Cadmium, Environmental Exposure and Health Outcomes

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Abbreviations:

BMD	Benchmark Dose
$\beta 2$-MG	$\beta 2$-Microglobulin
POD	Point of Departure
NAG	N-acetyl- β-D-glucosaminidase
NOAEL	No Observed Adverse Effect Level
LOAEL	Lowest Observed Effect Level
PTWI	Provisional Tolerable Weekly Intake

OUTLINE

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ABSTRACT

Objectives: To provide an update of the issues surrounding health risk assessment of exposure to cadmium in food.

Data Sources: We reviewed epidemiologic studies published during 2004-2009, concerning the bioavailability of cadmium in food, assessment of exposure and body burden estimate along with exposure-related effects in non-occupationally exposed populations.

Data Extraction and Synthesis: Bioavailability of ingested cadmium has been confirmed in studies on subjects with elevated dietary exposure and it is strengthened by the substantial amounts of cadmium accumulation in kidneys, eyes and other tissues and organs of environmentally exposed individuals. It is hypothesized that such accumulation results from the efficient absorption and systemic transport of cadmium, employing multiple transporters that are used for the body's acquisition of calcium, iron, zinc and manganese. Adverse effects of cadmium on kidney and bone have been observed in environmentally exposed populations at the frequencies higher than those predicted from models of exposure. There is increasing evidence implicating cadmium in the risk of diseases that involve other tissues and organ systems at cadmium concentrations not producing effects on bone or renal function.

Conclusions: Current population data raises a concern regarding the validity of a current "safe" intake level, using the kidney as a "sole" target in the assessment of health risk from ingested cadmium. The data also questions the validity of incorporating the default 5% absorption rate in the threshold-type risk assessment model, known as the Provisional Tolerable Weekly Intake (PTWI), to derive a safe intake level for cadmium.

INTRODUCTION

Cadmium is a contaminant in most human foodstuffs because of its high rates of soil-to-plant transfer, rendering diet a primary source of exposure among non-smoking, non-occupationally exposed populations (Clemens 2006; Franz et al. 2008; McLaughlin et al. 2006). A "safe" intake limit of 7µg cadmium per week per kg body weight was set based on the critical renal cadmium concentration of between 100 and 200 µg/g wet weight, corresponding to a urinary threshold limit of 5-10 µg/g creatinine (World Health Organization, 1989, 1993). However, numerous studies have revealed adverse kidney effects at urinary cadmium levels below 0.5 µg/g creatinine (Satarug and Moore 2004). Further, there is accumulating evidence linking environmental exposure to cadmium with increased cancer incidence. Excess cancer mortality was found associated with environmental exposure to cadmium in Japan and the US prospective studies (Arisawa et al. 2007; Menke et al. 2009; Nishijo et al. 2006). Increased endometrial cancer risk was observed in a Swedish cohort among those consumed cadmium above 15µg/day, mainly from cereals and vegetables (Akesson et al. 2008). These findings suggest a very large health burden associated with exposure to cadmium at the levels experienced by many populations worldwide.

This review will provide an update on cadmium exposure levels and the potential adverse health effects they may elicit on adult populations. It will focus first on key issues underpinning health-risk assessment of low-level cadmium in the diet. These include bioavailability of dietary origin, the 5% default absorption rate, thresholds and "safe" intake levels, and kidney as a specific target for cadmium accumulation. Second, it will review epidemiologic studies from 2004 to 2009 that link exposure levels to observed effects in classic targets (kidney and bone) along with newly identified potential target organs. Evidence will be summarized that links cadmium with diabetes, diabetic nephropathy, hypertension, peripheral arterial disease (PAD), myocardial infarction, diminished lung function, periodontal disease and age-related macular degeneration (AMD). Evidence from prospective studies are summarized which reveal potential causal relationships of cadmium exposure with life-prognosis (all-cause mortality) and excess cancer mortality, including evidence that cadmium is at least a co-morbidity factor if not a causative factor. Specifically, cadmium-cancer associations are summarized for the lung, pancreas, breast, endometrium, prostate and urinary bladder.

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FAO/WHO GUIDELINES FOR SAFE INTAKE

A major issue is if the guidelines established for the safe intake of cadmium adequately protect individuals from increased health risk. The FAO/WHO Joint Expert Committee on Food Additives (JECFA) has defined the **P**rovisional **T**olerable **W**eekly **I**ntake (PTWI) for a chemical with no intended function as an estimate of the amount of the chemical that can be ingested weekly over a lifetime without appreciable health risk. The PTWI value initially set for cadmium was 400–500 µg per person per week (WHO, 1989). These levels were based on a critical renal concentration of 100-200 µg Cd/g wet kidney cortex weight, attainable after a cadmium intake of 140–260 µg/d for over 50 yrs or 2000 mg over a lifetime. The PTWI model incorporates an oral absorption rate of 5% and a daily excretion rate of 0.005 % of total body burden. In 1992, the PTWI for cadmium was refined and subsequently expressed in terms of cadmium intake per kg body weight (WHO, 1993). This refinement also recognized that the model PTWI for cadmium did not include a safety factor and that there was only a very modest margin between the level of exposure in a normal diet and a level predicted to produce a potential effect on the kidney. Despite this narrow safety factor, the PTWI for cadmium was retained at 7 µg/kg body weight, which translates to 70 µg per day for a 70-kg person. A toxicokinetic model predicts, based on similar assumptions, that the renal cortical cadmium level of 50 µg/g wet weight could be attained at the cadmium intake of 1 µg /kg body weight/day over 50 yrs (Buchet et al. 1990). The renal cortical cadmium 50 µg/g wet weight corresponds to urinary cadmium 2 µg/g creatinine, but kidney effects have been observed at urinary cadmium levels < 0.5 µg/g creatinine (see Table 1). These findings argue that the current safe intake level does not provide a sufficient health protection and it needs to be lowered.

Studies by the author and coworkers (Satarug et al. 2000, 2003) examined the PTWI model by studying cadmium accumulation in kidneys and livers of environmentally exposed subjects. These studies suggested that the safe intake level for an adult should be below 30 µg per day. These studies included accumulation of cadmium in lung to account for exposure through inhalation. It was shown that cadmium accumulation in kidney cortex increased with age, reaching a plateau by 50 yrs of age (Satarug et al. 2002). An estimated dietary intake at 25–30 µg cadmium per day for the 41-50 age group would give rise to total cadmium body burden 18 mg. These studies predict that the estimated intake of 25-30 µg/day may produce adverse kidney effects in about 1 % of the adult population when variability in absorption and sensitivity to adverse effects among population members are considered in the analysis.

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THRESHOLD-BASED MODELS FOR SAFE INTAKE

If that the relative susceptibility of humans and animals is unknown at the time of derivation of PTWI, the Lowest Observed Adverse Effect Level (LOAEL) in the most sensitive species is used and adding an uncertainty factor of 100. The PTWI value then needs to be substantiated by additional experimental data, and if warranted, a larger uncertainty factor may be applied to the value. An alternative to LOAEL, the Benchmark Dose (BMD), has been used to derive urinary cadmium threshold. The BMD is defined as the exposure level that produces a change in a response, known as the Point Of Departure (POD). The lower 95% confidence limit of the BMD corresponding to a 5% (L5) or 10% (L10) level of each index of an adverse effect above the background level may also be calculated as a threshold. One study estimated the BMDL10 of urinary cadmium to be 0.6–1.2 µg/g creatinine (0.8–1.6 µg/day) in men and 1.2–3.6 µg/g creatinine (0.5–4.7 µg/day) in women, based on data from 828 Japanese subjects (410 men, 418 women), 40–59 yrs, who lived in the areas without apparent pollution (Uno et al. 2005). Another study estimated the BMD of urinary cadmium to be 0.6-1.1 µg/g creatinine, based on data from 790 Swedish women, 53-64 yrs (Suwazono et al. 2006). Data from selected studies found the POD for early kidney and bone effects to be between 0.5 and 3 µg/g creatinine (Jarup and Akesson 2009). Using the BMD-derived urinary cadmium threshold, the tolerable weekly intake for cadmium was found to be 2.5 µg/kg body weight, corresponding to 25 µg per day for a 70-kg person (European Food Safety Agency, 2009).

INTERNATIONAL FOOD LEGISLATION

In the early 1960's, the Joint FAO/WHO Codex Alimentarius Commission was established to detail international food legislation. In 2000, the Codex Committee for Food Additives and Contaminants (CCFAC) reached agreement on the principles for setting maximum levels (MLs) for cumulative food contaminants (Francesconi 2007). MLs were proposed for lead (Pb^{2+}) and cadmium (Cd^{2+}) in various food categories, including rice, soybean, peanuts and bivalve mollusks. The bioavailability and ML of cadmium became an issue because certain bivalve mollusks were known to be naturally high in cadmium content (Francesconi 2007). A high ML for cadmium was based on an early study on bluff oysters as discussed below.

CADMIUM SOURCES AND BIOAVAILABILITY

Mollusks and crustaceans: Bivalve mollusks and crustaceans are filter feeders that accumulate metals from the aquatic environment independent of environmental pollution and contaminated waters could further increase their content of metals (Whyte et al. 2009). Cadmium content of some Pacific

oysters was found to be 13.5 mg/kg dry weight while two-fold higher cadmium content was reported for some New Zealand bluff oysters (Copes et al. 2008). A bioavailability study has been conducted on 57 men and 19 women of 20-75 yrs of age who were associated with the oyster industries (McKenzie et al. 1986). The subjects were divided into groups 1, 2, 3 and 4, according to their average weekly oyster consumption rate at <6, 6–24, 24– <72 and ≥72 oysters, respectively. The estimate of cadmium intake (µg/day) for subjects in groups 1, 2, 3 and 4 were 34, 75, 116 and 250 respectively. The estimated consumption for all groups, except group 1, exceeded the FAO/WHO "safe" guideline. The blood cadmium was found to be higher in smokers than in non-smokers. Among non-smokers in group 4 (the highest consumption rate), the increase in blood cadmium attributable to oyster consumption was 1.2 µg/L. Blood selenium was also elevated by oyster consumption, but there was no effect on serum zinc or copper levels. The urinary cadmium, zinc and β2-microglobulin (β2-MG) levels were not affected, nor was there a relationship between cadmium intake and adverse renal effects, defined as glycosuria or proteinuria. There was no effect on the levels of cadmium, zinc and copper in hair. From this study, it was concluded by the authors' that interactions with selenium and other metals in oysters may result in diminished cadmium absorption. This study is extremely important since it has been used as the basis to argue for assigning high cadmium ML values to allow the marketing of oysters and their products which contain naturally high levels of cadmium. It is important to note also that there is no distinction between toxicity of natural *vs*. anthropogenic cadmium. It is this author's opinion that this study had several flaws. Mainly, although dietary selenium and zinc were measured in the analysis, other determinants of cadmium absorption were not considered, such as body iron stores and old age of the subjects. Furthermore, there is now evidence (see Tables 1-5) that the blood cadmium 1.2 µg/L attributed to oyster consumption among non-smokers in group 4 can now be considered at-risk since blood cadmium levels of less than 1 µg/L has been shown to be associated with adverse effects.

Recent studies by Copes and coworkers (2008) and Clark and coworkers (2007) reexamined this issue and their studies have shown effects of consumption of oysters on cadmium body burden and serum elemental composition (selenium, zinc, copper). The study of Copes and coworkers (2008) took into consideration the potential confounding effects of old age and cigarette smoking and restricted their study to relatively young age; non-smokers (33 men, 28 women) aged 33-64 yrs (mean 47.3 yrs). The estimated cadmium intake from oysters was 174 µg/week (24.8 µg/day). Significant increases in blood and urinary cadmium levels were found associated with duration of engagement in oysters farming, with the duration of at least 12 yrs during which time the on-average consumption rate was 18

oysters per week (87 g/wk). Average [range] blood cadmium for studied subjects was 0.83 [0.34-2.27] µg/L while the average urinary cadmium [range] was 0.76 [0.16-4.04] µg/g creatinine. The mean urinary cadmium 0.76 µg/g creatinine was 2.5-fold greater than that of US female non-smokers, mean age 55 yrs, as defined in the study by McElroy et al. (2007). Cadmium in shellfish diet was shown to be bioavailable in the study by Vahter and coworkers (1996) who found cadmium intake to be 11µg/day for women in the mixed-diet group and it was 28 µg/day for those in the high-shellfish diet group. No differences in blood or urine cadmium levels were observed between the two groups. However, an increase in blood cadmium of 63 % and an increase in urinary cadmium of 24% were found among those consuming the high-shellfish diet who had plasma ferritin levels <20 µg/L, when compared with those who consumed mixed diets and had the same low body iron stores. Thus, these studies strongly suggest that cadmium in oysters and shellfish is bioavailable and that long-term oyster consumption does result in a higher body burden of cadmium.

Oilseeds: Sunflower seeds, peanuts, flaxseed and linseed accumulate cadmium from the soil in the similar manner to that of the tobacco. Cadmium levels in sunflower kernels range from 0.2–2.5 mg/kg. Reeves and Vanderpool (1997) conducted a study on seventy-five male and female non-smokers, 30–70 yrs. Based on a self-reported food-frequency survey, subjects who reported consuming more than 28 g sunflower kernels per week were considered to be high consumers. Analysis of duplicate diet showed that on-average cadmium intake among controls was 36 µg/day, but intake was not determined for any of the high consumers. Blood and urinary cadmium levels were used as indicators of cadmium body burden. The expected increased cadmium body burden could not be demonstrated, probably due to the limited number of subjects and the short-term time frame of the study. However, evidence for kidney effects, reflected by urinary β2-MG and N-acetyl- β-D-glucosaminidase (NAG) levels, was found among high consumers of sunflower seeds. These data may indicate that cadmium in sunflower kernels possess a high nephrotoxic potential. Alternatively, they may indicate increased sensitivity to cadmium renal toxicity in the high sunflower-kernel consumers.

Offal: High cadmium levels (7–76 mg/kg wet weight) were found in the offal of dugongs and turtles that constituted the diet in the Torres Strait (Australia). Haswell-Elkins and coworkers (2007a) examined cadmium body burden in relation to offal consumption among residents in two communities with varying dugong and turtle catch statistics. Of 182 subjects, 12% had urinary cadmium > 2 µg/g creatinine and group mean urinary cadmium was 0.83 µg/g creatinine. Age accounted for 46% of total variation in urinary cadmium levels, while female gender and current smokers accounted for 7% and

4.7% of variation, respectively. In a second study, Haswell-Elkins and coworkers (2007b) found high cadmium body burden associated with higher consumption of turtle liver and kidney, and locally gathered clams, peanuts, and coconut. The sum of these foods, heavy smoking, age and waist circumference accounted for 40% of variation in cadmium body burden (*p*<0.05). Thus, it was shown that local offal consumption was linked with high cadmium body burden.

Cadmium levels in liver and kidney are higher than that in muscle and they are also higher in older animals (Prankel et al. 2005). Average cadmium in the liver and kidney of wild moose was 2.11 and 20.2 µg/g wet weight, respectively (Arnold et al. 2006). Notably, chronic, low-dose exposure situations produce a10-20-fold higher cadmium in kidney than liver. It is noteworthy that there appears to be no difference in bioavailability of ionic cadmium *vs*. protein bound cadmium.   In the human gastrointestinal tract, the protein bound to cadmium is digested and ionic cadmium released and thus speciation of cadmium in food would not be a basis for assigning high cadmium MLs for marketing purposes (Francesconi 2007). There has been no indication of decreases in food cadmium content over the past decade nor has there been a drastic change in dietary habits. The British study (Lyon et al. 1999) showed that human kidney cadmium levels were static over the 16-yr (1978 to 1993), but were higher than those found in studies done in the 19th and early 20th century. The distribution of kidney cadmium concentrations in the British study was skewed, with about 3.9 % of the 2700 samples above 50 µg/g kidney cortex wet weight, although the population mean value was only 19µg/g wet weight.

CADMIUM EXPOSUE AND EFFECTS OBSERVED

Kidney and Bone-Chronic High Dose Effects: Long-term exposure to high-dose cadmium causes Itai-itai disease. This disease affects mainly women and is characterized by severely impaired tubular and glomerular function, generalized osteomalacia and osteoporosis with resultant multiple bone fractures (Inaba et al. 2005). An estimate of cadmium intake, based on historic rice cadmium content, in the Itai-itai disease endemic area during 1960s was 600 µg/day and the threshold lifetime intake was estimated to be between 1580 and 2000 mg of cadmium (Kobayashi et al. 2002, 2006). It has been advanced in two reports that the lifetime threshold for early onset of the Itai-itai disease was less than a three-fold difference from the intake observed in areas with no apparent pollution (Inaba et al. 2005; Uno et al. 2005). This may reflect a small safety margin between population intake levels and the levels that produce overt effects.

Kidney and Bone-Chronic Low Dose Effects: Long-term exposure to low-dose cadmium has been linked to tubular impairment with a loss of reabsorptive capacity for nutrients, vitamins and

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minerals. These loses include zinc and copper bound to the metal binding protein metallothionein (MT), glucose, amino acids, phosphate, calcium, β2-MG, retinol-binding protein (RBP) (International Programme on Chemical Safety, 1992). The abnormal urinary excretion of low-molecular-weight proteins, calcium, amino acid, phosphate and glucose observed in cadmium-exposed individuals share some similarities with Fanconi's syndrome, a genetic disorder of renal tubular transport. Urinary markers for cadmium effects are cadmium itself, low-molecular-weight substances, and the enzymes of renal tubular origin, such as NAG (Teeyakasem et al. 2007). In general, the urinary cadmium level is considered to reflect the body burden over long-term exposure before development of kidney damage; whereas, blood cadmium is considered to be an indicator of recent exposure (IPCS, 1992). An exception is that blood cadmium is considered to provide a better estimate of body burden than urinary cadmium among those over 60 yrs of age.

Kidney and Bone-The Cadmibel Project: The Cadmibel study was one of the earliest studies on the effects of low-dose exposure with examination of 2,327 Belgian subjects between 1985 and 1989 (Buchet et al. 1990). The results demonstrated that there was a 10 % probability of having tubular impairment when urinary cadmium levels exceeded 2–4 µg/day. The result was derived from a logistic regression of urinary cadmium and various markers, including urinary calcium, amino acids, NAG, RBP and β2-MG. These markers demonstrated different thresholds for urinary cadmium levels. More than 10 % of values for each marker were abnormal when urinary cadmium (µg/day) exceeded 1.92 for calcium; 2.74 for NAG; 2.87 for RBP; 3.05 for β2-MG; and, 4.29 for amino acids. It was also shown that urinary calcium excretion increased by 10 mg/day for every 2-fold increment in urinary cadmium excretion. Increased susceptibility to cadmium among diabetic subjects was noted.

Kidney and Bone-Current Exposure Levels: There is compelling evidence linking tubular impairment with urinary calcium loss, rapid bone demineralization and osteoporosis (Table 1). It has been shown that tubular impairment among women, 53-64 yrs, was associated with blood and urinary cadmium levels of 0.38 µg/L and 0.67 µg/g creatinine, respectively (Akesson et al. 2005). It was also shown that glomerular impairment was associated with the urinary cadmium of 0.8 µg/g creatinine. An additional study using the same population showed body burden associated with decreased bone mineral density (Akesson et al. 2006). It was also shown that diabetic subjects had increased susceptibility to the renal effects of cadmium and that menopausal women were more susceptible to cadmium-induced bone effects. The risk for osteoporosis among women of 50 yrs of age or greater increased by 43% when urinary cadmium levels were compared between groups having urinary

cadmium below 0.5 and above 1.0 µg/g creatinine (Gallagher et al. 2008). In a prospective study on Flemish women, bone effects were found in those with a two-fold increase in body cadmium burden, but no tubular effects were documented in the population (Schutte et al. 2008b).

Tubular impairment and renal injury associated with increased risk of high blood pressure levels was found for subjects in Thailand, aged 16-60 yrs that had mean urinary cadmium of 0.39 µg/L and mean serum cadmium of 0.47 µg/L (Satarug et al. 2005). It was shown that a three-fold increase in urinary cadmium (0.39 to 1.12 µg/L) was associated with an 11%, 32% and 61% increase in the probability of having high blood pressure, renal injury and tubular impairment, respectively. The probability of having high blood pressure was increased by 20% among those with evidence of renal injury. The odds of tubular impairment were found to be 10.6-times higher when comparisons were made between urinary cadmium levels of 1-5 *vs*. >5 µg/g creatinine (Teeyakasem et al. 2007). Thomas and coworkers (2009) reported a dose-response relationship between urinary cadmium and "early" renal injury while Wu and coworkers (2008) found progressive tubular and glomerular impairment among those with urinary cadmium >10 µg/g creatinine. In the study of 14,778 US adults, aged >20 yrs, showing mean blood cadmium and lead of   0.41 µg/L and 1.58 µg/L, respectively, Navas-Acien and coworkers (2009) found that risk for albuminuria was 2.34 and it was 1.98 for lowered glomerular filtration rate, comparing those in the highest *vs*. the lowest quartiles of blood cadmium and lead. These findings suggest environmental exposure to cadmium and lead may constitute the risk factors for chronic kidney disease in the US.

Diabetes: A study by Schwartz and coworkers (2003) demonstrated a dose-response between urinary cadmium level and an increased risk of pre-diabetes and diabetes. The risk estimates for abnormal fasting glucose and diabetes were 1.48 and 1.24 when comparisons were made for urinary cadmium levels of <1 with those between 1.00-1.99 µg/g creatinine. These increased to 2.05 and 1.45 when comparisons were for urinary cadmium <1 with those of ≥2 µg/g creatinine. As noted by Edwards and Prozialeck (2009), since diabetic incidence is rising globally, reaching endemic levels in some nations, the potential role played by low-dose cadmium in prediabetes and diabetes warrants further research. In a study on Chinese subjects with type 2 diabetes between 44-78 yrs of age (66 yrs mean), tubular impairment was found with those having diabetes for 8.6 years (Chen et al. 2006). The risk for tubular impairment was increased by 3.34, based on a comparison of urinary cadmium of <1 *vs*. ≥1 µg/g creatinine and it was increased by 5.56, comparing those with low *vs*. high levels of circulating MT antibody. These data suggested increased susceptibility to cadmium tubular effects among diabetic

subjects with high MT antibody in plasma. The authors considered that mean urinary cadmium 0.38 µg/g creatinine and mean blood cadmium 0.61 µg/L were below threshold for glomerular effects. Afridi and coworkers (2008) reported higher blood and urinary cadmium among Pakistani men with type-2 diabetes aged 31-60 yrs who had on-average diabetes for 16 yrs.

Diabetic nephropathy: A dose-response relationship has been observed between urinary cadmium and albuminuria among Torres Strait subjects with type-2 diabetes (Haswell-Elkins et al. 2008). The geometric mean for urinary cadmium in diabetic subjects with albuminuria was 61% higher than those without whose average urinary cadmium level was 0.74 µg/g creatinine. The higher urinary cadmium levels among diabetic subjects could be the result of extensive kidney damage which leads to the release of cadmium in the kidney into the urine. One way to interpret this data is to suggest that the threshold urinary cadmium for people with diabetes should be no greater than 0.74 µg/g creatinine in order to prevent/delay the onset of diabetic renal complications. Such an interpretation considers that albuminuria is a predictor of glomerular impairment, end-stage renal failure and adverse cardiovascular outcomes. A similar threshold was suggested in another study which found glomerular impairment associated with the urinary cadmium 0.8 µg/g creatinine (Akesson et al. 2005).

Hypertension: A dose–response relationship was also observed between urinary cadmium and hypertension in a Korean subjects of which 26.2% of the subjects were hypertensive (Eum et al. 2008). In this study, mean blood cadmium was 1.67µg/L and the risk estimate for hypertension was 1.51 when comparing blood cadmium levels in the lowest *vs*. the highest tertile. An association was also found between blood cadmium and blood pressure levels in a US sample population, showing the mean blood cadmium 3.98-fold lower than those in the Korean study (Tellez-Plaza et al. 2008). The strength of the cadmium-blood pressure association was the greatest in non-smokers, intermediate in former smokers, and small or absent among current smokers. These findings support "pressor" effects, shown to be the characteristic of chronic exposure to low-dose cadmium (Satarug et al. 2005).

Blood vessels and the heart: A set of studies has found evidence linking an increased risk of PAD with low-dose cadmium exposure (Navas-Acien et al. 2004, 2005).   The risk for PAD was 1.07, 1.30, and 2.82 when comparing blood cadmium quartiles 2, 3 and 4 against the lowest quartile (*p* for trend = 0.01). Evidence that cadmium might be a key contributor to the high PAD risk was the finding that the risk of PAD for current smokers was 4.13-fold higher than those who never smoked; diminishing to 1.84 after controlling for cadmium. In this study subjects with PAD had 36% higher urinary cadmium than those without disease where average urinary cadmium of the sample group was

0.36 µg/L and the 25th and 90th percentile urinary cadmium level was 0.19 and 1.16 µg/L. Furthermore, the PAD risk was found to be 3.05, compared the 75th percentile urinary cadmium to that of the 25th percentile (Navas-Acien et al. 2005). It has also been shown that increased cadmium body burden is associated with lower aortic pulse wave velocity, lower pulse pressure and higher femoral distensibility among subjects from low and high cadmium exposure areas (Schutte et al. 2008b). Everett and coworkers (2008) found the risk of myocardial infarction in female subjects to be 1.8 when urinary cadmium >0.88 µg/g creatinine was compared to those <0.43 µg /g creatinine. The risk remained when the analysis was restricted to non-smokers.

Lung: Lampe and coworkers (2008) examined the potential effects of exposure to cadmium on lung function using a sample group of 96 men who underwent one to three lung function tests between 1994 and 2002. They found a reduction in forced expiratory volume in 1 sec (a reflection of lung function) associated with increased urinary cadmium among those who smoked. These data could be interpreted to suggest that lung disease in smokers may be mediated in part by cadmium because urinary cadmium is also a marker of cumulative smoking, an established risk factor in lung disease.

Periodontal tissues: A 3-fold increase in urinary cadmium (0.18 *vs*. 0.63 µg/g creatinine) was reported to be associated with a 54% higher prevalence odds ratio for periodontal disease among a sample of adults of which 15.4% had periodontal disease (Arora et al. 2009). The age-adjusted mean urinary cadmium for subjects with periodontal disease was 0.50 µg/g creatinine and 0.30 µg/g creatinine for non-affected individuals.

Ocular tissues: Higher urinary cadmium was found to be associated with AMD in smokers (Erie et al. 2007). Median urinary cadmium level of current and former smokers with AMD was 1.18 µg/g creatinine. This level was 1.97-, 2.03-, 2.07-fold higher than that of smokers without AMD, non-smokers with AMD and non-smokers without disease. Increased retinal cadmium content has also been found in male subjects with AMD (Will et al. 2008, 2009).

Mammary gland: Gundacker and coworkers (2007) have shown that breast milk samples of Austrian subjects contained on-average cadmium 0.086 µg/L and that breast milk cadmium content was lowered among non-smokers who took vitamins and mineral supplements ($p < 0.05$). In a study by Kippler and coworkers (2008), the median cadmium level in breast milk from Bangladeshi subjects was 1.6-fold higher than those in the Austrian study. This study observed a correlation between cadmium and elemental composition of milk, including manganese, iron and calcium levels, suggesting potential influence of cadmium on the mammary gland metal transport/secretion.

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Cadmium and Cancer: Cadmium is classified as a cancer causing agent in humans based on an elevated incidence of lung cancer and mortality data derived from the occupational groups with evidence of elevated exposure to cadmium. The occupational exposures have historically been through inhalation of cadmium (IARC, 1993). A consequence of this initial association of inhaled cadmium with cancer in occupationally exposed workers is that a carcinogenic risk from cadmium of dietary origin has long been ignored by regulatory agencies. However, literature to support a role for dietary cadmium that shows exposure levels associated with increased mortality risk and cancer mortality does exist as summarized in Table 4. In the Kakehashi cohort, a 2.5-fold increase was observed in cancer mortality among women with permanent tubular impairment (Nishijo et al. 2006). This study also noted increased mortality also from nephritis, nephrosis, heart failure and brain infarction in both men and women with severely impaired tubular function. Baseline-median urinary cadmium values for men and women in the Kakehashi cohort were 7.0 and 12.1 µg/g creatinine. This cohort was also used to establish a dose-response showing the lowest urinary cadmium of 3 µg/g creatinine associated with excess female mortality risk (Nakagawa et al. 2006). Similarly, Arisawa and coworkers (2007a) observed an increased mortality rate among subjects with permanent tubular impairment in the Nagasaki cohort I. They also observed a concurrent cancer mortality risk increase by 2.58-fold among those with tubular impairment. The determinants of increased mortality were renal injury, tubular impairment and renal insufficiency. These effects of cadmium were absent in cohort II study, most likely due to the selective loss of advanced cases and reduction in exposure after soil restoration which was undertaken between 1980 and 1983 (Arisawa et al. 2007b). Of note, the cadmium exposure levels in the Kakehashi cohort and Nagasaki cohort were close to the levels experienced by people in a cadmium pollution area in Thailand (Teeyakasem et al. 2007).

In contrast to the above studies, the cadmium exposure in the Belgian and the US cohorts were below those causing renal injury and yet increased mortality was observed in these studies. Nawrot and coworkers (2008) observed in the Belgian cohort the increase in mortality by 20% in low-exposure area and it was increased by 44% in high-exposure area. Further, mortality risks in those two areas were increased by 25% and 33% among those with a two-fold increase in blood cadmium who resided in low- and high exposure areas, respectively. Menke and coworkers (2009) observed in the US cohort, an increases in cancer mortality by 4.29-fold among men when a comparison was made between those with urinary cadmium levels <0.21 *vs.* > 0.48 µg/g creatinine. They also observed 1.68-fold increase in male all-cause mortality after adjustment for cadmium exposure from cigarette

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smoking. Mean urinary cadmium for men in the US cohort was 0.28 µg/g creatinine and it was 1.43-fold lower than that of women.

Cadmium as a Multi-Tissue Carcinogen: There are a substantial number of recent reports which demonstrate a linkage between cadmium and cancer in non-occupationally exposed populations (Table 5). In the 15-yr Belgian cohort, a 1.7-, 4.2- and 1.57-fold increase in lung cancer risk was observed among those with; two-fold increase in cadmium body burden, those living in a "high" exposure area, and two-fold increase in soil-cadmium content, respectively (Nawrot et al. 2006). Serum cadmium and a farming occupation have been associated with pancreatic cancer with the risk attributed to increased serum cadmium was 1.12 and it was 3.25 for farming occupation (Kriegel et al. 2006). A dose-response between breast cancer risk and cadmium exposure could be shown when individuals with urinary cadmium of ≤0.26 were compared to those with ≥ 0.58 µg/g creatinine, suggesting a 2.29-fold increase in risk (McElroy et al. 2006). In a prospective study, Akesson and coworkers (2008) found a 2.9-fold increase in endometrial cancer risk among those with cadmium intake greater than an average value 15 µg/day, 80% of which derived from cereals and vegetables. Several studies have examined prostate disease. A dose-response relationship was shown between urinary cadmium and abnormal serum levels of prostate specific antigen (PSA) (Zeng et al. 2004). It has also been shown that an increase in urinary cadmium to 1 µg/ g creatinine associated with a 35% increase in serum PSA level in men whose zinc intakes were less than 12.7 mg/day (Wijngaarden et al. 2008). Safe and adequate zinc intake for an adult is 15 mg/day. A 4.7-fold increase in prostate cancer risk could be shown in subjects where toe-nail cadmium was compared between individuals with less than 0.007 and those with greater than 0.03 µg cadmium/g tissue (Vinceti et al. 2007). In a study of bladder cancer, a 5.7-fold increase in risk was shown when a comparison was made between subjects with blood cadmium at the lowest *vs*. highest tertile (Kellen et al. 2007). The risk estimate was corrected for gender, age, smoking habits and workplace exposure. Mean blood cadmium for bladder cancer cases was 1.1 µg/L; 1.6-fold higher than the controls.

CADMIUM BODY BURDEN

Gender and Tissue Differential Cadmium Accumulation: Tissue collected from post mortem examinations has been used to define cadmium accumulation levels in tissues and organs of human subjects (Table 6). In an analysis of 61 environmentally exposed subjects between 2 and 89 yrs of age (mean 38.5 yrs), it was revealed that renal cadmium accumulation were greater in younger age groups with little increase or even a reduction in the older age groups (Satarug et al. 2002). It has been

suggested that younger individuals have high rates of renal cadmium accumulation due to a very high rate of dietary cadmium absorption (Horiguchi et al. 2004; Kikuchi et al. 2003). Conversely, a lack of renal cadmium accumulation in older individuals could be caused by a fall in dietary absorption rate plus a reduction in tubular re-absorptive capacity, associated with aging kidney. There have been limited studies on gender differences with regard to cadmium accumulation. In the above Australian study, it was shown that females had twice the level of cadmium in liver compared to male counterparts. There was also a trend for higher cadmium content in kidneys from female subjects. There have also been documented differences in cadmium accumulation between genders in a range of tissues and organs from 72 subjects, living in areas with no apparent cadmium pollution (Uetani et al. 2006). There have been several studies on human eyes. It was shown that the retinal pigment epithelium and choroids contained more cadmium than did the retina (Erie et al. 2005; Wills et al. 2008). These studies also noted that females, those of older age, and smokers had elevated levels of cadmium accumulation in their eye tissues. Additional studies have also demonstrated gender differences in ocular metal content in non-disease eyes and those afflicted with AMD (Wills et al. 2008, 2009).

Intestinal absorption of metals, body burden variability and metal transporters: Highly efficient absorption, transport and cellular uptake mechanisms have evolved in living organisms to ensure an optimal supply of essential metals. Such mechanisms are crucial for metals since they cannot be synthesized nor destroyed by the cells and must be "mined" from the external environment (Clemens 2006). As predicted from the U-shaped dose-response curve characteristics of essential metals, mechanisms have likely evolved for maintenance of homeostasis that are designed to prevent deficiency or overdose toxicity (Slikker et al. 2004). Cadmium has no known physiological function and no mechanism would have been expected to be evolved for its selective transport and homeostasis. In all likelihood, cadmium is acquired by transport mechanisms developed for essential metals. From physical and chemical properties, those metals are most likely to be zinc (Zn^{2+}), iron (Fe^{2+}), manganese (Mn^{2+}) and calcium (Ca^{2+}). There is a considerable range in the literature that defines the possible intestinal absorption rate for cadmium. It was estimated to be between 3 and 7% in humans and 0.3–3.5 % in rats and these values were used to assign an average 5% absorption rate in deriving a safe exposure level for cadmium (IPCS, 1992; WHO 1989). However, higher cadmium absorption rates (20-40%) were shown in balanced studies (Horiguchi et al. 2004; Kikuchi et al. 2003). These studies also observed enhanced rates among young subjects and they also considered the possible biliary

excretion and re-uptake *via* the entero-hepatic circulation. A substantial literature shows the influence of body iron stores on absorption rate and body burden of cadmium. Satarug and coworkers (2004) found a 3-4 fold increase in cadmium body burden among Thai women who had low iron stores when compared with those of the same age and of normal iron stores. Kippler and coworkers (2007) have found increased cadmium burden in Bangladeshi women associated with low iron stores only among those with adequate zinc status. An inverse correlation between serum iron and blood cadmium was observed among Canadian subjects with men showing higher serum iron, blood lead, and serum selenium compared to that of women who had higher serum copper and blood manganese than men (Clark et al. 2007; Copes et al 2008). The higher blood manganese in women might be expected since low iron stores have been found associated with enhanced manganese absorption (Finley 1999, Kippler et al. 2009). There are studies that have shown no influences of body iron stores, but these occurred in chronic high exposure situations where metal transporters would likely be saturated with metal. Current data thus suggest metal transporters could be one of the determinants of cadmium body burden and this factor perhaps explain the variability in blood cadmium levels observed by Björkman and coworkers (2000) in a cohort of 61 monozygotic and 103 dizygotic twin pairs.

CONCLUSIONS AND PERSPECTIVES

Recent epidemiologic studies involving an exposure-effect assessment have linked low-level cadmium exposure experienced by current populations with some adverse effects that are not restricted to kidney and bone, but in almost every organ and tissue where cadmium accumulates, including eye tissues. These data argue strongly for public health measures for reducing exposure. In the past, the wide variation in cadmium body burden among people has been attributed to cigarette smoking habits and the high pulmonary absorption rates for cadmium in cigarette smoke. However, as revealed in the present review, the difference in body burden of cadmium between smokers *vs*. non-smokers is less than three-fold. It is advanced that the signs of early renal injury and mild tubular impairment observed in chronic low-dose exposure situations viewed previously as "benign" could indeed be an early warning sign of subclinical or clinical morbidity and mortality. These notions are substantiated by the dose-response observed between cadmium body burden and all-cause mortality and cancer mortality in the Belgian and the US cohorts. It is also advanced that cadmium is secreted in breast milk and that calcium and zinc supplements could be considered in order to lower the breast milk cadmium content in minimizing potential effects of early-life exposure to cadmium.

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There are many issues that require further research. A precise risk estimate is needed to quantify the carcinogenic risk because the high prevalence of cadmium exposure means that even a small increase in risk could yield a large number of preventable cancer cases. The threshold-based PTWI model, while appearing as a reasonable method to derive a safe exposure level, to be valid it will require the appropriate inputs that are derived from the current stage scientific knowledge. Thus, revision of the current "safe" intake level for cadmium is much needed. A strong consideration should be given to a safety factor issue which is necessary to protect subpopulations with increased susceptibility, such as those with diabetes. Animal studies have shown that the symptoms of diabetic nephropathy and cadmium renal toxicity are enhanced when both the metal and the disease are present. The enhanced cadmium absorption noted for young age groups indicates new intake guidelines may need to be established for pediatric populations. The application of the Benchmark dose method should be expanded and applied to other toxicity endpoints to identify the organ other than kidney that should be considered as critical for deriving safe exposure levels. The potential genetically determined rates of cadmium absorption, uptake, accumulation and toxicity remain largely unexplored and needs to be the subject of future research. With the looming cancer and chronic disease epidemic worldwide, we encourage consideration given to cadmium exposure assessment, identification of potential exposure sources and determinant of cadmium body burden in future epidemiologic investigations to allow an estimate of total disease burden (cost) of the population exposure. There is a lack of therapeutically-effective chelating agents to enhance excretion of cadmium and this factor makes prevention of cadmium accumulation pivotal. The persistence of cadmium in the environment requires a long-term approach to minimize human exposure through environmental management and maintenance of lower cadmium levels wherever possible.

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Table 1. Exposure levels associated with kidney and bone effects.

Study Population	Exposure/Outcomes
Sweden, n820, aged 53-64 yrs, Akesson et al. 2005, 2006.	Blood and urinary cadmium at 0.38µg/L and 0.67 µg/g creatinine were associated with tubular impairment. Urinary cadmium at 0.8 µg/g creatinine was associated with glomerular impairment. Increased body burden of cadmium was associated with lowered bone mineral density, decreased serum parathyroid hormone and bone metabolism.
Thailand, n200, aged 16-60 yrs, Satarug et al. 2005.	A three-fold increase in body burden associated with 11%, 32% and 61% increases in the probability of having high blood pressure, renal injury and tubular impairment.
Thailand, n224, 30-87 yrs, Teeyakasem et al. 2007.	OR for tubular impairment was 10.6, comparing urinary cadmium 1-5 *vs*. >5 µg/g creatinine.
US, n4258 ≥ 50 yrs, Gallagher et al. 2008.	A 1.43-fold increase in osteoporosis risk, comparing urinary cadmium 1 *vs*. < 0.5 µg/g creatinine.
Belgium, n294 with mean age 49.2 yrs, Schutte et al. 2008b.	A 2-fold increase in body burden associated with increased bone re-sorption, urinary calcium loss, decreased proximal forearm bone density and low serum parathyroid hormone.
China, n148, 3-yr observation, Wu et al. 2008.	Progressive tubular and glomerular impairment observed among those with urinary cadmium >10 µg/g creatinine.
UK, n160, aged 18-86 yr, Thomas et al. 2009.	*Risk for early renal effects was increased by 2.6 fold and 3.6 fold, comparing urinary cadmium 0.3 *vs*. < 0.5 *vs*. ≥ 0.5 µg/g creatinine.
US, n14778 > 20 yrs, Navas-Acien et al. 2009.	Risk for albuminuria was 2.34 and it was 1.98 for lowered glomerular filtration rate, comparing those in the highest *vs*. the lowest quartiles of blood cadmium and lead.

The n values denote number of subjects in a study. *Early renal injury was defined as uurinary NAG > 2 IU/g creatinine.

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Table 2. Exposure levels associated with diabetes and hypertension.

Study Population	Exposure/Outcomes
US, *n*8722 aged ≥ 40 yrs, Schwartz et al. 2003.	OR for abnormal fasting glucose was 1.48, 2.05, comparing urinary cadmium <1 *vs*. 1.00-1.99 *vs*. ≥2 µg/g creatinine. OR for diabetes was 1.24, 1.45, comparing urinary cadmium <1 *vs*. 1.00-1.99 *vs*. ≥2 µg/g creatinine.
China, *n*229 aged 44-87 yrs with type 2 diabetes, mean diabetic duration 8.6 yrs, Chen et al. 2006.	OR for tubular impairment was 3.34, comparing urinary cadmium <1 *vs*. ≥1 µg/g creatinine and it was increased to 5.56, comparing those with low *vs*. high levels of circulating metallothionein antibody.
Pakistan, 238 men aged 31-60 yrs with type-2 diabetes, diabetic duration 16 yr, 196 controls, Afridi et al. 2008.	Diabetic subjects had higher levels of cadmium in hair, blood and urine than controls. Mean blood (urinary) cadmium among non-smoker controls *vs*. non-smoker cases was 4.2 (3.2) *vs*. 5.7 (4.6) µg/L.
Torres Strait, Australia, *n*182, Haswell-Elkins et al. 2008.	A dose-response between urinary cadmium and glomerular impairment was observed among type-2 diabetic subjects after adjustment for confounders.
Korea, *n*1902, Eum et al. 2008.	OR for hypertension was 1.51, comparing blood cadmium in the lowest *vs*. the highest tertile.
US, *n*10991 aged ≥ 20 yrs, Tellez-Plaza et al. 2008.	Mean difference in systolic blood pressure between blood cadmium in the 90th *vs*. 10th percentile was 1.36 mmHg [95% CI, -0.28 to 3.00] while the mean difference in diastolic blood pressure was 1.68 mmHg [95% CI, 0.57-2.78].

The *n* values denote number of subjects in a study.

Table 3. Exposure levels associated with effects on newly identified targets.

Targets/Study Population	Exposure/Outcomes
Blood vessels: US, *n*2125, *n*790, Navas-Acien et al. 2004, 2005	OR for PAD of 1.07, 1.30, and 2.82, when comparing blood cadmium quartiles 2, 3 and 4 *vs*. the lowest (*p* for trend = 0.01). OR for PAD of 3.05, when comparing urinary cadmium of the 75th *vs*. the 25th percentile.
Blood vessels: Belgium, *n*557, Schutte et al. 2008a	Increased body burden associated with lower aortic pulse wave velocity, lower pulse pressure and higher femoral distensibility.
Heart: US, *n* 4912, Everett et al. 2008.	OR for female myocardial infarction was 1.8, comparing urinary cadmium ≥ 0.88 *vs*. <0.43 µg/g creatinine.
Lung: US, *n*96, Lampe et al. 2008	Increased body burden was associated with reduced lung function among smokers.
Periodontal tissues: US, *n*11412, Arora et al. 2009.	A 3-fold increase in urinary cadmium associated with 54% higher prevalence odds for periodontal disease.
Eye: US, 53 cases, 53 controls, Erie et al. 2007.	Higher urinary cadmium associated with AMD in smokers.
Mammary gland: Austria, *n*124, Gundacker et al. 2007.	Intake of supplement was associated with lowered breast milk cadmium only in non-smokers.
Mammary gland: Bangladesh, *n*123, Kippler et al. 2008.	Manganese, iron and calcium in breast milk correlated with cadmium content.

The *n* values denote number of subjects in a study.

Table 4. Exposure levels associated with mortality and cancer mortality.

Study Population	Exposure/Outcomes
Kekehashi (Japan) cohort, *n*3178, 15-y observation**,** Nishijo et al. 2006, Nakagawa et al. 2006.	Hazard ratio for cancer mortality was 2.5, among women with permanent tubular impairment. Hazard ratio for all-cause mortality was 2.09 among women with urinary cadmium $\geq$ 3 µg/g creatinine.
Nagasaki (Japan) cohort I, *n*275**,** 23-y observation, Arisawa et al. 2007a.	OR for cancer mortality 2.58 among those with tubular impairment. OR for all-cause mortality was 1.41 among those with permanent tubular impairment.
Nagasaki cohort II, *n*329, 13-yr observation, Arisawa et al. 2007b.	No effects of body burden of cadmium on mortality were observed.
Belgian Cohort**,** *n*956, 20.3-y median observation, Nawrot et al. 2008.	Mortality increased by 20% and 44% in low and high exposure areas, among those with a two-fold increase in body burden. Mortality increased by 25% and 33% in low and high exposure areas, among those with a two-fold increase in blood cadmium.
US Cohort, *n*13958, Menke et al. 2009.	Male hazard ratio was 1.7 for all-cause mortality and it was 4.3 for cancer mortality, comparing urinary cadmium <0.21 *vs*. >0.48 µg/g creatinine.

The *n* values denote number of subjects in a study. Irreversible tubular impairment was defined as urinary β2-MG $\geq$ 1000 µg/g creatinine.

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Table 5. Exposure levels associated with cancer.

Cancer/Study Population	Exposure/Risk Estimate
Lung, Belgium, *n*994, 15-y observation, Nawrot et al. 2006.	Hazard ratio of 1.7, 2.6 and 1.6 was respectively attributed to a two-fold increase in body burden, living in "high" exposure area, and a two-fold increase in soil cadmium.
Pancreas, Egypt, 31 cases, 52 controls, Kriegel et al. 2006.	OR of 1.12 and 3.25 was respectively attributed to elevated serum cadmium and farming occupation.
Breast, US, 246 cases, 254 controls, McElroy et al. 2006.	OR of 2.3 when comparing urinary cadmium <0.26 *vs.* ≥ 0.58 μg/g creatinine.
Endometrium, Sweden, *n*30210, 16-yr observation, Akesson et al. 2008.	OR of 2.9 was attributed to cadmium intake >15 μg/day.
Prostate, China, *n*297, Zeng et al. 2004**.**	Dose-response between body burden and abnormal serum PSA levels.
Prostate, Italy, 45 cases, 58 controls, Vinceti et al. 2007.	OR of 4.7 when comparing nail cadmium content in the lowest *vs.* the highest quartile.
Prostate, US, *n*422, Wijngaarden et al. 2008.	An increase of urinary cadmium to 1 µg/g creatinine associated with a 35% increase in serum PSA.
Urinary bladder, Belgium, 172 cases, 395 controls, Kellen et al. 2007.	OR of 5.7 when comparing blood cadmium in the lowest *vs.* the highest tertile.

The *n* values denote number of subjects in a study.

Table 6. Cadmium accumulation in the body of environmentally exposed subjects

Study Population/Reference	Cadmium content (µg/g wet tissue weight	
	Men	Women
Australia, Satarug et al. 2002		
Lung	0.11 ± 0.19	0.17 ± 0.35
Liver	0.78 ± 0.71	1.36 ± 0.96*
Kidney cortex	14.6 ± 12.4	18.1 ± 18.0
Japan, Uetani et al. 2006		
Liver	7.9 ± 2.1	13.1 ± 2.1
Kidney cortex	72.1 ± 1.7	83.9 ± 2.2
Kidney medulla	18.3 ± 2.2	24.5 ± 2.1
Pancreas	7.4 ± 2.0	10.5 ± 2.1
Thyroid	10.6 ± 2.2	11.9 ± 2.0
Heart	0.3 ± 1.5	0.4 ± 2.0
Muscle	1.2 ± 2.1	2.2 ± 2.4
Aorta	1.0 ± 2.1	1.1 ± 1.9
Bone	0.4 ± 1.6	0.6 ± 1.8

Numbers are mean ± standard deviation (SD) values.
An Australian study comprised 43 men and 18 women, 2-89 yrs, mean age 38.5 yrs. Mean and SD values for cadmium content were in arithmetic units. *Indicates higher in women than men.
A Japanese study comprised 36 men and 36 women, 60-91 yrs, mean age 74 yrs. Mean and SD values for cadmium content were in geometric units.