cadmium oxide by inhalation." Toxicol Lett **22**(1): 53-61.	In female rats exposed to cadmium oxide aerosols (0.02 and 0.16 mg Cd/m^3) there was no effect on fertility. Viability and postnatal growth of offspring were decreased at 0.16 mg Cd/m^3; exploratory motor activity in 3-month-old pups was decreased in the 0.16 mg Cd/m^3 group and male offspring from the 0.02 mg Cd/m^3 group; dose-dependent decreases of avoidance acquisition were observed in female offspring but not in males; and ambulation was decreased in 5-month-old males from the 0.16 mg but increased in females from the 0.02 mg Cd/m^3 group.
Baranski, B. (1984). "Effect of exposure of pregnant rats to cadmium on prenatal and postnatal development of the young." J Hyg Epidemiol Microbiol Immunol **29**(3): 253-62.	In rats exposed to 1 mg Cd/m^3 for 4 months, fertility was decreased. In rats exposed orally from GD 7–16, congenital defects were seen at 40 mg Cd/kg. In rats exposed by inhalation during gestation, effects at ≥0.02 mg Cd/m^3 were decreased locomotor activity and altered conditioned-reflex response; effects at 0.16 mg Cd/m^3 were decreased offspring viability, lower body weight gain, and altered findings in negative-geotaxis test.
Baranski, B. (1986). "Effect Of Maternal Cadmium Exposure On Postnatal Development And Tissue Cadmium, Copper And Zinc Concentrations In Rats." Archives of Toxicology **58**(4): 255-260.	In rats exposed to 60 ppm cadmium in water during gestation, there was no effect on litter size, pup birth weight, body weight gain, viability, or physical or neuromuscular development. The author concluded that "there may be a relationship between reduced brain copper and zinc concentrations and central nervous system dysfunction in adult offspring of female rats exposed to cadmium during gestation."
Baranski, B. (1987). "Effect of Cadmium on Prenatal Development and on Tissue Cadmium, Copper, and Zinc Concentrations in Rats." Environmental Research **42**(1): 54-62.	In rats given cadmium-chloride (60 or 180 ppm cadmium orally from day one to day 20 of gestation, fetal length and body weight and blood hematocrit levels (at low dose) were decreased but gross fetal malformations were not reported. The author suggested that "changes in maternal metabolism, including tissue disposition of copper and zinc, reduced transplacental transport of nutrients, and decreased maternal blood flow to the placenta still

Reference	Findings/Conclusions
	may play an important role in the mechanism of cadmium fetotoxicity."
Bialonska, D., M. Zakrzewska, et al. (2002). "The long-term effect of cadmium exposure through food on the postnatal development of the bank vole (Clethrionomys glareolus Schreber, 1780)." Folia Biol (Krakow) **50**(3-4): 203-9.	In young voles fed cadmium at 35 µg/g food, "Cu and Fe levels were negatively correlated with cadmium concentrations, while a positive correlation was found between zinc and cadmium in the young animal bodies. Also found was higher offspring mortality in the group receiving 35 [µg/g] of cadmium in food. There was no difference in young animal body weight between the study groups."
Cardon, A. L., A. Rocha, et al. (2004). "Exposure to cadmium during gestation and lactation decreases cocaine self-administration in rats." Neurotoxicology **25**(5): 869-75.	Offspring from rats gavaged with 5.0 mg cadmium chloride during gestation and lactation self-administered significantly less cocaine than controls.
Danielsson, B. R. and L. Dencker (1984). "Effects of cadmium on the placental uptake and transport to the fetus of nutrients." Biol Res Pregnancy Perinatol **5**(3): 93-101.	"We conclude that inhibition of nutrient transfer to the fetus may be the underlying mechanism of growth retardation and possibly of the malformations produced by Cd. Vitamin B12 may be a sensitive indicator of early and subtle disturbances of placental function . . ."
Desi, I., L. Nagymajtenyi, et al. (1998). "Behavioral and neurotoxicological changes caused by cadmium treatment of rats during development." Journal Of Applied Toxicology **18**(1): 63-70.	In offspring of dams given 3.5, 7.0 or 14.0 mg/kg cadmium during part of the gestation and/or lactation period, there were dose and time dependent alterations in the spontaneous and evoked electrophysiological functions with prenatal exposure and dose-dependent decrease of horizontal and vertical exploratory activity and lower exploration frequency of the open-field center with pre- and postnatal exposure.
Deveci, E., Inal, et al. (1998). "Teratogenic effects of cadmium on rat skin." Hifuka Kiyo **93**(2): 155-9.	"After two weeks of confirming pregnancy, Wistar-albino rats (200-220 gr.) were given cadmium chloride intraperitoneally (i.p.) in a dosage of 2 mg/kg (in saline) for five days. . . Overall, considerable teratogenic effects of cadmium chloride were found on neonatal rat skin."
Ferm, V. H. and S. J. Carpenter (1967). "Teratogenic effect of cadmium and its inhibition by zinc." Nature **216**(5120): 1123.	No abstract available.
Ferm, V. H. and S. J. Carpenter (1968). "The relationship of cadmium and zinc in experimental mammalian teratogenesis." Lab Invest **18**(4): 429-32.	No abstract available.
Ferm, V. H. (1971). "Developmental malformations induced by cadmium. A study of timed injections during embryogenesis." Biol Neonate **19**(1): 101-7.	No abstract available.
Ferm, V. H. (1976). "Teratogenic effects and placental permeability of heavy metals." Curr Top Pathol **62**: 145-51.	No abstract available.

Reference	Findings/Conclusions
Ferm, V. H. and W. M. J. Layton (1979). "Reduction in cadmium teratogenesis by prior cadmium exposure." Environ Res **18**(2): 347-350.	"The administration of Cd 24-48 h prior to an optimal teratogenic dose reduces both the number and severity of congenital malformations in hamster embryos. I.p. administration is more effective in inducing this protective effect than is the s.c. route. Oral administration of Cd at the same pretreatment intervals does not seem to afford any protection."
Ferm, V. H. and D. P. Hanlon (1987). "Inhibition of Cadmium Teratogenesis by a Mercaptoacrylic Acid (MFA)." Experientia **43**(2): 208-210.	In hamsters, alpha-mercapto-beta-(2-furyl)-acrylic-acid (MFA) protected embryos from acute cadmium-sulfate teratogenesis on GD 6 and 7; resorption rates were increased in in Cd treated versus MFA treated animals.
Fernandez , E. L., et al. (2003). "Cadmium-induced changes in apoptotic gene expression levels and DNA damage in mouse embryos are blocked by zinc." Toxicol Sci **76**(1): 162-70.	"In summary, cadmium administered to pregnant mice increased primary DNA damage and activated the apoptotic pathway. These effects could be ameliorated by zinc pretreatment, and, because of that, it is possible that the mechanisms of cadmium-induced teratogenicity are related to zinc metabolism."
Fernandez, E. L., C. Svenson, et al. (2004). "Disturbing endoderm signaling to anterior neural plate of vertebrates by the teratogen cadmium." Reprod Toxicol **18**(5): 653-60.	In a study examining transcription factors involved in head formation in animals administered cadmium on on days 7, 8 and 9 p.c, "Stage specific down-regulation of Hesx1, Cerl, and Sox2, and an up-regulation of HNF3beta were observed. No effect was seen in Otx2 expression levels. Cell death was increased in the neuroepithelium of the cranial neural folds, and in areas where neural crest cells migrate, but not in the gut endoderm."
Gale, T. F. and W. M. Layton (1980). "The susceptibility of inbred strains of hamsters to cadmium-induced embryotoxicity." Teratology **21**(2): 181-6.	In a comparison of cadmium in one non-inbred (LVG) and five inbred (CB, LHC, LSH, MHA, PD4) strains of hamsters given a single iv dose (2 mg/kg) of cadmium sulfate on the 8th gestation day, "All six hamster strains developed significant resorption rates and external, internal, and skeletal abnormalities, e.g., exencephaly, microphthalmia, cleft lip, cleft palate, renal agenesis, rib fusions, etc. Significant interstrain differences were detected in only three categories of embryonic damage, i.e., resorptions, microphthalmia, and renal agenesis."
Gadzdik and Kaminsk (1985). "Ultrastructural study of development of the rat testis. II. After injecting CdCl2." Folia Morphol **33**(3): 218-22.	No abstract available.
Grawe, K. P., J. Pickova, et al. (2004). "Fatty acid alterations in liver and milk of cadmium exposed rats and in brain of their suckling offspring." Toxicol Lett **148**(1-2): 73-82.	In rats exposed to 0, 5, or 25 ppm cadmium (Cd) via drinking water for 17 days during lactation, changes in fatty acid composition were reported in milk and in pup brains.
Gulati, S., K. D. Gill, et al. (1986). "Effect of	In rats injected with cadmium at 1 and 2 mg

Reference	Findings/Conclusions
cadmium on lipid composition of the weanling rat brain." Acta Pharmacol Toxicol (Copenh) **59**(2): 89-93.	cadmium/kg body weight on the 3rd, 10th and 17th day after birth, ". . . cadmium treatment (a dose of only 2 mg Cd/kg) results in an appreciable decrease in myelin-specific lipids like nonesterified cholesterol, ethanolamine-containing lipids, cerebrosides and sulfatides leading to hypomyelination."
Gupta, A., R. C. Murthy, et al. (1993). "Neurochemical Changes in Developing Rat Brain after Preand Postnatal Cadmium Exposure." Bulletin of Environmental Contamination and Toxicology **51**(1): 12-17.	In rats given 50 parts per million cadmium as cadmium-acetate in their drinking water throughout gestation to weaning (21 days post partum), "the authors conclude that prenatal and lactational cadmium exposure suppresses DNA synthesis and thymidine-kinase activity in the developing brain. The cadmium induced zinc deficiency may be, at least in part, responsible for these effects."
Gutierrez-Reyes, E. Y., A. Albores, et al. (1998). "Increase of striatal dopamine release by cadmium in nursing rats and its prevention by dexamethasone-induced metallothionein." Toxicology **131**(2-3): 145-154.	Effects observed in nursing rats injected with $CdCl_2$ at 1 mg/kg per day for 5 days included increased striatal dopamine release (180% of controls) and turnover (150% of controls) at 13 days of age, increased striatal metallothionein content (161%) and lipid peroxidation (190%), and decreased striatal tyrosine hydroxylase activity (−28%). Some cadmium effects were prevented by dexamethasone.
Herba, E., D. Pojda-Wilczek, et al. (2000). "[The effect of prenatal exposure to cadmium on flash visual evoked potentials in rat offspring before and after injection of norepinephrine into the lateral brain ventricle]." Klin Oczna **102**(4): 233-6.	Prenatal cadmium exposure resulted in changes of visually evoked potentials in the rat.
Herba, E., D. Pojda-Wilczek, et al. (2001). "[The effect of serotonin on flash visual evoked potential in the rat prenatally exposed to cadmium]." Klin Oczna **103**(2-3): 81-4.	In a study examining changes in visually evoked potentials in rats prenatally exposed to cadmium, the study authors concluded, "Cadmium increases the serotonin sensibility in the CNS."
Herba, E., D. Pojda-Wilczek, et al. (2001). "[The effect of gamma-aminobutyric acid injected into lateral brain ventricle of rats after prenatal cadmium intoxication on flash visual evoked potentials (FVEP)]." Klin Oczna **103**(1): 5-8.	In a study examining changes in visually evoked potentials in rats prenatally exposed to cadmium, the study authors concluded, Cadmium increased the sensitivity of GABA-receptors in the OUN."
Herba, E., D. Pojda-Wilczek, et al. (2005). "[Visual evoked potentials (FVEP) after the prenatal exposure to heavy metals--experimentals studies]." Klin Oczna **107**(10-12): 599-602.	In a study examining prenatal exposure to cadmium or other heavy metals, study authors concluded "The heavy metals prolonged the latencies and diminished the amplitudes of flash visual evoked potentials, so may be, they are not only neurotoxic but also 'ophthalmotoxic' factors."
Holloway, W. R., Jr. and D. H. Thor (1988). "Cadmium exposure in infancy: effects on activity and social behaviors of juvenile rats." Neurotoxicol Teratol **10**(2): 135-42.	The authors of this rat study stated: "Male subjects receiving 2 mg/kg in infancy were significantly more active after weaning than littermates that had received 0 or 1 mg/kg doses, and on Day 29 they also engaged in significantly more rough and tumble

Reference	Findings/Conclusions
	play with a nontreated partner than did rats in the other groups. This effect of early cadmium exposure was also evident when males were tested with similarly treated subjects on Day 44. . . In contrast, females in the 1 and 2 mg/kg groups did not have increased activity or rough and tumble play fighting."
Holloway, W. R. J. and D. H. Thor (1988). "Social Memory Deficits in Adult Male Rats Exposed to Cadmium in Infancy." Neurotoxicol Teratol **10**(3): 193-198.	Abstract not available.
Holt, D. and M. Webb (1987). "Teratogenicity of ionic cadmium in the Wistar rat." Arch Toxicol **59**(6): 443-7.	The authors of a rat study stated "The foetotoxicity of i.p. injected Cd, however, increases with the dose over the range 1.25-2.0 mg Cd/kg body weight. The teratogenic response, which is also wider than that observed previously, is maximal after the injection of 1.25 mg Cd/kg body weight i.v. on gd 10 and i.p. on gd 12. Whilst the incidences of hydrocephalus, urogenital abnormalities, cleft palate and other less common defects are similar after dosing by both routes, the incidence, range and severity of skeletal malformations are greater after i.p. than after i.v. administration of Cd on gd 12."
Ishitobi, H. and C. Watanabe (2005). "Effects of low-dose perinatal cadmium exposure on tissue zinc and copper concentrations in neonatal mice and on the reproductive development of female offspring." Toxicol Lett **159**(1): 38-46.	In mice exposed to 1 and 10 ppm Cd in the drinking water from conception to 10 days after birth, it was reported that ". . . perinatal Cd exposure, even at low levels, affects the Zn and Cu concentrations of neonates and the reproductive functions of female offspring."
Ishizu, S., M. Minami, et al. (1973). "An experimental study on teratogenic effect of cadmium." Ind Health **11**(3): 127-139.	"Administration of 5 mg/kg of cadmium chloride to pregnant mice on 7 days of gestation produced a variety of malformations in the surviving fetuses. Exencephaly was found most among the fetuses and such exencephalic fetuses often exhibited open eye. Clefts palate and lack of tail or rachischisis were found in some other fetuses. Skeletal malformations were observed in the skull region, vertebral parts, ribs and tails. The total rate of malformation appearance exceeded about 80%. The lower the dose of cadmium chloride, the less the rate of malformation appearance: 19% for 2.5 mg/kg 1.0% or less for 0.63 mg/kg and none for 0.33 mg/kg."
Jahn, F. and W. Klinger (1989). "Influence of Prenatal Administration of Cadmium on Postnatal Development and Inducibility of Hepatic Monooxygenases in Rats." Pharmacology and Toxicology **64**(3): 291-292.	In offspring of rats ip treated from day seven through 21 of gestation with 0.5 mg/kg cadmium as cadmium sulfate, there were changes in the induction of hepatic monooxygenases.
Kanter, M., M. Yoruk, et al. (2003). "Effects of	"It is concluded that Cd exposure during pregnancy

Reference	Findings/Conclusions
cadmium exposure on morphological aspects of pancreas, weights of fetus and placenta in streptozotocin-induced diabetic pregnant rats." Biol Trace Elem Res **93**(1-3): 189-200.	may reduce the birth and placental weights and produce necrosis, degeneration, and degranulation in beta-cells of pancreatic islets, causing an increase in the serum glucose level. These changes might be severe in diabetic pregnant mothers."
Konecki, J., J. azejowski, et al. (2000). "Influence of chronic cadmium exposure during pregnancy on DNA synthesis in different organs of rat offspring." Med Sci Monit **6**(6): 1077-81.	"The synthesis of DNA in different organs of rat offspring, [the] dams [of which] were exposed to cadmium during pregnancy, was examined in this study. . .In most studied organs a significant increase of DNA synthesis was noted, pronounced especially in small intestine and bone marrow (over 2-fold increase in comparison with controls)."
Konecki, J., J. Slowinski, et al. (2003). "RNA and protein synthesis in different organs of rat offspring after chronic cadmium exposure during pregnancy." Int J Occup Med Environ Health **16**(1): 75-9.	In rats exposed to cadmium during pregnancy, "A strong induction of RNA synthesis in all four studied brain regions attracts special attention."
Kultima, K., Fern, et al. (2006). "Cadmium-induced gene expression changes in the mouse embryo, and the influence of pretreatment with zinc." Reprod Toxicol **22**(4): 636-46.	The authors of a study examining prenatal cadmium exposure in mice stated "We report nine genes with a transcriptional response induced by Cd, none of which was influenced by Zn pretreatment, and two genes induced only by combined maternal Cd exposure and Zn pretreatment."
Kuriwaki, J., M. Nishijo, et al. (2005). "Effects of cadmium exposure during pregnancy on trace elements in fetal rat liver and kidney." Toxicol Lett **156**(3): 369-76.	The authors of a study in which pregnant rats were exposed to cadmium stated, "These results suggest that Cd exposure inhibits Zn and Fe transportation from the placenta to fetus, as well as Cu, Ca, Na and K uptake and transportation across the placenta, possibly influencing fetal growth and metabolism."
Lee, G. S., X. Liao, et al. (2006). "Interactive effects of cadmium and all-trans-retinoic acid on the induction of forelimb ectrodactyly in C57BL/6 mice." Birth Defects Res A Clin Mol Teratol **76**(1): 19-28.	In mice treated on GD 9.5 with cadmium and/or retinoic acid (RA), "When RA was given simultaneously with cadmium, a significant increase in the incidence and severity of forelimb ectrodactyly (predominantly postaxial) was observed compared to the results with corresponding doses of cadmium or RA alone. When mice were exposed to subthreshold doses of both cadmium (0.5 mg/kg) and RA (1 mg/kg), the combined treatment exceeded the threshold, resulting in forelimb ectrodactyly in 19% of the fetuses. Moreover, coadministration of cadmium and RA at doses exceeding the respective thresholds showed a synergistic effect, that is, 92% of fetuses were found with the forelimb defect as opposed to 10% if the response were additive."
Lehotzky, K., G. Ungvary, et al. (1990). "Behavioral deficits due to prenatal exposure to cadmium chloride in CFY rat pups." Neurotoxicol Teratol **12**(2): 169-172.	The authors of a study that prenatally exposed rats to cadmium stated "The results suggest that doses of cadmium chloride that produce no overt toxicity in the dam can have long-lasting behavioral alterations in the offspring."

Reference	Findings/Conclusions
Leret, M. L., J. A. Millan, et al. (2003). "Perinatal exposure to lead and cadmium affects anxiety-like behaviour." Toxicology **186**(1-2): 125-30.	In weanling and adult rats neonatally exposed to metals, "Maternal co-exposure to lead and cadmium produced mainly alterations in dopaminergic and serotoninergic systems of hippocampus in both ages studied, while noradrenaline content in hypothalamus and hippocampus remained unchanged at 75 days of age. The intoxicated rats showed an increased on indices of anxiety on the elevated plus-maze."
Levin, A. A. and R. K. Miller (1980). "Fetal toxicity of cadmium in the rat: Maternal vs. fetal injections." Teratology **22**(1): 1-6.	Authors of a study in rats indicated "Following direct fetal injection, mean fetal body burdens of Cd were 74.6 ± 34.8 nmol, but the incidence of fetal death was only 11.5%. The high incidence of fetal death following maternal exposure to $CdCl_2$ is not solely explained by the direct effects of $CdCl_2$ on the fetus. Fetal toxicity of Cd may be due to some extra-fetal mechanism such as maternal toxicity or the observed placental necrosis."
Levin, A. A. and R. K. Miller (1981). "Fetal toxicity of cadmium in the rat: decreased utero-placental blood flow." Toxicol Appl Pharmacol **58**(2): 297-306.	Abstract not available.
Levin, A. A., J. R. Plautz, et al. (1981). "Cadmium: placental mechanisms of fetal toxicity." Placenta Suppl **3**: 303-18.	In a study of rats, it was concluded ". . . cadmium-induced fetal death was not the result of direct effects of cadmium but may be the result of a placental effect of the heavy metal. A proposed mechanism for the induction of fetal death is that high placental accumulations of cadmium result in trophoblastic damage which leads to a local circulatory response to the injured tissues and a decrease in uteroplacental blood flow. It is the decrease in nutrient and oxygen transport to the fetus that results from trophoblastic damage and blood flow alterations that ultimately induce fetal death."
Lutz, J. and S. L. Beck (2000). "Caffeine decreases the occurrence of cadmium-induced forelimb ectrodactyly in C57BL/6J mice." Teratology **62**(5): 325-31.	This study provides evidence that a subteratogenic dose of caffeine can ameliorate cadmium-induced forelimb ectrodactyly in the Cd-sensitive C57BL/6J inbred mouse strain.
Machemer, L. and D. Lorke (1981). "Embryotoxic effect of cadmium on rats upon oral administration." Toxicol Appl Pharmacol **58**(3): 438-43.	Abstract not available
Minetti, A. and C. A. Reale (2006). "Sensorimotor developmental delays and lower anxiety in rats prenatally exposed to cadmium." J Appl Toxicol **26**(1): 35-41.	In rats, gestational exposure to cadmium at 0.6 mg/kg bw "produced a delay in the development of the righting reflex and of the cliff aversion in the pups. No differences were observed in the development of the negative geotaxis, nor in the ages of eye and ear opening. Anxiety studies using an elevated plus maze showed a lower anxiety in all the offspring..."

Reference	Findings/Conclusions
Mori, K., K. Yoshida, et al. (2006). "Effects of perinatal exposure to low doses of cadmium or methylmercury on thyroid hormone metabolism in metallothionein-deficient mouse neonates." Toxicology **228**(1): 77-84.	The authors of a mouse study concluded, "Our study demonstrates that perinatal exposure to low doses of Cd or MeHg can induce changes in brain deiodinase activities in the neonates, suggesting that thyroid hormone metabolism in fetuses and neonates might be a potential target of Cd and MeHg."
Naruse, I. and Y. Hayashi (1989). "Amelioration of the teratogenicity of cadmium by the metallothionein induced by bismuth nitrate." Teratology **40**(5): 459-65.	In mice, "Pretreatment with bismuth nitrate (subcutaneously) ameliorated the teratogenicity, including exencephaly and abnormalities of the axial skeleton, caused by a single intraperitoneal injection of cadmium sulfate."
Nowak, P., J. Dabrowska, et al. (2006). "Prenatal cadmium and ethanol increase amphetamine-evoked dopamine release in rat striatum." Neurotoxicol Teratol **28**(5): 563-72.	In a study of rats prenatally exposed to cadmium, the study authors concluded "These findings clearly demonstrate that there is marked alteration in dopaminergic regulation after ontogenetic cadmium and ethanol co-exposure, which in this regard resembles the reaction of the striatonigral pathway on [amphetamine]-evoked [dopamine] release in rats with behavioral sensitization."
Padmanabhan, R. and M. S. Hameed (1990). "Characteristics of the limb malformations induced by maternal exposure to cadmium in the mouse." Reprod Toxicol **4**(4): 291-304.	Limb malformations were characterized in offspring of mice treated with cadmium during gestation.
Paniagua-Castro, N., G. Escalona-Cardoso, et al. (2007). "Glycine reduces cadmium-induced teratogenic damage in mice." Reprod Toxicol **23**(1): 92-7.	Authors of a mouse study concluded, ". . .lipid peroxidation was associated with cadmium-induced teratogenicity, and glycine inhibited the cadmium-induced effect by inhibiting placental transport of cadmium."
Petersson Grawe, K. and A. Oskarsson (2000). "Cadmium in milk and mammary gland in rats and mice." Arch Toxicol **73**(10-11): 519-27.	In rats "No effects were observed due to cadmium exposure on body weight in pups or dams. Cadmium treatment did not cause any effect on the lactose or protein concentration in milk, the concentrations of DNA, RNA or the ratio RNA/DNA in the mammary gland. Histological evaluation of mammary tissue did not reveal any abnormalities at any dose level."
Piasek, M., M. Blanusa, et al. (2004). "Low iron diet and parenteral cadmium exposure in pregnant rats: the effects on trace elements and fetal viability." Biometals **17**(1): 1-14.	Authors of a rat study concluded ". . . parenteral cadmium exposure during pregnancy causes perturbations in essential elements in maternal and fetal compartments. Acute cadmium exposure in the last trimester of gestation poses a risk for fetal viability especially when combined with low iron in maternal diet."
Picoli, L. C., I. S. Watanabe, et al. (2004). "Effect of cadmium on the floor of the mouth on rats during lactation." Pesqui Odontol Bras **18**(2): 105-9.	Retarded development was observed in rat pups the dams of which were given cadmium in drinking water during lactation.
Pillai, A. and S. Gupta (2005). "Effect of gestational and lactational exposure to lead and/or cadmium on reproductive	In rats sc dosed with 0.05 mg/kg bw/day lead acetate or cadmium acetate alone or in combination during premating, gestation, and lactation periods, "No

Reference	Findings/Conclusions
performance and hepatic oestradiol metabolising enzymes." Toxicol Lett **155**(1): 179-86.	change in the reproductive cyclicity was observed in any of the treated groups. The number of pregnancies was similar in all groups and no effect was observed on reproductive performance. The litter size, placental weights, pup weights, pup liver weights, maternal weights or maternal liver weights did not differ significantly."
Pillet, S., A. A. Rooney, et al. (2005). "Sex-specific effects of neonatal exposures to low levels of cadmium through maternal milk on development and immune functions of juvenile and adult rats." Toxicology **209**(3): 289-301.	In a study in which dams up to 10 $CdCl_2$ in drinking water during lactation, it was concluded that "...neonatal exposures to environmentally relevant levels of Cd through maternal milk represent a critical hazard liable to lead to both transitory and persistent immunotoxic effects."
Pond, W. G. and E. F. Walker, Jr. (1975). "Effect of dietary Ca and Cd level of pregnant rats on reproduction and on dam and progeny tissue mineral concentrations." Proc Soc Exp Biol Med **148**(3): 665-8.	In rats dosed with 200 ppm of Cd (as $CdCl_2$) through diet with two levels of dietary Ca (0.07% and 0.96%), "[the n]umber of live or stillborn pups per litter was not significantly affected by diet but high Cd significantly reduced pup birth weight. No grossly abnormal pups were noted."
Prigge, E. (1978). "Inhalative cadmium effects in pregnant and fetal rats." Toxicology **10**(3): 297-309.	Abstract not available.
Rady, P., et al. (1981). "Activity of pyruvate kinase and lactic acid dehydrogenase in mouse lung after transplacental exposure to carcinogenic and non-carcinogenic chemicals." Toxicol Lett **8**(4-5): 223-7.	Transplacental cadmium exposure did not affect enzyme activities in mouse lung.
Roelfzema, W. H., A. M. Roelofsen, et al. (1989). "Effects of Cadmium Exposure During Pregnancy on Cadmium and Zinc Concentrations in Neonatal Liver and Consequences for the Offspring." Arch Toxicol **63**(1): 38-42.	Abstract not available.
Rohrer, S. R., S. M. Shaw, et al. (1978). "Cadmium induced endothelial cell alterations in the fetal brain from prenatal exposure." Acta Neuropathol (Berl) **44**(2): 147-9.	"A 2.0 mg/kg dose of cadmium administered to maternal rats on day 20 of gestation caused the formation of vacuoles in the endothelial cells of capillaries in the fetal brain."
Rohrer, S. R., S. M. Shaw, et al. (1979). "Cadmium fetotoxicity in rats following prenatal exposure." Bull Environ Contam Toxicol **23**(1-2): 25-9.	Abstract not available.
Saltzman, R. A., R. K. Miller, et al. (1989). "Cadmium Exposure on Day 12 of Gestation in the Wistar Rat: Distribution, Uteroplacental Blood Flow, and Fetal Viability." Teratology **39**(1): 19-30.	In a study in which rats were exposed to cadmium during pregnancy, the authors conclude that "midgestational cadmium exposure, although it causes a transient decrease in placental blood flow, does not adversely affect fetal viability or growth. The differential fetolethal response to cadmium at mid and late gestation is not due to maternal dose."
Salvatori, F., C. B. Talassi, et al. (2004).	A study in rats reported that "Cd treatment during

Reference	Findings/Conclusions
"Embryotoxic and long-term effects of cadmium exposure during embryogenesis in rats." Neurotoxicol Teratol **26**(5): 673-80.	organogenesis (1) was not able to induce maternal toxicity; (2) induced external malformations; (3) increased significantly fetus anomalies and malformations, with reduced metacarpus ossification, cleft palate and right or left renal cavitation being observed in these animals; (4) did not modify pup body weight or weight gain during the lactation period; (5) improved testis descent and delayed the vaginal opening of pups; (6) did not modify ear unfolding, incisor eruption, eye opening, negative geotaxis or palmar grasp; (7) did not modify the open-field parameters and the stereotyped behavior of male or female pups; and (8) modified male sexual behavior and (9) reduced female sexual behavior."
Sasser, L. B., B. J. Kelman, et al. (1985). "The influence of maternal cadmium exposure or fetal cadmium injection on hepatic metallothionein concentrations in the fetal rat." Toxicol Appl Pharmacol **80**(2): 299-307.	The authors of a rat study concluded, "These data suggest that fetal rat liver is incapable of synthesizing [metallothionein] in response to Cd, possibly because Cd is not transported to the site of [metallothionein] synthesis in the fetal system."
Sato, F., T. Watanabe, et al. (1985). "Teratogenic effect of maternal zinc deficiency and its co-teratogenic effect with cadmium." Teratology **31**(1): 13-8.	"Injection of $CdCl_2$ produced a significant increase in the incidence of malformations in the marginally zinc-deficient mice, but not in zinc-replete animals. These results demonstrate that severe zinc deficiency is teratogenic in mice and that a marginal zinc intake influences the teratogenic potential of cadmium."
Saxena, D. K., R. C. Murthy, et al. (1986). "Embryotoxic and Teratogenic Effects of Interaction of Cadmium and Lindane in Rats." Acta Pharmacologica et Toxicologica **59**(3): 175-178.	In rats, "Neither cadmium nor lindane alone caused a significant loss of body weight during gestation. However, in the group exposed to both toxicants, a significant weight decrease was recorded. The only experimental group showing gross malformation was the cadmium plus lindane group, where uterine arms showed hemorrhages. This group also displayed intrauterine growth retardation. . . Number of embryonic deaths was higher in the group exposed to both toxicants, and those surviving showed marked reductions in ossification and incidence of reduced ossification in cranial bones, ribs, metacarpals, metatarsals, and caudal vertebrae. Also, significantly higher incidences of wavy ribs and scrambled sternebrae were detected in this group."
Scott, W. J., Jr., C. M. Schreiner, et al. (2005). "Cadmium-induced postaxial forelimb ectrodactyly: association with altered sonic hedgehog signaling." Reprod Toxicol **19**(4): 479-85.	"We show that exposure of the mouse embryo to Cd^{2+} disrupts Shh [sonic hedgehog] signaling as measured by polarizing activity of mouse limb bud ZPA [zone of polarizing activity] grafted to a host chick wing, and activity of a Gli:luciferase reporter exposed to limb bud lysates."

Reference	Findings/Conclusions
Smith, K. R. and J. R. Nation (2003). "Developmental exposure to cadmium alters responsiveness to cocaine in the rat." Drug Alcohol Depend **72**(1): 1-11.	Authors of a study in which rats were perinatally exposed to cadmium concluded "cocaine sensitization was attenuated in animals perinatally exposed to cadmium."
Sorell, T. L. and J. H. Graziano (1990). "Effect of oral cadmium exposure during pregnancy on maternal and fetal zinc metabolism in the rat." Toxicol Appl Pharmacol **102**(3): 537-45.	In a study examining effects of prenatal cadmium exposure in rats, the study authors concluded "These findings support the hypothesis that Cd-induced maternal zinc retention is responsible for fetal Zn deprivation and impaired fetal growth."
Soukupova, D., M. Dostal, et al. (1991). "Developmental toxicity of cadmium in mice. II. Immunotoxic effects." Funct Dev Morphol **1**(4): 31-6.	"It is concluded that in mice the maternal exposure to a single dose of cadmium results in postnatally manifested deviations of immune functions of their offsprings."
Soukupova, D. and M. Dostal (1991). "Developmental toxicity of cadmium in mice. I. Embryotoxic effects." Funct Dev Morphol **1**(2): 3-9.	In mice administered a single dose of $CdCl_2$, "The embryolethal effect, being highest after treatment with 6.0 mg/kg $CdCl_2$ on the 12th and 13th day of pregnancy (50.0 and 61.3%) was not significantly correlated to the day of treatment. Among survivors, foetuses with haemorrhagic bullae, limb malformations, exencephaly, cleft palate, open eyelids and tail deformities occurred. . . The administration of 2.0 and 4.0 mg/kg $CdCl_2$ on the 10th day of pregnancy induced fore limb polydactylies, whereas with the dose of 6.0 mg also oligodactylies were induced. The foetal body weight was reduced only by a dose of 6.0 mg $CdCl_2$ administered on the 12th day of pregnancy. Reduction of the thymus weight was a constant effect of treatment with the higher doses of cadmium from the 9th to the 14th day of pregnancy."
Tam, P. P. and W. K. Liu (1985). "Gonadal development and fertility of mice treated prenatally with cadmium during the early organogenesis stages." Teratology **32**(3): 453-62.	"The fertility of the male offspring was impaired by the prenatal cadmium insult, but the females were apparently fertile. The epididymal spermatozoa of the cadmium-affected offspring showed a lower fertilizing capacity in vitro."
Waalkes, M. P., J. A. Thomas, et al. (1982). "Induction of hepatic metallothionein in the rabbit fetus following maternal cadmium exposure." Toxicol Appl Pharmacol **62**(2): 211-8.	Abstract not available.
Wang, Y., U. Wimmer, et al. (2004). "Metal-responsive transcription factor-1 (MTF-1) is essential for embryonic liver development and heavy metal detoxification in the adult liver." Faseb J **18**(10): 1071-9.	"When the Mtf1 gene was excised by Cre recombinase after birth in liver and bone marrow and to a lesser extent in other organs, mice were viable under non-stress conditions but highly susceptible to cadmium toxicity, in support of a role of MTF-1 in coping with heavy metal stress."
Whelton, B. D., M. H. Bhattacharyya, et al. (1988). "Female reproduction and pup survival and growth for mice fed a cadmium-	The authors of a study in mice stated, "For sufficient diet groups, 50 ppm cadmium had no effect on fertility or pup survival during lactation, but caused

Reference	Findings/Conclusions
containing purified diet through six consecutive rounds of gestation and lactation." J Toxicol Environ Health **24**(3): 321-43.	a 15% decrease in litter size at birth and a 25% decrease in pup growth. Dietary deficiencies alone decreased all four measures of reproductive performance: fertility by 12%, litter size by 30%, pup survival by 18%, and pup growth by 42%. In addition, dietary deficiencies strikingly decreased the incidence of consecutive pregnancies. Combined effects of 50 ppm cadmium and dietary deficiencies were additive for all reproductive measures except fertility; for fertility, cadmium caused no decrease in the fertility of sufficient-diet animals, but caused a striking 45% decrease in deficient-diet animals."
Xu, B., Y. Jin, et al. (1993). "Lipid peroxidation induced by maternal cadmium exposure in mouse pups." Bull Environ Contam Toxicol **51**(5): 772-9.	Abstract not available.
Xu, B., Y. Jin, et al. (1993). "Lipid Peroxidation Induced by Administration of Cadmium to Female Mice in Their Pups." Fresenius Environmental Bulletin **2**(1): 1-6.	In mice "A statistically significant decrease in brain weights were seen in pups from animals exposed to 30 ppm Cd compared to unexposed controls, while those exposed to 75 ppm Cd demonstrated significantly decreased heart, liver, kidney, and brain weights. The lipid peroxidation concentrations were increased in all organs except the kidney in the pups of mice exposed to 75 ppm Cd."
Zenick, H., L. Hastings, et al. (1982). "Chronic cadmium exposure: relation to male reproductive toxicity and subsequent fetal outcome." J Toxicol Environ Health **9**(3): 377-87.	In male rats were exposed to 0, 17.2, 34.4, or 68.8 ppm Cd for 70 d, "No significant effects were observed on any of the parameters of reproductive toxicity or fetal outcome. These findings suggest that, at the doses employed in this study, Cd did not have significant deleterious effects on the male reproductive system."
Zhao, C. F. and H. M. Jiang (2001). "[Study on antagonism of manganese to cadmium toxicity in pregnant rats]." Chung Kuo Kung Kung Wei Sheng **17**(8): 709-10.	"The growth rate of rats, the proportion of living fetuses and their average weight in the manganese supplement group increased significantly compared with those of Cd - intoxication group, while the incidence of malformed fetuses and absorbed embryos decreased greatly (P less than 0.01)."
	In vitro Studies
Haberstroh, K. M. and C. M. Kapron (2006). "Activation of c-Jun N-terminal kinase by cadmium in mouse embryo neural cells in vitro." Environmental Toxicology and Pharmacology **22**(1): 1-7.	"These results demonstrate that $CdCl_2$ induces a rapid and transient activation of the JNK pathway in primary embryonic neuron cell cultures."
Li, Y. U. N. and R.-S. Wang (1998). "Application of mouse limb bud culture to study the influence of zinc on teratogenesis induced by cadmium." Journal Of West China University Of Medical Sciences **29**(3):	"As cadmium concentrations were increased from 0.1 to 1.0 [n]g/mL, the degree of morphogenetic differentiation and the area of the bone anlagen of limbs culture were significantly decreased. . . . As Zn concentrations increased from 1.0 to 10.0

Reference	Findings/Conclusions
259-263.	µg/mL, the degree of morphogenetic differentiation and the area of cartilaginous bone anlagen of limbs culture were improved or increased."
Li, Y. A., X. Wang, et al. (2000). "[Effects of cadmium chloride on the malignant transformation of human embryo lung fibroblasts]." Wei Sheng Yan Jiu **29**(1): 34-6.	Positve findings were obtained in numerous genetic toxicity tests.
Matsuoka, M., H. Igisu, et al. (2004). "Requirement of MKK4 and MKK7 for CdCl2- or HgCl2-induced activation of c-Jun NH2-terminal kinase in mouse embryonic stem cells." Toxicol Lett **152**(2): 175-81.	"These findings suggest that the full activation of JNK by toxic metal exposure requires both MKK4 and MKK7, and these upstream kinases might contribute differentially in JNK activation between mouse ES cells exposed to $CdCl_2$ and $HgCl_2$."
Minta, M. and B. Wlodarczyk (2003). "Effect of Some Environmental Contaminants on Differentiation in Micromass Culture of Rat Embryo Limb Buds Cells." Reprod Toxicol **17**(4): 500.	In an in vitro test, a mean ID_{50} value was estimated at 2.95 µg/mL for cadmium.
Paksy, K., Z. Forgacs, et al. (1999). "In vitro comparative effect of Cd2+, Ni2+, and Co2+ on mouse postblastocyst development." Environ Res **80**(4): 340-7.	In a study of postblastocyst development of mouse preembryos, "Significant adverse effect on the development stages were observed at 2.2 µM (Cd^{2+})."
Ridd, K., D. J. Alexander, et al. (2004). "Foetal rat lung epithelial (FRLE) cells: partial characterisation and response to pneumotoxins." Toxicol In Vitro **18**(1): 79-88.	"Toxins that damage ATII cells in vivo (cadmium chloride, cobalt chloride and paraquat) were found to induce cytotoxicity in FRLE cells."
Warren, S., S. Patel, et al. (2000). "The effect of vitamin E exposure on cadmium toxicity in mouse embryo cells in vitro." Toxicology **142**(2): 119-26.	In a study of mouse embryo cells, it was concluded, "Cadmium toxicity in these cultured cells was found to be both time and concentration dependent. Prior exposure to 50 µM alpha-tocopherol or 25 or 50 µM alpha-tocopherol acetate resulted in a marked reduction in the toxicity of 5 µM $CdCl^2$.
Wlodarczyk, B., B. Biernacki, et al. (2001). "Postimplantation whole embryo culture assay for hamsters: an alternative to rat and mouse." ScientificWorldJournal **1**: 227-34.	Cadmium chloride induced dose-related embryotoxic and teratogenic effects in hamster embryos.

B. Reproductive Toxicity

Human

A total of 37 human reproductive toxicity studies for cadmium were identified, and 24 of those were published in 1999 or later. Many of the endpoints reported in the ATSDR profile (sperm parameters, fertility, hormone levels) were assessed in the more recent studies. One of the most frequently reported endpoints in the more recent studies was possible associations between cadmium and spermatogenesis or sperm quality; as was noted in the ATSDR profile, results were variable. One study reported no endocrine effects in males. The more recent studies examining cadmium effects on female reproduction reported effects on menstrual cycle, abortion, stillbirth, placental function, and increased testosterone levels. No associations were reported between cadmium

exposure and endometriosis or preeclampsia. Other studies looked at the possible contribution of cadmium to birth complications, decline in milk quality, and placental changes observed in women who smoke. Placental function was examined in many in vitro studies. Human reproductive studies are summarized in Table 4.

Experimental animal

A total of 130 experimental animal reproductive toxicity studies were identified, 88 of which were published in or after 1999. Among the most frequently reported effects in the more recent studies were decreases in sperm count or quality, disruption of spermatogenesis, and testicular lesions. These effects were not observed in all studies and, as reported in the ATSDR profile, appear to be dose dependent. Some studies reported that susceptibility to cadmium may vary by species or strain. Other effects reported for the male reproductive system included changes in testicular gene expression (included androgen-regulated and metallothionein-related genes), genotoxicity or alterations in DNA repair enzymes, lipid peroxidation, changes in enzyme activity, and in some cases, prostate effects. Some studies reported toxicity interactions between cadmium and lead. Other studies reported protective effects of zinc. Studies also examined possible mechanisms related to cadmium-induced carcinogenicity in reproductive organs. Endocrine-related effects such as changes in hormone levels and altered gonadotropin binding and steroidogenic activity were reported in some of the more recent studies. A recent study conducted in ovariectomized rats reported estrogenic effects including increased uterine weight, increased growth and development of the mammary gland, changes in hormone regulation, and endometrial proliferation. Another study in female rats reported possible effects in the pituitary-hypothalamic axis. Effects on placental histopathology were also reported in the more recent studies of female rats. Experimental animal reproductive studies are summarized in Table 5. In vitro studies reported possible mechanisms of cadmium-induced toxicity on placenta, ovary and ovarian steroidogenesis, uterus, sperm, Sertoli cells, gametes, and Leydig cells.

Table 4. Human Reproductive Toxicity Studies

Reference	Findings/Conclusions
In vivo and ex vivo studies	
Akinloye, O., A. O. Arowojolu, et al. (2006). "Cadmium toxicity: a possible cause of male infertility in Nigeria." Reprod Biol **6**(1): 17-30.	"The strong deleterious effect of cadmium on spermatogenesis may be due to the systemic and cellular toxicity. A possible relationship between this element and the HPG axis is also suggested."
Armstrong, B. G. and G. Kazantzis (1985). "Prostatic Cancer and Chronic Respiratory and Renal Disease in British Cadmium Workers a Case Control Study." Br J Ind Med **42**(8): 540-545.	No abstract available.
Benoff, S., I. R. Hurley, et al. (1997). "A potential role for cadmium in the etiology of varicocele-associated infertility." Fertil Steril **67**(2): 336-47.	"Cadmium was elevated and zinc was decreased in the seminal plasma of men with varicocele. The content of these metals in semen and blood was not correlated. Cadmium exposure in vitro reduced mannose receptor expression, acrosome exocytosis, and cytoskeletal formation by fertile donor sperm."
Benoff, S. H., C. Millan, et al. (2004). "Bilateral increased apoptosis and bilateral	"The percentage of apoptotic nuclei and cadmium levels were high in some men with varicocele.

accumulation of cadmium in infertile men with left varicocele." Hum Reprod **19**(3): 616-27.

There was a concordance of these values in both testes despite the presence of left-sided varicocele only. These values were inversely related to an increase in sperm concentration after varicocelectomy."

Benoff, S., L. O. Goodwin, et al. (2005). "Deletions in L-type calcium channel alpha1 subunit testicular transcripts correlate with testicular cadmium and apoptosis in infertile men with varicoceles." Fertil Steril **83**(3): 622-34.

"Expression of undeleted L-type calcium channel mRNAs correlates with normal testes cadmium and increased sperm count after varicocelectomy. Apoptosis is lower in such cases."

Chia, S. E., C. N. Ong, et al. (1992). "Blood concentrations of lead, cadmium, mercury, zinc, and copper and human semen parameters." Arch Androl **29**(2): 177-83.

In men visiting an andrology clinic, "asthenozoospermic subjects had significantly (p less than .025) higher blood cadmium levels than normozoospermic subjects."

Chia, S. E., B. Xu, et al. (1994). "Effect of cadmium and cigarette smoking on human semen quality." Int J Fertil Menopausal Stud **39**(5): 292-8.

"Cigarette smoking appears to affect sperm density, especially in heavy smokers. Cadmium in cigarettes could be a possible causative agent for the low sperm density among smokers."

Drbohlav, P., V. Bencko, et al. (1998). "[Detection of cadmium and zinc in the blood and follicular fluid in women in the IVF and ET program]." Ceska Gynekol **63**(4): 292-300.

In women attending a fertility clinic, "The assessed mean levels (μg/L) of cadmium in blood (2.88 ± 2.71) and follicular fluid (1.25 ± 0.55) in the group of conception cycles did not differ significantly from mean blood levels (2.82 ± 2.22) and follicular levels (1.16 ± 0.55) of non-conception cycles."

Gennart, J. P., J. P. Buchet, et al. (1992). "Fertility of Male Workers Exposed to Cadmium, Lead, or Manganese." American Journal of Epidemiology **135**(11): 1208-1219.

In a study of workers exposed to cadmium, "Cadmium exposure did not significantly affect birth rate. The probability of a live birth was not significantly affected by cadmium or manganese exposure, odds ratios (ORs) 0.97 and 0.91, respectively."

Heilier, J. F., V. Verougstraete, et al. (2004). "Assessment of cadmium impregnation in women suffering from endometriosis: a preliminary study." Toxicol Lett **154**(1-2): 89-93.

In a study examining blood and urine cadmium levels in women, the study authors concluded, "These data, therefore, do not support a role for cadmium in the onset or the growth of endometriosis or deep endometriotic (adenomyotic) nodules of the recto-vaginal septum."

Hovatta, O., E. R. Venalainen, et al. (1998). "Aluminium, lead and cadmium concentrations in seminal plasma and spermatozoa, and semen quality in Finnish men." Hum Reprod **13**(1): 115-9.

In a study of Finnish men, "The concentrations of cadmium and lead were low and did not show any correlation with parameters of semen analysis."

Kasperczyk, A., S. Kasperczyk, et al. (2002). "[Lead and cadmium concentration in human semen]." Ginekol Pol **73**(5): 449-53.

The authors of a study examining lead and cadmium in normozoospermic men and teratozoospermic, asthenozoospermic, and oligozoospermic men stated "We did not find any difference in concentration of these elements in both groups. We found a positive correlation between lead and cadmium in seminal plasma."

Mason, H. J. (1990). "Occupational cadmium exposure and testicular endocrine function." Hum Exp Toxicol **9**(2): 91-4.

In workers who were exposed to cadmium for 1 year or longer, "The lack of testicular endocrine effects was in contrast to significant dose-related changes

	in renal glomerular and tubular function. . .”
Milnerowicz, H., J. Zalewski, et al. (2000). "[Levels of Cd, Pb in blood and Zn, Cu, Cd, Pb in amniotic fluid of tobacco smoking women during pregnancy complicated oligohydramnios or premature rupture of membranes]." Ginekol Pol **71**(4): 311-6.	“Twice lower concentration of Zn and Cd and ten times lower concentration of Pb in amniotic fluids in examined women than women in normal pregnancy were observed. The women, with oligohydramnios in earlier period of gestation, smoked many more cigarettes and cotinine and Cd were much higher. Both these facts had relevance with each other certainly. The stillborns were many more in this group. The different distribution of Cd, Pb, Zn in pregnant women with PROM and oligohydramnios, comparing with women in normal pregnancy was demonstrated.”
Milnerowicz, H. and M. Chmarek (2005). "Influence of smoking on metallothionein level and other proteins binding essential metals in human milk." Acta Paediatr **94**(4): 402-6.	“The level of cadmium was four times higher in the milk of smoking women than in non-smokers. The concentration of total protein was lower in smoking . . . than in non-smoking mothers. . . The level of metallothionein was over twice as low in smokers (5.1 ± 1.9 μg/mL) than in non-smokers (13.4 ± 3.0 μg/mL; $P \leq 0.001$), and an inverse correlation between MT level and cadmium concentration ($r = -0.86$; $P = 0.001$) was noticed.”
Nagata, C., Y. Nagao, et al. (2005). "Urinary cadmium and serum levels of estrogens and androgens in postmenopausal Japanese women." Cancer Epidemiol Biomarkers Prev **14**(3): 705-8.	In a study of Japanese women, the authors concluded, “Data suggested that cadmium exposure is associated with increased testosterone levels. As high testosterone levels have been associated with the risk of breast cancer, the involvement of cadmium exposure in breast cancer risk should be evaluated in future studies.”
Nishijo, M., S. Satarug, et al. (2004). "The gender differences in health effects of environmental cadmium exposure and potential mechanisms." Mol Cell Biochem **255**(1-2): 87-92.	“. . . six risk factors in Cd health effects in women have been identified; (1) more serious type of renal tubular dysfunction, (2) difference in calcium metabolism and its regulatory hormones, (3) kidney sensitivity; difference in P450 phenotype, (4) pregnancy, (5) body iron store status, and (6) genetic factors.”
Noack-Fuller, G., C. De Beer, et al. (1993). "Cadmium, lead, selenium, and zinc in semen of occupationally unexposed men." Andrologia **25**(1): 7-12.	“Sperm motility ($r = 0.53$, $P < 0.02$), linear ($r = 0.76$, $P < 0.001$) and curvilinear velocity ($r = 0.64$, $P < 0.002$) were significantly correlated with semen cadmium levels.”
Pant, N., G. Upadhyay, et al. (2003). "Lead and cadmium concentration in the seminal plasma of men in the general population: correlation with sperm quality." Reprod Toxicol **17**(4): 447-50.	“An increase in lead and cadmium levels was observed in infertile men and there was a significant negative correlation of cadmium and lead semen concentration with sperm motility and sperm concentration in oligoasthenospermic men.”
Pant, N., A. K. Banerjee, et al. (2003). "Correlation of lead and cadmium in human seminal plasma with seminal vesicle and prostatic markers." Hum Exp Toxicol **22**(3): 125-8.	“No associations were observed between cadmium and biochemical markers or sperm quality.”
Ronco, A. M., G. Arguello, et al. (2005).	“This study confirms that cigarette smoking increases

"Increased levels of metallothionein in placenta of smokers." Toxicology **208**(1): 133-9.	cadmium accumulation in placental tissue and suggests that this element has a stimulatory effect on placental MT [metallothionein] production."
Telisman, S., Cvitkovi, et al. (2000). "Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men." Environ Health Perspect **108**(1): 45-53.	"The overall study results indicate that even moderate exposures to Pb (BPb < 400 µg/L) and Cd (BCd < 10 µg/L) can significantly reduce human semen quality without conclusive evidence of impairment of male reproductive endocrine function."
Timbrell, J. A. (2000). "Urinary creatine as a biochemical marker of chemical induced testicular damage." Arh Hig Rada Toksikol **51**(3): 295-303.	"Urinary creatine was found to be the most sensitive indicator of testicular damage detected by histopathology after both 2-methoxyethanol and cadmium exposure."
Vigeh, M., K. Yokoyama, et al. (2006). "Lead and other trace metals in preeclampsia: a case-control study in Tehran, Iran." Environ Res **100**(2): 268-75.	No association was reported between cadmium and preeclampsia.
Wu, S. Y., J. Tian, et al. (2004). "[The effect of cadmium pollution on reproductive health in females]." Zhonghua Liu Xing Bing Xue Za Zhi **25**(10): 852-5.	In a study conducted in China, "Both prevalence rates of abnormal menstrual cycle and dysmenorrhea in unmarried women in Cd-pollution area (19.1% vs. 42.6%) were significantly higher than those in control area (5.7% vs. 18.9%) and the rates of sterility in married women in Cd-pollution area (6.3%) were significantly higher than those in control area (1.1%). During the first two pregnancies, rates of queasiness, disgorgement, spontaneous abortion and stillbirth in married women in polluted area were 44.7%, 31.7%, 10.27% and 4.23%, significantly higher than those 26.5%, 17.8%, 2.85% and 1.05% in control area, with significant differences (P < 0.05). Results from cumulative odds model analysis showed that: living in Cd-pollution area was a possible risk factor related to female reproductive health (OR = 2.072), after the other risk factors being under control."
Yaman, M., G. Kaya, et al. (2007). "Comparison of trace element concentrations in cancerous and noncancerous human endometrial and ovary tissues." Int J Gynecol Cancer **17**(1): 220-8.	Results for cadmium were not reported in the abstract.
Younglai, E. V., W. G. Foster, et al. (2002). "Levels of environmental contaminants in human follicular fluid, serum, and seminal plasma of couples undergoing in vitro fertilization." Arch Environ Contam Toxicol **43**(1): 121-6.	"Cadmium was detected in eight of 21 (38.1%) samples of follicular fluid. . . Cadmium was also found in the follicular fluid of these pregnant subjects."
Zeng, X., T. Jin, et al. (2004). "Impact of cadmium exposure on male sex hormones: a population-based study in China." Environ Res **96**(3): 338-44.	The authors of a Chinese study stated "We conclude that oral Cd exposure is not a critical determinant of hormone homeostasis in males, but lifestyle and some biological factors, such as age and BMI, are important. The relationship found between urinary Cd and high T levels may be of importance for male

	reproductive morbidity and should be investigated further."
Zhang, Y., Y. Zhao, et al. (2004). "Effects of zinc, copper, and selenium on placental cadmium transport." Biol Trace Elem Res **102**(1-3): 39-49.	In a study of Chines women, "The placental cadmium concentration was from 0.082 to 3.97 µg/g dry weight. . . It was concluded that the essential elements copper, selenium, and zinc might significantly affect placental cadmium transport."
	In vitro studies
Abe, T., K. Yamamura, et al. (1998). "Concentration-dependent differential effects of N-acetyl-L-cysteine on the expression of HSP70 and metallothionein genes induced by cadmium in human amniotic cells." Biochim Biophys Acta **1380**(1): 123-32.	"Our present data suggest that changes in intracellular redox status, as reflected by GSH concentration, have more important effects on the induction of HSP70 mRNA rather than that of MT-II mRNA in human amniotic cells exposed to cadmium."
Boadi, W. Y., J. Urbach, et al. (1992). "Effect of cadmium on some enzyme activities in first-trimester human placentae." Toxicol Lett **60**(2): 155-64.	"Cd at low dose levels increased significantly the activities of placental phases I and II enzymes in a time- and dose-dependent manner. . . However, the G-6-PD activity was inhibited at all the dose levels of Cd . . ."
Boadi, W. Y., R. Shurtz-Swirski, et al. (1992). "Secretion of human chorionic gonadotropin in superfused young placental tissue exposed to cadmium." Arch Toxicol **66**(2): 95-9.	"These results indicate that Cd may affect the normal placental function, as reflected in its hCG secretion pattern."
Boadi, W. Y., J. Urbach, et al. (1992). "Enzyme activities in the term human placenta: In vitro effect of cadmium." Pharmacol Toxicol **71**(3 PART 1): 209-212.	Cd at low doses had a stimulatory effect on aryl hydrocarbon hydroxylase (AHH) (a phase I enzyme) on a quinone reductase and catecholamine-O-methyltransferase (COMT) (both phase II enzymes). . .Only the activities of AHH and COMT showed a biphasic response, (i.e., increases at the lower dose levels and decreases with the higher ones), whereas that of quinone reductase continually increased with all the dose levels of the metal administered. Glucose-6-phosphate dehydrogenase (G-6-PD) activity was found to be inhibited at all the dose levels of Cd tested . ."
Parrish, A. R., K. Sallam, et al. (2002). "Culturing precision-cut human prostate slices as an in vitro model of prostate pathobiology." Cell Biol Toxicol **18**(3): 205-19.	In slices of human prostate, ". . . $CdCl_2$ demonstrated a dose-response effect ranging from proliferation to complete cellular necrosis."
Piasek, M., J. W. Laskey, et al. (2002). "Assessment of steroid disruption using cultures of whole ovary and/or placenta in rat and in human placental tissue." Int Arch Occup Environ Health **75 Suppl**: S36-44.	"Results of the research on cadmium-induced steroidogenic effects using cultures of whole rat ovary and/or placenta as well as human placental tissues point to cadmium as an endocrine disruptor that may compromise pregnancy outcome and fetal viability."
Wier, P. J., R. K. Miller, et al. (1990). "Toxicity of cadmium in the perfused human placenta." Toxicol Appl Pharmacol **105**(1): 156-71.	"Thus, the human placenta is a site for toxic action of cadmium and is at least as sensitive as the rodent placenta to the actions of cadmium. In addition, these human studies demonstrated a selectivity in

	the toxic effects with a maintenance of carbohydrate metabolism and amino acid uptake even after 12 hr of exposure with placental Cd burdens of 151 +/- 37 nmol/g, but with the earliest (within 4 hr) dose-related functional alterations occurring in protein hormone production and zinc transfer followed by later changes in morphology with a tissue Cd burden of 46.5 ± 4.0 nmol/g."
Yang, K., L. Julan, et al. (2006). "Cadmium reduces 11 beta-hydroxysteroid dehydrogenase type 2 activity and expression in human placental trophoblast cells." Am J Physiol Endocrinol Metab **290**(1): E135-E142.	"Thus the present study identifies placental 11 beta-HSD2 [11 beta-hydroxysteroid dehydrogenase type 2] as a novel molecular target of cadmium. It also reveals a molecular mechanism by which this endocrine disruptor may affect human placental function and, consequently, fetal growth and development."

Table 5. Experimental Animal Reproductive Toxicity Studies

Reference	Findings/Conclusions
	In vivo
Abe, T., O. Yamamoto, et al. (2000). "Cadmium-induced mRNA expression of Hsp32 is augmented in metallothionein-I and -II knock-out mice." Arch Biochem Biophys **382**(1): 81-8.	Expression of the Hsp32 was assessed in testis of transgenic mice deficient in the MT-I and -II genes and in control mice injected with cadmium chloride ($CdCl_2$). $CdCl_2$ induced little increase of the MT-I mRNA and little induction and no augmentation in expression of the *Hsp32* gene, and no increased expression of Hsp32 protein. The authors suggested ". . . organs of low stress response to cadmium such as the testis and lung may be vulnerable target sites for cadmium toxicity and carcinogenesis.
Abshire, M. K. and M. P. Waalkes (1994). "Cadmium-Induced Oxidative Tissue Damage in Mice: Role of Mouse Strain and Tissue Metallothionein Levels." Toxic Substances Journal **13**(2): 141-152.	In mice given 60 µmol/kg Cd intraperitoneally, lipid peroxidation was observed in testis of an NFS strain but not BALB/cAnNCr strain.
Agarwal, A. K. "Metabolic Alterations in Liver and Testes of Adult and Newborn Rats Following Cadmium Administration." Bulletin of Environmental Contamination and Toxicology **40**(4): 569-575.	Cadmium chloride was given by ip injection to adult rats at 1 mg/kg twice a day for 3 days or to newborn rats at 5 mg/kg, on day 2 after birth and every 2 days for 14 days. "Cadmium administration decreased the levels of glucose-6-phosphate dehydrogenase and 6-phosphogluconic dehydrogenase in testes of adult rats. . . Newborn animals did not show any changes in enzyme activities or levels of NADH or NADPH."
Agarwal, A., I. Ikemoto, et al. (1997). "Prevention of testicular damage by free-radical scavengers." Urology **50**(5): 759-63.	For rats given 1 mg/kg body weight of $CdCl_2$, it was concluded that ". . . $CdCl_2$ induces impairment of testicular function and causes a marked reduction in testicular LDH-X activity; that LDH-X activity is a biological marker of testicular damage; and that, except at high doses of $CdCl_2$, this damage can be prevented by oxypurinol or SOD."
Aoki, A. and A. P. Hoffer (1978).	No abstract available.

Reference	Findings/Conclusions
"Reexamination of the lesions in rat testis caused by cadmium." Biol Reprod **18**(4): 579-91.	
Ates, I., H. S. Suzen, et al. (2004). "The oxidative DNA base damage in testes of rats after intraperitoneal cadmium injection." Biometals **17**(4): 371-7.	In rats ip injected with $CdCl_2$ 0.5 or 1.25 mg/kg bw, "There was a significant dose-response relationship in 2-OH adenine, Fapy guanine and 8-OH guanine, especially in the second week suggesting the inhibition of XPA protein by cadmium after first week. In contrast, the observation of a significant decrease of 5-OH cytosine levels after first week showed that cadmium could not affect the enzymes repairing the cytosine base lesions."
Baranski, B. and K. Sitarek (1987). "Effect of Oral and Inhalation Exposure to Cadmium on the Oestrous Cycle in Rats." Toxicology Letters **36**(3): 267-273.	No abstract available.
Bench, G., M. H. Corzett, et al. (1999). "Cadmium concentrations in the testes, sperm, and spermatids of mice subjected to long-term cadmium chloride exposure." Cytometry **35**(1): 30-6.	"Because cadmium was not incorporated into sperm chromatin at levels above 0.02 μg/g dry weight, the data cast doubt on hypotheses that suggest that reduced male fertility may result from incorporation of cadmium into sperm chromatin."
Berry, N. R., R. F. Axford, et al. (1999). "The effect of a low dose of cadmium on spermatogenesis in rams." Small Ruminant Research **31**(2): 97-102.	In rams fed 7.5 mg/day Cd, "There were no treatment effects on the spermatozoa concentration in the semen or output per ejaculate, the proportion of live spermatozoa, their progressive linear or vertical motility, wave motion at the periphery of the semen sample or testis circumference."
Bialkowski, K., A. Bialkowska, et al. (1999). "Cadmium(II), unlike nickel(II), inhibits 8-oxo-dGTPase activity and increases 8-oxo-dG level in DNA of the rat testis, a target organ for cadmium(II) carcinogenesis." Carcinogenesis **20**(8): 1621-4.	In male F344/NCr rats given a single s.c. dose of 20 μmol Cd(II) acetate, there was an ". . . early and progressive increase (from 130% at 2 h to 200% at 48 h versus the controls) of the 8-oxo-dG level in testicular DNA ($P < 0.05$ or better). . . Thus, Cd(II), unlike Ni(II), is able to inhibit 8-oxo-dGTPase activity and to raise 8-oxo-dG levels in rat testicular DNA."
Biswas, N. M., R. Sen Gupta, et al. (2001). "Effect of atenolol on cadmium-induced testicular toxicity in male rats." Reprod Toxicol **15**(6): 699-704.	In rats sc injected with 0.45 mg/kg bw cadmium chloride. "adrenal weight, adrenal Δ5-3β-hydroxysteroid dehydrogenase (Δ5-3β-HSD) activity, serum corticosterone, and brain noradrenaline were increased significantly while testicular Δ5-3β-HSD and 17β-HSD activities, serum testosterone, and accessory sex organs weight were decreased."
Bizarro, P., S. Acevedo, et al. (2003). "Ultrastructural modifications in the mitochondrion of mouse Sertoli cells after inhalation of lead, cadmium or lead-cadmium mixture." Reprod Toxicol **17**(5): 561-6.	In CD-1 mice that inhaled 0.01 M lead acetate, 0.006 M cadmium chloride, or Pb-Cd mixture for 4 weeks, "Cadmium chloride caused the most severe mitochondrial alteration compared to lead acetate, whereas the mixture was more aggressive compared with each metal alone."

Reference	Findings/Conclusions
Bonda, E., T. Wlostowski, et al. (2004). "Testicular toxicity induced by dietary cadmium is associated with decreased testicular zinc and increased hepatic and renal metallothionein and zinc in the bank vole (Clethrionomys glareolus)." Biometals **17**(6): 615-24.	In a study in which the bank vole was exposed subchronically to dietary Cd at 0.9 µmol/g, young (1-month-old) animals but not adult (5 months old) animals displayed testicular histopathology and apoptosis of testicular cells. The study authors stated, "The data indicate that dietary Cd produces testicular lesions indirectly, through decreasing testicular Zn, which seems to be due to the sequestration of this element by the Cd-induced hepatic and renal MT."
Boujelben, M., F. Ghorbel, et al. (2006). "Lipid peroxidation and HSP72/73 expression in rat following cadmium chloride administration: interactions of magnesium supplementation." Exp Toxicol Pathol **57**(5-6): 437-43.	Lipid peroxidation was observed in testes of rats exposed to $CdCl_2$ at 2.5mg/day/kg body weight for 10 days.
Chellman, G. J., Z. A. Shaikh, et al. (1985). "Resistance to cadmium-induced necrosis in testes of inbred mice: possible role of a metallothionein-like cadmium-binding protein." Toxicol Appl Pharmacol **79**(3): 511-23.	In mice iv injected with $CdCl_2$, marked interstitial hemorrhage and seminiferous tubule necrosis was observed in testes from 129/J strain mice, but not in A/J strain mice.
Chen, L., W. H. Ren, et al. (2002). "[Effects of chronic cadmium loading on the testis and endocrine function of reproduction in male rats]." Sheng Li Xue Bao **54**(3): 258-62.	In rats orally dosed with ≥5 mg/kg bw of cadmium for over 6 weeks, "It is suggested that the gradual accumulation of cadmium in testis tissue induced by chronic cadmium loading results in changes in some enzyme activity, a decrease in sperm production, and defect of endocrine function activity in the testis."
Corpas, I. and M. T. Antonio (1998). "Study of alterations produced by cadmium and cadmium/lead administration during gestational and early lactation periods in the reproductive organs of the rat." Ecotoxicol Environ Saf **41**(2): 180-8.	"Administration of cadmium (10 mg/liter) and cadmium + lead (300 mg/liter) via drinking water to Wistar rats during gestation and early lactation until delivery and (5 days after parturition) damaged pup reproductive systems."
Damek-Poprawa, M. and K. Sawicka-Kapusta (2004). "Histopathological changes in the liver, kidneys, and testes of bank voles environmentally exposed to heavy metal emissions from the steelworks and zinc smelter in Poland." Environ Res **96**(1): 72-8.	"No damage was found in the tissues of the bank voles from the Borecka forest or in the testes of animals from other areas."
Deveci, E., A. Onen, et al. (1999). "Effects of cadmium chloride on placenta of rat during pregnancy." Singapore J Obstet Gynecol **30**(2): 66-9.	In rats iv injected with 2 mg/kg/day of cadmium chloride dissolved in 1 mL isotonic saline solution on GD 9-21, placental microscopic changes such as vascularization, congestion, hemorrhage and edema were observed.
Di Sant'Agnese, P. A., K. D. Jensen, et al. (1983). "Placental toxicity of cadmium in the rat: an ultrastructural study." Placenta **4**(2): 149-63.	"Pregnant rats on day 18 of gestation were injected s.c. with 40 [n]mol/kg $CdCl_2$, which caused fetal death and placental necrosis."

Reference	Findings/Conclusions
El-Demerdash, F. M., M. I. Yousef, et al. (2004). "Cadmium-induced changes in lipid peroxidation, blood hematology, biochemical parameters and semen quality of male rats: protective role of vitamin E and beta-carotene." Food Chem Toxicol **42**(10): 1563-71.	In rats gavaged with 5 mg/kg bw cadmium chloride, there were decreases in sperm concentration, percent motility, weight of testes and epididymis, and increases in dead and abnormal sperm.
Favino, A., A. H. Baillie, et al. (1966). "Androgen synthesis by the testes and adrenal glands of rats poisoned with cadmium chloride." J Endocrinol **35**(2): 185-92.	No abstract available.
Favino, A., A. Cavalleri, et al. (1968). "Testosterone excretion in cadmium chloride induced testicular tumours in rats." Med Lav **59**(1): 36-40.	No abstract available.
Fende, P. L. and R. J. Niewenhuis (1977). "An electron microscopic study of the effects of cadmium chloride on cyptorchid testes of the rat." Biol Reprod **16**(3): 298-305.	In testes of rats s.c. injected with $CdCl_2$, "Edema associated with Cd injury was visible at 3 h and the damage progressed in both cryptorchid and scrotal testes after 5 h and 24 h. The primary ultrastructural effects consisted of changes in the endothelial cell junctions of intratesticular capillaries, which progressed from a decrease in membrane-associated electron density at 3 h to actual separation of endothelial cells 6 h after Cd injection. These changes were more pronounced at each time period in the cryptorchid than in the scrotal testis."
Foote, R. H. (1999). "Cadmium affects testes and semen of rabbits exposed before and after puberty." Reprod Toxicol **13**(4): 269-77.	In male rabbits exposed to cadmium chloride (Cd) when 12 or 27 weeks old, "Cd given at 12 weeks of age in doses of 0.08 mmol/kg s.c., 0.20 mmol/kg orally, and 0.02 mmol/kg i.v. tended to depress sperm output of these males when adults." In limited comparisons to adults ". . . testicular sensitivity was slightly less than for young males. Androgenic function usually was maintained, as indicated by normal libido and seminal volumes even in males with reduced spermatogenesis. Necropsies confirmed previous findings of hyperemia, hemorrhaging, necrosis, and destruction of all spermatogenic elements in severely affected males."
Gouveia, M. A. (1988). "The testes in cadmium intoxication: morphological and vascular aspects." Andrologia **20**(3): 225-31.	In Wistar rats injected with 1 mg/ml of cadmium chloride ($CdCl_2$) intra-peritoneally, "vascular labeling was evidenced as early as 4 hours after $CdCl_2$, injection; 24 hours later severe oedema with leakage of particles to the interstitium and also into the tubules was patent. Fourteen days after $CdCl_2$ administration, atrophy of the testes with necrosis of the tubules, fibrosis of the interstitium and vascular thrombosis was found, compatible with chemical

Reference	Findings/Conclusions
	castration."
Gunn, S. A., T. C. Gould, et al. (1963). "The selective injurious response of testicular and epididymal blood vessels to cadmium and its prevention by zinc." Am J Pathol **42**: 685-702.	No abstract available
Gunn, S. A., T. C. Gould, et al. (1965). "Strain differences in susceptibility of mice and rats to cadmium-induced testicular damage." J Reprod Fertil **10**(2): 273-5.	No abstract available
Gunn, S. A., T. C. Gould, et al. (1965). "Strain Differences In Susceptibility Of Mice And Rats To Cadmium-Induced Testicular Damage." Journal of Reproduction and Fertility **10**: 273-275.	In experiments in which mice and rats injected with 0.03 mmol/kg cadmium chloride, "Necrosis was consistently seen in random bred CD-1-mice and in 10 inbred strains. Experiments with lower doses revealed that the amount of cadmium needed to produce minimal testicular damage varied within these susceptible strains. . . All rats showed characteristic testicular injury but there were indications that the dose of cadmium needed to produce minimal testicular damage differed."
Gunnarsson, D., G. Nordberg, et al. (2003). "Cadmium-induced decrement of the LH receptor expression and cAMP levels in the testis of rats." Toxicology **183**(1-3): 57-63.	"In the dose-response experiment Male Sprague Dawley rats received a single sc injection of $CdCl_2$ (1, 5 or 10 μmol/kg body weight) and were sacrificed 48 h after injection. A statistically significant decrease in luteinizing hormone (LH) receptor mRNA level in the testicular tissue was demonstrated at the highest dose (10 μmol/kg). In the temporal-response experiment rats were given 10 μmol/kg of $CdCl_2$ s.c. and sacrificed 0.48, 4.8, 48 or 144 h after injection. LH receptor mRNA levels as well as cyclic adenosine monophosphate (cAMP) levels were found to be significantly lowered at 48 and 144 h."
Gunnarsson, D., M. Svensson, et al. (2004). "Pronounced induction of testicular PGF(2 alpha) and suppression of testosterone by cadmium-prevention by zinc." Toxicology **200**(1): 49-58.	In a study in which adult male rats were injected with cadmium, the authors concluded "The present findings establish that cadmium can cause a strong induction of testicular $PGF_{2\alpha}$ production, which might help to explain the well-known antisteroidogenic effect of this heavy metal."
Gunnarsson, D., G. Nordberg, et al. (2007). "Differential effects of cadmium on the gene expression of seven-transmembrane-spanning receptors and GAPDH in the rat testis." Toxicol Lett **168**(1): 51-7.	In a study in which adult male rats were injected with 10 μmol/kg cadmium, the authors concluded "These data suggest that the influence of Cd on testicular gene expression involves a specific effect on the LH receptor and not a general effect on seven-transmembrane-spanning receptors. Also, data indicate that the increased expression of GAPDH may be secondary to Cd-induced testosterone deprivation, suggesting future studies of androgen-regulated genes in the toxicity of Cd."
Haffor, A. S. and F. M. Abou-Tarboush (2004).	In mice ingesting 1 mg/kg cadmium daily for 4 weeks,

Reference	Findings/Conclusions
"Testicular cellular toxicity of cadmium : transmission electron microscopy examination." J Environ Biol **25**(3): 251-8.	"Ultrastructure examination revealed, vascular endothelial, interstitial, and Sertoli cells damage[]. Early impairments of germinal cellular differentiation resulted in deformations in all parts of late spermatid. There were dislocation of acrosomal granules, nuclear damage associated with chromatin heterogeneity, detached spermatid from the apical process of Sertoli cell, disarrangement of the mitochondria, abnormal oriented tail piece, and abnormal microtubules complex."
Hew, K. W., G. L. Heath, et al. (1993). "Cadmium in vivo causes disruption of tight junction-associated microfilaments in rat Sertoli cells." Biol Reprod **49**(4): 840-9.	The authors of a rat study concluded that "a single cadmium chloride dose of 1 mg/kg results in the disruption of basal Sertoli cell microfilament bundles in the rat seminiferous epithelium, and that the action of cadmium is cell-specific and stage-specific."
Hew, K. W., W. A. Ericson, et al. (1993). "A single low cadmium dose causes failure of spermiation in the rat." Toxicol Appl Pharmacol **121**(1): 15-21.	The authors of a rat study stated "These results indicate that a single cadmium chloride dose of 1 mg/kg results in failed spermiation in rat seminiferous tubules, without discernible change to the surrounding endothelium. We conclude that cadmium begins to act during early stage VIII of spermatogenesis to induce failure of spermiation, and the action of cadmium is spermatogenic stage-specific."
Hoffmann, L., H. P. Putzke, et al. (1985). "Carcinogenic Effects of Cadmium on the Prostate of the Rat." J Cancer Res Clin Oncol **109**(3): 193-199.	Abstract not available.
Jiang, S. Y., X. Zhuang, et al. (2003). "[Effect of subchronic cadmium exposure on DNA damage of testicle cells in mice and protective effect of zinc sulfate]." Chung Kuo Kung Kung Wei Sheng **19**(12): 1450-2.	In a study in which mice were injected with cadmium chloride (0.4, 0.8, 1.6 mg/kg) for 7 weeks, the study authors concluded "Cadmium exposure may induce the DNA damage of testes cells, zinc sulfate could improve the subchronic pathological damage in testes induced by cadmium in a certain degree, but the protective effect of zinc was not showed in DNA damage level."
Iscan, M., A. O. Ada, et al. (2002). "Combined effects of cadmium and nickel on testicular xenobiotic metabolizing enzymes in rats." Biol Trace Elem Res **89**(2): 177-90.	In male rats given 3.58 mg $CdCl_2$, there were decreases in activities of testicular ethoxyresorufin *O*-deethylase and glutathione *S*-transferase, decreased reduced glutathione (GSH) level, and increased lipid peroxidation. Authors concluded that "combination of Cd and Ni does not have a synergistic effect on testicular xenobiotic metabolizing enzymes, and in contrast, Ni has an ameliorating effect on pathological disturbances caused by Cd alone in the rat testis."

Reference	Findings/Conclusions
Johnson, M. D., N. Kenney, et al. (2003). "Cadmium mimics the in vivo effects of estrogen in the uterus and mammary gland." Nat Med **9**(8): 1081-4.	"Exposure to cadmium increased uterine wet weight, promoted growth and development of the mammary glands and induced hormone-regulated genes in ovariectomized animals. In the uterus, the increase in wet weight was accompanied by proliferation of the endometrium and induction of progesterone receptor (PgR) and complement component C3. In the mammary gland, cadmium promoted an increase in the formation of side branches and alveolar buds and the induction of casein, whey acidic protein, PgR and C3. In utero exposure to the metal also mimicked the effects of estrogens. Female offspring experienced an earlier onset of puberty and an increase in the epithelial area and the number of terminal end buds in the mammary gland."
Kar, A. B., R. P. Das, et al. "Prevention of Cadmium Induced Changes in the Gonads of Rat by Zinc and Selenium A Study in Antagonism between Metals in the Biological System." Proceedings of the National Institute of Sciences of India, Part B. Biological Sciences **26**: 40-50.	"Results indicate that degenerative changes induced by cadmium in the rat gonads are prevented by zinc and selenium, and that cadmium is possibly antagonized by zinc and selenium at two different sites."
Karbownik, M., E. Gitto, et al. (2001). "Induction of lipid peroxidation in hamster organs by the carcinogen cadmium: melioration by melatonin." Cell Biol Toxicol **17**(1): 33-40.	In hamsters, "Forty-eight hours after cadmium injection, lipid peroxidation increased in brain, heart, kidney, testes, and lung. Melatonin slightly, but not significantly, reduced cadmium-induced lipid peroxidation in testes."
Kasprzak, K. S. and K. Bialkowski (2000). "Inhibition of antimutagenic enzymes, 8-oxo-dGTPases, by carcinogenic metals. Recent developments." J Inorg Biochem **79**(1-4): 231-6.	"After developing an assay for 8-oxo-dGTPase activity, we confirmed the inhibition by Cd(II) in cultured cells and in the rat testis, the target organ for cadmium carcinogenesis. 8-Oxo-dGTPase inhibition was accompanied by an increase in the 8-oxo-dG level in testicular DNA."
Kasprzak, K. S., Y. Nakabeppu, et al. (2001). "Intracellular distribution of the antimutagenic enzyme MTH1 in the liver, kidney and testis of F344 rats and its modulation by cadmium." Exp Toxicol Pathol **53**(5): 325-35.	"A particularly strong expression of MTH1 was observed for the first time in the perinuclear acrosomic bodies of spermatocytes and in the acrosomic vesicles of sperm heads. Treatment of rats with a single sc dose of 20 μmol Cd(II)/kg body wt. produced histopathologic changes in these organs accompanied by redistribution of the cellular MTH1 protein between the cytoplasm and nuclei."
Lafuente, A., E. Alvarez-Demanuel, et al. (1999). "Pubertal dependent effects of cadmium on episodic prolactin secretion in male rats." Arch Toxicol **73**(1): 60-3.	"Prepubertal cadmium administration decreased mean serum prolactin levels and the absolute amplitude of the prolactin pulses. Subchronic exposure to cadmium of adult rats decreased mean serum prolactin levels, the absolute amplitude of the prolactin pulses and their duration, and the mean half-life of the hormone."

Reference	Findings/Conclusions
Lafuente, A., N. Marquez, et al. (1999). "Cadmium affects the episodic luteinizing hormone secretion in male rats: Possible age-dependent effects." Toxicology Letters **104**(1-2): 27-33.	In a study examining luteinizing hormone secretion in male rats, "Cadmium administration, from day 30 to 60 of life, decreased the pulse frequency and mean half-life of the hormone."
Lafuente, A., aacute, et al. (2000). "Pubertal and postpubertal cadmium exposure differentially affects the hypothalamic-pituitary-testicular axis function in the rat." Food Chem Toxicol **38**(10): 913-23.	In a study examining cadmium effects on norepinephrine, serotonin, luteinizing hormone, and follicle stimulating hormone in rats , it was concluded "These data suggest that cadmium exerts age-dependent effects on the hypothalamic-pituitary-testicular axis function, and a disruption of the regulatory mechanisms of the hypothalamic-pituitary-gonadal axis emerges."
Lafuente, A., A. Gonzalez-Carracedo, et al. (2004). "Cadmium exposure differentially modifies the circadian patterns of norepinephrine at the median eminence and plasma LH, FSH and testosterone levels." Toxicol Lett **146**(2): 175-82.	In a study examining norepinephrine, luteinizing hormone, follicle stimulating hormone, and testosterone in rats, it was concluded "These data suggest that cadmium exerts differential effects at the median eminence, the pituitary and the testes, that may explain the changes in the 24-h pattern of plasma testosterone levels."
Lee, K. F., K. M. Lau, et al. (1999). "Effects of cadmium on metallothionein-1 and metallothionein-II mRNA expression in rat ventral, lateral, and dorsal prostatic lobes: Quantification by competitive RT-PCR." Toxicology And Applied Pharmacology **154**(1): 20-27.	In rats treated with cadmium, "The susceptibility of VP [ventral prostate] to Cd toxicity/carcinogenicity may therefore be explained by low levels of Cd-induced expression rather than lack of induction of MTs."
Levy, L. S., F. J. Roe, et al. (1973). "Absence of prostatic changes in rats exposed to cadmium." Ann Occup Hyg **16**(2): 111-8.	Abstract not available.
Levy, L. S. and J. Clack (1975). "Further studies on the effect of cadmium on the prostate gland: I. Absence of prostatic changes in rats given oral cadmium sulphate for two years." Ann Occup Hyg **17**(3-4): 205-212.	In rats exposed to $3CdSO_4 \cdot 8H_2O$ at up to 0.8 mg/kg bw each week (0.35 mg Cd/kg) for 2 years, "No macroscopic or microscopic change attributable to treatment was seen in the prostate or any other organ or tissue."
Liao, X., N. Terada, et al. (2006). "Immunohistochemical study of serum albumin in normal and cadmium-treated mouse testis organs by "in vivo cryotechnique"." Histol Histopathol **21**(1): 35-40.	In mice, "Twenty-four and 48 hrs after Cd-treatment, some enlarged spaces and vesicular formations in the seminiferous epithelium were observed on the HE-stained sections. The albumin immunolocalization was detected not only in the basal compartments, but also in the adluminal compartments between Sertoli cells and germ cells."
Liu, J., C. Corton, et al. (2001). "Genetic background but not metallothionein phenotype dictates sensitivity to cadmium-induced testicular injury in mice." Toxicol Appl Pharmacol **176**(1): 1-9.	The authors of a mouse study concluded "Thus, this study demonstrates that it is genetic strain, not MT genotype, that is mechanistically important in determining susceptibility to Cd-induced testicular injury."
Mason, K. E., J. A. Brown, et al. (1964). "Cadmium-Induced Injury of the Rat Testis."	In rats given graded, subcutaneous doses of cadmium-chloride, " . . . Injury to the testis is found to

Reference	Findings/Conclusions
Anatomical Record **149**: 135-148.	represent an ischemic necrosis secondary to rapid production of intertubular edema, increased intratesticular pressure, with or without associated hemorrhage, and ultimate interference with testicular blood supply and drainage."
Mason, K. E. and J. O. Young (1966). "Effectiveness of Selenium and Zinc in Protecting against Cadmium-Induced Injury of the Rat Testis." Selenium in Biomedicine: 19671967.	"Single subcutaneous injections of 0.45 milligram cadmium-chloride . . . consistently produce testis injury in adult rats weighting 250 to 375 grams. Half-equimolar selenium-dioxide . . . injected at the same time as cadmium . . . or 45 times equimolar zinc-acetate . . . injected one day before cadmium, approximates minimal amounts for protection against cadmium."
Mason, K. E. and J. O. Young (1967). "Effects of cadmium upon the excurrent duct system of the rat testis." Anat Rec **159**(3): 311-23.	Abstract not available.
Massanyi, P., V. Uhrin, et al. (1999). "Histological changes in the oviduct of rabbits after administration of cadmium." Journal Of Animal And Feed Sciences **8**(2): 255-261.	Complete abstract not available.
Motas, G., et al. (2004). "Ultrastructural Alterations In Reproductive Organs Induced By Subchronic Exposure To Lead And Cadmium." Toxicol Appl Pharmacol **197**(3): 273.	"We observed that treated Wistar rats during 30 days with cadmium chloride (250 ppm) and lead acetate (500 ppm) in drinking water suffered ultrastructural alterations at reproductive level . . . It is observed, in exposed animal to cadmium, the presence of intranuclear inclusions bodies, as well as a great number of myelin figures into cytoplasm, that probably represent an active but unsuccessful attempt to isolate or to expel the metal from the cell. At testicular level, we observed vascular and perivascular edema in capillaries in both experiments, which could be explained by the changes that cadmium induces at the endothelial cell junctions when interacting with calcium. . . we found additive effects of the injuries observed in treated animals separately to lead and cadmium."
Mou, S. H., L. Yan, et al. (2006). "[Effect of fluorine, selenium and cadmium on lipid peroxide and microelements in rat's testicle]." Chung Kuo Kung Kung Wei Sheng **22**(3): 336-7.	"Fluorine, cadmium can accelerate the activity of GSH-Px in the testicle of rat, which can diminish the antioxidative ability of the testicle. But selenium had no obvious effect on them, when two of the fluorine, selenium and cadmium coexist, they can reduce the content of lipid peroxide and the effect is even stronger when three of them coexist."
Mukherjee, S., S. K. Das, et al. (2001). "Acute cadmium toxicity and male reproduction." Adv Reprod **5**(1): 19-33.	The authors of a study in which rats were injected with 1.0 mg Cd/kg body weight stated, "These data demonstrate that Cd-induced male infertility is not due to the perturbation of GnRH regulated gonadotropin secretion. However, it exerts its

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	adverse effects on PRL, the ability of the Leydig cells to synthesize and secrete testosterone, a key regulator of spermatogenesis and sperm maturation in adult animals. Furthermore, our data also suggest that Cd induces the production of antisperm antibodies as a result of the damage to the blood-testis barrier.
Nampoothiri, L. P. and S. Gupta (2006). "Simultaneous effect of lead and cadmium on granulosa cells: a cellular model for ovarian toxicity." Reprod Toxicol **21**(2): 179-85.	In a study of hormone binding in granulosa cells of rats ip treated with lead or cadmium acetate at 0.05 mg/kg bw for 15 days, "both lead and cadmium caused a significant reduction in gonadotropin binding, which altered steroidogenic enzyme activity of granulosa cells."
Oliveira, H., J. Loureiro, et al. (2006). "Flow cytometry evaluation of lead and cadmium effects on mouse spermatogenesis." Reprod Toxicol **22**(3): 529-35.	In mice treated with cadmium and evaluated for spermatogenic effects, "The highest doses of $CdCl_2$ decreased the number of haploid (1C) cells and increased the number of diploid (2C), S phase and tetraploid (4C) cells."
Omaye, S. T. and A. L. Tappel (1975). "Effect of cadmium chloride on the rat testicular soluble selenoenzyme, glutathione peroxidase." Res Commun Chem Pathol Pharmacol **12**(4): 695-711.	"Thirty-six hours after male rats were injected with 25 [n]moles cadmium chloride/mL/kg of body weight they exhibited decreased plasma and testicular glutathione (GSH) peroxidase activity, testicular atrophy and necrosis, and increased testicular thiobarbituric acid-reactive products. Seven days after injection, only the plasma GSH peroxidase activity returned to normal."
Oner, H., M. Karatepe, et al. (2005). "Effects on rat testes of the thiosemicarbazone derivative Schiff base (4-(1-phenylmethylcyclobutane-3-yl)-2-(2-hydroxybenzylidenehydrazino)thiaz ole) and its cadmium(II) complex." Cell Biochem Funct **23**(6): 427-33.	In rats treated with the cadmium complex of 4-(1-phenyl-methylcyclobutane-3-yl)-2-(2-hydroxybenzylidene-hydrazino) thiazole (L), there were degenerative changes in testes.
Oteiza, P. I., V. N. Adonaylo, et al. (1999). "Cadmium-induced testes oxidative damage in rats can be influenced by dietary zinc intake." Toxicology **137**(1): 13-22.	The authors of a rat study concluded, "These results support the concept that zinc deficiency increases the susceptibility of testes to cadmium-mediated free radical damage."
Ozawa, N., N. Goda, et al. (2002). "Leydig cell-derived heme oxygenase-1 regulates apoptosis of premeiotic germ cells in response to stress." J Clin Invest **109**(4): 457-67.	Cadmium was used in the study of stress response in testicular cells.
Parizek, J. and Z. Zahor (1956). "Effect of cadmium salts on testicular tissue." Nature **177**(4518).	Abstract not available.
Patra, R. C., D. Swarup, et al. (1999). "Effects of cadmium on lipid peroxides and superoxide dismutase in hepatic, renal and testicular tissue of rats." Vet Hum Toxicol **41**(2): 65-7.	In rats "Daily i.p. administration of 0.5 mg cadmium (Cd)/kg body weight to rats for 3 mo enhanced lipid peroxidation and inhibited superoxide dismutase (SOD) activity in liver, kidney and testes."

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Pillai, A., Laxmipriya, et al. (2002). "Effect of low level exposure of lead and cadmium on hepatic estradiol metabolism in female rats." Indian J Exp Biol **40**(7): 807-11.	In female rats ip dosed with lead acetate and cadmium acetate separately and in combination (0.025, 0.05 and 0.1 mg/kg body wt) for 15 days, "The metabolizing enzymes (17β-hydroxysteroid oxidoreductase and UDP glucoronyl transferase) activities decreased with increasing dose showing significant change compared to control."
Pillai, A., L. Priya, et al. (2003). "Effects of combined exposure to lead and cadmium on the hypothalamic-pituitary axis function in proestrous rats." Food Chem Toxicol **41**(3): 379-84.	In a study in which female rats were ip dosed with either lead acetate or cadmium acetate alone or in combination at 0.05 mg/kg daily for 15 days, the study authors concluded "These data suggest that the metal accumulation disrupts the regulatory mechanisms of the hypothalamic-pituitary axis where the effects produced by the combined treatment of metals are not additive."
Rehm, S. and M. P. Waalkes (1988). "Cadmium-induced ovarian toxicity in hamsters, mice, and rats." Fundam Appl Toxicol **10**(4): 635-47.	The effects of sc administered cadmium on the female reproductive tract was examined in Syrian hamsters (Cr:RGH), 4 mouse strains, and 2 rat strains. "Uterine and cervical stromal hemorrhages were seen only in immature hamsters at doses of greater than or equal to 30 [n]mol $CdCl_2$/kg. Of the mice, only the DBA/2NCr strain showed significant CdCl2-induced ovarian hemorrhages, and these hemorrhages occurred at doses also producing lethal liver toxicity. Lesions of the uterus were rare. Rats showed dose- and age-dependent toxicity in the ovaries, uterus, cervix, and liver. $CdCl_2$ exposure in mature rats induced uterine lesions only in F344 rats, while acute ovarian and hepatic toxicity was less severe in mature animals of both strains. No lesions were noted after 7 days in mature WF rats."
Rehm, S. and M. P. Waalkes (1988). "Mixed Sertoli-Leydig cell tumor and rete testis adenocarcinoma in rats treated with CdCl2." Vet Pathol **25**(2): 163-6.	Abstract not available.
Ren, X. Y., Y. Zhou, et al. (2003). "Expression of metallothionein gene at different time in testicular interstitial cells and liver of rats treated with cadmium." World J Gastroenterol **9**(7): 1554-8.	In rats treated with cadmium, "Cd-induced expression of MT [metallothionein] isoforms is not only tissue dependent but also time-dependent. The inability to induce the metal-detoxicating MT-protein in response to Cd, may account for a higher susceptibility of testes to Cd toxicity and carcinogenesis compared to liver."
Ren, X. Y., Y. Zhou, et al. (2003). "Metallothionein gene expression under different time in testicular Sertoli and spermatogenic cells of rats treated with cadmium." Reprod Toxicol **17**(2): 219-27.	In a study in which rats were exposed to Cd prior to examining testicular and liver cells, it was concluded, "These results indicate: (1) that Cd-induced MT [metallothionein] mRNA expression is cell- and time-dependent; (2) that the inability to induce the metal-detoxicating MT protein in response to Cd, might account for higher susceptibility of testes to Cd toxicity and

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	carcinogenesis relative to liver."
Roe, F. J., C. E. Dukes, et al. (1964). "Cadmium Neoplasia: Testicular Atrophy and Leydig Cell Hyperplasia and Neoplasia in Rats and Mice Following the Subcutaneous Injection of Cadmium Salts." Br J Cancer **18**: 674-81.	Abstract not available.
Roelfzema, H. W., H. J. Hacker, et al. (1989). "Effects of Cadmium Exposure on Glycogen Phosphorylase Activity in Rat Placenta as Demonstrated by Histochemical Means." Histochemistry **91**(4): 305-308.	Abstract not available.
Santos, F. W., T. Oro, et al. (2004). "Cadmium induced testicular damage and its response to administration of succimer and diphenyl diselenide in mice." Toxicol Lett **152**(3): 255-63.	In mice given a single dose of $CdCl_2$ (2.5 mg/kg or 5 mg/kg, intraperitoneally), there was lipid peroxidation and changes in antioxidant enzyme activities in testes.
Santos, F. W., G. Zeni, et al. (2005). "Efficacy of 2,3-dimercapto-1-propanesulfonic acid (DMPS) and diphenyl diselenide on cadmium induced testicular damage in mice." Food Chem Toxicol **43**(12): 1723-30.	In mice given a single dose of $CdCl_2$ (2.5 mg/kg or 5 mg/kg, intraperitoneally), there was lipid peroxidation and changes in enzyme activities in testes.
Santos, F. W., Gra, et al. (2006). "Sub-chronic administration of diphenyl diselenide potentiates cadmium-induced testicular damage in mice." Reprod Toxicol **22**(3): 546-50.	"Male mice were dosed with 2.5 mg/kg $CdCl_2$ (2.5 mg/kg) with or without [diphenyl selenide] (5 µmol/kg) at 30 min post-exposure using a model of five weekly subcutaneous injections. . . .Animals exposed to $CdCl_2$ and $CdCl_2$ plus [diphenyl selenide] displayed a reduction in body weight gain and testicular weight. Progressive damage and histolopathological changes in the testis were not remedied with, but rather were potentiated by, [diphenyl selenide] therapy."
Saxena, D. K., R. C. Murthy, et al. (1989). "Zinc protects testicular injury induced by concurrent exposure to cadmium and lead in rats." Res Commun Chem Pathol Pharmacol **64**(2): 317-29.	Rats ". . . coexposed to lead and cadmium exhibited much more pronounced pathological changes and reduced sperm counts compared to the animals exposed to either of the metals alone. Zinc supplementation to the lead + cadmium exposed rats revealed the protective effect of zinc on these parameters."
Saygi, S., G. Deniz, et al. (1991). "Chronic effects of cadmium on kidney, liver, testis, and fertility of male rats." Biol Trace Elem Res **31**(3): 209-14.	"All the cadmium-treated male rats showed pathological testicular alterations, and liver and kidney damage after chronic exposure. . . .At the end of the 52-wk period, reproductive capacity of the cadmium-treated rats was investigated and was found to be lost in 39.89% of the animals."
Schroeder, H. A. and M. Mitchener (1971). "Toxic effects of trace elements on the reproduction of mice and rats." Arch Environ Health **23**(2): 102-6.	Abstract not available.
Sen Gupta, R., J. Kim, et al. (2004). "Effect of	The authors of a study in rats exposed to 0.2 or 0.3

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ascorbic acid supplementation on testicular steroidogenesis and germ cell death in cadmium-treated male rats." Mol Cell Endocrinol **221**(1-2): 57-66.	mg/100 g bw cadmium concluded "These results indicate that ascorbic acid have protective roles in vivo on the Cd-induced overall testicular damage including impaired steroidogenesis and germ cell death possibly through scavenging the reactive oxygen species generated by Cd administration."
Sen Gupta, R., E. Sen Gupta, et al. (2004). "Vitamin C and vitamin E protect the rat testes from cadmium-induced reactive oxygen species." Mol Cells **17**(1): 132-9.	In rats, "Cadmium administration caused an increase in reactive oxygen species (ROS) by elevating testicular malondialdehyde (MDA) and decreasing the activities of testicular antioxidant enzymes. . . The activities of testicular Δ5-3β and 17β-hydroxysteroid dehydrogenases (HSD) as well as serum testosterone level were also lowered. . ."
Shimada, H., S. Yamaguchi, et al. (2002). "Cadmium exposure decreases androgen-dependent metabolism of acetohexamide in liver microsomes of male rats through its testicular toxicity." Arch Toxicol **76**(1): 8-12.	Exposure of male rats to cadmium at 1.23 mg/kg (2.0 mg/kg as $CdCl_2$ induced testicular hemorrhage and atrophy and diminished serum testosterone levels.
Su, N., W. J. Zhu, et al. (2005). "[Sub chronic Effects of Cadmium Chloride on the Spermatogenesis of the Adult Rats Exposed Orally]." Shengzhi Yu Biyun **25**(3): 143-8.	"This study demonstrates that subchronic dietary exposure of cadmium ion can damage the spermatogenetic epithelium and the function of spermatogenesis of adult SD rat. The toxic damage is dose-dependent."
Swarup, D., R. Naresh, et al. (2007). "Changes in plasma hormones profile and liver function in cows naturally exposed to lead and cadmium around different industrial areas." Res Vet Sci **82**(1): 16-21.	No associations were reported between cadmium blood levels and reproductive hormones in blood of cows.
Valverde, M., T. I. Fortoul, et al. (2000). "Induction of genotoxicity by cadmium chloride inhalation in several organs of CD-1 mice." Mutagenesis **15**(2): 109-14.	DNA damagae that varied by organ was reported in the examination of several organs (including testis) in mice inhaling cadmium chloride.
Villanueva, O., R. M. Vigueras, et al. (2005). "Zinc-induced survival of Leydig cells in Fischer rats (Rattus norvegicus) treated with cadmium chloride." Comp Med **55**(6): 533-8.	In rats sc injected with $CdCl_2$ 20 μmol /kg weekly for 5 weeks, with or without zinc acetate, ". . . the number of surviving Leydig cells was significantly lower in the cadmium group (7.34% = 0.095 × $10^9/cm^3$) than in the cadmium-zinc group (20.85%) or control animals (91.2%). Moreover, the concentrations of serum testosterone and LH were significantly higher in the cadmium group than in any of the other groups."
Waalkes, M. P., S. Rehm, et al. (1988). "Cadmium carcinogenesis in male Wistar [Crl:(WI)BR] rats: dose-response analysis of tumor induction in the prostate and testes and at the injection site." Cancer Res **48**(16): 4656-63.	In a study of rats sc injected with $CdCl_2$, "Results indicate that $CdCl_2$ can induce preneoplastic lesions of the prostate that appear to develop into tumors only at doses well below those causing marked degeneration of the testes and atrophy of the prostate."
Waalkes, M. P., S. Rehm, et al. (1992). "Cadmium exposure in rats and tumours of the prostate." IARC Sci Publ(118): 391-400.	"In the first study, sc cadmium exposure increased prostatic tumour incidence only at doses below the threshold for cadmium induction of testicular

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	dysfunction (5.0 [n]mol/kg). In a second study, prostatic tumours were elevated at higher doses of cadmium (30 [n]mol/kg, sc) if testicular dysfunction was prevented by zinc treatment. Finally, dietary cadmium (25-200 µg/g) increased prostatic neoplastic lesions."
Waalkes, M. P., M. Anver, et al. (1999). "Carcinogenic effects of cadmium in the noble (NBL/Cr) rat: induction of pituitary, testicular, and injection site tumors and intraepithelial proliferative lesions of the dorsolateral prostate." Toxicol Sci **52**(2): 154-61.	"These results show that cadmium induces proliferative lesions in the dorsolateral prostate of the Noble rat, a model having a presumed relevance to human prostate cancers."
Waalkes, M. P., M. R. Anver, et al. (1999). "Chronic toxic and carcinogenic effects of oral cadmium in the Noble (NBL/Cr) rat: induction of neoplastic and proliferative lesions of the adrenal, kidney, prostate, and testes." J Toxicol Environ Health A **58**(4): 199-214.	"These results indicate that oral cadmium can induce proliferative lesions in the prostate and kidney of the Noble rat. The finding of proliferative lesions of dorsolateral prostate in rats has presumed relevance to human prostate cancers."
Wade, M. G., W. G. Foster, et al. (2002). "Effects of subchronic exposure to a complex mixture of persistent contaminants in male rats: systemic, immune, and reproductive effects." Toxicol Sci **67**(1): 131-43.	A study examined animals exposed to a mixture of organochlorines (2,3,7,8-tetrachlorodibenzo-*p*-dioxin [TCDD], polychlorinated biphenyls [PCBs],*p,p′*-dichlorodiphenoxydichloroethylene [*p,p′*-DDE],*p,p′*-dichlorodiphenoxytrichloroethane [*p,p′*-DDT], dieldrin, endosulfan, methoxychlor, hexachlorobenzene, and other chlorinated benzenes, hexachlorocyclohexane, mirex and heptachlor) as well as metals (lead and cadmium). The study authors concluded "These data suggest that additive or synergistic effects of exposure to contaminants resulting in residue levels representative of contemporary human tissue levels are unlikely to result in adverse effects on immune function or reproductive physiology in male rats."
Wang, W. X., H. Z. Liao, et al. (2004). "[Study on reproductive toxicity of subcbronic cadmium exposure in male rats]." Chung Kuo Kung Kung Wei Sheng **20**(5): 562-3.	The authors of a study in rats concluded, "Subchronic cadmium exposure can induce male sexual glands injury, especially to the testis. The mechanism may relate to peroxidative injury, the lack of protection effect of MT."
Wong, C. H., D. D. Mruk, et al. (2004). "Regulation of blood-testis barrier dynamics: an in vivo study." J Cell Sci **117**(Pt 5): 783-98.	In rats, "It was shown that the $CdCl_2$-induced disruption of the blood-testis barrier (BTB) associated with a transient induction in testicular TGF-beta$_2$ and TGF-beta$_3$ (but not TGF-beta$_1$) and the phosphorylated p38 mitogen activated protein (MAP) kinase, concomitant with a loss of occludin and zonula occludens-1 (ZO-1) from the BTB site in the seminiferous epithelium."
Wong, C. H., D. D. Mruk, et al. (2005). "Blood-testis barrier dynamics are regulated	"In this study, we have shown that by administering dimethylaminopurine, a c-Jun N-terminal protein

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by α_2-macroglobulin via the c-Jun N-terminal protein kinase pathway." Endocrinology **146**(4): 1893-908.	kinase (JNK) inhibitor, to the testis, JNK activity was blocked specifically and α_2-[macroglobulin] production was inhibited, worsening the cadmium chloride-induced damage to the epithelium."
Xu, C., J. E. Johnson, et al. (1996). "In vivo studies of cadmium-induced apoptosis in testicular tissue of the rat and its modulation by a chelating agent." Toxicology **107**(1): 1-8.	"Characteristic DNA migration patterns (laddering) provide evidence of apoptosis (programmed cell death) in testicular tissue of rats administered $CdCl_2$ at a level of 0.03 mmol/kg 48 h previously."
Xu, G., G. Zhou, et al. (1999). "Apoptosis and p53 gene expression in male reproductive tissues of cadmium exposed rats." Biometals **12**(2): 131-9.	In a study of rats sc injected with $CdCl_2$ "The results indicated that Cd can induce apoptosis in testes via p53-independent pathway. . . Since p53 is a tumor suppressor gene which can inhibit tumorigenesis, the consequence of a Cd-induced decrease of p53 in testes may have a relation to the known risk of Cd tumorigenesis in this tissue."
Xu, L., S. Wang, et al. (2000). "[Protection of metallothionein on the peroxidative injury in testis induced by cadmium]." Wei Sheng Yan Jiu **29**(2): 78-9.	In a study of rats, "It was concluded that MT might play an important role in protecting testis from oxidative damage. The toxicity of cadmium on male reproduction might be related to the unbalance of anti-oxidation system including MT."
Xu, L. C., S. Y. Wang, et al. (2000). "[Enzymology study of toxicity effects of cadmium on rat testis]." Chung Kuo Kung Kung Wei Sheng **16**(2): 119-20.	The authors of a rat study concluded "These results suggest cadmium toxicity on male reproductive system is associated to activities of testicular enzymes. ALP and LDH-X are sensitive biochemical endpoints reflecting cadmium toxicity on male reproductive system."
Xu, L. C., S. Y. Wang, et al. (2001). "Effects of cadmium on rat sperm motility evaluated with computer assisted sperm analysis." Biomed Environ Sci **14**(4): 312-7.	The authors of a rat study concluded, "Cadmium may reduce sperm motility at a dose far below the dose affecting sperm production at this time point. The motility of sperm is an early and sensitive endpoint for the assessment of cadmium toxicity on male reproduction."
Yadav, N., R. K. Dogra, et al. (2005). "Prevention of acute cadmium toxicity by Picroliv." Hum Exp Toxicol **24**(10): 529-36.	The authors of a rat study concluded, "Picroliv (12 mg/kg, oral) followed by a single dose of Cd as cadmium chloride ($CdCl_2$) (3 mg/kg, ip) revealed marked suppression of oxidative stress in liver and testes. . . Hepatic and testicular histopathological damage was also minimized."
Yan, H., C. E. Carter, et al. (1997). "Cadmium-induced apoptosis in the urogenital organs of the male rat and its suppression by chelation." J Toxicol Environ Health **52**(2): 149-68.	"Cadmium-induced apoptosis is shown to occur, in vivo, in several organs of the male Wistar rat urogenital system, 48 h after cadmium administration ip at a dose of 0.03 mmol/kg."
Yang, X. F., S. Y. Wang, et al. (2000). "Changes in tissue metals after cadmium intoxication and intervention with chlorpromazine in male rats." Biomed Environ Sci **13**(1): 19-25.	In study that examined cadmium induced effects in rat tissues including testes, it was concluded "These data suggest that the intervention of cadmium with tissue essential metals may play a role in cadmium toxicity in rats, and calmodulin inhibitors to some extent can reduce the adverse effect of cadmium by

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	decreasing the cadmium load in tissues and reversing the unbalance of essential metals."
Yang, H. S., D. K. Han, et al. (2006). "Effects of alpha-tocopherol on cadmium-induced toxicity in rat testis and spermatogenesis." J Korean Med Sci **21**(3): 445-51.	The authors of a study in rats concluded, "These findings indicate that α-tocopherol treatment can protect testicular tissue and preserve spermatogenesis from the detrimental effects of cadmium but its effectiveness is dependent on the dose of cadmium exposed."
Yiin, S. J., C. L. Chern, et al. (1999). "Cadmium induced lipid peroxidation in rat testes and protection by selenium." Biometals **12**(4): 353-9.	The authors of a rat study concluded "Data suggest that lipid peroxidation was associated with cadmium toxicity in testes and that the addition of selenium was found to be effective in attenuation of this effect."
Yoruk, M., M. Kanter, et al. (2003). "Localization of glycogen in the placenta and fetal and maternal livers of cadmium-exposed diabetic pregnant rats." Biol Trace Elem Res **96**(1-3): 217-26.	"It was concluded that Cd exposure during pregnancy might produce a glycogen localization in the placenta of diabetic rats."
Zahor, Z. and C. Povy sil (1979). "Cadmium necrosis in transplanted testicles as evidence for persistence of original vessels in the graft." Am J Pathol **97**(2): 223-33.	"The testicles of newborn rats were transplanted subcutaneously to the external ears of mature male rats. Four and 8 weeks later the hosts received a subtoxic dose of cadmium chloride. Forty-eight hours thereafter focal, but evidently cadmium-induced necroses occurred in the grafts."
Zhou, T., G. Zhou, et al. (1999). "Cadmium-induced apoptosis and changes in expression of p53, c-jun and MT-I genes in testes and ventral prostate of rats." Toxicology **142**(1): 1-13.	The authors of a study in rats reported, "It was observed that cadmium markedly induced apoptosis in the testes at the dose of 5 μmol/kg while 10 and 20 μmol/kg cadmium caused more necrosis than apoptosis. Apoptosis in the ventral prostate was markedly induced by all the doses of cadmium and there was an obvious time- and dose-dependent relationship between apoptotic index . . . and cadmium treatment."
Zhou, T., X. Jia, et al. (2004). "Cadmium at a non-toxic dose alters gene expression in mouse testes." Toxicol Lett **154**(3): 191-200.	In mice, sc injection with 5 μmol/kg $CdCl_2$ "did not produce overt histopathological changes, but clearly altered the expression of some genes that are likely to be important in toxicity responses."
Zhu, S. L., L. Chen, et al. (2002). "[Study of the Effect of Chronic CdCl2 Intoxication Sperm Production and Motility of Rats]." Shengzhi Yu Biyun **22**(1): 14-17.	In a study in which rats were given feed containing cadmium at 5 or 10 mg/kg feed, it was concluded, "Chronic cadmium exposure results in direct toxic effects on sperm production in testes and motility of sperm in caudal epididymides in rats."
	In vitro or ex vivo studies
Abe, T., S. Gotoh, et al. (1999). "Attenuation by glutathione of hsp72 gene expression induced by cadmium in cisplatin-resistant human ovarian cancer cells." Biochem Pharmacol **58**(1): 69-76.	"Our findings suggest that increased GSH biosynthesis in CDDP-resistant cancer cells may be involved in the attenuation of HSF activation by $CdCl_2$."
Abel, J., N. de Ruiter, et al. (1991).	Freshly isolated and purified rat Leydig cells and a

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"Comparative study on metallothionein induction in whole testicular tissue and isolated Leydig cells." Arch Toxicol **65**(3): 228-34.	murine tumor Leydig cell line respond to cadmium by increased synthesis of metallothionein and increased Mt-mRNA content.
Barfield, J. P., C. H. Yeung, et al. (2005). "The effects of putative K+ channel blockers on volume regulation of murine spermatozoa." Biol Reprod **72**(5): 1275-81.	In flow cytometric forward scatter measurements taken to indicate relative sperm size, exposure to 0.2 mM cadmium resulted in significantly higher forward scatter values.
Boadi, W. Y., J. Urbach, et al. (1992). "In vitro exposure to mercury and cadmium alters term human placental membrane fluidity." Toxicol Appl Pharmacol **116**(1): 17-23.	"In conclusion, exposure of placental cells to Hg and Cd caused accumulation of the metals in the membranes and lowered the membrane fluidity, which may affect membrane function and cause damage to the developing fetus."
Chu, Z. and S. M. Moenter (2006). "Physiologic regulation of a tetrodotoxin-sensitive sodium influx that mediates a slow afterdepolarization potential in gonadotropin-releasing hormone neurons: possible implications for the central regulation of fertility." J Neurosci **26**(46): 11961-73.	In GnRH neurons, cadmium affected function of calcium channels.
Chung, N. P. and C. Y. Cheng (2001). "Is cadmium chloride-induced inter-sertoli tight junction permeability barrier disruption a suitable in vitro model to study the events of junction disassembly during spermatogenesis in the rat testis?" Endocrinology **142**(5): 1878-88.	"Based on these results, it is apparent that $CdCl_2$-induced inter-Sertoli TJ disassembly is a potential in vitro model to study the events of junction disassembly."
Dalton, T. P., L. He, et al. (2005). "Identification of mouse SLC39A8 as the transporter responsible for cadmium-induced toxicity in the testis." Proc Natl Acad Sci U S A **102**(9): 3401-6.	"We show here that ZRT-, IRT-like protein (ZIP)8 expression in cultured mouse fetal fibroblasts leads to a >10-fold increase in the rate of intracellular Cd influx and accumulation and 30-fold increase in sensitivity to Cd-induced cell death."
Fiorini, C., A. Tilloy-Ellul, et al. (2004). "Sertoli cell junctional proteins as early targets for different classes of reproductive toxicants." Reprod Toxicol **18**(3): 413-21.	In the SerW3 Sertoli cell line, cadmium chloride ". . . affected intercellular junctions by either reducing the amount or inducing aberrant intracellular localization of these membranous proteins."
Foote, R. H. (1999). "Fertility of rabbit sperm exposed in vitro to cadmium and lead." Reprod Toxicol **13**(6): 443-9.	In a study examining fertility of rabbit sperm exposed to Cd^{2+} or Pb^{2+} in vitro, ". . . . neither Cd^{2+} nor Pb^{2+} affected hyperactivation, or presumably associated capacitation. . . No effect of 0.1 mM Cd^{2+} on fertilizing ability of sperm was found (75% fertilization with control sperm and 78% with treated sperm)."
Leoni, G., L. Bogliolo, et al. (2002). "Influence of cadmium exposure on in vitro ovine gamete dysfunction." Reprod Toxicol **16**(4): 371-77.	"The results suggest that in vitro cadmium at the lowest dose tested affects the physiological function of both ovine gametes but at higher dose tested can compromise cell viability."
Milosevic, M., S. Petrovic, et al. (2005). "Effects of metal ions on plasma membrane Mg2+-atpase in rat uterus and ovaries." Ann	"The in vitro effects of cadmium and mercury were investigated on the Mg^{2+}-ATPase activity of plasma membranes from the rat ovary and uterus.

Reference	Findings/Conclusions
N Y Acad Sci **1048**: 445-8.	ATP hydrolyzing activities were significant and dose-dependent-inhibited in both plasma membrane preparations by both metals."
Mlynarcikova, A., S. Scsukova, et al. (2004). "Inhibitory effect of cadmium and tobacco alkaloids on expansion of porcine oocyte-cumulus complexes." Cent Eur J Public Health **12 Suppl**: S62-4.	In porcine oocyte-cumulus complexes, cadmium suppressed FSH-induced cumulus expansion and inhibited synthesis and accumulation of hyaluronic acid in the cell/matrix compartment.
Piasek, M. and J. W. Laskey (1999). "Effects of in vitro cadmium exposure on ovarian steroidogenesis in rats." J Appl Toxicol **19**(3): 211-7.	Authors of in vitro study of ovarian cells concluded "Cadmium appears to interfere with the ovarian steroidogenic pathway in rats at more than one site."
Priya, P. N., A. Pillai, et al. (2004). "Effect of simultaneous exposure to lead and cadmium on gonadotropin binding and steroidogenesis on granulosa cells: an in vitro study." Indian J Exp Biol **42**(2): 143-8.	In a study in which rat granulosa cells were exposed to cadmium or lead it was concluded, "These results suggest that both Pb and Cd can cause a reduction in LH and FSH binding, which significantly alters steroid production in vitro and exerts a direct influence on granulosa cell function."
Smida, A. D., X. P. Valderrama, et al. (2004). "Cadmium stimulates transcription of the cytochrome p450 side chain cleavage gene in genetically modified stable porcine granulosa cells." Biol Reprod **70**(1): 25-31.	"We conclude that Cd^{2+} has a dual action in stable porcine granulosa cells: low concentrations activate, whereas high concentrations inhibit, expression of the $p450_{scc}$ gene and progesterone synthesis."
Sorenson, D. R. and M. Brabec (2003). "The response of adult rat sertoli cells, immortalized by a temperature-sensitive mutant of SV40, to 1,2-dinitrobenzene, 1,3-dinitrobenzene, 2,4-dinitrotoluene, 3,4-dinitrotoluene, and cadmium." Cell Biol Toxicol **19**(2): 107-19.	"From these observations, we conclude that this cell line can serve as a model for studying toxic mechanisms in adult Sertoli cells."
Vrsansk, aacute, et al. (2003). "Components of cigarette smoke inhibit expansion of oocyte-cumulus complexes from porcine follicles." Physiol Res **52**(3): 383-7.	In oocyte-cumulus complexes (OCC) isolated from large antral porcine follicles, "there were comparable inhibitory effects of cadmium and nicotine on the synthesis and accumulation of hyaluronic acid in the cell/matrix compartment of OCC. The inhibitory effect of tested compounds on the cumulus expansion was accompanied by decreased progesterone synthesis by cumulus cells during 42 h incubation of OCC with FSH."
Yang, J. M., M. Arnush, et al. (2003). "Cadmium-induced damage to primary cultures of rat Leydig cells." Reprod Toxicol **17**(5): 553-60.	"These results indicate that cadmium is directly toxic to primary Leydig cells, and that the decreased percentage of normal cells and the increased level of DNA damage in cadmium-exposed Leydig cells may be responsible for decreased testosterone secretion."
Yang, P. M., S. J. Chiu, et al. (2004). "Effect of cadmium on cell cycle progression in Chinese hamster ovary cells." Chem Biol Interact **149**(2-3): 125-36.	"Cell cycle progression was retarded as a function of Cd concentration."
Yuan, C., M. Kadiiska, et al. (2000). "Possible	In Chinese hamster ovary cells, ". . . Cd may have a

Reference	Findings/Conclusions
role of caspase-3 inhibition in cadmium-induced blockage of apoptosis." Toxicol Appl Pharmacol **164**(3): 321-9.	generalized inhibitory effect on apoptosis, possibly by inhibiting caspase-3. Inhibition of apoptosis by Cd may allow a greater portion of genetically damaged cells to survive, or give selective growth advantages, and has implications as a potential nongenotoxic mechanism of Cd carcinogenesis."

C. Human Exposure

A total of 59 exposure studies were identified and 33 of those were published in 1999 or later. I majority of the more recent studies reported cadmium levels in biological samples such as blood, cord blood, placenta, milk, hair, and nails. Some of the studies examined cadmium levels in individuals who smoked or lived in proximity from unspecified mining operations. One study reported cadmium levels in infant foods. A limited number studies estimated cadmium intake and those values ranged from 0.1 to 3.9 µg/kg bw/week (0.014–0.56 µg/kg bw/day). As noted above, I WHO had estimated human intake at 1–4 µg/kg bw/day. Exposure studies are summarized in Table 6

Table 6. Exposure Studies

Reference	Findings/Conclusions
Abadin, H. G., B. F. Hibbs, et al. (1997). "Breast-feeding exposure of infants to cadmium, lead, and mercury: a public health viewpoint." Toxicol Ind Health **13**(4): 495-517.	Cadmium was detected in human milk at < 1 µg/L.
Al-Saleh, I., N. Shinwari, et al. (2003). "Heavy metal concentrations in the breast milk of Saudi women." Biol Trace Elem Res **96**(1-3): 21-37.	Cadmium was measured at 1.732 µg/L in the milk of Saudi mothers.
Anwar, M. (2005). "Arsenic, cadmium and lead levels in hair and toenail samples in Pakistan." Environ Sci **12**(2): 71-86.	"I mean hair and toenail cadmium levels in the present study were 0.08 ppm and 0.05 ppm, respectively. I correlation coefficient between log-transformed values of hair and toenail cadmium levels was 0.17 (P = 0.034)."
Ataniyazova, O. A., R. A. Baumann, et al. (2001). "Levels of certain metals, organochlorine pesticides and dioxins in cord blood, maternal blood, human milk and some commonly used nutrients in the surroundings of the Aral Sea (Karakalpakstan, Republic of Uzbekistan)." Acta Paediatr **90**(7): 801-8.	"I levels of metals in cord and maternal blood were consistent with concentrations observed in European countries."
Baranowska, I. (1995). "Lead and cadmium in human placentas and maternal and neonatal blood (in a heavily polluted area) measured by graphite furnace atomic absorption spectrometry." Occup Environ Med **52**(4): 229-32.	". . . the following mean concentrations of cadmium and lead were found: in venous blood Pb = 72.50 ng/mL, Cd = 4.90 ng/mL; in placenta Pb = 0.50 µg/g, Cd = 0.11 µg/g; in cord blood Pb = 38.31 ng/mL, Cd = 1.13 ng/mL."
Bonithon-Kopp C, Huel G, Grasmick C, Sarmini H, Moreau T. Effects of pregnancy	There is a significant decrease of blood cadmium during the first trimester of

Reference	Findings/Conclusions
on the inter-individual variations in blood levels of lead, cadmium and mercury. Biol Res Pregnancy Perinatol. 1986;7(1):37-42.	pregnancy.
Bussières D, et al. (2004). "Exposure of a Cree population living near mine tailings in northern Quebec (Canada) to metals and metalloids." Arch Environ Health **59**(12): 732-41.	"Blood cadmium increased with age and smoking ($R^2 = 0.61$). No influence of mine residues was observed among residents of Oujé-Bougoumou, but lifestyle exposure associations were noted for both communities."
Butler Walker, J., J. Houseman, et al. (2006). "Maternal and umbilical cord blood levels of mercury, lead, cadmium, and essential trace elements in Arctic Canada." Environ Res **100**(3): 295-318.	"[Geometric mean] blood Cd in moderate smokers (1–8 cigarettes/day) and in heavy smokers (> 8 cigarettes/day) was 7.4-fold higher and 12.5-fold higher, respectively, than in nonsmokers."
Casey CE, Robinson MF. Copper, manganese, zinc, nickel, cadmium and lead in human foetal tissues. Br J Nutr. 1978 May;39(3):639-46.	"Cd was detected in most of the tissue samples and concentrations were within the range 0.01-0.58 microgram/g..."
Dabeka, R. W. and A. D. McKenzie (1988). "Lead Cadmium Levels in Commercial Infant Foods and Dietary Intake by Infants 0-1-Year-Old." Food Addit Contam **5**(3): 333-342.	No abstract available.
Eklund, G. and A. Oskarsson (1999). "Exposure of cadmium from infant formulas and weaning foods." Food Addit Contam **16**(12): 509-19.	"The mean weekly intakes of dietary cadmium were estimated to vary between 0.10 and 3.05 µg/kg body weight of the child, if the recommended amount of formula were to be consumed at the recommended age, and if the child were of average weight. This estimation however does not include the contribution of cadmium from drinking water."
El-Agha, O. and I. G. Gokmen (2002). "Smoking habits and cadmium intake in Turkey." Biol Trace Elem Res **88**(1): 31-43.	"The blood cadmium concentration of female smokers were found to be highest (mean: 2.62 ± 0.72; median: 0.90 ng/mL Cd) and that of nonsmokers lowest (mean: 0.67 ± 0.57; median: 0.44 ng/mL Cd)."
Falcon, M., P. Vinas, et al. (2002). "Environmental exposures to lead and cadmium measured in human placenta." Arch Environ Health **57**(6): 598-602.	"The authors found significantly higher lead and cadmium levels in placentas of women living in urban-industrial areas than in placentas of women living in rural areas."
Fiala, J., D. Hruba, et al. (1998). "Cadmium and zinc concentrations in human placentas." Cent Eur J Public Health **6**(3): 241-8.	"Cadmium and zinc levels in placentae of 688 women who delivered their children in two university hospitals in Brno and in the regional hospital in Znojmo during January-June 1992 were determined using AAS analytical method. Average value of zinc (54.6 micrograms/g) and cadmium (18.02 ng/g) concentrations found out in our file are in accord with those ones

Reference	Findings/Conclusions
	reported in literature."
Florek, E., W. Piekoszewski, et al. (2004). "[Determination of cadmium in urine of tobacco smoking pregnant women]." Przegl Lek **61**(10): 1109-12.	"Cadmium concentration in smokers was 1.6 ± 2.6 ng/mL and ranged from 0 to 11.5 ng/mL. In urine of woman who do not smoke and are not expos[ed] to ETS, [it] was 1.1 ± 2.2 ng/mL, [] range 0–2.5 ng/mL and was not statistically different from concentration of cadmium in urine of smoking pregnant woman. In any one non-smoking woman, concentration of cadmium was not higher than 5 ng/mL, but in 11.8% of smoking women this level was exceeded."
Gelinas Y, Lafond J, Schmit JP. Multielemental analysis of human fetal tissues using inductively coupled plasma-mass spectrometry. Biol Trace Elem Res. 1997 Winter;59(1-3):63-74.	Cadmium was measured in fetal tissues. Results were not given in the abstract.
Gross, S. B., D. W. Yeager, et al. (1976). "Cadmium in liver, kidney, and hair of humans, fetal through old age." J Toxicol Environ Health **2**(1): 153-67.	"Cadmium concentrations were measured in the liver, kidney, and hair of 107 individuals from the Cincinnati area."
Honda, R., K. Tawara, et al. (2003). "Cadmium exposure and trace elements in human breast milk." Toxicology **186**(3): 255-9.	In Japanese mothers examined 5–8 days post-partum, "Geometrical mean Cd concentrations were 0.28 (geometrical standard deviation = 1.82) μg/l in breast milk and 1.00 (1.93) μg/g creatinine in urine."
Kantola, M., R. Purkunen, et al. (2000). "Accumulation of cadmium, zinc, and copper in maternal blood and developmental placental tissue: differences between Finland, Estonia, and St. Petersburg." Environ Res **83**(1): 54-66.	"The data demonstrate an inverse accumulation of Zn and Cd throughout the pregnancy in the placenta and maternal blood samples. Zn may act as a positive marker or even an enzymatic enhancement for the human placental vital functions. Smoking, parity, age, and especially the place of residence affect the Cd, Zn, and Cu contents and ratios in placenta and mother's blood."
Kantola, M., R. Purkunen, et al. (2004). "Selenium in pregnancy: is selenium an active defective ion against environmental chemical stress?" Environ Res **96**(1): 51-61.	"When the cadmium concentrations were high in placenta, as in smokers, the transfer of selenium from blood to placenta was increased, decreasing the selenium levels in blood. On the other hand, the high selenium concentrations in blood were connected to lower cadmium concentrations in placenta also in nonsmokers."
Krachler M, Li FS, Rossipal E, Irgolic KJ. Changes in the concentrations of trace elements in human milk during lactation. J Trace Elem Med Biol. 1998 Nov;12(3):159-76.	There is no information on cadmium in the abstract except that it was measured in human milk.
Krachler, M., E. Rossipal, et al. (1999). "Trace	"Concentrations of the toxic elements Cd and

Reference	Findings/Conclusions
element transfer from the mother to the newborn--investigations on triplets of colostrum, maternal and umbilical cord sera." Eur J Clin Nutr **53**(6): 486-94.	Pb decreased in the order colostrum (Pb 2.6 µg/L; Cd 0.6 µg/L), maternal sera (0.8 µg/L; 0.3 µg/L), umbilical cord sera (0.4 µg/L; 0.2 µg/L)."
Krachler, M., E. Rossipal, et al. (1999). "Concentrations of trace elements in arterial and venous umbilical cord sera." Trace Elements And Electrolytes **16**(1): 46-52.	The study may report cadmium levels in newborns.
Kuhnert, P. M., P. Erhard, et al. "Analysis Of Cadmium In Whole Blood And Placental Tissue By Furnace Atomic Absorption Spectroscopy." Trace Substances in Environmental Health XVI, pages: 19821982.	"Cadmium concentrations in the blood and placental tissue of the nonsmokers were 2.2 and 13.7 ng/g, respectively. The corresponding cadmium concentrations in the smokers were 3.5 and 18.1 ng/g, respectively."
Kuhnert, P. M., B. R. Kuhnert, et al. (1982). "Cadmium levels in maternal blood, fetal cord blood, and placental tissues of pregnant women who smoke." Am J Obstet Gynecol **142**(8): 1021-5.	"On the basis of the Cd data on cord blood and placental tissues, the fetuses of pregnant women who smoke apparently receive very little additional exposure to Cd; however, this does not lessen concern for the fetus."
Lagerkvist BJ, Nordberg GF, Soderberg HA, Ekesrydh S, Englyst V, Gustavsson M, Gustavsson NO, Wiklund DE. Placental transfer of cadmium. IARC Sci Publ. 1992;(118):287-91.	"There were no significant differences in cadmium levels, as between exposed women and controls, and blood levels were low, even in an industrial area. The most important environmental exposure seemed to be smoking. There was... a significant increase in cadmium levels during pregnancy among non-smoking women in both groups...The cadmium levels in the newborn babies were about 70% of those in the mothers."
Lagerkvist BJ, Soderberg HA, Nordberg GF, Ekesrydh S, Englyst V. Biological monitoring of arsenic, lead and cadmium in occupationally and environmentally exposed pregnant women. Scand J Work Environ Health. 1993;19 Suppl 1:50-3.	"There were no significant differences in the [blood] Cd levels between the smelter and reference towns, except for non- and ex-smokers at the onset of pregnancy. No difference between the two areas was seen among the smokers, whose cadmium levels were twice those of non- and ex-smokers."
Lauwerys, R., J. P. Buchet, et al. (1978). "Placental transfer of lead, mercury, cadmium, and carbon monoxide in women. I. Comparison of the frequency distributions of the biological indices in maternal and umbilical cord blood." Environ Res **15**(2): 278-89.	In a study examining cadmium, lead, and mercury levels in pregnant women in Belgium it was noted, "A barrier of some importance was demonstrated for cadmium. Statistical correlations bear out these contentions; there was a lower correlation between maternal blood cadmium and umbilical blood cadmium concentrations (*r* + .38) than for the other 2 metals (*r* .6)."
Leotsinidis, M., A. Alexopoulos, et al. (2005). "Toxic and essential trace elements in human milk from Greek lactating women: association with dietary habits and other	Colostrum from Greek women contained Cd at 0.190 ± 0.150 µg/L. "Cadmium and lead weekly intakes were found to be below the Maximum Tolerable Weekly Intakes as they

Reference	Findings/Conclusions
factors." Chemosphere **61**(2): 238-47.	have been established for infants by WHO or NRC."
Loiacono NJ, Graziano JH, Kline JK, Popovac D, Ahmedi X, Gashi E, Mehmeti A, Rajovic B. Placental cadmium and birthweight in women living near a lead smelter. Arch Environ Health. 1992 Jul-Aug;47(4):250-5.	"A higher mean placental Cd concentration... was found in [smelter-]exposed women (n = 106), compared with those who were not exposed (n=55); the observed Cd concentrations were comparable to concentrations reported previously for smoking and nonsmoking women..."
Mokhtar, G., E. Hossny, et al. (2002). "In utero exposure to cadmium pollution in Cairo and Giza governorates of Egypt." East Mediterr Health J **8**(2-3): 254-60.	In Egypt, "The serum cadmium levels of mothers ranged from 0.4 to 2.2 µg/L (mean 0.73 µg/L) and of infants from 0.2 to 1.5 µg/L (mean 0.66 µg/L). Infant cadmium levels were about 70% of maternal levels in most pairs. Serum cadmium was significantly higher in mothers and babies passively exposed to tobacco smoke. Five-minute Apgar scores were negatively correlated with cord blood cadmium levels."
Moreno-Rojas, R., P. J. Sanchez-Segarra, et al. (2001). "Cadmium content in infant formulas. Toxicological evaluation." Nahrung **45**(5): 357-9.	The mean concentrations of cadmium were 1.97 ± 0.84, 1.86 ± 0.65, and 2.98 ± 2.59 µg/kg for "beginner," "continuation," and "special infant formulas," respectively.
Nishijo, M., K. Tawara, et al. (2004). "Cadmium and nutritional intake in pregnant Japanese women." Toxicol Lett **148**(3): 171-6.	In a study of Japanese women, the study authors concluded, "These results indicate that Cd exposure levels of pregnant women with low energy intake, especially less fat intake, were higher than those of women with more energy and fat intake. In particular, blood Cd may be affected by protein and iron intake in pregnant women with increased [] nutrient demand."
Odland, J. O., E. Nieboer, et al. (1999). "Self-reported ethnic status of delivering women, newborn body mass index, blood or urine concentrations of toxic metals, and essential elements in sera of Norwegian and Russian Arctic populations." Int J Circumpolar Health **58**(1): 4-13.	In Norwegian and Russian populations, "Blood cadmium concentrations were strongly related to smoking frequency."
Oldereid, N. B., Y. Thomassen, et al. (1993). "Concentrations of lead, cadmium and zinc in the tissues of reproductive organs of men." J Reprod Fertil **99**(2): 421-5.	"Unlike lead, the tissue concentrations of cadmium increased with increasing age in all of the reproductive organs examined. Of these, the epididymides and seminal vesicles contained the highest concentrations. . . The age-dependent increase in testicular cadmium did not become apparent until after the fourth decade, when any potentially deleterious impact on male fertility has less relevance"
Oldereid, N. B., Y. Thomassen, et al. (1994).	"It appears that tobacco consumption may have

Reference	Findings/Conclusions
"Seminal plasma lead, cadmium and zinc in relation to tobacco consumption." Int J Androl **17**(1): 24-8.	to exceed 20 cigarettes/day before a noticeable increase in seminal cadmium can be recorded."
Oskarsson, A., A. Widell, et al. (2004). "Cadmium in food chain and health effects in sensitive population groups." Biometals **17**(5): 531-4.	"The contribution of Cd from locally produced food to the total dietary intake in humans was relatively low and varied. . ."
Ostrea, E. M., Jr., E. Tan, et al. (1998). "Exposure to environmental pollutants adversely affects fetal outcome." Pediatr Res **43**(4 Pt 2).	"By meconium analysis, we have quantitated fetal exposure . . . to heavy metals (lead, mercury and cadmium) by atomic absorption spectrometry (mg/g meconium). Subjects consisted of 200 mother/infants dyads from 7 nurseries in Manila."
Radisch, B., W. Luck, et al. (1987). "Cadmium concentrations in milk and blood of smoking mothers." Toxicol Lett **36**(2): 147-52.	"The median blood and milk concentrations in nonsmokers were 0.54 and 0.07 μg/L, respectively; these values rose to 1.54 and 0.16 μg/L in blood and milk of mothers smoking more than 20 cigarettes per day. Milk concentrations of cadmium were approximately 10% of corresponding blood concentrations. The cadmium exposure of infants nursed by nonsmoking as well as by smoking mothers was far below the exposure of formula-fed infants or the provisional acceptable weekly intake level set by the WHO."
Razagui, I. B. and I. Ghribi (2005). "Maternal and neonatal scalp hair concentrations of zinc, copper, cadmium, and lead: relationship to some lifestyle factors." Biol Trace Elem Res **106**(1): 1-28.	In hair samples from mothers and infants Cd was measured at "0.49 μg/g (0.47–0.69 μg/g) in the mothers and 0.57 μg/g (0.55–0.86 μg/g) in the neonates. . . . Cigarette smoking . . . was associated with lower Zn and higher Cd and Pb concentrations and in lower Zn/Cd and Zn/Pb molar concentration ratios."
Roca de Togores, M., Farr, et al. (1999). "Cadmium and lead in infant cereals--electrothermal-atomic absorption spectroscopic determination." Sci Total Environ **234**(1-3): 197-201.	In infant cereals from Spain, "The cadmium and lead contents of milk-free infant cereals range from 6.6 to 35.8 ng/g and from 36.1 to 305.6 ng/g, respectively, while the ranges corresponding to milk-added infant cereals are 2.9–40.0 ng/g for cadmium and 53.5–598.3 ng/g for lead."
Roels, H. A., J. P. Buchet, et al. (1979). "[Evaluation of the exposure of different groups of the Belgian population (fetus, children, adult men and women) to heavy metals]." Arch Belg Med Soc **37**(9-10): 589-625.	Abstract not available.
Saadi, E. and R. Sikorski (1998). "[Levels of cadmium in pubic hair of women with threatened abortion and in full-term	"The concentrations of cadmium in pubic hair were elevated in women living in town and were statistically significant higher in

Reference	Findings/Conclusions
pregnancy]." Ginekol Pol **69**(12): 878-83.	smokers in comparison to nonsmokers."
Salvato, N. (1997). "Cadmium analysis in baby foods." Annali Di Chimica **87**(5-6): 295-303.	Measurement of cadmium levels in samples of liver, meat, fish, rice and cocoa powder alone or as part of infant foods reported "Concentrations of cadmium are higher in liver, with values exceeding the set limit of 0.09 mg/kg"
Satarug, S., P. Ujjin, et al. (2004). "Influence of body iron store status and cigarette smoking on cadmium body burden of healthy Thai women and men." Toxicol Lett **148**(3): 177-85.	"Thus, iron status and cigarette smoking were found to be determinants of Cd body burden in young adult Thai women and men."
Schrey, P., J. Wittsiepe, et al. (2000). "Dietary intake of lead, cadmium, copper and zinc by children from the German North Sea island Amrum." Int J Hyg Environ Health **203**(1): 1-9.	In German children, the median cadmium intake was reported at 2.7 µg/(kg bw × week) [range: 1.7–4.4 µg/(kg bw × week)].
Schulte-Lobbert, F. J. and G. Bohn (1977). "Determination of cadmium in human milk during lactation." Arch Toxicol **37**(2): 155-7.	"The levels in colostrum were some 50–65% higher than in transitional and mature milk."
Sharma, R. and S. Pervez (2005). "Toxic metals status in human blood and breast milk samples in an integrated steel plant environment in Central India." Environ Geochem Health **27**(1): 39-45.	In India, "The order of occurrence of these metals in blood and milk samples thus found is Mn > Pb > Hg > As > Cd."
Silberstein, T., M. Hallak, et al. (2001). "Toxic trace elements (TE) can be found in the maternal and fetal compartments." Am J Obstet Gynecol **184**(1).	Levels of cadium in amniotic fluid were equilibrated with levels in maternal blood.
Telisman S, Jurasovic J et al. Cadmium in the blood and seminal fluid of nonoccupationally exposed adult male subjects with regard to smoking habits. Int Arch Occup Environ Health. 1997;70(4):243-8.	"Significant correlations were found between smoking habits, i.e., the number of cigarettes per day, and an increase in [blood] Cd in smokers...and in all 120 subjects...as well as between smoking habits and an increase in [seminal fluid] Cd in smokers."
Truska, P., L. Rosival, et al. (1989). "Blood and placental concentrations of cadmium, lead, and mercury in mothers and their newborns." J Hyg Epidemiol Microbiol Immunol **33**(2): 141-7.	"The mean plasma values (arithmetic mean) of cadmium. . . in industrial area was 0.53 . . . [µg/dL] in maternal blood and 0.30 . . . [µg/dL] in cord blood."
Tsukahara, T., T. Ezaki, et al. (2003). "No significant effect of iron deficiency on cadmium body burden or kidney dysfunction among women in the general population in Japan." Int Arch Occup Environ Health **76**(4): 275-81.	"The current level of iron deficiency among women in the general population in Japan may not induce significant increase in Cd body burden or Cd-induced tubular dysfunction."
Turconi, G., M. Guarcello, et al. (2004). "Evaluation of xenobiotics in human milk and ingestion by the newborn--an epidemiological survey in Lombardy	Cadmium values were below detection limits (2 µg/L) in 87.4% of breast milk samples in Italy.

Reference	Findings/Conclusions
(Northern Italy)." Eur J Nutr **43**(4): 191-7.	
Turker, G., K. Ergen, et al. (2006). "Concentrations of toxic metals and trace elements in the meconium of newborns from an industrial city." Biol Neonate **89**(4): 244-50.	In meconium samples, the median concentration (interquartile range) of cadmium was 2.3 (55.6) µg/g dry wt.
Ursinyova, M. and V. Masanova (2005). "Cadmium, lead and mercury in human milk from Slovakia." Food Addit Contam **22**(6): 579-89.	The average concentrations of Cd in milk samples taken on the 4th postpartum day was 0.43 µg/kg and that in infant formula (n = 10) was 0.40 µg/kg. . . the calculated average dietary intake of Cd in newborn babies from human milk and from infant formula was far lower than the appropriate provisional tolerable weekly intake values recommended by WHO/FAO.
Varga, B., B. Zsolnai, et al. (1993). "Age dependent accumulation of cadmium in the human ovary." Reprod Toxicol **7**(3): 225-8.	"Cd levels in the ovary increased linearly between 30 and 65 years of age."
Wilhelm, M., J. Wittsiepe, et al. (2002). "Dietary intake of cadmium by children and adults from Germany using duplicate portion sampling." Sci Total Environ **285**(1-3): 11-9.	In a study of cadmium intake in the German population, it was concluded "Compared to the provisional tolerable weekly intake (PTWI) of 7 µg/(kg bw × week) proposed by the WHO, the dietary intake of cadmium was rather high. The geometric mean and maximum intake values for the different groups ranged between 24.3–55.7% and 62.7–120.7 respectively of the PTWI. We therefore conclude, that the cadmium exposure of the population needs to be reduced in order to minimize the risk of adverse health effects related to this metal."
Wilhelm, M., J. Wittsiepe, et al. (2005). "Consumption of homegrown products does not increase dietary intake of arsenic, cadmium, lead, and mercury by young children living in an industrialized area of Germany." Sci Total Environ **343**(1-3): 61-70.	In a study of cadmium intake by German children, the geometric mean weekly intake was 2.3 µg/(kg bw × week) and corresponded to the percentage of the provisional tolerable weekly intake (PTWI) as 32%.
Yapici, G., G. Can, et al. (2006). "Lead and cadmium exposure in children living around a coal-mining area in Yatagan, Turkey." Toxicol Ind Health **22**(8): 357-62.	In a coal-mining area in Turkey, "The mean blood cadmium level of all children was 1.31 ± 0.72 µg/dL. The blood cadmium level was found to be >0.5 µg/dL, which is considered to be toxic, in 85% of all children."
Zadorozhnaja, T. D., R. E. Little, et al. (2000). "Concentrations of arsenic, cadmium, copper, lead, mercury, and zinc in human placentas from two cities in Ukraine." J Toxicol Environ Health A **61**(4): 255-63.	In placental samples from women in the Ukraine, "Cadmium was detected in almost all samples, with a median of 5.2 ng/g."
Zenzes, M. T., S. Krishnan, et al. (1995).	Cadmium was detected in follicular fluid.

Reference	Findings/Conclusions
"Cadmium accumulation in follicular fluid of women in in vitro fertilization-embryo transfer is higher in smokers." Fertil Steril **64**(3): 599-603.	

D. Other Relevant Studies

The literature search identified additional studies that could be relevant to a cadmium evaluation. Thirty-two toxicokinetics study provide information on topics such exposures to fetuses or sucking animals, bioavailability of cadmium from infant diets, and exposure of reproductive organs. A total of 44 reviews were also identified. References for toxicokinetics studies and reviews are listed below.

Toxicokinetics:

Ahokas, R. A., W. K. Herman, et al. (1976). "Placental Accumulation of Cadmium." Gynecol Invest **7**(1/2): 66-67.

Ahokas, R. A. and J. R. Dilts Pv (1977). "Cadmium Uptake in the Rat Embryo as a Function of Gestational Age." Gynecol Invest **8**: 46-47.

Ahokas, R. A. and P. V. Dilts, Jr. (1979). "Cadmium uptake by the rat embryo as a function of gestational age." Am J Obstet Gynecol **135**(2): 219-22.

Boadi, W. Y., S. Yannai, et al. (1991). "Transfer and accumulation of cadmium, and the level of metallothionein in perfused human placentae." Arch Toxicol **65**(4): 318-23.

Brako, E. E., A. K. Wilson, et al. (2003). "Cadmium pathways during gestation and lactation in control versus metallothoinein 1,2-knockout mice." Toxicol Sci **71**(2): 154-63.

Buchet, J. P., H. Roels, et al. (1978). "Placental transfer of lead, mercury, cadmium, and carbon monoxide in women. II. influence of some epidemiological factors on the frequency distributions of the biological indices in maternal and umbilical cord blood." Environ Res **15**(3): 494-503.

Cerulli, N., L. Campanella, et al. (2006). "Determination of Cd, Cu, Pb and Zn in neoplastic kidneys and in renal tissue of fetuses, newborns and corpses." J Trace Elem Med Biol **20**(3): 171-9.

Chan, H. M. and M. G. Cherian (1993). "Mobilization of hepatic cadmium in pregnant rats." Toxicol Appl Pharmacol **120**(2): 308-14.

Chatterjee, M. S., M. Abdel-Rahman, et al. (1988). "Amniotic fluid cadmium and thiocyanate in pregnant women who smoke." J Reprod Med **33**(5): 417-20.

Danielsson, B. R. (1984). "Placental transfer and fetal distribution of cadmium and mercury after treatment with dithiocarbamates." Arch Toxicol **55**(3): 161-7.

Danielsson, B. R. G., L. Dencker, et al. (1984). "Accumulation Of Toxic Metals In Male Reproduction Organs." Archives of Toxicology, Supplement **7**: 177-180.

Eklund, G., K. P. Grawe, et al. (2001). "Bioavailability of cadmium from infant diets in newborn rats." Arch Toxicol **75**(9): 522-30.

Eklund, G., A. Linden, et al. (2003). "Bioavailability of cadmium from in vitro digested infant food studied in Caco-2 cells." J Agric Food Chem **51**(14): 4168-74.

Eklund, G., J. Tallkvist, et al. (2004). "A piglet model for studies of gastrointestinal uptake of cadmium in neonates." Toxicol Lett **146**(3): 237-47.

Ferm, V. H., D. P. Hanlon, et al. (1969). "The permeability of the hamster placenta to radioactive cadmium." J Embryol Exp Morphol **22**(1): 107-13.

Ferm, V. H. and D. P. Hanlon (1974). "Placental transfer of zinc in the Syrian hamster during early embryogenesis." J Reprod Fertil **39**(1): 49-52.

Haouem, S. and R. Sakly (2005). "Lactational transfer of cadmium from Meriones shawi shawi mothers to their pups and its effects on calcium homeostasis and bone calcium in pups." Ann Nutr Metab **49**(5): 296-9.

King, L. M., W. A. Banks, et al. (1999). "Differences in cadmium transport to the testis, epididymis, and brain in cadmium-sensitive and -resistant murine strains 129/J and A/J." J Pharmacol Exp Ther **289**(2): 825-30.

King, L. M., W. A. Banks, et al. (2000). "Differential zinc transport into testis and brain of cadmium-sensitive and -resistant murine strains." J Androl **21**(5): 656-63.

Lau, J. C., M. G. Joseph, et al. (1998). "Role of placental metallothionein in maternal to fetal transfer of cadmium in genetically altered mice." Toxicology **127**(1-3): 167-78.

Leazer, T. M., Y. Liu, et al. (2002). "Cadmium absorption and its relationship to divalent metal transporter-1 in the pregnant rat." Toxicol Appl Pharmacol **185**(1): 18-24.

Levin, A. A., R. W. Kilpper, et al. (1987). "Fetal toxicity of cadmium chloride: the pharmacokinetics in the pregnant Wistar rat." Teratology **36**(2): 163-70.

Liu, Y., J. Liu, et al. (2001). "Metallothionein-null and wild-type mice show similar cadmium absorption and tissue distribution following oral cadmium administration." Toxicol Appl Pharmacol **175**(3): 253-9.

Olsson, I. M., S. Jonsson, et al. (2001). "Cadmium and zinc in kidney, liver, muscle and mammary tissue from dairy cows in conventional and organic farming." J Environ Monit **3**(5): 531-8.

Perez-Coll, C. S., J. Herkovits, et al. (1999). "Metallothionein induction and cadmium uptake in Bufo arenarum embryos following an acclimation protocol." Environmental Pollution **106**(3): 443-448.

Roels, H., G. Hubermont, et al. (1978). "Placental Transfer of Lead, Mercury, Cadmium, and Carbon Monoxide in Women. III. Factors Influencing the Accumulation of Heavy Metals in the Placenta and the Relationship Between Metal Concentration in the." Environmental Research **16**:

236-247.

Rohrer, S. R., S. M. Shaw, et al. (1978). "The maternal distribution and placental transfer of cadmium in zinc deficient rats." Bull Environ Contam Toxicol **19**(5): 556-63.

Sugiura, Y., M. Kashiba, et al. (2005). "Cadmium exposure alters metabolomics of sulfur-containing amino acids in rat testes." Antioxid Redox Signal **7**(5-6): 781-7.

Trottier, B., J. Athot, et al. (2002). "Maternal-fetal distribution of cadmium in the guinea pig following a low dose inhalation exposure." Toxicol Lett **129**(3): 189-97.

Waalkes, M. P. and L. A. Poirier (1985). "Interactions of cadmium with interstitial tissue of the rat testes. Uptake of cadmium by isolated interstitial cells." Biochem Pharmacol **34**(14): 2513-8.
Waisberg, M., W. D. Black, et al. (2005). "The effect of pharmacologically altered gastric pH on cadmium absorption from the diet and its accumulation in murine tissues." Food Chem Toxicol **43**(5): 775-82.

Zakrzewska, M., D. Bialonska, et al. (2002). "Cadmium accumulation in fetus and placenta of bank voles (Clethrionomys glareolus, Schreber 1780)." Bull Environ Contam Toxicol **69**(6): 829-34.

Reviews from authoritative sources:

ATSDR (1999). "Toxicological Profile for Cadmium (update)." Agency for Toxic Substances and Disease Registry U.S. Public Health Service **390**.

Critera group for occupational standards. (2003). "Scientific basis for Swedish occupational standards. XXIV. Consensus report for Cadmium." Arbete och Hälsa **16**(2003): 31-47.

WHO (1992). "Cadmium." Environmental Health Criteria **134**(1992).

WHO (2001). "Safety evaluation of certain food additives and contaminants. Cadmium." WHO Food Additives Series **46**(2001): 247-305.

Who (1985). "Who Environmental Health 2. Effects of Occupational Factors on Reproduction." World Health Organization. Who Environmental Health **0**(0).

WHO (1992). "Cadmium - environmental aspects." Environmental Health Criteria **135**(1992).

Other reviews:

Archibong, A. E. and E. R. Hills (2000). "Male fertility as affected by cadmium: immunocontraceptive potential." Adv Reprod **4**(2-3).

Cogswell, M. E., P. Weisberg, et al. (2003). "Cigarette smoking, alcohol use and adverse pregnancy outcomes: implications for micronutrient supplementation." J Nutr **133**(5 Suppl 2).

Ferm, V. H. "Effects Of Metal Pollutants Upon Embryonic Development." Reviews on Environmental Health **1**(3): 238-259.

Ferm, V. H. (1972). "The Teratogenic Effects of Metals on Mammalian Embryos." Advances in

Teratology **5**: 51-75.

Goyer, R. A., J. Liu, et al. (2004). "Cadmium and cancer of prostate and testis." Biometals **17**(5): 555-8.

Hastings, L. and M. L. Miller (1998). "Developmental neurotoxicity of cadmium." Handbook of Developmental Neurotoxicology: 517-38.

Henson, M. C. and P. J. Chedrese (2004). "Endocrine disruption by cadmium, a common environmental toxicant with paradoxical effects on reproduction." Exp Biol Med (Maywood) **229**(5): 383-92.

Holt, D. and M. Webb (1986). "Comparison of some biochemical effects of teratogenic doses of mercuric mercury and cadmium in the pregnant rat." Arch Toxicol **58**(4): 249-54.

Jarup, L., M. Berglund, et al. (1998). "Health effects of cadmium exposure--a review of the literature and a risk estimate." Scand J Work Environ Health **24 Suppl 1**: 1-51.

Jarup, L. (2003). "Hazards of heavy metal contamination." Br Med Bull **68**: 167-82.

Kazantzis, G. "Mutagenic And Carcinogenic Effects Of Cadmium." Toxicological and Environmental Chemistry **8**(4): 267-278.

Kazantzis, G. "The Mutagenic and Carcinogenic Effects of Cadmium: An Update." Toxicological and Environmental Chemistry **15**: 1-2.

Klemmt, L. and A. R. Scialli (2005). "The transport of chemicals in semen." Birth Defects Res B Dev Reprod Toxicol **74**(2): 119-31.

Kumar, S., A. K. Gautam, et al. (2000). "Occupational exposure and male reproductive dysfunction: a growing concern." Indian Journal of Occupational and Environmental Medicine **4**(2): 89-95.

Levin, A. A., R. K. Miller, et al. "Heavy Metal Alterations Of Placental Function: A Mechanism For The Induction Of Fetal Toxicity In Cadmium." Reproductive and Developmental Toxicity of Metals, Clarkson, T. W., G. F. Nordberg, and P. R. Sager, Editors: 19831983.

McDiarmid, M. A. and K. Gehle (2006). "Preconception brief: occupational/environmental exposures." Matern Child Health J **10**(5 Suppl): 123-8.

Mehennaoui, S., A. Delacroix-Buchet, et al. (1999). "Comparative study of cadmium transfer in ewe and cow milks during rennet and lactic curds preparation." Arch Environ Contam Toxicol **37**(3): 389-95.

Mlynarcikova, A., M. Fickova, et al. (2005). "Ovarian intrafollicular processes as a target for cigarette smoke components and selected environmental reproductive disruptors." Endocr Regul **39**(1): 21-32.

Nordberg, M. (2004). "Environmental exposure and preventive measures in Sweden and EU." Biometals **17**(5): 589-92.

Nordberg, G. F. (2004). "Cadmium and health in the 21st century--historical remarks and trends for the future." Biometals **17**(5): 485-9.

Olea, N., F. Olea-Serrano, et al. (1999). "Inadvertent exposure to xenoestrogens in children." Toxicology And Industrial Health **15**(1-2): 151-158.

Oskarsson, A., I. Palminger Hallen, et al. (1998). "Risk assessment in relation to neonatal metal exposure." Analyst **123**(1): 19-23.

Paran'ko, N. M., E. N. Belitskaia, et al. (2002). "[Contribution of heavy metals to the development of reproductive disorders]." Gig Sanit **1**: 28-30.

Perera, F. P., W. Jedrychowski, et al. (1999). "Molecular epidemiologic research on the effects of environmental pollutants on the fetus." Environmental Health Perspectives **107**(SUPPL. 3): 451-460.

Prozialeck, W. C., J. R. Edwards, et al. (2006). "The vascular endothelium as a target of cadmium toxicity." Life Sci **79**(16): 1493-506.

Queiroz, E. K. and W. Waissmann (2006). "Occupational exposure and effects on the male reproductive system." Cad Saude Publica **22**(3): 485-93.

Ragan, H. A. and T. J. Mast (1990). "Cadmium inhalation and male reproductive toxicity." Rev Environ Contam Toxicol **114**: 1-22.

Rohrer, S. R., S. M. Shaw, et al. "Cadmium Teratogenesis And Placental Transfer." Cadmium Toxicity, Mennear, J. H., Editor: 19791979.

Satarug, S. and M. R. Moore (2004). "Adverse health effects of chronic exposure to low-level cadmium in foodstuffs and cigarette smoke." Environ Health Perspect **112**(10): 1099-103.

Satoh, M., H. Koyama, et al. (2002). "Perspectives on cadmium toxicity research." Tohoku J Exp Med **196**(1): 23-32.

Semczuk, M. and A. Semczuk-Sikora (2001). "New data on toxic metal intoxication (Cd, Pb, and Hg in particular) and Mg status during pregnancy." Med Sci Monit **7**(2): 332-40.

Shiverick, K. T. and C. Salafia (1999). "Cigarette smoking and pregnancy I: ovarian, uterine and placental effects." Placenta **20**(4): 265-72.

Singh, R. and S. V. Rana (2002). "Influence of antioxidants on metallothionein-mediated protection in cadmium-fed rats." Biol Trace Elem Res **88**(1): 71-7.

Vahter, M., M. Berglund, et al. (2002). "Metals and women's health." Environ Res **88**(3): 145-55.

Vahter, M., M. Berglund, et al. (2004). "Toxic metals and the menopause." J Br Menopause Soc **10**(2): 60-4.

Waalkes, M. P. and S. Rehm (1994). "Cadmium and prostate cancer." Journal Of Toxicology And Environmental Health **43**(3): 251-269.

Waalkes, M. P. (2000). "Cadmium carcinogenesis in review." J Inorg Biochem **79**(1-4): 241-4.

Waalkes, M. P. (2003). "Cadmium carcinogenesis." Mutat Res **533**(1-2): 107-20.

Zenzes, M. T. (2000). "Smoking and reproduction: gene damage to human gametes and embryos." Hum Reprod Update **6**(2): 122-31.

III. Summaries of Selected Human Studies

A. Exposure

Kuhnert et al. (1988), supported by NIH, evaluated placentas from smoking and nonsmoking women for zinc and cadmium concentration. Smoking status was assessed by questionnaire and verified by measurement of maternal plasma thiocyanate. The relationship between placental zinc, cadmium, and zinc/cadmium ratio was evaluated with respect to maternal age, divided into 5-year increments from 20 to 40 years, and parity. The placentas came from 98 women who smoked and 151 women who did not smoke. **[Gestational age, route of delivery, and the presence of obstetrical complications were not indicated.]**

Placental tissue was used after perfusion with saline to remove blood. Membranes and blood vessels were excluded from the tissue samples, which were analyzed for zinc and cadmium by atomic absorption spectrophotometry. The spectrophotometer required repair after the first 161 samples after which the sensitivities of the zinc and cadmium measurements were altered. Analyses involving zinc or cadmium were reported only for the first 161 samples. Because the machine repair did not change the zinc/cadmium ratio, analyses involving the ratio used data from all 249 placentas. Data were analyzed using simple correlation and repeated measures ANOVA.

There was an increase in placental cadmium with parity among smokers ($r = 0.42$) but not among nonsmokers. Placental cadmium was not significantly altered by maternal age independent of parity. Placental zinc decreased with parity ($r = -0.14$) and age ($r = -0.20$) in smokers and nonsmokers. The placental zinc/cadmium ratio decreased with age but not with parity in smokers and nonsmokers. The zinc/cadmium ratio was always higher in nonsmokers than in smokers with the oldest nonsmokers having a mean zinc/cadmium ratio greater than the youngest smokers.

The authors concluded that the greater effect of smoking on birth weight in infants of older mothers, which had been shown in a previous study, may be mediated by an age- or parity-related decrease in maternal zinc stores, an increase in placental cadmium due to accumulation of cadmium in smokers over time, or a combination of the two effects.

Krachler et al. (1999a), supported by the Austrian Society for the Promotion of Children's Health, measured trace elements in umbilical cord blood, infants, and adults in Slovenia. Umbilical cord blood was collected from 20 newborns. Blood samples were collected from exclusively breast-fed 5 infants (mean age 3.5 months), 6 formula-fed infants (mean age 3.1 months), and 20 healthy adults (mean age 25 years). **[Cigarette smoke exposure was not mentioned.]** Additional samples were collected from older adults with a variety of medical illnesses **[not discussed here]**. Serum was obtained by centrifugations and analyzed for cadmium and other elements by inductively coupled plasma-mass spectrometry. Results for cadmium are shown in Table 7. The authors did not express conclusions related to cadmium.

Table 7. Cadmium Concentration in the Serum of Newborns, Infants, and Adults

	Cadmium concentration, µg/L	
Source of serum	Mean ± SD	Median
Umbilical cord blood	0.4 ± 0.3	0.3
Breast-fed infants	0.4 ± 0.1	0.4
Formula-fed infants	0.3 ± 0.1	0.4
Healthy adults	Not reported	0.2

From Krachler et al. (1999a)

Krachler et al. (1999b), supported by the Austrian Society for the Promotion of Children's Health, measured trace elements in umbilical cord serum, maternal serum, and colostrum in 29 Solvenian mother-infant pairs. The women in the study were nonsmokers (5 were former smokers) who had given birth normally at term. Maternal blood was sampled within 20 minutes before delivery and colostrum was collected from 27 of the women at some time during the first 3 days postpartum. Cadmium and other elements were measured by inductively coupled plasma-mass spectrometry. Cord and maternal serum concentrations were compared with Student *t*-test.

Results are presented in Table 8. There was no significant difference between maternal and umbilical cord serum in cadmium concentration. No conclusions were drawn with respect to cadmium except that concentrations in maternal and umbilical cord serum are within the reported range for normal adults.

Table 8. Cadmium Concentrations in Umbilical Cord and Maternal Serum and in Colostrum

	Cadmium concentration, µg/L			
Sample	Mean ± SD	Median	Interquartile range	Full range
Umbilical cord serum	0.3 ± 0.3	0.2	<0.08–0.3	<0.08–1.3
Maternal serum	0.3 ± 0.3	0.3	0.1–0.4	<0.08–1.3
Colostrum	0.6 ± 0.5	0.6	0.2–0.8	<0.18–1.9

From Krachler et al. (1999b)

Sarasua et al. (2000), from the CDC, evaluated the relationship between urine cadmium concentration and immune system endpoints in children and adults living near sites with cadmium and lead contamination of the soil. Blood lead was also measured. The subjects were evaluated in four age groups (6–35 months, 36–71 months, 6–15 years, and 16–75 years) and were compared to demographically matched individuals not living near contaminated sites. Urine cadmium was corrected for urine creatinine concentration. Because >60% of the children had undetectable urine cadmium and 20% had low urine creatinine, the evaluation of cadmium and immune markers was restricted to adults. **[The abstract suggests that this study contains information on developmental effects of cadmium, but on reading the study, no such results were presented.]**

Ostrea et al. (2002), support not indicated, evaluated meconium samples for the presence of cadmium and other environmental contaminants. Meconium was collected during the first 2 days of life from 426 infants born in Manila. Cadmium was measured by atomic absorption spectrometry. Cadmium standards of 0.1, 0.3, and 0.5 ppm were also run. The limit of detection was 1.5 ppm. **[It is not clear why standards below the limit of detection were run.]** The recovery of cadmium in spiked samples was ~100%. Infant exposure was defined as yes or no based on the presence of detectable cadmium in the meconium. Associations between cadmium exposure and maternal and fetal factors (from hospital records) were evaluated with multiple chi-

squared tests. **[Sixteen factors appeared to have been evaluated for association with 3 different metals.]**

Cadmium was detected in 8.5% of meconium samples with a mean concentration of 12 ppm **[mg/kg]** and a range of 2.09–27.39 ppm **[mg/kg]**. Cadmium positivity was associated with the hospital of birth an d with parity >3. A significant association between cadmium positivity and maternal cigarette smoking was not identified. The authors suggested that with increasing parity, the placenta becomes less effective at excluding cadmium from the fetus.

Åkesson et al. (2002), supported by the Swedish Environmental Protection Agency, the Council for Swedish Forestry and Agricultural Research, and the Lund University Medical Faculty, evaluated the relationship between iron status and cadmium concentration in blood, urine, and placenta in pregnant and postpartum Swedish women. The original sample consisted of 254 women in early pregnancy of whom 15% smoked cigarettes. Blood and urine samples were collected at 11 weeks gestation (210 subjects), 36 weeks gestation (123 subjects), during early lactation (99 subjects), and 15 months postpartum (56 subjects). Not all subjects contributed specimens at all time points. Placentas (106 subjects) and cord blood samples (32 subjects) were collected at delivery. Blood cadmium was measured by atomic absorption spectrometry with a limit of detection of 0.05 µg/L. Urine and placental cadmium concentrations were measured by inductively coupled plasma mass spectrophotometry, adjusted in urine to a specific gravity of 1.018 g/mL. Iron status was assessed using serum ferritin and soluble transferrin receptor. Soluble transferrin receptor concentrations are inversely proportional to tissue iron content. Spearman correlation coefficients were calculated for cadmium concentrations and iron measures. Correlation coefficients were also calculated for cadmium concentrations and the transferrin receptor/ferritin ratio.

Concentrations of cadmium in nonsmoking women in early pregnancy and in placenta are shown in Table 9. **[Cadmium measurements at other times were not shown. Data from smoking women were not used.]** Blood and urine cadmium concentrations were inversely correlated with serum ferritin at all time points. Transferrin receptor was correlated with urine cadmium concentration at the 15 month post-partum measurement. Increasing urine cadmium was seen with increasing maternal age, particularly among multiparous women. Placental cadmium content but not cadmium concentration was correlated with the transferrin receptor/ferritin ratio in late pregnancy and with transferrin receptor in cord serum. The authors concluded that an increased cadmium burden during pregnancy is associated with low iron stores, especially in older, parous women.

Table 9. Blood, Urine, and Placental Cadmium in Nonsmoking Women

Matrix	Median, µg/L or µg/kg	Range, µg/L or µg/kg
Blood	0.16	<0.05[a]–0.73
Urine	0.31	0.11–1.1
Placenta	4.8	1.1–18.6

[a]Limit of detection
From Åkesson et al. (2002)

Mokhtar et al. (2002), support not indicated, measured serum cadmium concentrations in maternal and umbilical cord blood from 100 Egyptian maternal-infant pairs. Information on smoking, residence, and pregnancy history was obtained by questionnaire. There were 61 women exposed to passive cigarette smoke and 38 women not exposed to cigarette smoke. One woman was an active smoker. Statistical analyses were performed using Student *t*-test, the Wilcoxon rank-sum test, and an unspecified test of correlation.

Serum cadmium concentrations are summarized in Table 10. Serum cadmium concentrations were higher in mothers and infants exposed to passive cigarette smoke than unexposed mother-infant pairs. There was no statistical difference in serum cadmium concentration between mothers and infants within pairs. Umbilical cord serum cadmium concentration was inversely correlated with 5-minute Apgar score ($r = -0.35$). Serum cadmium was not significantly associated with birth order, gestational age, birth weight, crown-heel length, or head circumference of the infants. There was no difference in serum cadmium concentration by rural or urban residence. The authors concluded that intrauterine exposure to cadmium is evident and called for studies on long-term effects of exposure.

Table 10. Serum Cadmium Concentrations in 100 Egyptian Mother-Infant Pairs

	Serum cadmium, µg/L (mean ± unspecified error)	
Pairs	Maternal serum	Umbilical cord serum
Entire sample (n = 100)	0.7 ± 0.3, range 0.4–2.2	0.7 ± 0.2, range 0.2–1.5
Nonsmokers (n = 38)	0.6 ± 0.14	0.5 ± 0.14
Passive smokers (n = 61)	0.8 ± 0.31	0.7 ± 0.19
Active smoker (n = 1)	1.9	1.5

From Mokhtar et al. (2002)

Zhang et al. (2004), supported by the International Atomic Energy Agency, investigated determinants of cadmium placental transport in women from Da-Ye county in the Hubei Province of China. These women were selected due to cadmium contamination of water and soil in the county by a nonferrous metal smelter. Subjects included 47 healthy pregnant women without occupational exposure to cadmium and without exposure to vitamin or mineral supplements. Information on medical and reproductive history, smoking, ethanol, medication, and gestational age was collected by questionnaire. Maternal blood was sampled within 3 days prior to delivery, and umbilical cord blood was sampled immediately after delivery. Placentas were freeze-dried, ground, and stored as a powder for later analysis. Cadmium in blood and placenta and copper in blood were measured by inductively coupled plasma-mass spectrometry. Blood zinc was determined by flame atomic absorption spectrometry, and blood selenium was determined by atomic fluorescence spectrometry. Maternal blood zinc, copper, and selenium concentrations were trichotomized as low, normal, or high based on published reference values. ANOVA was used to compare maternal blood, cord blood, and placental cadmium concentrations in the groups established by low, normal, or high levels of other elements. Stepwise multiple linear regression was used to adjust for maternal age, gestational age, and lactation history. **[Exposure to cigarette smoke was not mentioned in the analysis except to say that few of the women had a history of smoking.]**

The median (range) maternal blood cadmium concentration was 1.72 (0.80–25.20) µg/L, and the median (range) cord blood cadmium concentration was 0.40 (0.020–1.48) µg/L. Geometric mean ± SD cadmium concentration was 2.26 ± 1.75 µg/L in maternal blood and 0.47 ± 1.28 µg/L in umbilical cord blood. Maternal blood cadmium was significantly higher than umbilical cord blood cadmium, although the values were correlated ($P = 0.061$). Median (range) placental cadmium was 0.14 (0.082–3.97) µg/g dry weight, and geometric mean SD placental cadmium was 0.27 ± 1.32 µg/g dry weight. Placental cadmium concentration was correlated with maternal blood cadmium concentration ($r = 0.64$) but not with umbilical cord blood cadmium.

ANOVA showed significantly higher placental cadmium in women with low blood zinc and lower placental cadmium in women with low blood selenium than in women with normal blood zinc and selenium, respectively. Multiple regression showed that maternal age and blood

concentrations of zinc, selenium, and copper could explain 20% of the variance in maternal blood cadmium. Maternal blood cadmium and copper concentrations could explain 9% of the variance in cord blood cadmium concentration. Maternal age and blood cadmium, zinc, and selenium concentrations could explain 78.1% of the variance in placental cadmium concentration. The authors concluded that there were significant associations between essential trace elements and placental cadmium transport and that improvement of maternal nutritional status may reduce cadmium transfer to the fetus.

Lyon et al. (2002), support not indicated, measured concentrations of cadmium in liver from children of different ages. The liver samples were obtained at autopsy in children from birth to 6 years of age. Many of the samples were taken for the purpose of evaluating a possible relationship between antimony and sudden infant death syndrome, but additional samples were added from children dying of other causes. There were 10 children who had been born prematurely and who died prior to reaching an age equivalent to 40 gestation weeks, 19 neonates age 0–1 month, 111 infants age >1–12 months, and 17 children age >12 months. Cadmium concentration was determined using inductively coupled mass spectrometry.

The results are summarized in Table 11. The authors commented that the relatively low concentrations of cadmium up to 1 year of age is consistent with a low rate of placental transfer and low concentrations of cadmium in human milk and in formula. The increase in cadmium after 1 year of age occurs with increasing exposure to dietary cadmium and environmental contact with cadmium from mouthing behaviors.

Table 11. Liver Cadmium Concentration (ng/g wet weight) at Autopsy in Children

Age	Median	Range
Premature[a]	1.45	0.6–4.6
0–1 month	2.6	0.15–8.8
>1–12 months	2.7	1.0–10.85
>12 months	56.5	4.6–412

[a]Dying before the equivalent of 40 weeks gestation
From Lyon et al. (2002)

Honda et al. (2003), supported by Kanazawa Medical University, measured cadmium and other elements in milk from 68 Japanese women. Milk samples were collected after infant nursing on day 5 of life (day 8 if the woman had been delivered by cesarean section). Information on occupational exposure to cadmium, residence in a cadmium-contaminated area, and cigarette smoking was obtained by questionnaire. Urine was also collected for cadmium determination. **[No reference is made to the questionnaire data in the results. This study may have included subjected reported in Nishijo et al. (2002).]** Cadmium was measured by flameless atomic absorption spectrometry. Other elements measured included calcium, magnesium, sodium, potassium, phosphorous, and zinc. Statistical analyses used Student *t*-test, Welch test, and Spearman correlation.

The geometrical mean ± SD cadmium concentration in milk was 0.28 ± 1.82 µg/L (range 0.07–1.23 µg/L). Urine cadmium geometrical mean ± SD was 1.00 ± 1.93 µg/g creatinine (range 0.28–5.13 mg/g creatinine). Milk cadmium concentration was not affected by maternal age, parity, or route of delivery. Milk cadmium and urine cadmium were significantly correlated. Milk calcium concentration was inversely correlated with milk cadmium concentration ($r = -0.248$). There were no significant correlations between the milk concentration of cadmium and that of any other element. The authors concluded that the inverse relationship between milk cadmium and calcium may reflect an effect of cadmium on calcium metabolism in bone and kidney.

Nishijo et al. (2004a), supported by Kanazawa Medical University, measured blood and urine cadmium concentration in pregnant Japanese women and obtained information on the diet consumed by these women. Blood and urine samples were obtained from 50 women at 30–32 weeks gestation during a routine prenatal visit. Three-day food diaries were given and reviewed with each subject by a dietician. Cadmium concentrations were measured by flameless atomic absorption spectrometry, and urine values were corrected for creatinine concentration. Relationships between cadmium measures and features of the diet were evaluated using Spearman correlation. Multiple regression was used to adjust for age.

Mean ± SD blood cadmium concentration was 0.93 ± 0.46 µg/L. Geometric mean ± SD urine cadmium concentration was 1.05 ± 1.64 µg/g creatinine. Urine and blood cadmium were correlated (r = 0.354). There were 9 women who smoked prior to pregnancy; their cadmium measurements did not differ from those in the nonsmokers. There was no significant correlation between cadmium measures and indices of anemia. Urine but not blood cadmium was correlated with age. When adjusted for age, blood cadmium concentration was inversely correlated with total energy, protein, fat, and iron intake, and intake of green vegetables. The authors concluded that their results were consistent with increased absorption of cadmium in the presence of iron deficiency, because green vegetables are an important source of iron in Japan. The authors identified rice as an important source of cadmium in Japan and indicated that rice is displaced in the Japanese diet by fatty foods. Low fat diet, then, could be an indicator of less displacement of rice from the diet.

Butler Walker et al. (2006), supported by the Government of the Northwest Territories and Health Canada, measured concentrations of cadmium and other elements in maternal and umbilical cord blood in Arctic Canada. Women enrolled in prenatal clinics were given questionnaires on lifestyle and diet. A maternal blood sample was drawn between 36 weeks gestation and discharge from the hospital post-partum. Umbilical cord blood was drawn at delivery. Cadmium concentration was measured in blood samples using graphite furnace atomic absorption spectrometry. Other elements measured included mercury, lead, copper, selenium, and zinc. Statistical analyses were performed using ANOVA with post-hoc Tukey t-test. Cigarette smoking was trichotomized as none, moderate (≤8 cigarettes/day), or heavy (>8 cigarettes/day). Consumption of traditional foods was analyzed as none, moderate (<115 g/day), or heavy (>115 g/day) without regard to the species consumed.

There were 523 women in the study, although not all women contributed both maternal blood and umbilical cord blood samples. Cadmium was detectable in 84.7% of maternal blood samples and 26% of umbilical cord blood samples (limits of detection 0.2 µg/L). Values are summarized in Table 12. **[The number of subjects in subcategories are noted not to add to the total number in the larger categories.]** Maternal blood cadmium concentration was significantly related to smoking. The role of consumption of traditional food (largely game) in maternal blood cadmium was characterized as "small." **[It was not clear if there was a statistically significant relationship between consumption of traditional foods and blood cadmium concentration.]** The authors concluded that most cadmium exposure in this population was from cigarette smoking.

Table 12. Cadmium Concentration and Maternal and Cord Blood in Arctic Canada

	Cadmium concentration, µg/L	
Source	Mean ± SD (range)	Geometric mean ± SD
Maternal blood		
Smokers + nonsmokers (n = 385)[a]	1.72 (<0.2–8.5)	0.76
All smokers (n = 192)	2.91 ± 1.75 (<0.2–8.54)	2.24± 4.08
Heavy smokers (n = 80)	3.66 ± 1.95 (0.4–8.54)	3.13 ± 2.44
Moderate smokers (n = 109)	2.43 ± 1.35 (<0.2–6.18)	1.86 ± 3.9
Nonsmokers (n = 191)	0.52 ± 0.69 (<0.2–6.55)	0.25 ± 1.91
Umbilical cord blood (n = 402)[a]	0.2 (<0.2–7.5)	0.08

[a]Standard deviations not provided.
From Butler Walker et al. (2006)

B. Developmental Effects

Huel et al. (1981), supported by the French National Institute of Health and Medical Research, measured cadmium and lead in maternal and neonatal hair. Subjects were drawn from 110 births in eastern France in a rural area near chemical and metallurgical facilities. Hair was taken from the occipital region, washed, and prepared for metal determination by atomic absorption spectrometry. Some samples were discarded, leaving samples from 108 mothers, 105 newborns, and 103 mother-newborn pairs. Comparisons involved several maternal and neonatal factors. **[The source of the maternal and neonatal data, other than hair measurements, was not discussed. Statistical methods were not always explicitly discussed, although paired *t*-tests, chi-squared, and multiple regression were used. There does not appear to have been adjustment for multiple comparisons.]**

The geometric mean (5^{th}–95^{th} percentile) maternal hair cadmium was 0.43 (0.04–4.11) ppm **[mg/kg]**, and newborn hair cadmium was 0.54 (0.06–6.87) ppm. There was no statistical difference between these 2 values. Maternal and infant hair cadmium concentrations were significantly correlated ($r = 0.481$). In a regression analysis, infant hair cadmium and lead were significantly correlated. There was no significant relationship between maternal or neonatal hair cadmium and maternal age or parity. Neonatal but not maternal hair cadmium was higher in the presence of maternal hypertension (neonatal hair cadmium 0.79 ppm in hypertensive pregnancies [n = 13] and 0.52 ppm in normotensive pregnancies [n = 74]. **[The kind of central tendency and the distribution were not given.]**

Geometric mean infant hair cadmium [interquartile range] was higher in small-for-dates infants (1.04 [0.22–4.32] ppm; n = 9) than normal infants (0.46 [0.16–1.24] ppm; n = 66). There was no significant difference in infant hair cadmium in infants born prematurely or in infants with malformations compared to normal infants, and maternal hair cadmium was not significantly different in any of these infant outcome groups. The authors noted that in the 24 infants who were either preterm, small-for-dates, or malformed, 10 infants had hair cadmium concentrations >1.9 ppm. This proportion was significantly higher than the proportion with this high a hair cadmium concentration in the normal-infant group. When small-for-dates infants were excluded and adjustments were made for infant sex, gestational age, and maternal weight, there was a significant inverse correlation between hair cadmium **[presumably neonatal, but not stated]** and birth weight ($r = -0.26$). The authors concluded that there may be an interrelationship between maternal smoking, cadmium, hypertension, and birth weight. **[The connection with smoking was based on previous literature. Only 13 mothers in this study smoked, most smoked <5 cigarettes/day, and smoking does not appear to have been considered in the analyses.]**

Kuhnert (P.M.) et al. (1987a), supported by NIH, evaluated measures of cadmium and zinc in smoking and nonsmoking pregnant women. Subjects consisted of 65 smokers and 84 nonsmokers selected without regard to the presence of pregnancy complications. **[Some of these subjects were also reported in B.R. Kuhnert et al., 1987b.]** Smoking status was ascertained based on the medical record and a questionnaire and was confirmed with measurement of plasma thiocyanate. After delivery, cord blood was collected for determination of plasma and red blood cell zinc levels and placentas were collected for measurement of tissue cadmium and zinc concentration. Maternal blood was collected within an hour of delivery for measurement of whole blood cadmium and plasma and red blood cell zinc. Cadmium was measured using graphite furnace atomic absorption spectrometry, and zinc was measured using flame absorption spectrometry. Zinc intake was estimated in 29 randomly selected smokers and 37 randomly selected nonsmokers using a 7-day food frequency questionnaire. Statistical analysis was performed using simple correlation, Student *t*-test, chi-squared, and step-wise multiple regression.

The mean birth weight in the infants of smokers was 391 g less than that of the infants of nonsmokers. There were more small for gestational age infants in the smoking than the nonsmoking group. There was no difference between smokers and nonsmokers in dietary zinc intake. Whole blood cadmium concentration was 66% higher in smoking than nonsmoking mothers (mean ± SD: 1.33 ± 0.8 ng/g in smokers, 0.80 ± 0.4 ng/g in nonsmokers). Placental cadmium was 48% higher in smoking than nonsmoking mothers (mean ± SD: 12.0 ± 7.5 ng/g in smokers, 8.1 ± 5.0 ng/g in nonsmokers). There were no significant differences in smoking and nonsmoking mothers with respect to plasma or red blood cell zinc or between their infants in plasma zinc. Placental zinc was 9% higher in smokers than nonsmokers, and infant red blood cell zinc was 8% lower in smokers than nonsmokers. In smokers, maternal whole blood cadmium significantly predicted placental zinc and placental cadmium. In nonsmokers, maternal blood cadmium significantly predicted placental cadmium. Infant red blood cell zinc was significantly predicted by maternal plasma thiocyanate, a surrogate for number of cigarettes smoked.

The authors concluded that there is a cadmium/zinc interaction in smoking women that may adversely impact fetal zinc status. They hypothesized than cadmium-associated increases in placental metallothionein may result in increased zinc-binding and less zinc transport to the fetus.

Kuhnert (B.R.) et al. (1987b), supported by NIH, evaluated the relationship between birth weight and measures of cadmium and zinc in smoking and nonsmoking pregnant women. Subjects consisted of 77 smokers and 125 nonsmokers selected without regard to the presence of pregnancy complications. **[Subjects included women reported in P.M. Kuhnert et al., 1987a.]** Smoking status was ascertained based on the medical record and a questionnaire and was confirmed with measurement of plasma thiocyanate. After delivery, cord blood was collected for determination of plasma and red blood cell zinc levels and placentas were collected for measurement of tissue cadmium and zinc concentration. Maternal blood was collected within an hour of delivery for measurement of whole blood cadmium and plasma and red blood cell zinc. Cadmium was measured using graphite furnace atomic absorption spectrometry, and zinc was measured using flame absorption spectrometry. Statistical analysis was performed using simple correlation, Student *t*-test, and step-wise multiple regression. Variables adjusted in the regression included maternal age, gestational age, parity, gravidity, race, and maternal red blood cell count.

The mean birth weight in the infants of smokers was 391 g less than that of the infants of nonsmokers. Gestational age made the largest contribution to birth weight. In smokers, maternal plasma thiocyanate and whole blood cadmium concentrations were negatively correlated with birth weight and placental zinc/cadmium radio was positively correlated with birth weight. Red blood cell zinc in cord blood was positively correlated with birth weight in the offspring of

smokers and nonsmokers. In the step-wise multiple regression analysis, gestational age accounted for >11% of birth weight variance in smokers and in the entire sample. Maternal plasma thiocyanate concentration, a surrogate for number of cigarettes smoked, accounted for 5.8% of the variance in birth weight among smokers and 12.2% of the variance in birth weight in the entire sample. Maternal whole blood cadmium accounted for 8.5% of the birth weight variance among smokers and 2.5% of the birth weight variance in the entire sample.

The authors concluded that the negative effect of maternal smoking on birth weight may be mediated by a cadmium-associated disturbance in zinc availability.

Sikorski et al. (1988), support not indicated, measured cadmium in maternal and umbilical cord blood in 100 maternal-infant pairs delivered at term. There were 37 nonsmokers and 63 current smokers. The median number of cigarettes smoked daily was 6, and the smoker sample was divided into those smoking ≤6 cigarettes/day and those smoking >6 cigarettes/day. Blood was analyzed for cadmium concentration by atomic absorption spectrometry. Statistical analysis was by sign-rank test, Student *t*-test, and chi-squared. There were no differences between groups in maternal age, parity, or gestational age at delivery. Birth weight was ~12% lower in the offspring of women smoking >6 cigarettes/day than of nonsmoking women or women smoking ≤6 cigarettes/day with a mean decrement of ~400 g. Cadmium concentrations in maternal and cord blood were correlated. In the nonsmoking group, 27% of maternal and 32.4% of cord blood samples had detectable cadmium concentrations **[limits of detection not given]**. Signficantly more mothers (61.9%) and infants (57.1%) in the smoking group had detectable blood cadmium concentrations. The highest maternal blood cadmium concentration in nonsmokers was ~0.02 ppm **[mg/L]**, and the highest maternal blood cadmium concentration in smokers was ~0.9 ppm **[mg/L]**. The highest cord blood cadmium concentration in the nonsmoking group was ~0.03 ppm **[mg/L]**, and the highest cord blood cadmium concentration in smokers was ~0.15 ppm **[mg/L]**. **[Cadmium concentration was presented graphically as cumulative percentage of the sample reaching a given concentration.]** There was no significant association between cadmium concentration in maternal or cord blood and measures of fetal growth. The authors concluded that they could not document a placental barrier to cadmium transport to the fetus and that the decreased fetal size associated with cigarette smoking was unlikely to be due to cadmium.

Laudanski et al. (1991), supported by the Polish Medical Academy, the Swedish Medical Research Council, and the University of Lund, evaluated reproductive history in women from a rural area in eastern Poland with elevated soil levels of lead and cadmium. Interviews were conducted with 405 of the 814 women age 17–75 living in this area. A comparison group consisted of 269 women from a nearby village that was considered to have normal levels of lead and cadmium in the soil. Subjects were interviewed regarding demographic information and reproductive history. The interviewer was aware of exposure status. Physical examinations were performed on a subset of women in both groups. Subjects had blood drawn for determination of lead and cadmium concentrations by atomic absorption spectrometry. **[Soil concentrations of lead and cadmium were not reported.]** Statistical comparisons were made using chi-squared and *t*-tests.

The groups were comparable in demographic features. Plasma lead was similar in both groups (mean 6–7 µg/dL). Blood cadmium was higher in the study group than the control group (mean ± SD: 29 ± 1.2 µg/L in the study group, 2.5 ± 1.4 µg/L in the control group). There were no differences between groups in proportion of women with miscarriages, stillbirths, or preterm labor, or in women with 0, 1, 2, or 3 pregnancies. There was a smaller proportion of women with >3 pregnancies and >3 deliveriesin the study than the control group (study group 39%, control group 52%).

The authors concluded that cadmium exposure could be responsible for a decrease in the proportion of women with >3 pregnancies and >3 deliveries.

Loiacono et al. (1992), supported by NIEHS, UPA, the Lucille B. Markey Charitable trust, and the Andrew Mellon Foundation, compared placental cadmium concentration and birth weight in 2 towns in the former Yugoslavia. The towns were Titova Mitrovica, which is near a lead smelter, and Pristina, 40 km to the south and considered unexposed to smelter activities.[1] The initial sample included 602 pregnancies from Titova Mitrovica and 900 pregnancies from Pristina. Maternal blood samples at mid-pregnancy and delivery and umbilical cord blood samples were collected for measurement of lead **[not discussed here]**. Placentas were collected from most of the subjects and frozen for subsequent analysis. After exclusion of placentas that thawed in transit to the laboratory, placentas from smoking mothers, twins, stillbirths, pregnancies of unknown gestational age or gestational age outside 28–44 weeks, pregnancies not born in calendar year 1986, and placentas with suspected contamination, there were 106 placentas from Titova Mitrovica and 55 placentas from Pristina that were analyzed for cadmium concentration by graphite furnace atomic absorption spectrometry. Possible relationships between placental cadmium, birth weight, and gestational age were analyzed by multiple regression adjusting for ethnicity, maternal age, infant sex, maternal height, parity, maternal education, and mid-pregnancy maternal blood lead concentration.

Placental cadmium was higher in Titova Mitrovica than Pristina (mean ± SD 0.73 ± 0.52 nmol/g dry weight **[82 ± 58 µg/kg]** in Titova Mitrovica and 0.50 ± 0.19 nmol/g dry weight **[56 ± 21 µg/kg]** in Pristina). In Titova Mitrovica, placental cadmium concentration was significantly correlated with midpregnancy and delivery maternal blood lead and with umbilical cord blood lead (r = 0.21–0.26) but not with placental lead concentration. There was no significant correlation between placental cadmium concentration and birth weight or gestational age. The sample size was adequate to provide an 80% likelihood of detecting a birth weight difference of 245 g and a gestational age difference of 8 days. The authors concluded that cadmium exposure may not be associated with reduced birth weight and that previous studies showing an association between cadmium and birth weight in smokers may have been confounded by exposure other components of cigarette smoke. The authors discussed the results of Kuhnert et al. (1987a,b) in which maternal blood thiocyanate was used as a marker of smoking and suggested that thiocyanate is a marker of recent smoking whereas placental cadmium is a longer-term marker of cigarette smoke exposure.

Fréry et al. (1993) evaluated cadmium in placentas and hair from 102 mother-infant pairs. Subject mothers had uncomplicated singleton pregnancies and were interviewed 3 days after delivery for information on social category and smoking. Placental tissue and occipital hair samples were assayed for cadmium by atomic absorption spectrometry with a graphite furnace. Placentas were fixed in formalin, sectioned at 1 cm intervals, and evaluated systematically by a pathologist for macroscopic changes. Statistical methods included the Wilcoxon test, Spearman correlation coefficient, and linear regression. Birth weight was adjusted for sex, gestational age, and maternal height and weight.

Parenchymal calcifications of the placenta were associated with a 39% increase in median placental cadmium and a 24% decrease in median newborn hair cadmium. Median placental cadmium in the absence of parenchymal calcifications was 8.5 ng/g wet weight and in the presence of parenchymal calcifications was 11.8 ng/g wet weight. The relationship between

[1] These towns are now in Kosovo, Servia. Titova Mitrovica has been renamed Kosovska Mitrovica.

placental calcifications and cadmium levels remained significant when controlled for maternal smoking. Overall, cadmium levels in placenta or in maternal or newborn hair were not significantly related to birth weight; however, in the presence of placental calcification, newborn hair cadmium was inversely association with birth weight ($r = -0.49$, $P < 0.01$). In the presence of placental calcifications, there was a 473 g mean difference in birth weight between the first and fourth quartiles of newborn hair cadmium. The authors concluded that the inverse association of infant hair but not placental cadmium with birth weight suggested that direct fetal rather than placental toxicity of cadmium may be responsible for birth weight alterations. They further suggested that in the presence of placental calcifications, cadmium toxicity for the fetus may be higher than in the absence of calcifications, although they could not suggest a mechanism by which placental calcifications would increase cadmium toxicity.

Tabacova et al. (1994), from the National Center of Hygiene, Ecology, an Nutrition, Bulgaria, NIEHS, and the Clinic of Occupational Diseases, Bulgaria, evaluated 71 prenatal patients living near a copper smelter in Bulgaria. Subjects were interviewed after 24 weeks of gestation and medical records were reviewed to identify threatened abortion, anemia, hyperemesis, or toxemia. Five patients were excluded based on preexisting medical disorders. Blood lead and cadmium and urine arsenic were determined by flameless atomic absorption spectrophotometry. Lipid peroxides, glutathione, and catalase were measured in blood, and catalase was measured in erythrocytes. Women with and without complications of pregnancy were compared with respect to blood metal concentrations and anti-oxidant related biochemical results. Statistical analysis included Spearman rank correlation and chi-squared test.

Of the 66 subjects, only 19 had no obstetric complication. There were no differences in blood cadmium concentration in women with toxemia, anemia, threatened abortion, and women without complications (hyperemesis was not evaluated, because too few women had this diagnosis). The mean blood cadmium concentrations were 0.21–0.32 µg/L in these groups. There were increases in lipid peroxides in women with toxemia. The authors concluded that there are signs of oxidative stress in toxemia and other complications of pregnancy in a metal-contaminated environment, and they suggested that the association may be facilitated by interference of metals with glutathione. **[Total, reduced, and oxidized glutathione blood concentrations were not altered in women with toxemia compared to women without complications.]**

Galicia-García et al. (1997), support not indicated, measured cadmium in maternal, cord, and fetal blood in 49 mother-infant pairs in Mexico City. Blood was analyzed by graphite furnace atomic absorption spectrometry. Cigarette smoking and other potential cadmium exposures were assessed by questionnaire. Regression analysis was used to assess the relationship between blood cadmium and possible sources of cadmium exposure. Maternal-cord blood and infant-cord blood cadmium concentrations were correlated but maternal-infant blood cadmium concentrations were not correlated. Mean cadmium concentrations in the three blood types were 1.2–1.4 µg/L. Blood cadmium concentration was ~24% higher in maternal blood in women who smoked **[estimated from a graph]**, but cord blood and infant blood associated with maternal smoking did not show cadmium elevations. Only cord blood cadmium concentration was inversely correlated with birth weight ($P = 0.06$). This relationship was not altered when smoking was considered. The authors concluded that birth weight decrements may be due to placental cadmium and that cord blood cadmium may be a reflection of the placental cadmium burden.

Odland et al. (1999), supported by the University of Tromsø and the Royal Norwegian Ministry of Foreign Affairs, evaluated the relationship between maternal and cord blood cadmium concentration and birth weight in maternal-infant pairs in northern Norway and Russia. Blood was collected from mothers immediately post-partum. A questionnaire and medical records were

used to assess cigarette smoking, reproductive history, and dietary information. Samples were obtained from 148 Russian and 114 Norwegian mother-infant pairs. Cadmium was measured using electrothermal atomic absorption spectrometry. Lead was also measured **[not discussed here]**. Concentrations below the limits of detection for cadmium (1.0 nM **[0.112 µg/L]**) were assigned a value of 0.5 nM **[0.056 µg/L]**. Statistical analysis used the Wilcoxon test, ANOVA, and multiple linear regression.

Russian and Norwegian subjects did not differ with respect to maternal blood cadmium (median concentration 1.8–2.2 nM **[0.20–0.25 µg/L]**) or cord blood cadmium (median concentration 0.5 nM **[0.056 µg/L]**). Nearly 90% of the cord blood cadmium concentrations were below the limits of detection. Neither maternal nor cord blood cadmium concentration was correlated with birth weight or infant body-mass index. There was a significant association between number of cigarettes smoked and maternal blood cadmium ($r = 0.30$). The authors concluded that it was difficult to establish an effect of cadmium on birth weight independent of cigarette smoking.

Odland et al. (2004), supported by the University of Tromsø and the Royal Norwegian Ministry of Foreign Affairs, presented additional analyses of the data reported in Odland et al. (1999) and other publications. **[The values presented in this paper were slightly different from those previously reported.]** A multivariate regression was used to evaluate possible relationships between birth weight or infant body-mass index and maternal age, body-mass index, country of origin, smoking, and concentrations in maternal blood at delivery and placenta of several elements, including cadmium. Median (range) maternal blood cadmium concentration was 2.0 (0.5–35.2) nM **[0.225 (0.056–3.96) µg/L]**, neonatal cord blood cadmium was 0.5 (0.5–4.8) nM **[0.056 (0.056–0.540) µg/L]**, and placental cadmium was 0.032 (0.011–0.201) µg/g. Maternal blood and placental cadmium concentrations were correlated. There was no significant association between any cadmium measurement and birth weight or infant body-mass index.

Osada et al. (2002), support not indicated, measured cadmium concentration in maternal and cord blood and placental tissues in Japanese mother-infant pairs. All women were nonsmokers and had delivered at 34 weeks gestation or later. There were 30 mother-infant pairs in which birth weight was normal for gestational age and 21 pairs in which birth weigh was less than 1.5 SD below the mean for gestational age on a Japanese standard birth weight curve. Blood samples were collected from mothers, umbilical arteries, and umbilical veins after delivery and serum separated by centrifugation. Placental tissue was sampled after removal of the deciduas basalis and chorionic plate. Placental and serum samples were freeze dried prior to analysis. Cadmium was measured with inductively coupled plasma mass spectrometry. **[Nine other trace elements were also measured; not discussed here.]** Comparisons between measurements in maternal-infant pairs with and without fetal growth restriction were made using the Wilcoxon/Kruskal-Wallis test.

Cadmium concentrations are illustrated in Figure 1. There were no significant differences between measurements with and without fetal growth restriction. The authors did not express conclusions related to cadmium.

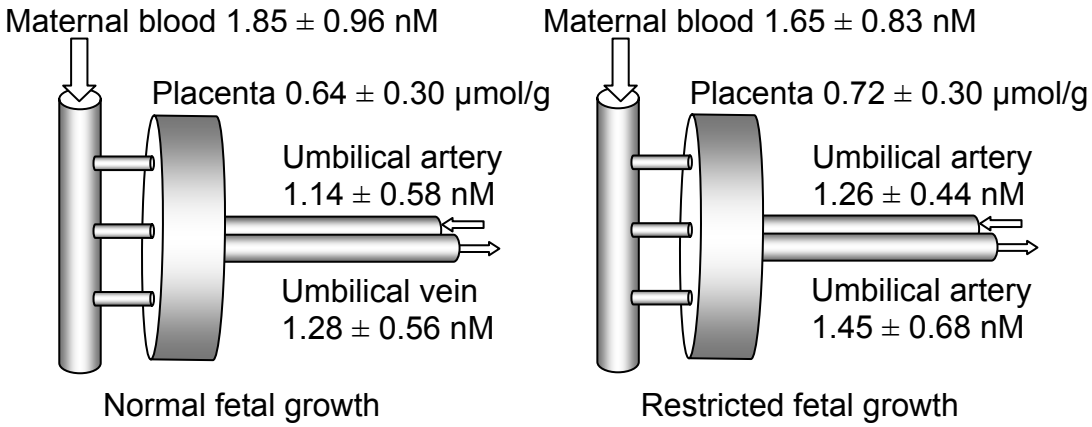

Figure 1. Concentration of cadmium in samples from 30 maternal-infant pairs with normal fetal growth and 21 maternal-infant pairs with restricted fetal growth.
Data shown as mean ± SD. To convert nM to µg/L or µmol/g to µg/kg, multiply by 0.112. Drawn from data in Osada et al. (2002).

Nishijo et al. (2002), supported by Kanazawa Medical University, measured cadmium in urine and milk from 57 Japanese women who delivered after 30 weeks gestation. Urine and milk were collected on the 5th or 8th post-partum day. Smoking, residence, and occupation were ascertained by questionnaire. Cadmium was measured by flameless atomic absorption spectrometry. Statistical analysis used *t*-test, Welch test, chi-squared, and multiple regression.

Subjects were divided on the basis of urine cadmium measurements into those with values above and below 2 nmol/mmol creatinine. This division was based on a previous report showing that individuals with the higher value had a 10% incidence of proteinuria. On univariate analysis, the 12 women with the higher level of urine cadmium were significantly older, delivered 2 weeks earlier, had lighter babies, and were more likely to have delivered prematurely. The association of urine cadmium concentration and birth weight disappeared when adjusted for gestational age. Urine cadmium concentration was significantly correlated with milk cadmium concentration, which ranged from ~1–10 nM **[0.11–1.1 µM; estimated from a graph]**. The authors stated in the Discussion section that geometric mean cadmium did not change between the early third trimester, 5th postpartum day, and 1 month postpartum in a subgroup of 8 subjects and that urinary cadmium and that in an unspecified number of these subjects, urinary cadmium 5 days postpartum was highly correlated with blood cadmium at 30–32 weeks gestation **[data not shown]**. Smoking did not influence milk cadmium concentration, but there were only 8 women who indicated that they smoked, and 6 of them said they quit smoking in early pregnancy.

The authors concluded that cadmium is associated with lower birth weight due to decreased gestational age and that cadmium can be transmitted to the infant through milk.

Falcón et al. (2003), supported by the Séneca Foundation of Murcia, Spain, measured placental cadmium in 96 women. Women who gave birth without complications to healthy singletons were interviewed after delivery about reproductive and medical history, medication and occupational exposure, and eating habits. Placentas were assayed for cadmium by atomic absorption spectrometry, and lipid peroxidation was measured by determination of malondialdehyde after

thiobarbituric acid treatment. Differences between means were assessed using the Mann-Whitney test and correlation was evaluated using the Spearman coefficient. Multiple linear regression was used to evaluate sources of variance in birth weight and other infant somatic measurements.

There were 61 women who did not smoke or who stopped smoking after learning they were pregnant, and there were 35 women who continued to smoke during pregnancy. Median birth weight was 328 g less in the infants of smoking compared to nonsmoking women. Infant length, head circumference, and abdominal circumference were also reduced in offspring of smoking compared to nonsmoking women. The placental cadmium concentration was higher in smoking than nonsmoking women (mean ± SD: smokers 51.0 ± 26.4 ng/g; nonsmokers 33.6 ± 16.6 ng/g). Placental cadmium concentration was significantly correlated with the number of cigarettes smoked but not with birth weight or other infant somatic measurements. Placental lipid peroxidation was significantly correlated with birth weight and abdominal circumference, but was not correlated with number of cigarettes smoked or with placental cadmium concentration.

The authors concluded that the decrease in infant size in smokers is probably not mediated by placental cadmium.

Carillo-Ponce et al. (2004), support not indicated, measured serum cadmium, lead, and zinc in newborns with neural tube defects and matched control newborns. The infants were born in a region of Mexico that had been contaminated with lead, cadmium, and arsenic from mining operations. The 31 cases of neural tube defect were matched with the next 2 liveborn infants of the same sex without a known congenital anomaly. Demographic information and medical history were obtained by interview with the mother. The children of women with epilepsy, diabetes mellitus, or first trimester fever or radiation were excluded. A peripheral blood sample was obtained from each child in the first day of life. Cadmium was measured using a graphite furnace atomic absorption spectrometer. Statistical analyses were performed using the Student *t*-test, chi-squared, and linear regression.

Mean cadmium concentration was similar in case children with neural tube defects and controls (mean ± SD 6.18 ± 5.9 µg/L in cases and **[6]**.16 ± 0.4 µg/L in controls). The serum cadmium concentration across all newborns ranged from 0 to 0.99 µg/L. Serum cadmium was inversely correlated with serum zinc ($r = -0.2742$ **[from a table; the text gives the correlation coefficient as −0.02742]**. Serum lead was not different between the cases and controls, but serum zinc was lower in case than control infants. The authors concluded that their study did not support the report of Jiang (1991), which found children with neural tube defects to have mothers with elevated serum cadmium concentrations.

Godschalk et al. (2005), support not indicated, evaluated 9 smoking and 16 nonsmoking women at the time of delivery. The smoking women smoked an average of 9 cigarettes/day. Maternal blood and umbilical cord blood were sampled after delivery. Mononuclear cells were isolated by centrifugation. Blood was hydrolyzed and centrifuged **[speed not given]**. The supernatant was analyzed for cadmium, lead, and zinc concentration in a graphite furnace atomic absorption spectrophotometer. DNA was isolated **[presumably from the mononuclear cells]** and DNA adducts were estimated using ^{32}P post-labeling analysis. *HPRT* variant frequency was determined in lymphocytes from cord blood. Simple and multiple regression and non-parametric statistical tests were used to analyze the data.

Maternal blood cadmium was significantly higher in smokers than in nonsmokers (mean ± SEM: 0.69 ± 0.14 µg/L in smokers, 0.33 ± 0.07 µg/L in nonsmokers). No significant difference was detected in cord blood cadmium concentration by maternal smoking status. Blood zinc and lead

concentrations were not found to differ by maternal smoking status in either maternal or cord blood samples. Aromatic DNA adducts were present in significantly higher amounts in maternal mononuclear cells in smokers than in nonsmokers (mean ± SEM: 0.99 ± 0.31 per 10^8 nucleotides in smokers, 0.43 ± 0.12 per 10^8 nucleotides in nonsmokers). No significant smoking-related difference was identified in adduct quantification in cord blood. Cord blood lymphocyte *HPRT* variant frequency was increased in the offspring of smokers compared to nonsmokers (mean ± SEM: 6.6 ± 1.4 per 10^6 lymphocytes in smokers, 2.3 ± 0.4 per 10^6 lymphocytes in nonsmokers). The authors reported a positive correlation between *HPRT* variant frequency and DNA adduct level ($R = 0.31$, $P = 0.16$). The ratio between *HPRT* variant frequency and DNA adducts was calculated (representing the efficiency by which adducts are turned into mutations). This ratio was correlated with cadmium concentration ($R = 0.61$, $P = 0.001$) and with cadmium/zinc ratio ($R = 0.57$, $P = 0.002$). The ratio between *HPRT* variant frequency and DNA adducts was independent of maternal smoking status. **[It is assumed but not stated that the comparisons were made in umbilical cord blood and monocytes.]**

The authors concluded that the conversion of pro-mutagenic DNA lesions to mutations could be enhanced by exposure to cadmium. They hypothesized that DNA repair proteins with zinc-finger motifs may be impaired by an increased cadmium/zinc ratio.

Nishijo et al. (2004b), supported by Kanazawa Medical University, evaluated the relationship between maternal blood cadmium concentration at 30–32 weeks gestation and subsequent newborn infant size. Fifty-five Japanese subjects had blood samples drawn during a routine prenatal visit and completed a questionnaire concerning smoking and possible residential or occupational exposure to cadmium. The subjects included 1 current smoker and 9 ex-smokers. Comparisons of maternal blood cadmium concentration between groups with various maternal characteristics were made by Student *t*- or Welch test. Spearman correlation was used to evaluate the relationship between maternal blood cadmium concentration and infant size. Multiple regression analysis was used to further characterize relationships between maternal blood cadmium concentration and infant size.

The mean (range) maternal blood cadmium concentration was 9.29 (1.43–39.6) nM **[1.04 (0.16–4.45) µg/L]**. Maternal cadmium concentration was correlated with maternal age ($r = 0.287$). There was no statistically significant relationship between gestational age, parity, preeclampsia, or preterm labor and maternal blood cadmium concentration. Maternal blood cadmium concentration was not higher in the woman who smoked or in women with residential or occupational cadmium exposure than in other women. There was no significant relationship between indices of iron-deficiency anemia and blood cadmium concentration. There was a significant inverse correlation between maternal blood cadmium concentration and infant length ($r = -0.337$) but not weight ($r = -0.233$). Infant length was predicted by maternal blood cadmium concentration in the multiple regression model adjusted for gestational age and maternal weight. There were 8 infants whose mothers had blood cadmium concentrations > 13.4 nM **[1.51 µg/L]**. These infants had a significantly lower birth weight than infants whose mothers had blood cadmium concentrations < 13.4 nM **[data were not shown]**. The authors concluded that maternal blood cadmium may influence newborn size.

Ronco et al. (2005), supported by the International Atomic Energy Agency, measured cadmium, zinc, iron, and copper in placentas from 20 smokers and 20 nonsmokers in Chile. Medical and diet history and information on occupational and environmental exposure to metals was collected by questionnaire. Smoking status was determined by questionnaire and measurement of urine cotinine. Placentas were collected after delivery. Samples were collected from the maternal side of the placenta (the decidua) and the fetal side (the chorionic plate) and the remainder of the

placenta was homogenized and used to represent total placenta. Cadmium and copper determinations were made by graphite furnace atomic absorption spectrometry. Zinc and iron were measured by instrumental neutron activation analysis. Metal concentrations were compared with Student *t*-test and the relationship between metal concentrations and infant birth weight were evaluated with Pearson correlation.

Smokers consumed 5–10 cigarettes/day. Smokers and nonsmokers did not differ significantly in age, parity, maternal size (height, weight, body-mass index), or placental weight. Infants born to smokers were a mean 280 g lighter than infants born to nonsmokers. There were no differences in gestational age at delivery in the two groups. Zinc and cadmium concentrations were higher in the placenta samples (total, maternal side, and fetal side) of smokers than nonsmokers. Mean ± SD total placental cadmium was 0.06 ± 0.02 µg/g dry weight in smokers and 0.02 ± 0.01 µg/g dry weight in the placentas of nonsmokers. In smokers but not nonsmokers, cadmium concentration on the maternal side of the placenta (0.05 ± 0.02 µg/g dry weight) was higher than on the fetal side (0.04 ± 0.01 µg/g dry weight). Placental cadmium concentration was inversely correlated with infant birth weight in smokers ($r = -0.8$) and nonsmokers ($r = -0.4$). The authors concluded that the increase in placental cadmium concentration may produce a decrease in fetal growth by making less zinc available to the fetus. They hypothesized that cadmium exposure may cause an increase in placental metallothionein, resulting in retention of zinc in the placenta.

Friel et al. (2005), supported by the Canadian Institute of Health Research and the Janeway Child Health Research Foundation, measured zinc and cadmium concentration is tissues obtained at autopsy of infants with and without anencephaly. There were 33 anencephalic infants of whom all but 2 were stillborn and 22 control infants of whom all but 2 were liveborn. Samples of liver, kidney, sciatic nerve, pancreas, and muscle were collected from the right side of the infant and prepared for measurement of cadmium and zinc by inductively coupled plasma mass spectrometry. Not all tissues were obtained from all infants. Differences in cadmium and zinc content between anencephalic and control groups were evaluated with *t*-tests.

Anencephalic infants were delivered at a mean ± SD gestational age of 25 ± 8 weeks, and control infants were delivered at 298 ± 8 weeks. Two-thirds of the anencephalic infants were female compared to about half of the control females. The cadmium concentrations of tissues are summarized in Figure . Sciatic nerve cadmium in anencephalic fetuses was 3% of the mean control values, but specimens were obtained form only 4 control infants, resulting in marked variability and a lack of statistical significant difference between the groups. Liver concentration of cadmium in anencephalic infants (15 ± 5 ppb **[µg/kg]**) was lower than liver concentration of cadmium in control infants (54 ± 16 ppb). Live zinc was 1.6 times higher in anencephalic than control infants. The authors noted the difference between their cadmium results and those of Limin and Wenzhen (1992), which had shown a higher concentration of cadmium in the liver of anencephalic than control infants. They concluded that cadmium may not be important in the development of anencephaly or may have different significance in Canada (their study) than in China (Limin and Wenzhen study).

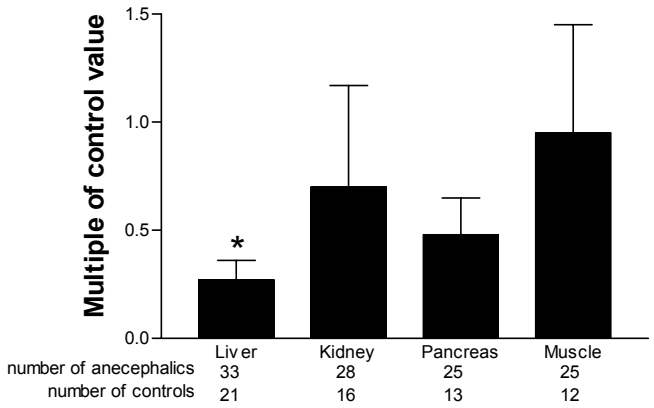

Figure 2. Tissue cadmium concentration in anencephalic fetuses as a fraction ± SD of the mean value in tissues from control fetuses.
*Significantly different from control tissue mean, $P < 0.05$. From Friel et al. (2005)

Brender et al. (2006), supported by the CDC, evaluated maternal exposure to cadmium, arsenic, lead, and mercury in women who gave birth to a child with a neural tube defect. This case-control study was conducted in Texas near the border with Mexico and included 225 cases (women who gave birth to an affected child) and 378 controls (women delivering a normal child during the same time period in the same geographic area). Subjects were interviewed 5–6 weeks after delivery using a standardized questionnaire to collect information on medical and reproductive history, residential history, environmental and occupational exposures, and use of medications or vitamins. About 1 year after the estimated time of conception, women submitted urine specimens for measurement of cadmium concentration. The 1-year time period was selected to account for possible seasonal variations in exposure. Cadmium was determined with inductively coupled plasma mass spectrometry and concentrations were reported without regard to creatinine or any other adjustment for urine dilution. Parental occupational exposures were estimated based on questionnaire information. Residence at the time of conception was used to estimate drinking water exposure to cadmium based on records maintained by the state for the public water supply serving the subject's residence. The subject's address at conception was used to estimate air exposures based on data obtained from the EPA Toxic Release Inventory for industries within 2 miles of the subject's residence. Median urine cadmium concentrations in cases and controls were compared using the Mann-Whitney test. Adjusted odds ratios were calculated using logistic regression. Urine cadmium concentration results were dichotomized at the 95th percentile for Mexican Americans in the 1999-2000 National Health and Nutrition Examination Survey (NHANES).

Median urine cadmium concentration did not differ by case or control status. The median urine cadmium concentration was 0.4–0.5 µg/L in these women with a range of 0.1–1.5 µg/L. There was no significant difference between case and control women in the proportion above the NHANES 95th percentile for urine cadmium concentration. Estimated maternal or paternal exposure to cadmium at work was not significantly associated with case or control status. There was no difference in the proportion of cases and controls with drinking water cadmium ≥ 5 µg/L or living within 2 miles of a facility that emitted cadmium into the air. The authors concluded that exposure to cadmium does not appear to be a risk factor for neural tube defect.

Vigeh et al. (2006), supported by the Japan Society for the Promotion of Science and the University of Tokyo, evaluated the possible relationship between maternal or umbilical cord blood cadmium concentration and pre-eclampsia. Subjects included 396 subjects who gave birth

in Tehran. Umbilical cord blood was sampled at delivery and maternal blood was sampled post-partum. Cadmium and other elements were measured by inductively coupled plasma-mass spectrometry. Preeclampsia was diagnosed based on hypertension and proteinuria in 31 subjects. None of the preeclamptic women were smokers, and 2 of the non-preeclamptic women were smokers. Data were analyzed using the Wilcoxon rank-sum test, chi-squared, and Fisher test.

Mean ± SD (range) cadmium in maternal blood was 0.5 ± 0.21 (0.2–1.1) µg/L in preeclamptic women and 0.54 ± 0.16 (0.1–2.6) µg/L in non-preeclamptic women. Mean ± SD (range) cadmium in umbilical cord blood was 0.34 ± 0.39 (0.0–1.30) µg/L in preeclamptic pregnancies and 0.34 ± 0.44 (0.0–6.3) µg/L in non-preeclamptic pregnancies. There was no statistical effect of preeclampsia on maternal or umbilical cord blood cadmium concentrations. The authors did not express conclusions relative to cadmium.

Windham et al. (2006), supported by the Agency for Toxic Substances and Disease Registry, the Centers for Disease Control and Prevention, and the California Department of Health Services, evaluated possible associations between a diagnosis of autistic spectrum disorder and exposure to environmental cadmium and other substances. Children with autistic spectrum disorder in 6 countries in the San Francisco Bay area were identified through active surveillance coordinated by CDC and from computerized records of Kaiser Permanente. Control children from the 6 counties were selected from birth certificate records and matched 2:1 with cases by sex and month of birth. Addresses and demographic data were obtained from birth certificates. The final sample included 284 children with autism and 657 control children.

Exposure was assessed using EPA estimates of exposure to "hazardous air pollutants" by census tract in 1996, which was the year closest to the birth year of the children (1994) for which estimates were available. Of the 33 compounds in the EPA data base, 25 were selected for further evaluation. Six of these compounds showed little variation across the census tracts of interest in this study, and these compounds were excluded from further consideration. Exposures to many of the other compounds were highly correlated. Compounds were considered individually and in groups. Cadmium was included with arsenic, chromium, lead, manganese, mercury, and nickel in a metals group.

To express the magnitude of exposure to a group, the exposure quartiles of the members of the group were added to produce an exposure index. For metals, a census tract could have a score that ranged from 7 (each metal present in a concentration equivalent to its first or lowest quartile) to 28 (each metal present in a concentration equivalent to its fourth or highest quartile). Associations between exposure status and autism were evaluated using logistic regression adjusting for race, parental age, parental education, maternal parity, low birth weight, and preterm delivery. **[Possible exposures to tobacco, ethanol, and other drugs were not considered.]** The first and second exposure quartiles were taken as the referent group for comparison with the third and fourth quartiles. The quartile cut points were determined from the control distribution of individual chemical exposures or, for grouped chemicals, the control distribution of exposure indices.

There was no statistical difference between autistic subjects and controls in the mean estimated air concentration of cadmium. There was a statistically significant association between autism and estimated exposure to metals as a group and to cadmium at the third and fourth quartiles (Table).

Table 13. Adjusted Odds Ratios (95% Confidence Intervals) for Autism and Cadmium-Related Exposures in Air

Exposure	Third quartile	Fourth quartile
Metals	1.68 (1.17–2.41)	1.50 (1.05–2.12)
Cadmium	1.43 (1.01–2.04)	1.54 (1.08–2.20)

From Windham et al. (2006)

Estimated exposures to cadmium and mercury were correlated ($r = 0.76$). When exposure to mercury and cadmium were included in the same model, there was a statistically significant association between autism and the fourth quartile of exposure to mercury but not cadmium. The authors concluded that there may be an association of autism with high ambient air concentrations of metals.

C. Human Placental Cell Culture

Boadi et al. (1992a), supported by the German Society for Radiation and Environmental Research and the Israeli Technion V.P.R. Fund-Steigman Research Fund, measured enzyme activities in first trimester human placental tissue after culture with cadmium. Ten placentas were collected at termination of pregnancy between 8 and 12 weeks gestation. Explants (50 mg) were cultured in cadmium chloride with cadmium concentrations of 0, 0.75, 1.5, 3, 6, or 12 µg/mL **[mg/L]**. The tissue was incubated for 6 or 24 hours following which it was homogenized and centrifuged and the supernatant used for analysis of enzyme activity. Arylhydrocarbon hydrolase activity was assessed by oxidation of benzo[*a*]pyrene, quinone reductase by reduction of 2,6-dichlorophenolindophenol, catechol-*O*-methyl transferase by methylation of 2-hydroxyestrone, and glucose-6-phosphate dehydrogenase by reduction of NADPH. Statistical analysis was performed using 2-way ANOVA for the effects of cadmium, the duration of exposure to cadmium, and the interaction. **[The number of explants evaluated per experiment is unclear and is reported in different places as 6, 8, or 10.]**

Arylhydrocarbon hydroxylase activity was increased by cadmium culture for 6 or 24 hours, reaching maximum activity after culture with cadmium 3 µg/mL. At higher cadmium concentrations, enzyme activity was decreased. Quinone reductase and catechol-*O*-methyl transferase activity appeared to increase with increasing cadmium dose **[assessed graphically; statistical analysis not reported]**. Glucose-6-phosphate dehydrogenase activity was decreased by cadmium in a concentration-dependent manner at both incubation durations. The authors concluded that the increased activity of arylhydrocarbon hydroxylase, quinone reductase and catechol-*O*-methyl transferase may be beneficial in facilitating the detoxification of xenobiotics compounds but that the inhibition of glucose-6-phosphate dehydrogenase may be harmful by inhibiting energy metabolism and steroid production.

Boadi et al. (1992b), supported by the German Society for Radiation and Environmental Research and the Israeli Technion V.P.R. Fund-Steigman Research Fund, measured placental membrane fluidity after in vitro exposure to cadmium. Human placentas were collected after term vaginal deliveries from nonsmoking women who did not take medications. Placental pieces (100–150 mg) were incubated for 6 or 24 hours with cadmium at 0, 6, or 12 µg/mL **[mg/L]**. Incubations with mercury were also carried out **[not discussed here]**. Viability was assessed by measuring glucose utilization, human chorionic gonadotropin production, and LDH concentration in the media. Following incubation of placental pieces, microvillus cell membranes were extracted, and fluidity was assessed by steady-state fluorescence polarization with 1,6-diphenyl-1,3,5-hexatriene as a probe. Alkaline phosphatase was measured to assess the degree of membrane enrichment in the preparations compared to a placental mince. Phospholipid and cholesterol content of the membranes was measured. Cadmium concentrations in the placental

tissue were measured by graphite furnace atomic absorption spectrometry. Statistical analysis was by 1-way ANOVA followed by Student *t*-test.

Viability of the cultured placental pieces was not affected by incubation with cadmium. Alkaline phosphatase measurement suggested that the membrane preparations were enriched 18-fold compared to a placental mince. There was no evidence of decreased viability of the placental tissue after incubation with cadmium. Membrane fluidity was not altered after a 6-hour incubation with cadmium at either concentration but was decreased to a similar extent by both concentrations at 24 hours. Mean ± SD tissue cadmium increased from 0.026 ± 0.01 ng/mg protein in the control cultures to 3.995 ± 0.43 ng/mg protein in tissue cultured in cadmium 6 μg/mL and 5.631 ± 0.61 ng/mg protein in tissue cultured in cadmium 12 μg/mL. There were no significant changes in the tissue content of cholesterol or phospholipid with cadmium exposure.

The authors concluded that the decrease in placental membrane fluidity associated with cadmium exposure in vitro may have been due to cadmium-mediated oxidation of double bonds in membrane fatty acids. They suggested that a decrease in membrane fluidity may be important in decreasing the function of membrane-associated enzymes.
Jolibois et al. (1999a), supported by NIH and Tulane/Xavier, evaluated the effects of cadmium on progesterone production by cultured human trophoblast. Cytotrophoblast was isolated from term placentas obtained at cesarean section. Cytotrophoblast was placed in culture, resulting in the development of syncytiotrophoblast within 96 hours. Cultures were exposed to cadmium chloride at 0, 5, 10, or 20 μM **[cadmium 0, 0.56, 1.12, or 2.25 mg/L]** for 96 hours. Other cultures were exposed from 72 hours, when 70% of the cells are expected to be syncytial, until 96 hours, when 90% of the trophoblast is syncytial and progesterone production normally peaks. Cell viability was assessed by trypan blue exclusion. At 72 or 96 hours, media were collected for evaluation of progesterone concentration by radioimmunoassay. Other trophoblast cultures were exposed to cadmium chloride at the same concentrations for 24, 48, 72, or 96 hours and cell cadmium concentration measured by graphite furnace atomic absorption spectrometry. Trophoblast that had been cultured for 96 hours with cadmium 0 or 20 μM **[cadmium 2.25 mg/L]** was evaluated histologically after fixation in Bouin fluid and staining with hematoxylin and eosin. Statistical analyses were performed by linear regression and *t*-test.

Accumulation of cadmium in trophoblast was time dependent but not clearly concentration-dependent. In some placentas at some time points, cadmium at the middle concentration accumulated to a greater extent than at the high concentration. Progesterone produced by cultured trophoblast was decreased by cadmum in a concentration-dependent manner in cultures exposed for the first 72 hours and in cultures exposed from 72 to 96 hours. The highest cadmium concentration decreased progresterone production to 35–38% of the control concentration at 72 and 96 hours. Histologic evaluation after exposure to this concentration of cadmium did not show evidence of impaired syncytial development. The authors concluded that an increase in cellular uptake of cadmium by trophoblast is associated with a decrease in progesterone production.

Jolibois et al. (1999b), supported by NIH and Tulane/Xavier, evaluated the effects of cadmium on progesterone production by cultured human trophoblast. Cytotrophoblast was isolated from term placentas obtained at cesarean section. Cytotrophoblast was placed in culture, resulting in the development of syncytiotrophoblast within 96 hours. Cultures were exposed to cadmium chloride at 0, 5, 10, or 20 μM **[cadmium 0, 0.56, 1.12, or 2.25 mg/L]** for 96 hours. Cell viability was assessed by conversion of MTT to formazan. Additional trophoblast was cultured for 96 hours with cadmium chloride at 0, 5, 10, 20, 40, or 80 μM **[cadmium 0, 0.56, 1.12, 2.25, 4.49, or 8.98 mg/L]** following which DNA was extracted and subjected to electophoresis. DNA laddering was interpreted as evidence of apoptosis. Time-response analysis of DNA laddering was

performed using exposure to cadmium 10 µM **[1.12 mg/L]** for 48, 72, or 96 hours. Trophoblast cultured with cadmium chloride 0 or 20 µM **[cadmium 2.25 mg/L]** for 96 hours was imaged using immunocytochemical staining for desmoplakin, a component of desmosomes, to identify cell membranes and propidium iodide to identify nuclei. Syncytial maturation was assessed by counting the number of nuclei associated with mononucleated and multinucleated cells. Additional trophoblast was exposed to cadmium chloride 0, 5, 10, or 20 µM **[cadmium 0, 0.56, 1.12, or 2.25 mg/L]** for 96 hours following which RNA was extracted and RT-PCR used to quantify LDL-receptor mRNA. Statistical analyses were performed by ANOVA and Student *t*-test.

Trophoblast viability as assessed by MTT conversion was not impaired by culture with cadmium at concentrations up to 20 µM **[2.25 mg/L]**. DNA laddering was present in all cultures at 96 hours but the number of bands was similar in the control cultures and at all concentrations of cadmium. The time-response study showed that laddering had begun to appear in cultured cells at 48 hours but was not different in control or cadmium-exposed trophoblast. Imaging of cultured trophoblast showed no impairment of syncytial maturation at a cadmium concentration of 20 µM [**2.25 mg/L**]. Expression of LDL-receptor mRNA was inhibited by cadmium in a concentration-dependent manner with transcripts 56, 47, and 27% of control at 5, 10, and 20 µM cadmium. The authors concluded that cadmium exposure of trophoblast decreases LDL-receptor transcription without interfering with cell viability or syncytial maturation. They cited previous work showing a decrease in trophoblast production of progesterone in culture in the presence of cadmium and suggested that inhibition of LDL-receptor transcription may be a mechanism by which there is less cholesterol available to the trophoblast for steroid biosynthesis.

Piasek et al. (2001), supported by the Croatian Ministry of Science and Technology, evaluated cadmium in placentas from 56 nonsmoking and smoking Croatian women. Smoking status was assessed by a questionnaire that was also used to obtain information on passive smoke exposure, rural or urban residence, occupation, and diet. There were 29 nonsmokers and 27 smokers (2 women in each group did not have placental samples for metal analysis). Placentas were collected after delivery and frozen until analysis for progesterone by radioimmunoassay and cadmium by electrothermal atomic absorption spectrometry. Placental lead, iron, zinc, and copper were also assayed. Effects of smoking were analyzed using ANOVA.

No significant effect of smoking on birth weight was identified. The mean progesterone concentration in the placental tissue from smoking women was 41% lower than the progesterone concentration in placental tissue from nonsmoking women. Placental cadmium was 79% higher in smoking than nonsmoking women (mean ± SEM: 28.5 ± 2.05 ng/g in smokers, 15.9 ± 1.44 ng/g in nonsmokers). Reported passive smoking was not shown to have an effect on placental cadmium. The authors concluded that cigarette smoking is associated with increased cadmium body burden, including placental accumulation, and that the placentas of smokers contain less progesterone than the placentas of nonsmokers. They speculated that cadmium may interfere with transcriptional regulation of steroid synthesis or with intracellular trafficking of cholesterol into mitochondria.

Ronco et al. (2006), supported by the International Atomic Energy Agency and the Chilean Commission for Nuclear Energy, measured cadmium, zinc, and metallothionein concentrations in the placentas of smoking and nonsmoking Chilean women. Twenty placentas were collected after delivery of normal pregnancies. Questionnaires were used to assess smoking status, which was confirmed using urine cotinine concentration. Women were designated as nonsmokers (never smokers, n = 10) or smokers (smoking throughout pregnancy, n = 10). Homogenized whole placentas were used for analysis. Cadmium was measured by graphite furnace atomic absorption

spectrometry, zinc by instrumental neutron activation analysis, and metallothionein-1 and -2 by HPLC with UV detection. Fractions from the HPLC column were analyzed by atomic absorption spectrometry with inductively coupled plasma for cadmium, which was used to quantify metallothionein-1 and -2. Metallothionein-1 and -2 were also quantified by Western blot. Comparisons between concentrations in the placentas of smokers and nonsmokers were made with Mann-Whitney *U*-test.

Results are summarized in Table 14. Based on the smoking-associated differences in cadmium in the metallothionein peak, the authors concluded that placental metallothionein 2 was increased by smoking. This increase resulted in a 2-fold increase in total metallothionein in the placentas of smokers. The potential pool of metallothioneins bound to cadmium or zinc was estimated assuming that 1 mol metallothionein bound 7 mol cadmium or zinc. The authors concluded that because metalliothionein-2 was increased in smokers and only a small proportion of the metallothionein bound cadmium, there was an increase in the capacity to bind zinc. The authors recognized that the zinc estimated not to be bound to metallothioneins was similar in both groups, but suggested that a small difference in zinc accessibility to the fetus might have meaningful effects on fetal growth.

Table 14. Characteristics of Placentas From Smokers and Nonsmokers

Endpoint	Smokers	Nonsmokers
Median cadmium in metallothionein-1 peak, ng	53	44.8
Median cadmium in metallothionein-2 peak, ng[a]	58.1	7.4
Median metallothionein-1, nmol/g wet weight	1.06	0.90
Median metallothionein-2, nmol/g wet weight[a]	1.16	0.15
Median total metallothionein, nmol/g wet weight[a]	2.2	1.1
Median (range) placental cadmium, pmol **[ng]**/g wet weight[a]	80 (62–102) **[9.0 (7.0–11.5)]**	36 (27–46) **[4.0 (3.0–5.2)]**
Estimated metallothioneins bound to cadmium, pmol/g wt weight	11.4	5.1
Estimated metallothioneins not bound to cadmium, pmol/g wt weight	2189	1095
Median (range) placental zinc, nmol/g wet weight	140 (111–157)	128 (79–179)
Estimated zinc-metllothionein-1, nmol/g wt weight	7.4	6.3
Estimated zinc-metllothionein-2, nmol/g wt weight	8.1	1.05
Estimated zinc bound to total metallothioneins nmol/g wt weight	15.5	7.35
Estimated zinc not bound to total metallothioneins nmol/g wt weight	124.5	120.7

[a]Significant difference between smokers and nonsmokers by Mann-Whitney *U*-test
From Ronco et al. (2006)

D. Male Reproductive Toxicity

Gennart et al. (1992), supported by the European Coal and Steel Community, evaluated the fertility of Belgian men with occupational exposure to cadmium. The subjects had worked in 1 of 2 cadmium smelters. Some of these workers were also exposed to lead. Other groups of workers were selected based on exposure to lead or manganese **[not discussed here]**. An unexposed comparison group consisted of men working in factories or in the maintenance department of the smelters. Control men were excluded if their blood lead concentration exceeded 20 µg/dL or if their urinary cadmium concentration exceeded 20 µg/g creatinine. Subjects were excluded if their medical histories included conditions that might interfere with reproductive function or if they

were unmarried. Information was collected by questionnaire on subject age, residence, education, health history, occupational history, smoking, and use of coffee and alcohol. Each man was also asked to identify his wife's dates of birth, date of marriage, the number of his children born alive, and his children's dates of birth. Blood and urine samples were collected at the time of the questionnaire for determination of blood lead and zinc protoporphyrin and urinary cadmium and creatinine **[analytical methods not given]**. Subjects were excluded from the cadmium group if their blood lead concentration was >30 µg/dL.

Birth rates were calculated in 4 age strata (<25, 25–29, 30–34, and ≥35 years), and relative risk of exposure was calculated using Cochran and Mantel-Haenszel methods. The ratio between the observed and expected birth rate was calculated according to the wife's age group, parity, and interval since previous birth. Logistic regression was used to calculate risk estimates for conception within each person-year of presumed fertility (defined as a year of marriage prior to the wife's 41st birthday). Exposure was entered into the model as a categorical value or, if possible, a continuous variable. Educational level, smoking, and alcohol use were entered into the model in a stepwise fashion.

There were 83 cadmium-exposed and 138 unexposed subjects. Men in the cadmium group were older than in the reference group (mean ± SD 51.6 ± 10.7 years in the cadmium group, 41.8 ± 11.2 years in the reference group). There was no significant difference in the ages of the wives or the years of marriage. There was no difference in the percentage of smokers in either group (cadmium 80.7%, reference group 68.8%). The mean ± SD duration of occupational exposure in the cadmium group was 24.0 ± 13 years (range 1.1–52.3 years). Mean ± SD (range) blood lead was 18.6 ± 5.8 (8.0–30.0) µg/dL in the cadmium group and 10.4 ± 3.3 (4.4–19.0) µg/dL in the reference group. Mean ± SD (range) urinary cadmium was 6.94 ± 4.56 (2.07–24.15) µg/g creatinine in the cadmium group and 0.71 ± 0.52 (0.09–1.99) µg/dL in the reference group.

The birth rate in the cadmium-exposed group was greater than that in the reference group; however, this effect was due to the older age of the cadmium-exposed workers. When adjusted for age, there was no different in birth rates between cadmium and unexposed workers and no effect of the onset of cadmium work on birth rate. The authors commented that the cadmium-exposed workers appeared to have been exposed to excessive cadmium because 25% of them had renal impairment, as evidenced by a serum creatinine >1.3 mg/dL. They concluded that the lack of evidence of adverse effects of cadmium on male fertility in workers was consistent with experimental animal data.

Xu et al. (1993), supported by the National University of Singapore, measured blood and seminal fluid cadmium and performed semen analyses in 221 Singaporean men in a fertility clinic. Men were excluded from participation if they had a history of urinary tract infection, sexually transmitted disease, or testicular examination or if they had abnormal findings on andrological examination. Information on smoking, alcohol, and occupational exposures was obtained by questionnaire. **[These factors were not further mentioned.]** Semen samples were collected after 3 days of sexual abstinence and blood samples were collected the same day. Semen analysis was performed and, if the remaining volume of semen permitted, cadmium concentration was measured by graphite furnace atomic absorption spectrometry. Blood cadmium concentration was measured using the same technique. Lead, zinc, and selenium were also measured in blood and seminal fluid **[not discussed here]**. Statistical methods were not specified but appeared to include linear regression.

Mean ± SD cadmium concentration in blood in 191 subjects was 1.25 ± 0.9 µg/L and in seminal fluid in 74 subjects was 0.61 ± 0.21 µg/L. Blood cadmium concentration was inversely correlated

with sperm density ($r = -0.15$), but was not significantly correlated with other semen analyses parameters. There was no significant correlation between blood cadmium concentration and sperm density in men with sperm density ≥ 20 million/mL, but blood cadmium concentration was significantly inversely correlated with sperm density in men with sperm density < 20 million/mL ($r = 0.230$). Seminal fluid cadmium concentration was inversely correlated with semen volume ($r = -0.29$) and morphologically normal sperm ($r = -0.21$; $P = 0.055$). The authors concluded that cadmium exposure may have adverse effects on the male reproductive system.

Keck et al. (1995), support not indicated, measured seminal fluid cadmium concentration in fertile and infertile German men. Subjects included 12 men with proven fertility, 44 men with unexplained infertility who were selected based on normal semen analyses, and 118 infertile men who were unselected for semen analysis results. In addition, 2 infertile men with known occupational exposure to cadmium were studied. Information on smoking status and the daily number of cigarettes smoked was available for the infertile men. Semen analyses were performed after 2–7 days sexual abstinence. Seminal fluid cadmium concentration was measured by graphite furnace atomic absorption spectrometry. Blood samples were collected for determination of serum testosterone and 17β-estradiol by radioimmunoassay, and LH, FSH, and prolactin by immunofluorometric assay. Statistical analyses were performed using Student *t*-test, Mann-Whitney *U*-test, and multiple regression analysis.

There were no significant differences between the fertile and infertile groups in seminal fluid cadmium concentrations, which were 0.38–0.44 µg/L (range of group means). The 2 patients with known cadmium exposure had seminal fluid cadmium concentrations of 2.99 and 3.56 µg/L. There was no significant correlation between seminal fluid cadmium concentration and any semen analysis endpoint. In patients with normal sperm density, seminal fluid cadmium concentration was higher in smokers than in nonsmokers (mean ± SD 0.55 ± 0.81 in smokers and 0.42 ± 0.67 µg/L in nonsmokers). Seminal fluid cadmium concentration in infertile men was weakly correlated with daily number of cigarettes smoked ($r = 0.17$; $P = 0.04$). There were no group differences in serum hormone measurements; no attempt to correlated hormone values with seminal fluid cadmium was reported. FSH values for the 2 men with known cadmium exposure were elevated, but the authors could not conclude that cadmium exposure was responsible for the elevation. The authors also could not conclude what level of cadmium in seminal fluid was associated with impaired fertility.

Telišman et al. (1997), supported by the International Lead Zinc Research Organization, Inc., studied blood and seminal fluid cadmium concentrations in 120 Croatian men who were not exposed occupationally to cadmium. There were 42 smokers and 78 nonsmokers, ascertained by questionnaire. The 42 nonsmokers included 9 former smokers. Blood and semen samples were collected after 4 days of sexual abstinence. Cadmium concentrations were measured by electrothermal atomic absorption spectrometry. Statistical analyses included the Mann-Whitney *U*-test and regression analysis.

Blood and seminal fluid cadmium concentrations were significantly higher in smokers than nonsmokers (Table 15). The 9 former smokers appeared to have blood and seminal fluid cadmium concentrations that were somewhat higher than never smokers **[statistical testing not reported]**. Among smokers, there was a significant correlation between number of cigarettes smoked and blood cadmium concentration ($r = 0.296$) and seminal fluid cadmium ($r = 0.378$). The authors noted that there was considerable variability in seminal fluid cadmium concentration at any given level of blood cadmium concentration, and they suggested that these 2 measurements may not reflect the same dynamic aspects of cadmium accumulation. **[These data were republished as part of Telišman et al. (2000).]**

Table 15. Blood and Seminal Fluid Cadmium Concentrations in Croatian Men

	Median (range) cadmium concentration, µg/L	
Tissue	Nonsmokers	Smokers
Blood	0.46 (0.19–1.49)	4.33 (0.49–13.33)
Semen	0.54 (0.17–1.67)	0.85 (0.29–3.56)
From Telišman et al. (1997)		

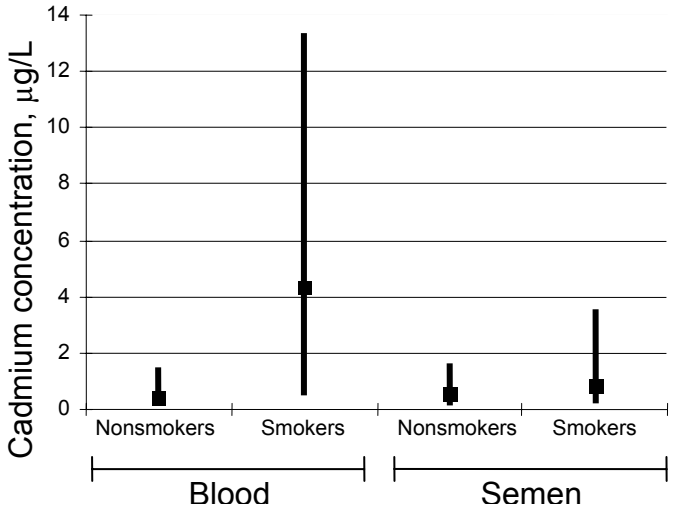

Figure 3. Median and range cadmium concentrations in blood and seminal fluid from 42 nonsmoking and 76 smoking Croatian men.
From Telišman et al. (1997, 2000).

Telišman et al. (2000), supported by EPA and the International Lead Zinc Research Organization, Inc., studied blood and seminal fluid cadmium concentration and semen analysis endpoints in Croatian men. Subjects included 98 men with occupational exposure to lead and 51 subjects without occupational exposure to lead. **[The focus of the study was lead, but information on cadmium was also reported.]** None of the men had known occupational exposure to cadmium. There were 95 smokers and 54 nonsmokers. Information on age, smoking, alcohol use, and marital status was collected by examination, and an andologist performed a history and physical examination to exclude men with genital tract abnormalities. Blood samples were collected for measurement of blood lead and cadmium concentration, serum zinc and copper concentration, erythrocyte protoporphyrin, δ-aminolevulinic acid dehydratase activity, and serum concentrations of FSH, LH, prolactin, testosterone, and 17β-estradiol. Semen was collected after 4 days sexual abstinence for routine semen analysis and for measurement of lactate dehydrogenase, fructose, zinc, acid phosphatase, and citric acid. In a subset of 118 subjects with adequate seminal fluid volume, seminal fluid concentrations of lead and cadmium were measured. Blood and seminal fluid cadmium were measured by electrothermal atomic absorption spectrometry. Statistical methods included Mann-Whitney *U*-test, Pearson and Spearman correlation, and stepwise multiple regression.

Blood cadmium concentration was higher in smokers than nonsmokers. Median (range) blood cadmium in smokers was 4.33 (0.49–13.33) µg/L and in nonsmokers was 0.46 (0.16–2.85) µg/L. There was a statistically significant correlation between smoking and blood cadmium

concentration (r = 0.777). There was a correlation between blood cadmium concentration and abnormal sperm morphology (r = 0.158), serum LH concentration (r = 0.185), decreased prolactin (r = −0.168), and testosterone (r = 0.295). **[These statistically significant correlations came from a table in which 210 univariate comparisons were made between 10 indices of exposure and 21 semen endpoints.]** In the stepwise multiple regression, blood cadmium concentration was a significant contributor to decreased sperm motility, morphologically abnormal sperm, and serum testosterone.

Blood and semen cadmium concentrations in the 118 men with semen measurements are shown in Figure 3. **[The means and ranges for blood and seminal fluid cadmium in smokers and nonsmokers were identical to those reported by Telišman et al. (1997).**] There was a statistically significant difference between smokers and nonsmokers in cadmium concentrations in both tissues. In stepwise multiple regression in this subset, blood cadmium concentration was significantly correlated with morphologically abnormal sperm (r = 0.260) but seminal fluid cadmium concentration was not significantly correlated with any semen analysis endpoint. Seminal fluid cadmium concentration was correlated with seminal fluid zinc, acid phosphatase, and citric acid concentration. The authors postulated that cadmium exposure may have adverse effects on testicular function through alterations in zinc availability secondary to metallothionein induction. They suggested that seminal fluid cadmium may increase prostate function.

Jurasović et al. (2004), supported by the Croatian Ministry of Science and Technology, evaluated blood cadmium and semen analyses in 123 Croatian men. Subjects were randomly selected from men presenting to an andrology clinic for semen analysis either as prospective semen donors or as part of a fertility evaluation. None of the subjects were occupationally exposed to metals and none had clinical evidence of hypogonadism or prostatitis. Information on smoking, alcohol, medical history, and diet was obtained by questionnaire. There were 61 smokers and 62 nonsmokers. Semen was collected after 4 days of sexual abstinence for evaluation by computer-aided sperm analysis. A blood sample was collected on the same morning as the semen sample. Blood cadmium and lead concentrations were determined by atomic absorption spectrometry, δ-Aminolevulinic acid dehydratase activity, erythrocyte protoporphyrin, hematocrit, hemoglobin, glutathione peroxidase, and serum concentrations of copper, zinc, selenium, FSH, LH, prolactin, testosterone, and 17β-estradiol were also measured. Seminal fluid was analyzed for LDL-C_4, fructose, zinc, acid phosphatase, and citric acid. Testis size was measured **[method not indicated]**. Statistical analysis was performed using the Mann-Whitney U-test, Spearman correlation, and multiple regression.

Median (range) blood cadmium concentration was 0.85 (0.20–11.93) µg/L in the entire sample, 2.94 (0.49–11.93) µg/L in the smokers, and 0.59 (0.20–3.71) µg/L in the nonsmokers. There was significant difference between the blood cadmium concentrations in smokers and nonsmokers, and smoking was significantly correlated with blood cadmium concentration (r = 0.808). Blood cadmium was inversely correlated with serum selenium (r = −0.196) and glutathione peroxidase (r = −0.189). In multiple regression analysis, blood cadmium concentration was significantly correlated with serum 17β-estradiol, FSH, and testosterone and inversely correlated with testis size. There were no significant associations between blood cadmium concentration and semen characteristics. The authors concluded that it is necessary to adjust for the presence of other metals and for potential confounding factors when studying the possible effects of a given metal on reproduction.

Xu et al. (2003), supported by the Anhui Provincial Natural Science Foundation and the China Medical Board, evaluated semen analyses, seminal cadmium, and 8-hydroxydeoxyguanosine in 56 healthy men. The subjects did not smoke or use ethanol. Semen specimens were collected after

3 days of sexual abstinence and routine semen analysis were performed. The remaining semen was frozen until further analysis. Thawed semen was centrifuged for separation of seminal fluid, which was analyzed for cadmium, lead, and selenium by atomic absorption spectrometry. DNA was extracted from sperm and assayed by HPLC for 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage, and dehydroxyguanosine. 8-Hydroxydeoxyguanosine was expressed as parts per million parts of deoxyguanosine. Statistical analysis was performed using an unspecified test of correlation with and without age as a covariate.

Geometric mean (95% confidence interval) seminal fluid cadmium concentration was 0.77 (0.48–1.22) µg/L. Cadmium concentration was inversely correlated with sperm concentration and total sperm/ejaculate ($r \approx -0.28$, with and without adjustment for age). Seminal fluid cadmium concentration was significantly correlated with sperm 8-hydroxydeoxyguanosine content ($r \approx 0.55$, with and without adjustment for age). The authors concluded that seminal fluid cadmium may adversely affect sperm quality and is associated with oxidative DNA damage to sperm.

Pant et al. (2003a), supported by the Indian Council of Medical Research, measured cadmium in the seminal plasma of fertile and infertile Indian men. Fertile subjects included 50 men "of proven fertility" **[criteria not given]** with sperm concentration ≥20 million/mL and sperm motility >50%, and infertile men included 50 partners of women who presented for failure to conceive without a diagnosis of a female fertility problem having been made. Semen was collected after 3 days sexual abstinence. Seminal fluid cadmium and lead concentrations were measured by atomic absorption spectrometry. Statistical analyses were performed using Student *t*-test, chi-squared, multiple regression analysis adjusting for smoking and duration of marriage, and Pearson correlation. **[Adjustment of cadmium results for seminal fluid lead concentration does not appear to have been made.]**

The proportion of smokers and duration of marriage were higher among infertile than fertile men. Mean ± SD seminal fluid cadmium in fertile men was 50.0 ± 35.9 µg/L and in infertile men was 104 ± 85.6 µg/L, a significant difference on univariate analysis but not significantly different when adjusted for years of marriage and cigarette smoking. A significant association was not found between seminal cadmium concentration and sperm concentration <20 million/mL or sperm motility <40%. In men with oligoasthenospermia (concentration <20 million/mL and motility <50%), there was a significant correlation between sperm concentration, motility, and seminal cadmium concentration. after adjustment for smoking and duration of marriage. The authors concluded that an increase in cadmium and lead concentration in semen may contribute to decreased semen quality.

Pant et al. (2003b), supported by the Indian Council of Medical Research, evaluated seminal fluid concentrations of lead and cadmium and markers of seminal vesicle and prostatic function. Subjects included 40 fertile men with sperm concentration >20 million/mL and motility >50% and 40 infertile men with sperm concentration <20 million/mL and motility <50%. **[It was not indicated whether fertility was determined only by semen analysis results.]** None of the men were occupationally exposed to cadmium or lead. **[Smoking was not mentioned]**. Semen was collected after 2–7 days sexual abstinence for routine semen analysis. Cadmium and lead concentrations were measured in seminal fluid by atomic absorption spectrometry. Fructose, acid phosphatase activity, and γ-glutamyl transferase activity were determined by spectrophotometer **[methods not given]**. Statistical analyses used Mann-Whitney *U*-test and Pearson correlation.

The seminal fluid cadmium concentration was higher in infertile than fertile men with a mean ± SD value of 115.6 ± 93.7 µg/L in infertile men and 50.7 ± 37.7 µg/L in fertile men. There were no significant correlations between seminal fluid cadmium concentration and seminal fluid

measured of fructose, acid phosphatase activity, or γ-glutamyl transferase activity. The authors did not express conclusions relative to cadmium.

Akinloye et al. (2006), support not indicated, measured serum and seminal fluid cadmium concentration in 60 infertile and 40 fertile Nigerian men. The infertile men belonged to couples seeking consultation for infertility and were subdivided into 40 oligospermic men with sperm concentration <20 million/mL and 20 men with azoospermia. The fertile men were sperm donors and the partners of currently or recently pregnant women. Men who smoked or used ethanol were excluded from the study. Routine semen analyses were performed **[days of sexual abstinence not indicated]**. LH, FSH, prolactin, and testosterone were measured in serum and seminal fluid by enzyme immunoassay. Cadmium in serum and seminal fluid was measured by atomic absorption spectrometry. Statistical analyses used ANOVA with Student *t*-test and Pearson correlation.

Oligospermic and azoospermic men had higher LH, FSH, and prolactin serum concentrations than control men. Serum testosterone concentrations were higher in azoospermic than control men. Serum and seminal fluid cadmium concentrations were higher in azoospermic than oligospermic or control men (Figure 4). **[The serum and seminal fluid cadmium concentrations were about 3 orders of magnitude higher than those reported in many other studies. The authors reported the results in mg/L (converted in the figure to µg/L), but it is possible that there was an error in the paper and that the units should have been µg/L.]** Serum cadmium concentration was inversely correlated with sperm concentration, motility, progressive motility, viability, and morphology (*r* values 0.320–0.605) but was not significantly correlated with serum or seminal fluid LH, FSH, prolactin, or testosterone. Seminal fluid cadmium concentration was correlated with seminal fluid FSH (*r* = 0.355) but not with any sperm measures or with other hormone concentrations in serum or in seminal fluid. The authors concluded that cadmium may have a role in infertility in Nigerian men.

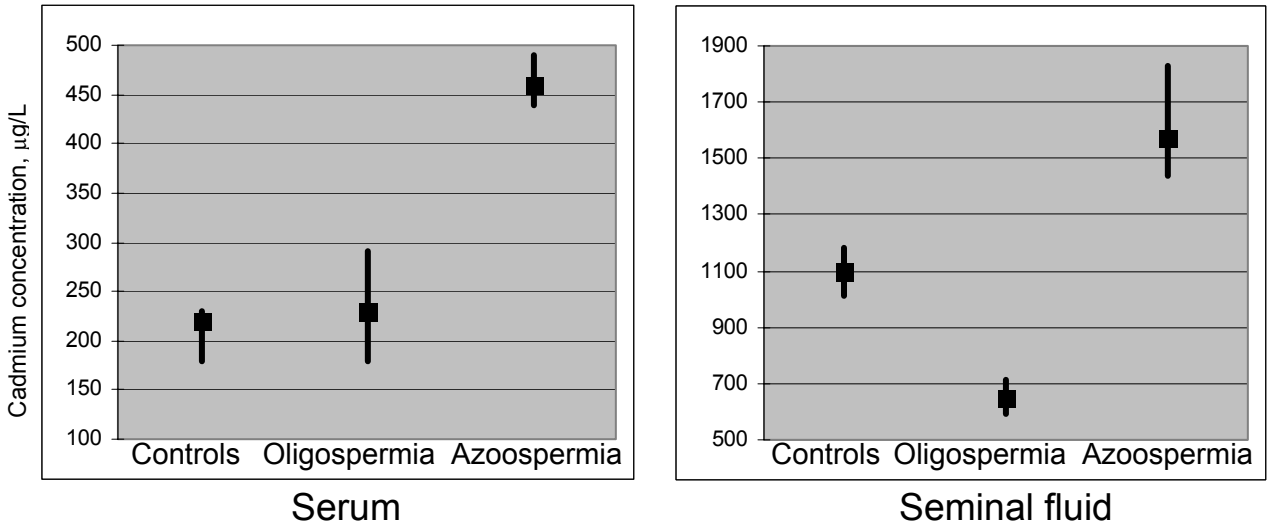

Figure 4. Serum and seminal fluid cadmium concentration in normal control men and infertile men with oligospermia and azoospermia.
Data expressed as mean and 95% confidence limits. Note the different scales for the 2 graphs. Concentrations were presented as mg/L and converted to µg/L for comparison to other studies. Drawn from Akinloye et al. (2006).

E. References for summaries

Åkesson A, Berglund M, Schütz A, Bjellerup P, Bremme K, Vahter M. Cadmium exposure in pregnancy and lactation in relation to iron status. Am J Public Health. 2002 Feb;92(2):284-7.

Akinloye O, Arowojolu AO, Shittu OB, Anetor JI. Cadmium toxicity: a possible cause of male infertility in Nigeria. Reprod Biol. 2006;6:17-30.

Boadi WY, Urbach J, Brandes JM, Yannai S. Effect of cadmium on some enzyme activities in first-trimester human placentae. Toxicol Lett. 1992a Apr;60(2):155-64.

Boadi WY, Urbach J, Brandes JM, Yannai S. In vitro exposure to mercury and cadmium alters term human placental membrane fluidity. Toxicol Appl Pharmacol. 1992b Sep;116(1):17-23.

Brender JD, Suarez L, Felkner M, Gilani Z, Stinchcomb D, Moody K, Henry J, Hendricks K. Maternal exposure to arsenic, cadmium, lead, and mercury and neural tube defects in offspring. Environ Res. 2006 May;101(1):132-9.

Butler Walker J, Houseman J, Seddon L, McMullen E, Tofflemire K, Mills C, Corriveau A, Weber JP, LeBlanc A, Walker M, Donaldson SG, Van Oostdam J. Maternal and umbilical cord blood levels of mercury, lead, cadmium, and essential trace elements in Arctic Canada. Environ Res. 2006 Mar;100(3):295-318. Epub 2005 Aug 3.

Carrillo-Ponce M de L, Martínez-Ordaz VA, Velasco-Rodríguez VM, Hernández-García A, Hernández-Serrano MC, Sanmiguel F. Serum lead, cadmium, and zinc levels in newborns with neural tube defects from a polluted zone in Mexico. Reprod Toxicol. 2004 Dec;19(2):149-54.

Falcón M, Viñas P, Perez-Cárceles MD, Luna A. Placental cadmium and lipid peroxidation in smoking women related to newborn anthropometric measurements. Arch Environ Contam Toxicol. 2003 Aug;45(2):278-82.

Fréry N, Nessmann C, Girard F, Lafond J, Moreau T, Blot P, Lellouch J, Huel G. Environmental exposure to cadmium and human birthweight. Toxicology. 1993 Apr 30;79(2):109-18.

Friel JK, Longerich H, Jackson SE, Pushpananthan C, Wright JR Jr. Possible altered mineral metabolism in human anencephalic fetuses. Mutat Res 2005;25:103-109.

Galicia-Garcia V, Rojas-Lopez M, Rojas R, Olaiz G, Rios C. Cadmium levels in maternal, cord and newborn blood in Mexico City. Toxicol Lett. 1997 Mar 14;91(1):57-61.

Gennart JP, Buchet JP, Roels H, Ghyselen P, Ceulemans E, Lauwerys R. Fertility of male workers exposed to cadmium, lead, or manganese. Am J Epidemiol. 1992 Jun 1;135(11):1208-19.

Godschalk R, Hogervorst J, Albering H, Mercelina-Roumans P, van Schooten FJ, de Haan J, Kleinjans J. Interaction between cadmium and aromatic DNA adducts in hprt mutagenesis during foetal development. Mutagenesis. 2005 May;20(3):181-5.

Honda R, Tawara K, Nishijo M, Nakagawa H, Tanebe K, Saito S. Cadmium exposure and trace elements in human breast milk. Toxicology. 2003 Apr 22;186(3):255-9.

Huel G, Boudene C, Ibrahim MA. Cadmium and lead content of maternal and newborn hair: relationship to parity, birth weight, and hypertension. Arch Environ Health. 1981 Sep-Oct;36(5):221-7.

Jolibois LS Jr, Burow ME, Swan KF, George WJ, Anderson MB, Henson MC. Effects of cadmium cell viability, trophoblastic development, and expression of low density lipoprotein receptor transcripts in cultured human placental cells. Reprod Toxicol. 1999b Nov-Dec;13(6):473-80.

Jolibois LS Jr, Shi W, George WJ, Henson MC, Anderson MB. Cadmium accumulation and effects on progesterone release by cultured human trophoblast cells. Reprod Toxicol. 1999a May-Jun;13(3):215-21.

Jurasović J, Cvitković P, Pizent A, Čolak B, Telišman S. Semen quality and reproductive endocrine function with regard to blood cadmium in Croatian male subjects. Biometals. 2004;17:735-43.

Keck C, Bramkamp G, Behre HM, Muller C, Jockenhovel F, Nieschlag E. Lack of correlation between cadmium in seminal plasma and fertility status of nonexposed individuals and two cadmium-exposed patients. Reprod Toxicol. 1995 Jan-Feb;9(1):35-40.

Krachler M, Rossipal E, Micetic-Turk D. Concentrations of trace elements in sera of newborns, young infants, and adults. Biol Trace Elem Res. 1999a May;68(2):121-35.

Krachler M, Rossipal E, Micetic-Turk D. Trace element transfer from the mother to the newborn--investigations on triplets of colostrum, maternal and umbilical cord sera. Eur J Clin Nutr. 1999b Jun;53(6):486-94.

Kuhnert BR, Kuhnert PM, Debanne S, Williams TG. The relationship between cadmium, zinc, and birth weight in pregnant women who smoke. Am J Obstet Gynecol. 1987b Nov;157(5):1247-51.

Kuhnert BR, Kuhnert PM, Zarlingo TJ. Associations between placental cadmium and zinc and age and parity in pregnant women who smoke. Obstet Gynecol. 1988 Jan;71(1):67-70.

Kuhnert PM, Kuhnert BR, Erhard P, Brashear WT, Groh-Wargo SL, Webster S. The effect of smoking on placental and fetal zinc status. Am J Obstet Gynecol. 1987a Nov;157(5):1241-6.

Laudanski T, Sipowicz M, Modzelewski P, Bolinski J, Szamatowicz J, Razniewska G, Akerlund M. Influence of high lead and cadmium soil content on human reproductive outcome. Int J Gynaecol Obstet. 1991 Dec;36(4):309-15.

Loiacono NJ, Graziano JH, Kline JK, Popovac D, Ahmedi X, Gashi E, Mehmeti A, Rajovic B. Placental cadmium and birthweight in women living near a lead smelter. Arch Environ Health. 1992 Jul-Aug;47(4):250-5.

Lyon TD, Patriarca M, Howatson G, Fleming PJ, Blair PS, Fell GS. Age dependence of potentially toxic elements (Sb, Cd, Pb, Ag) in human liver tissue from paediatric subjects. J Environ Monit. 2002 Dec;4(6):1034-9.

Mokhtar G, Hossny E, el-Awady M, Zekry M. In utero exposure to cadmium pollution in Cairo and Giza governorates of Egypt. East Mediterr Health J. 2002 Mar-May;8(2-3):254-60.

Nishijo M, Nakagawa H, Honda R, Tanebe K, Saito S, Teranishi H, Tawara K. Effects of maternal exposure to cadmium on pregnancy outcome and breast milk. Occup Environ Med. 2002 Jun;59(6):394-6.

Nishijo M, Tawara K, Honda R, Kuriwaki J, Nakagawa H, Tanebe K, Saito S. Cadmium and nutritional intake in pregnant Japanese women. Toxicol Lett. 2004a Mar 21;148(3):171-6.

Nishijo M, Tawara K, Honda R, Nakagawa H, Tanebe K, Saito S. Relationship between newborn size and mother's blood cadmium levels, Toyama, Japan. Arch Environ Health. 2004b Jan;59(1):22-5.

Odland JØ, Nieboer E, Romanova N, Thomassen Y, Lund E. Blood lead and cadmium and birth weight among sub-arctic and arctic populations of Norway and Russia. Acta Obstet Gynecol Scand. 1999 Nov;78(10):852-60.

Odland JØ, Nieboer E, Romanova N, Thomassen Y. Elements in placenta and pregnancy outcome in arctic and subarctic areas. Int J Circumpolar Health. 2004 May;63(2):169-87.

Osada H, Watanabe Y, Nishimura Y, Yukawa M, Seki K, Sekiya S. Profile of trace element concentrations in the feto-placental unit in relation to fetal growth. Acta Obstet Gynecol Scand. 2002 Oct;81(10):931-7.

Ostrea EM, Morales V, Ngoumgna E, Prescilla R, Tan E, Hernandez E, Ramirez GB, Cifra HL, Manlapaz ML. Prevalence of fetal exposure to environmental toxins as determined by meconium analysis. Neurotoxicology. 2002 Sep;23(3):329-39.

Pant N, Banerjee AK, Pandey S, Mathur N, Saxena DK, Srivastava SP. Correlation of lead and cadmium in human seminal plasma with seminal vesicle and prostatic markers. Hum Exp Toxicol. 2003b;22:125-8.

Pant N, Upadhyay G, Pandey S, Mathur N, Saxena DK, Srivastava SP. Lead and cadmium concentration in the seminal plasma of men in the general population: correlation with sperm quality. Reprod Toxicol. 2003a;17:447-50.

Piasek M, Blanuša M, Kostial K, Laskey JW. Placental cadmium and progesterone concentrations in cigarette smokers. Reprod Toxicol. 2001 Nov-Dec;15(6):673-81.

Ronco AM, Arguello G, Muñoz L, Gras N, Llanos M. Metals content in placentas from moderate cigarette consumers: correlation with newborn birth weight. Biometals. 2005 Jun;18(3):233-41.

Ronco AM, Garrido F, Llanos MN. Smoking specifically induces metallothionein-2 isoform in human placenta at term. Toxicology. 2006 Jun 1;223(1-2):46-53.

Sarasua SM, Vogt RF, Henderson LO, Jones PA, Lybarger JA. Serum immunoglobulins and lymphocyte subset distributions in children and adults living in communities assessed for lead and cadmium exposure. J Toxicol Environ Health A. 2000 May 12;60(1):1-15.

Sikorski R, Radomanski T, Paszkowski T, Skoda J. Smoking during pregnancy and the perinatal cadmium burden. J Perinat Med. 1988;16(3):225-31.

Tabacova S, Little RE, Balabaeva L, Pavlova S, Petrov I. Complications of pregnancy in relation to maternal lipid peroxides, glutathione, and exposure to metals. Reprod Toxicol. 1994 May-Jun;8(3):217-24.

Telišman S, Cvitković P, Jurasović J, Pizent A, Gavella M, Ročić B. Semen quality and reproductive endocrine function in relation to biomarkers of lead, cadmium, zinc, and copper in men. Environ Health Perspect. 2000 Jan;108(1):45-53. PMID: 10620523 [PubMed - indexed for MEDLINE]

Telišman S, Jurasović J, Pizent A, Cvitković P. Cadmium in the blood and seminal fluid of nonoccupationally exposed adult male subjects with regard to smoking habits. Int Arch Occup Environ Health. 1997;70(4):243-8.

Vigeh M, Yokoyama K, Ramezanzadeh F, Dahaghin M, Sakai T, Morita Y, Kitamura F, Sato H, Kobayashi Y. Lead and other trace metals in preeclampsia: a case-control study in Tehran, Iran. Environ Res. 2006 Feb;100(2):268-75. Epub 2005 Jul 18.

Windham GC, Zhang L, Gunier R, Croen LA, Grether JK. Autism spectrum disorders in relation to distribution of hazardous air pollutants in the san francisco bay area. Environ Health Perspect. 2006 Sep;114(9):1438-44.

Xu B, Chia SE, Tsakok M, Ong CN. Trace elements in blood and seminal plasma and their relationship to sperm quality. Reprod Toxicol. 1993 Nov-Dec;7(6):613-8.

Xu DX, Shen HM, Zhu QX, Chua L, Wang QN, Chia SE, Ong CN. The associations among semen quality, oxidative DNA damage in human spermatozoa and concentrations of cadmium, lead and selenium in seminal plasma. Mutat Res. 2003 Jan 10;534(1-2):155-63.