Adverse Health Effects of Chronic Exposure to Low-Level Cadmium in Foodstuffs and Cigarette Smoke

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Cadmium is a cumulative nephrotoxicant that is absorbed into the body from dietary sources and cigarette smoking. The levels of Cd in organs such as liver and kidney cortex increase with age because of the lack of an active biochemical process for its elimination coupled with renal reabsorption. Recent research has provided evidence linking Cd-related kidney dysfunction and decreases in bone mineral density in nonoccupationally exposed populations who showed no signs of nutritional deficiency. This challenges the previous view that the concurrent kidney and bone damage seen in Japanese itai-itai disease patients was the result of Cd toxicity in combination with nutritional deficiencies, notably, of zinc and calcium. Further, such Cd-linked bone and kidney toxicities were observed in people whose dietary Cd intakes were well within the provisional tolerable weekly intake (PTWI) set by the Joint Food and Agriculture Organization/World Health Organization Expert Committee on Food Additives of 1 µg/kg body weight/day or 70 µg/day. This evidence points to the much-needed revision of the current PTWI for Cd. Also, evidence for the carcinogenic risk of chronic Cd exposure is accumulating and Cd effects on reproductive outcomes have begun to emerge. *Key words:* bone density, cadmium, calcium, cancer, dietary intake, estrogen, food legislation, iron, maximum limit, nephrotoxicant, proteinuria, zinc. *Environ Health Perspect* 112:1099–1103 (2004). doi:10.1289/ehp.6751 available via *http://dx.doi.org/* [Online 25 March 2004]

Cadmium is a ubiquitous environmental pollutant of increasing worldwide concern. Food crops grown on Cd-containing soils or on soils naturally rich in this metal constitute a major source of nonworkplace exposure to Cd other than exposure from cigarette smoking [International Programme on Chemical Safety (IPCS) 1992; Jarup et al. 1998; Satarug et al. 2000a, 2003; World Health Organization (WHO) 1989]. Approximately 0.001% of Cd in the body is excreted per day, mostly in urine. Such extremely slow excretion rate of Cd is due to a lack of an active biochemical mechanism for elimination coupled with renal reabsorption. Cd accumulation occurs in various tissues and organs, with the most extensive accumulation occur in kidney cortex (IPCS 1992; Jarup et al. 1998; WHO 1989). Renal Cd concentration is strongly age related, and usually it reaches a plateau at 50 years of age, consonant with an age-related degeneration of kidney reabsorption function (Satarug et al. 2002). The average concentration of Cd in liver and kidney cortex in Australian subjects 41–50 years of age was 1.4 µg/g liver wet weight (ww) and 26 µg/g kidney cortex ww (Satarug et al. 2002). The corresponding mean concentration was 2 µg/g liver ww and 70 µg/g kidney cortex ww in Japanese subjects (Yoshida et al. 1998) and 1.6 µg/g liver ww and 41 µg/g kidney cortex ww in Canadian subjects (Benedetti et al. 1999).

The manifestations of Cd nephrotoxicity, including proteinuria, calciuria, aminoaciduria, glycosuria, and tubular necrosis, have been detected at renal Cd concentrations of ≥ 50 µg/g tissue ww. Cd persists in the kidneys of humans for many years (half-life of 30 years). This provides an opportunity for Cd toxicity to occur with no additional exposure, when the previously bound (nontoxic) Cd is displaced and released (Satarug et al. 2000b). An increase in mortality risk by 40–100% has been noted for individuals with signs of Cd-linked nephropathy (Arisawa et al. 2001; Jarup et al. 1998). In addition to its well-known nephrotoxicity, chronic exposure to low-level Cd has been associated with a number of pathologies, such as end-stage renal failure, early onset of diabetic renal complications, osteoporosis, deranged blood pressure regulation, and increased cancer risk (IARC 1993; IPCS 1992; Jarup et al. 1998; Nakagawa and Nishijo 1996).

In this commentary we highlight clinically relevant outcomes of chronic exposure to environmental Cd and discuss international food legislation. We also comment on recent studies involving Cd dose (burden)–response analysis. Most of these studies, however, have not included Cd intake data. In such instances, we applied a toxicokinetic model of Cd in an attempt to relate Cd burden (urinary Cd excretion) to Cd intake and observed adverse health outcomes. This model predicts that a Cd level of 50 µg/g kidney cortex ww, corresponding to urinary Cd excretion of 2–4 µg/day, may be attained after 50 years of intake of about 1 µg Cd/kg body weight/day (Buchet et al. 1990). This figure is equivalent to the current guideline for safe intake levels of dietary Cd (WHO 1993).

Provisional Tolerable Weekly Intake for Cd

In 1989, the Food and Agriculture Organization/World Health Organization (FAO/WHO) Joint Expert Committee on Food Additives (JECFA) set the provisional tolerable weekly intake (PTWI) for Cd at 7 µg/kg body weight/week, corresponding to 1 µg/kg body weight/day, or 70 µg/day (WHO 1989). However, Cd-linked kidney toxicity occurred in higher-than-expected frequencies in human populations whose dietary Cd intakes were well within the current PTWI, suggesting that the current PTWI is not sufficiently restrictive to protect the general population. At its 41st meeting in 1993, the JECFA recognized that the model on which the PTWI for Cd was based did not include a safety factor, and thus the PTWI for Cd has a very modest safety margin between exposure in normal diet and exposure that produces adverse effects (WHO 1993). The PTWI or the tolerable daily intake (TDI) for a contaminant is usually derived from the lowest observed adverse effect level (LOAEL) in the most sensitive species, using an uncertainty factor of 100, provided that the relative susceptibility of humans and animals is unknown at the time of derivation of the tolerable intake. The PTWI or TDI value needs to be substantiated by experimental data, and a larger uncertainty factor is applied when a LOAEL is the point of departure.

International Food Legislation

The Joint FAO/WHO Codex Alimentarius Commission was established in the early 1960s to detail international food legislation

(Berg and Licht 2002). In 2000, the Codex Committee for Food Additives and Contaminants (CCFAC) reached agreement on the principles for setting maximum limits (MLs) for contaminants (Codex Alimentarius Commission 2000). MLs were proposed for lead and Cd in various food categories, including peanuts and bivalve mollusks, which have been traded internationally (Berg and Licht 2002). At the 35th CCFAC meeting in 2003, the proposed draft of MLs for Cd in rice, soybean, mollusks, and peanuts (Codex Alimentarius Commission 2003) was circulated to Codex member countries and international organizations for additional consideration and comments.

Bivalve mollusks and crustaceans are known to have the ability to accumulate Cd from the aquatic environment, and their Cd contents are usually > 1–2 mg/kg ww (Kikuchi et al. 2002; Kruzynski 2004; Storelli and Marcotrigiano 2001). Such high Cd concentrations in the mollusks and crustaceans have raised considerable concerns for frequent consumers whose dietary Cd intake easily exceed the PTWI for Cd (Kruzynski 2004). The European Community has set the ML for Cd in bivalve mollusks at 1 mg/kg ww (1 ppm), and Australia, New Zealand, and Hong Kong have an ML for Cd in mollusks of 2 ppm (Codex Alimentarius Commission 2000). Canada and the United States have not established ML values for Cd.

Estimated dietary Cd intakes vary widely in different countries. Most of such estimates show that intakes were within the PTWI. In European countries, dietary Cd intake estimates were between 10 and 30 μg/day, corresponding to 17–50% of the PTWI (Nasreddine and Parent-Massin 2002). In Australia, a dietary Cd intake of 7–9 μg/day was derived from the food Cd content database and national consumption data, but the measured levels of Cd accumulation in kidneys of Australians suggest greater dietary Cd intake of 20–30 μg/day (Satarug et al. 2002, 2003). Approximately two-thirds of dietary Cd intake is derived from plant products, and animal products provide the remaining one-third of total Cd intake. Because foodstuffs are the main source of human intake of Cd, greater efforts need to be made to reduce exposure to dietary Cd. Thus, the maximum level for Cd in a foodstuff should be set as low as reasonably achievable. Attempts to reduce human exposure to dietary Cd by risk reduction measures supported by international legislation (ML) should not be relaxed. Efforts should continue toward better agricultural practices such as defining the areas, culture methods, species, and harvest times that would minimize Cd residues. There is no distinction between toxicity of natural or anthropogenic Cd.

Enteral versus Pulmonary Cd Absorption

The dietary Cd absorption rate in humans has been estimated at 5% (IPCS 1992; WHO 1989). However, interindividual variation in Cd absorption has been shown to be much greater than the previous estimate; Cd absorption rates increase to 20–30% in some individuals (Kikuchi et al. 2003; Satarug et al. 2004). The metal transporter protein Nramp2, known also as DMT1, has been shown to be involved in Cd absorption (Tallkvist et al. 2001). Increased expression of the intestinal DMT1 was found in iron deficiency and hemochromatosis (Zoller et al. 1999, 2001). Increased expression of the metal transporter protein DMT1, in general, would provide individuals with a greater capacity to absorb Fe and possibly Cd. This provides a likely explanation for a 3.4-fold increase in Cd body burden in women with low Fe stores seen in our recent study on Thai subjects (Satarug et al. 2004). Olsson et al. (2002) also observed an increased rate of Cd absorption in individuals with low body Fe stores. Thus, special consideration should be given to ensure adequate Fe intakes to reduce Cd absorption. In addition to increased dietary Cd absorption and Cd load, there is evidence for increased sensitivity to Cd toxicities in women (Nishijo et al. 2004; Vahter et al. 2002).

Cd is an integral constituent of tobacco because of the propensity of the *Nicotiana* species to concentrate Cd independent of soil-Cd content. Tobacco Cd content varies widely, but a typical range is 1–2 μg/g dry weight, equivalent to 0.5–1 μg/cigarette. Cd oxide generated during the burning of cigarettes is highly bioavailable. Approximately 10% of the inhaled Cd oxide is deposited in lung tissues, and another 30–40% is absorbed into systemic blood circulation of smokers. Smokers have 4–5 times higher Cd levels in blood and 2–3 times greater amounts of Cd in their kidneys than do nonsmokers.

Adverse Health Effects of Chronic Cd Intake

Cd and chronic (end-stage) renal failure. Hellstrom et al. (2001) determined the incidence of end-stage renal disease in a Swedish population using data from individuals undergoing renal replacement therapy (RRT). The age-standardized rate ratio for RRT was, respectively, 1.4, 1.9, and 2.3, in low-, moderate-, and high-exposure groups, defined by employment history together with distance of residence from a Cd battery plant. Workers in the Cd battery plant or the residents of Cd-polluted areas near the plant comprised the high-exposure group, whereas those residing < 2 km or between 2 and 10 km from the plant comprised the moderate-exposure and low-exposure groups, respectively. The rate ratio for

RRT in women was 2.3; this value was higher than the RRT rate ratio of 1.5 in men of the same age (Hellstrom et al. 2001). Cd levels in RRT patients were not determined, but the Cd urinary excretion of approximately 1 μg/g creatinine derived from residents of contaminated areas in Sweden suggests intake of less than the PTWI. Thus, Cd exposure, even at levels lower than the PTWI, may contribute to chronic renal failure, which occurred at a higher rate in women than in men of the same age and area (Hellstrom et al. 2001).

Cd and bone fragility. In a cross-sectional study in Belgium, Buchet et al. (1990) observed that urinary calcium excretion rose by 10 mg/day for every 2-fold increment in urinary Cd excretion. Jarup et al. (1998) reported that urinary Ca excretion was increased by 90% in Swedish women 50–70 years of age whose urinary Cd excretion exceeded 1 μg/g creatinine. In a Chinese population including residents from low- and high-exposure areas based on Cd concentrations in rice of 0.07 mg/kg and 3.71 mg/kg, respectively, Wu et al. (2001) observed that the prevalence of calciuria was increased by 10% in subjects whose urinary Cd excretion exceeded 2 μg/g creatinine. These findings have led to the hypothesis that prolonged urinary Ca loss caused by Cd is sufficient to promote skeletal demineralization, which may lead to increases in bone fragility and risk of fractures.

A prospective study in Belgium. In a prospective study (median follow-up of 6.6 years) of a Belgian population, Staessen et al. (1999) observed a 2-fold increase in urinary Cd correlated with a 0.01-g/cm^2 decrease in bone density ($p < 0.02$) in postmenopausal women. The risks associated with doubled urinary Cd were 1.73 ($p = 0.007$) for fractures in women and 1.60 ($p = 0.08$) for height loss in men. Mean urinary Cd excretion at baseline of 1 μg/day suggests that Cd intake did not exceed the PTWI. Thus, chronic exposure to low-level Cd increases bone fragility and risk of fractures in women, despite the nonsignificant change in men. These female-linked effects are consistent with the previously described studies linking Cd absorption with reduced Fe stores.

Cross-sectional studies in Japan and China. Honda et al. (2003) used a calcaneal bone stiffness index to estimate bone density mass of a group of adult Japanese women whose mean (range) of urinary Cd concentration was 2.87 (0.25–11.4) μg/g creatinine. Bone density mass showed an inverse correlation with urinary Cd, after adjusting for age, body weight, and menstrual status. A 2-fold increase in urinary Cd was accompanied by a decrease in bone density mass equivalent to a 1.7-year increase in age. However, the authors found no correlation between bone mass and kidney dysfunction as assessed by urinary

excretion of β2-microglobulin (β2-MG) and *N*-acetyl-β-D-glucosaminidase. This suggests that Cd may produce a primary bone effect independent from its kidney effects. Ikeda et al. (2000) reported geometric mean concentrations for Cd intake, derived from food duplicates, and urine samples of 24.7 µg/day (40% from rice) and 3.94 µg/g creatinine, respectively. It is reasonable to infer from these data that Cd intake of the Japanese subjects (Honda et al. 2003) was within the PTWI.

Aoshima et al. (2003) observed a correlation between renal and bone effects in a group of Japanese women whose mean (range) of urinary Cd excretion was 17.2 (5.7–37) µg/g creatinine. These concentrations were higher than those reported by Honda et al. (2003). Serum markers of bone formation, but not urinary markers of bone resorption, showed correlation with Cd-related renal tubular dysfunction assessed by glomerular filtration rate and fractional excretion rates for β2-MG. Thus, bone formation might be affected by renal tubular dysfunction induced by Cd.

Nordberg et al. (2002) recorded mean urinary Cd excretion values of 14.5, 4.8, and 2.4 µg/g creatinine for Chinese subjects living in areas with high, moderate, and low (control) Cd pollution areas, respectively. Based on rice Cd content, average total Cd intakes of these subjects in the high and moderate pollution areas and the control areas were 545, 106, and 22 mg, respectively (Jin et al. 2002). These concentrations were lower than a 2,000-mg lifetime cumulative exposure limit (WHO 1989), but decreased bone density was found in postmenopausal women with elevated urinary Cd excretions or blood Cd and among men with elevated blood Cd (Jin et al. 2002). This Chinese study suggests a link between kidney and bone toxicities, which was not evident in the Japanese study by Honda et al. (2003). The reasons for the discrepancies are not known, but it may be related to genetic differences in kidney sensitivity to Cd or to higher levels of protective factors, such as vitamin C status, in Japanese subjects compared to Chinese subjects. It may also be due to higher Cd internal doses in Chinese subjects than in Japanese subjects. Kobayashi et al. (2002) provided a thorough analysis of total Cd intake and relative risk estimates of adverse renal effects.

Cross-sectional studies in Sweden. In a study in Sweden, Alfven et al. (2000) found inverse relationships between urinary Cd excretion and tubular proteinuria, and forearm bone mineral density (BMD). This was particularly apparent in the subjects older than 60 years. The odds ratios (ORs) for osteoporosis in men were 2.2 in the medium-dose group (0.5–3 µg Cd/g creatinine) and 5.3 in the highest dose group (≥ 3 µg Cd/g creatinine) compared with the lowest dose group

(< 0.5 µg Cd/g creatinine). For women, the OR for osteoporosis was 1.8 in the medium-dose group, but the OR for osteoporosis could not be determined for women in the highest dose group because no women excreted urinary Cd at levels ≥ 3 µg Cd/g creatinine.

In another study, Alfven et al. (2002) reported that the group with the highest blood Cd levels (≥ 1 µg/L) had a 4-fold greater risk of having renal dysfunction (proteinuria) compared with the group with the lowest blood Cd levels (≤ 0.5 µg/L). In the older age group (> 60 years), the risk of low BMD for the group with the highest blood Cd was 3-fold greater than that for the group with the lowest blood Cd levels. Blood Pb levels did not correlate with proteinuria or BMD.

Cd and reproductive outcomes. There is abundant literature on effects of smoking on pregnancy outcome, for example, early delivery and low birth weight. However, Cd exposure data were lacking in those early studies to reveal association between the maternal Cd exposure from smoking and adverse pregnancy outcomes, given the fact that cigarette smoke contains more than 3,000 substances, including the metallic elements Cd, Pb, nickel, and cobalt. The result of the study by Nishijo et al. (2002) suggested that there is a relationship between maternal Cd exposure and adverse reproductive outcomes, akin to the effects of smoking. Preterm and cesarean section deliveries were found to occur approximately 4 times more frequently in women with higher Cd burdens (urinary Cd ≥ 2 µg/g creatinine) than in those with lower Cd burdens (urinary Cd < 2 µg/g creatinine). In addition, Nishijo et al. (2002) found an inverse correlation between maternal urinary Cd excretion and gestational age, after adjustment for maternal age. The height and weight of the infants of women in the higher urinary Cd group were significantly lower than those of infants of women with lower urinary Cd. The smaller size of infants was attributed to early delivery, possibly induced by Cd. No correlation was evident between fetal development and maternal Cd exposure. This is consistent with data on neonatal Cd content revealed by a British study in which liver samples collected at autopsy from 157 subjects, < 1 day to 6 years of age showed that liver Cd levels are negligible in neonates but increased in older children (Lyon et al. 2002). The negligible amounts of Cd in neonatal liver provide direct evidence that Cd does not cross the human placental barrier, and hence the fetus seems to be well protected from Cd exposure *in utero.* However, Cd exposure in the United Kingdom (Lyon et al. 2002) was much lower than in Japan (Nishijo et al. 2002).

Cd in breast milk. Nishijo et al. (2002) reported that Cd concentrations in breast milk from women in their higher and lower

Cd exposure groups were 0.52 µg/L and 0.31 µg/L, respectively. They observed a positive correlation between maternal Cd burden and breast milk Cd concentration. This correlation was confirmed in a subsequent study involving analysis of Cd in urine and in breast milk samples collected 5–8 days postpartum (Honda et al. 2003). Cd in breast milk reflected maternal Cd exposure. Further analysis of breast milk samples for Ca, zinc, copper, magnesium, sodium, potassium, and phosphorus revealed an inverse correlation between Cd and Ca in breast milk, suggesting that higher levels of Cd result in lower levels of Ca in breast milk. Implications of early-life Cd exposure warrant further research; a study in rats revealed that exposure to Cd in early life resulted in rapid weight gain and early onset of puberty (Johnson et al. 2003).

Cd and human cancers. Cd in respirable forms was classified as a cancer-causing agent in humans by the WHO (1993), based on consistent reports of an association between Cd exposure and lung cancer (IARC 1993). This is supported by a study in rats in which Cd exposure by inhalation resulted in pulmonary cancer (Waalkes 2003). It is noteworthy that Cd displays multitissue carcinogenicity in rats and that cigarette smoking, which provides a substantial additional source of Cd, has been identified as a risk factor in many common human cancers. Thus, the possibility that Cd is involved in cancers at other sites cannot be excluded, given the long residence time of Cd in tissues and organs.

Renal cell cancer. Pesch et al. (2000) found that excess risks for renal cell cancer after high exposure to Cd were greater in women (OR = 2.6) than in men (OR = 1.4). This suggests a high susceptibility of female kidneys to Cd carcinogenesis. This observation could be predicted because the rate of uptake and tissue accumulation of Cd in women is higher than in men, as discussed above. An association between renal cancer and Cd exposure was also seen by Hu et al. (2002) using questionnaire data from histologically confirmed cases and population controls in eight Canadian provinces. The authors observed a borderline significant increased risk of renal cancer associated with duration of Cd exposure (OR = 1.9) only in men. This Canadian survey could not establish the association between Cd exposure and renal cancer in women because of the small number of women who had been exposed to Cd.

Breast cancer. Band et al. (2002) found that the risk of breast cancer (OR = 1.69) was increased in women who had been pregnant and who had started smoking within 5 years of menarche. The risk rose sharply in nulliparous women who smoked ≥ 20 cigarettes daily (OR = 7.08) and had smoked for ≥ 20 cumulative pack-years (OR = 7.48).

These findings underscore the need for smoking prevention (low Cd exposure) in early adolescence. In support of a potential role for Cd exposure in breast cancer, Cd has been shown to mimic estrogenic effects in breast tissues of rats (Johnson et al. 2003). In Cd-exposed female rats, mammary glands were larger than those of unexposed rats. These changes were also seen in rats whose endogenous estrogen sources (ovaries) had been removed (Johnson et al. 2003).

Prostate and colorectal cancers. Exposure to Cd is one of the identified risk factors of prostate cancer together with obesity and consumption of animal fat and red meat, whereas vegetable and cereal consumption and vitamin D are protective factors (Ekman 1999); high blood vitamin D_3 concentrations were associated with lowered prostate cancer risk. A certain genetic variant of vitamin D receptor has been associated with a 4.6-fold greater risk of prostate cancer compared with the wild-type receptor (Ingles et al. 1997). Of relevance, Cd exposure has been shown to interfere with renal vitamin D_3 synthesis (Chalkley et al. 1998). Consistent with carcinogenicity of Cd, human prostate epithelial cells transformed to cancer cells after repeated Cd exposure (Achanzar et al. 2001; Nakamura et al. 2002). As with prostate cancer, vitamin D has been found to be a protective factor against colorectal cancer (Lamprecht and Lipkin 2003), whereas cigarette smoking is one of the risk factors, although involvement of Cd has never been investigated. Colorectal cancer is a major type of cancer seen in people with genetic defects in the mismatch repair system. Interestingly, Jin et al. (2003) reported a 2,000-fold increase in the gene mutation rate in yeast cells whose DNA-mismatch repair mechanism was suppressed by low-level Cd. Exposure of colon cells to bile and fecal Cd thus may contribute to the development of colorectal cancer in some individuals whose diets contain high Cd.

Conclusion

Cd remains an environmental pollutant of continuing concern. Dose–response analyses and risk estimates indicate that adverse health outcomes due to chronic Cd exposure occur at renal concentrations that are much lower than the previous estimate of 180–200 µg/g kidney cortex and at intake levels lower than the current PTWI. In addition, Cd-linked toxicities are found more frequently in women than in men. High rates of soil-to-plant transfer of Cd coupled with continuing mobilization of small amounts of the metal from nonbioavailable geologic matrices into biologically accessible situations predicts that human exposure to dietary Cd will gradually increase in the next 10–20 years. There is a lack of therapeutically effective chelating agents to reduce Cd burden, and this factor makes exposure minimization pivotal. The persistence in the environment of this metal requires a long-term approach to minimizing human exposure through environmental management and maintenance of lower Cd levels wherever possible. International food legislation, through setting the ML for a cumulative toxin such as Cd in agricultural products, is one of the strategies for exposure minimization.

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