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# Effects of low-dose perinatal cadmium exposure on tissue zinc and copper concentrations in neonatal mice and on the reproductive development of female offspring

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**Abstract**

It has been suggested that the toxic effects of cadmium (Cd) are the result of interactions with essential metals, such as zinc (Zn) and copper (Cu). Previous studies have shown altered Zn and/or Cu levels in the tissues of rodents that drank water supplemented with >50 ppm Cd. To evaluate the effects of lower level Cd exposure on maternal and neonatal Zn and Cu levels and on the reproductive organs of female offspring, mice were exposed to 0, 1 and 10 ppm Cd in the drinking water from conception to 10 days after birth. The Cd concentrations in the brains of the offspring were higher in the exposed group than in the control group at birth. In the kidneys and livers, the Cd concentrations were higher in the Cd-exposed group 10 days after birth. At birth, increased Zn concentrations were observed in the kidneys and livers of the Cd-exposed offspring, although the Cd concentrations in these tissues did not differ between the exposed and non-exposed groups. The hepatic Cu concentrations of the exposed mice tended to be lower than those of the control mice at birth and were significantly lower 10 days after birth. In addition, Cd exposure tended to delay the timing of vaginal opening and perturbed the estrous cycles of the female offspring. These findings suggest that perinatal Cd exposure, even at low levels, affects the Zn and Cu concentrations of neonates and the reproductive functions of female offspring.


*Keywords:* Cadmium; Low-dose exposure; Zinc; Copper; Offspring

## 1. Introduction

Cadmium (Cd) is a heavy metal that is dispersed throughout the modern environment, mainly as the result of pollution from a variety of sources. The high concentrations of Cd in the soil and water supply mean that it is readily detectable in meat, fish, grains, vegetables and fruits. Foodstuffs represent the main contributor to Cd intake in the general (non-occupational) human population. Total human intake of Cd from foods has been estimated as 2.8–4.2 μg/kg body-weight (BW) per week, which

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equates to approximately 40–60% of the current provisional tolerable weekly intake (PTWI) of 7 μg/kg BW per week. Strikingly, among the foods that contribute to Cd levels, there is a higher average concentration of Cd in Japanese rice samples (0.061 mg/kg) than in rice samples from other countries (0.017 mg/kg) (JECFA, 2005).

In the case of human pregnancy, maternal exposure to Cd is associated with low birth-weight (Kuhnert et al., 1988; Frery et al., 1993) and is linked with an increased incidence of spontaneous abortion (Shiverick and Salafia, 1999). In addition, Cd has been shown to produce a variety of adverse reproductive outcomes in exposed animals. Cd administration at doses of 1–40 mg/kg BW to rodents impairs implantation (Baranski et al., 1982), decreases litter size (Baranski et al., 1982; Samarawickrama and Webb, 1981), produces resorptions (Machemer and Lorke, 1981; Samarawickrama and Webb, 1981), and causes fetal or embryonic death (Levin and Miller, 1980; Rohrer et al., 1979). Fetal growth retardation (Baranski, 1987; Hastings et al., 1987) and congenital malformations (Chernoff, 1973; Gale and Ferm, 1973) in the offspring of Cd-exposed (0.04–4 mg/kg BW or 60–180 ppm) rats have been widely reported.

The passage to offspring of maternally administered Cd depends on the particular developmental stage. Cd that is administered to pregnant animals is possibly transferred to the fetus via the placenta, and to neonates through the milk. When low to moderate doses are taken up during pregnancy, the placenta acts to restrict the entry of Cd into the fetus (Sonawane et al., 1975; Whelton et al., 1993). However, Cd at sufficiently high dosages can cross the placental barrier (Sonawane et al., 1975). The transfer of Cd to milk is also restricted (Bhattacharyya, 1983; Pitrzak-Flis et al., 1978). In mice, of the small amount of Cd that is passed from dam to offspring during gestation and lactation, the major portion is transferred during lactation (Whelton et al., 1993). Moreover, the Cd level in the brain increases after neonatal exposure to a moderate dose of 50 ppm Cd (Gupta et al., 1993), in contrast to gestational exposure, which does not lead to elevated Cd levels in the brain (Baranski, 1987; Murthy et al., 1986; Sowa and Steibert, 1985). However, the entry of Cd into the neonatal brain at lower doses of Cd, as occurs during lactation, has not been fully elucidated.

The mechanism of Cd-mediated fetotoxicity is not fully understood. However, some studies have suggested that the toxic effects of Cd may be mediated by altered metabolism of zinc (Zn) and copper (Cu) (Baranski, 1986; Sorell and Graziano, 1990). Adequate availability of both Zn and Cu is essential for normal growth and development. Insufficient Zn availability in fetal or early postnatal life is teratogenic (Hurley and Swenerton, 1966), retards growth (Beach et al., 1980; Sandstead et al., 1972), and alters cognitive function (Sandstead et al., 1972). Fetal or neonatal Cu deficiency is also teratogenic (Keen et al., 1982), reduces brain catecholamine levels (Feller and O'Dell, 1980), and decreases myelination in the central nervous system (Zimmerman et al., 1976). Gestational exposure to oral Cd levels of >50 ppm in the drinking water results in decreased Zn and Cu levels in the fetal liver (Baranski, 1987; Sorell and Graziano, 1990; Sowa and Steibert, 1985; Roelfzema et al., 1988, 1989), brain (Baranski, 1987; Sowa and Steibert, 1985), kidney and intestine (Sowa and Steibert, 1985), as well as in the entire bodies (Petering et al., 1979; Pond and Walker, 1975), and in these tissues of neonates (Baranski, 1986) and adult offspring (Baranski, 1986; Roelfzema et al., 1989). However, both increased (Waalkes et al., 1982) and unaltered (Sowa et al., 1982) concentrations of Zn and Cu in the fetus have been reported following maternal Cd exposure (0.25 mg/kg BW in the former and 100 ppm in the drinking water in the latter). Moreover, little is known about the effects on offspring of perinatal Cd exposure at levels lower than those used in the previous studies.

Recently, an estrogen-like activity for Cd has been suggested by Garcia-Morales et al. (1994), who showed that Cd mimics the effects of estrogens by decreasing the level of estrogen receptor (ER) mRNA and transcription of the ER gene. It has also been demonstrated that Cd activates ER-α through interaction with the hormone-binding domain of the receptor, to which it binds with high affinity, thereby blocking the binding of estradiol (Stoica et al., 2000). In addition, female offspring that have been exposed in utero to Cd experience an earlier onset of puberty (indicated by earlier vaginal opening) as well as increases in the epithelial area and number of terminal end buds in the mammary glands (Johnson et al., 2003). It has been shown that just two injections of Cd at 0.5 μg/kg or 5 μg/kg body-weight into dams produce changes in the