

Cadmium exposure in the population: from health risks to strategies of prevention

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Abstract We focus on the recent evidence that elucidates our understanding about the effects of cadmium (Cd) on human health and their prevention. Recently, there has been substantial progress in the exploration of the shape of the Cd concentration-response function on osteoporosis and mortality. Environmental exposure to Cd increases total mortality in a continuous fashion without evidence of a threshold, independently of kidney function and other

classical factors associated with mortality including age, gender, smoking and social economic status. Pooled hazard rates of two recent environmental population based cohort studies revealed that for each doubling of urinary Cd concentration, the relative risk for mortality increases with 17% (95% CI 4.2–33.1%; $P < 0.0001$). Tubular kidney damage starts at urinary Cd concentrations ranging between 0.5 and 2 μg urinary Cd/g creatinine, and recent studies focusing on bone effects show increased risk of osteoporosis even at urinary Cd below 1 μg Cd/g creatinine. The non-smoking adult population has urinary Cd concentrations close to or higher than 0.5 μg Cd/g creatinine. To diminish the transfer of Cd from soil to plants for human consumption, the bioavailability of soil Cd for the plants should be reduced (external bioavailability) by maintaining agricultural and garden soils pH close to neutral (pH-H₂O of 7.5; pH-KCL of 6.5). Reducing the systemic bioavailability of intestinal Cd can be best achieved by preserving a balanced iron status. The latter might especially be relevant in groups with a lower intake of iron, such as vegetarians, and women in reproductive phase of life. In exposed populations, house dust loaded with Cd is an additional relevant exposure route. In view of the insidious etiology of health effects associated with low dose exposure to Cd and the current European Cd intake which is close to the tolerable weekly intake, one should not underestimate the importance of the recent epidemiological evidence on Cd toxicity as to its medical and public health implications.

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Introduction

Cadmium (Cd) is an ever-present and global environmental pollutant. During the twentieth century, the Cd concentration in human bones rose 10-fold in France (Jaworowski et al. 1985). Populations worldwide have a low-level intake through their food, causing an age-related cumulative increase in the body burden of this toxic metal (Järup et al. 1998c). Environmental exposure levels to Cd, that are substantially above the background, occur in areas with current or historical industrial contamination for instance in regions of Belgium, Sweden, UK, Japan, and China.

We review the most substantial lines of research that recently (since 1999) have been pursued and elucidate our understanding about human health effects of Cd at the population level. Hence, we describe possible strategies of prevention for populations at risk.

External and internal exposure to Cd

Exposure to Cd occurs through intake of contaminated food or water, or by inhalation of polluted air. Occupational exposures are found in industries such as electroplating, welding, smelting and refining, pigment production, and battery manufacturing. Other respiratory exposure to Cd can occur through inhalation of cigarette smoke (Järup et al. 1998c) or indoor dust contaminated with Cd (Hogervorst et al. 2007).

In the non-anthropogenic influenced environment, Cd concentration is generally low and is not related with the concentration of other elements except zinc. Daily human intakes are from 10 µg Cd/kg body weight (humans exposed to high Cd concentrations) to 0.1 µg/kg b.w. (Järup et al. 1998c). In order to keep the urinary Cd concentration below 1 µg Cd/g creatinine in 95% of the population by age of 50 years, a weekly dietary Cd exposure should stay below 2.5 µg Cd/kg body-weight (CONTAM 2009).

The average dietary intake of Cd in adults across European countries was estimated to be between 1.9 and 3.0 µg/kg b.w. per week, and the highly exposed adults have estimates in the range of 2.5–3.9 µg/kg b.w. per week (CONTAM 2009). The CONTAM Panel noted that such average dietary intake in European countries is close to or slightly exceeding the threshold of 2.5 µg/kg b.w. (CONTAM 2009). Furthermore, it was noticed that subgroups of the population, such as vegetarians, women in reproductive phase of life, smokers and people living in highly contaminated areas may exceed the tolerably weekly intake by about 2-fold.

Cd inhalation is a far smaller contributor to total Cd body burden except in some industrial settings, smokers or highly environmentally exposed subjects. Smokers absorb amounts of Cd comparable to those from food, about 1–3 µg of Cd per day. It has been reported that one cigarette contains about 1–2 µg of Cd and that about 10% of the Cd content is inhaled when the cigarette is smoked (Nordberg et al. 2007). A logic preventive measure is to stop smoking and to avoid passive exposure to tobacco smoke (Bolte et al. 2008). Recent data show low Cd concentrations (<5 ng Cd/m³) in the air of most European cities (Nawrot et al. 2009), however, close to some metallurgic plants values exceeding the WHO limit value (5 ng Cd/m³) are still reported (e.g. measuring station OBE01, Beerse, Belgium, 27 ng Cd/m³; <http://www.vmm.be>, accessed on November, 2009). Belgium is no exception, and similar levels of environmental exposure likely persist in the United States and other European countries close to non-ferrous sites.

Soil polluted with Cd, can be taken up by the wind and thereby generating polluted dust particles. The particles that contain Cd are generally bigger than 10 µm. They are too large to reach the lung alveoli, but they will end up in the gastrointestinal tract by mucociliary clearance from the naso-pharynx and bronchi (Alfaro-Moreno et al. 2007). One can prevent this way of Cd exposure by installing a well-closed cover of plants on the contaminated soils. House dust historically enriched by Cd is a relevant route of exposure in polluted areas (Hogervorst et al. 2007). In a population living in the vicinity of zinc refiners, a 2-fold increase in the metal loading rate in house dust was associated with increases in blood Cd (+2.3%) and urinary Cd (+3.0%), independent of the intake of

locally grown vegetables (Hogervorst et al. 2007). Gastrointestinal absorption of Cd is estimated to be around 5–8%, but may increase in cases of iron deficiency (Flanagan et al. 1978). Inhalation absorption of Cd is generally higher than gastrointestinal absorption. It ranges 10–50%, however, the absorption of Cd from cigarette smoke is between 25 and 50% (Nordberg et al. 2007).

Once absorbed, Cd binds avidly to metallothionein. Cd is stored mainly in the kidneys and the liver, and also in testes. The half-life in the body is 10–30 years. In general, nonsmokers have urinary Cd concentrations of 0.02–0.7 µg/g creatinine, which increase with age in parallel with the accumulation of Cd in the kidney (Järup et al. 1998c; Staessen et al. 2001).

Urinary excretion of Cd is a biomarker of lifetime Cd exposure. Cd excretion in 24-h urine is rather stable in solute composition and is therefore the gold standard to measure Cd in the urinary matrix. However, a lower participation rate and/or incomplete sampling together with practical reasons might incite to choose for spot urine. As spot urine samples vary in dilution of the solute within individuals, often urinary analytes are standardized to 1 g of creatinine. However, creatinine might be influenced by muscle mass, physical exercise, and the dietary intake of proteins. The mean urinary Cd level in the US population averaged 0.18 µg/g creatinine (95th percentile: 0.79 µg/g creatinine) (CDC 2005). In the Belgian population urinary Cd averaged 0.80 µg/g creatinine to 1.00 µg/g creatinine for those in the vicinity of zinc smelters (Nawrot et al. 2008). Japanese women living in non-polluted areas had urinary Cd concentrations that were considerably higher and ranged from 0.25 to 11.4 µg/g creatinine (with a geometric mean of 2.87 µg/g creatinine) (Ezaki et al. 2003). Recent biomonitoring in a population living close to mining sites of Katanga (Congo) revealed urinary Cd values of 0.75 µg/g creatinine (Banza et al. 2009).

The Cd level in blood mainly reflects the last few months of exposure. Differences in hematocrit levels may cause some variability of the Cd concentration in whole blood. Hematocrit levels in women range normally from 35 to 47% and for men from 39 to 50%. To control for this variability, whole blood Cd may be standardized for hematocrit. Non-smoking adults living in non-polluted areas have blood Cd

concentrations that vary between 0.1 and 1.0 µg Cd/l in whole blood.

Cd related morbidity

Osteoporosis

Osteoporosis is usually an age-related bone disorder. Evidence accumulates that besides kidney the bone is a primary target organ of Cd toxicity as well. Clinical features associated with osteoporosis include increased morbidity (pain, physical impairment, decreased quality of life), increased risk of new fractures and increased mortality (Van der Klift et al. 2002). Studies among populations from Belgium (Staessen et al. 1999; Schutte et al. 2008b), Sweden (Järup et al. 1998a; Alfvén et al. 2000; Åkesson et al. 2006), Japan (Honda et al. 2003) and China (Zhu et al. 2004; Jin et al. 2004; Wang et al. 2003) showed associations between osteoporosis and low-level environmental Cd exposure. The generally accepted interpretation has been that Cd-induced renal tubular damage (Staessen et al. 1994) decreases the calcium reabsorption in the nephron, resulting in hypercalciuria and decreased bone mineral density, and hence increased fracture risk (Järup et al. 1998c; Staessen et al. 1994) particularly in postmenopausal women (Schutte et al. 2008b; Staessen et al. 1999) or men in the older age group (Järup and Alfvén 2004). However, a recent study also found a dose–response association between odds of osteoporosis in young men (mean age 45) and urinary Cd (Nawrot et al. 2010). A selection of recent studies focusing on the association between Cd exposure and bone effects is given in Table 1.

A striking observation, considering the first epidemiological argument of Cd-induced bone effects, was the clear-cut interference of low-level Cd exposure with calcium metabolism. The Belgian Cadmibel study showed for a 2-fold increase in the urinary Cd excretion that the urinary calcium excretion rose on average by 0.25 mmol/24 h (Buchet et al. 1990). Hypercalciuria should be considered an early tubulotoxic effect, because it may exacerbate the development of osteoporosis, especially in the elderly. Some years later, mineral density and fracture incidence were assessed in 506 participants of the initial population cohort (Staessen et al. 1999).

Table 1 Selected studies on bone density and osteoporosis in association with cadmium exposure

Reference	Population	Effect measure	Effect size	Mean exposure/observed threshold
Staessen et al. (1999)	General population, $n = 506$. Prospective study, median follow-up 6.6 years, Belgium	Fractures/bone density	Each doubling in UCd associated with 1.73 times higher risk of fracture in women (interaction with postmenopausal status)	Geometric mean UCd concentration: 8.6 nmol/day Threshold: $\sim 1 \mu\text{g Cd/g crt}$
Wang et al. (2003)	General population ($n = 790$), China	Osteoporosis (T-score < -2.5) Fractures	Odds: 2.09 (95% CI 1.08–4.03) for the highly polluted area versus control area Each $\mu\text{g UCd/g crt}$ 18% (95% CI 1.0–38%) higher risk	UCd 2.3–13 $\mu\text{g Cd/g crt}$ (control vs. polluted area) Average exposure 0.74 $\mu\text{g UCd/g crt}$
Alfvén et al. (2004)	General population $n = 1,021$. Retrospective study, Sweden		Hazard ratio reached 3.5 (90% CI 1.1–11) in the group of subjects with UCd between 2 and 4 $\mu\text{g/g crt}$ compared with $<0.5 \mu\text{g UCd/g crt}$.	Significant effects observed from 2 $\mu\text{g UCd/g crt}$
Jim et al. (2004)	General population ($n = 790$), China	Osteoporosis (Z-Score < -2)	Prevalence of osteoporosis: $\leq 2 \mu\text{g UCd/g crt}$: 2.4% (lowest group), 5 $\mu\text{g UCd/g crt}$: 2.5%, 10 $\mu\text{g UCd/g crt}$: 6%, 20 $\mu\text{g UCd/g crt}$: 14.8%	$>2 \mu\text{g Cd/g crt}$ Kidney damage observed
Åkesson et al. (2006)	General population ($n = 820$), women, Sweden	Bone-mineral density (BMD) Urinary deoxyypyridinoline (UDP)	BMD: $-0.011 \text{ g/cm}^2/\mu\text{g Cd/l}$ UDP: 16 nmol// $\mu\text{g Cd/l}$	Median UCd: 0.67 $\mu\text{g/g crt}$ Stronger associations in postmenopausal women
Gallagher et al. (2008)	General population. NHANES ($n = 4,257$). US women 50–90 year of age	Osteoporosis (T-score < -2.5)* based on Hip bone measurements	15% increase in prevalence of osteoporosis per 1 $\mu\text{g Cd/g crt}$ in urine	Significant associations at UCd levels $<1 \mu\text{g/g crt}$
Schutte et al. (2008a, b)	General population. ($n = 294$) women, Belgium. Prospective cohort	Effects independent of tubular kidney function Effects on BMD continuous Effects on biomarkers of bone resorption (UHP, ULP)	Effect sizes associated with a doubling of UCd exposure were +8.4% for UHP, +6.9% for ULP, 0.77 mmol/day for urinary calcium, -0.009 g/cm^2 for proximal forearm BMD	Effects independent of tubular kidney function Continuous effects in both pre- and postmenopausal women. Stronger effects observed in postmenopausal women Mean UCd level 11 nmol/l ($\sim 1.2 \mu\text{g Cd/g crt}$)
Nawrot et al. (2010)	Occupationally exposed young men ($n = 83$), mean age 45 years. Cross-sectional	BMD, osteoporosis (T-score < 2.5)* defined in three bone sites (forearm, hip and lumbar spine)	Compared with the lowest (0.5 $\mu\text{g UCd/g crt}$) tertile of UCd, the odds were 4.8- and 9.9-fold higher in the middle (0.5–1.9 $\mu\text{g UCd/g crt}$) and highest tertile ($>1.9 \mu\text{g Cd/g crt}$ in urine)	Effects independent of tubular kidney function Lowest effects observed between 0.5 and 1.9 $\mu\text{g Cd/g crt}$ in urine

BMD bone-mineral density, UCd urinary cadmium, crt creatinine, UHP hydroxylysypyridinoline, ULP lysypyridinoline

*Osteoporosis was defined as a T-score or Z-score to define age- and gender-specific threshold

Cadmium was negatively associated with bone mineral density in postmenopausal women. A 2-fold increase in urinary Cd excretion at baseline was associated with 73% increased risk of fractures in women [95% confidence interval (CI) 1.16–2.57]. The corresponding results for men were 1.20 (0.75–1.93) (Staessen et al. 1999). Data from Sweden showed a doubling of the risk for osteoporosis for urinary Cd levels of 0.5–3 $\mu\text{g Cd/g creatinine}$ (middle tertile) compared with the lowest tertile (<0.5 $\mu\text{g Cd/g}$) (Alfvén et al. 2000). In addition, an increased risk of fractures was also noted in the Swedish Oscar study, demonstrating an elevated hazard ratio already at exposure levels of 2–4 $\mu\text{g/g creatinine}$ (Alfvén et al. 2004). Studies in China have reported that osteoporosis is related to kidney dysfunction, especially to tubular damage and its severity (Wang et al. 2003; Jin et al. 2004). Although women are believed to be more susceptible than men, a study in middle-aged men (mean age 45 years) exposed to Cd in an occupational setting showed a dose-dependent increase of osteoporosis. This is the first study that assessed the bone mineral density at three sites on the skeleton including forearm, lumbar spine and hip. Osteoporosis was defined according to T-score less than -2.5 (in this case $<0.56 \text{ g/cm}^2$) in one of the measured bone sites. Compared with the lowest tertile of urinary Cd, the risks were 4.8- and 9.9-fold higher in the middle (0.51–1.88 $\mu\text{g/g creatinine}$) and highest tertile ($>1.88 \mu\text{g/g creatinine}$), respectively. Only four (5%) men in this population had evidence of renal tubular dysfunction (β_2 -microglobuline $>300 \mu\text{g/g creatinine}$) (Nawrot et al. 2010).

A study using data from National Health and Nutrition Examination Surveys (NHANES) reported an increased risk for hip osteoporosis in 3,207 women aged 50 years and older [OR = 1.43 (95% CI 1.03–2.0)] at urinary Cd levels between 0.50 and 1.00 $\mu\text{g/g creatinine}$ as compared with the reference ($<0.5 \mu\text{g/g creatinine}$) (Gallagher et al. 2008). Dose–response relationships were reported on urinary Cd as a continuous variable expressed in $\mu\text{g per g creatinine}$ [OR = 1.15 (95% CI 1.00–1.33)]. Recent data provide more insight into the mechanisms supporting a direct osteotoxic effect of Cd independent of the status of kidney function in that urinary excretion of pyridinium crosslinks from bone collagen is increased (Schutte et al. 2008b). The shape of this association was linear with effects observed at low levels (Table 1). The

Cd-induced bone effect is not mediated via impaired activation of vitamin D (Engstrom et al. 2009).

Kidney

Microproteins in urine are sensitive biomarkers of Cd-induced renal damage reflecting a tubulotoxic effect. Among them β_2 microglobulin, a small plasma protein, which passes the glomerular filter and subsequently almost completely reabsorbed in the renal tubules if no Cd-induced damage is present. Depending on the biomarker of nephrotoxicity thresholds of urinary Cd can range from about 2 $\mu\text{g/g creatinine}$ for the onset of early biochemical alterations (e.g. hypercalciuria) to 10 $\mu\text{g/g creatinine}$ for the development of the classic tubular microproteinuria (Roels et al. 1999). A cross-sectional analysis of 14,778 subjects (NHANES) showed that subjects in the highest quartile of blood Cd ($>0.6 \mu\text{g/l}$) were almost two times more likely to exhibit albuminuria ($\geq 30 \text{ mg/g creatinine}$) and 32% more likely to have reduced glomerular filtration rate ($<60 \text{ ml/min/1.73 m}^2$) (Navas-Acien et al. 2009).

Epidemiological evidence shows higher susceptibility for persons with diabetes to develop Cd-induced renal dysfunction. A study of 122 men and women aged 18–85 exposed to Cd by consuming seafood (coast of Australia) found a statistically significant correlation between urinary Cd levels and albuminuria in individuals with type II diabetes, but found no such correlation in non-diabetic individuals (Haswell-Elkins et al. 2008). In 820 Swedish women between the ages of 53 and 64, multiple linear regression analysis showed statistically significant associations between urinary α_1 -microglobulin and urinary Cd with significant effect-modification for diabetes (Åkesson et al. 2005).

Although there is strong evidence that elevated levels of tubular biomarkers of renal dysfunction are associated with urinary cadmium, a surrogate of the Cd body burden, there is less agreement about the clinical significance and predictivity of these changes. Prospective epidemiological evidence from Belgium (Nawrot et al. 2008) and U.S. (Menke et al. 2009) suggests that the increased Cd related mortality was directly related to the toxic effects of Cd, rather than being mediated by renal dysfunction, as suggested by the Japanese studies (Nishijo et al. 2006; Arisawa et al. 2007).

Diabetes

The Third National Health and Nutrition Examination Survey (NHANES III), which examined 8,722 U.S. citizens over age 40, revealed a significant association between elevations in urinary Cd levels and increases in fasting blood glucose levels (110–126 mg/dl) (Schwartz et al. 2003). To exclude the effect of tubular kidney function (defined as urine albumin, ≤ 30 $\mu\text{g/ml}$), the investigators restricted the analysis to persons without evidence of renal damage, but this restriction revealed the same conclusions. However, until now prospective evidence linking Cd exposure with higher prevalence of diabetes is lacking. Persons with diabetes appear to be more susceptible for the Cd-induced renal effects (see paragraph on kidney).

Cancer

Three lines of evidence explain why the International Agency for the Research on Cancer classified Cd as a human carcinogen. First, as reviewed by Verougstraete et al. (2003) several (Kazantzis et al. 1992; Sorahan and Lancashire 1997; Järup et al. 1998b; Sorahan and Waterhouse 1983) albeit not all studies (Sorahan et al. 1995) in workers showed a positive association between the risk of lung cancer and occupational exposure to Cd. Figure 1 summarizes the findings of these five largest occupational cohort studies. The combined estimate showed an increased risk of 20% in workers exposed to Cd compared with those not exposed (Verougstraete et al. 2003). Second, data from rats showed that the pulmonary system is a target site for carcinogenesis after Cd inhalation. However, exposure to toxic metals in animal studies has usually been much higher than those reported in humans environmentally exposed to toxic metals. Third, several *in vitro* studies have shown plausible toxicodynamic pathways, such as increased oxidative stress (as reviewed in this special issue by Cuypers et al. 2010), modified activity of transcription factors (Watkin et al. 2003), and inhibition of DNA repair (Jin et al. 2003). Most errors that arise during DNA replication can be corrected by DNA polymerase proof reading or by postreplication mismatch repair. As reviewed in this special issue by Hartwig (2010), inactivation of the DNA repair machinery is an important primary effect, because repair systems are required to deal with the constant

DNA damage associated with normal cell function. The latter mechanism might indeed be relevant for environmental exposure because Jin et al. (2003) found that chronic exposure of yeast to environmentally relevant concentrations of Cd can result in extreme hypermutability. In this study, the DNA-mismatch repair system was already inhibited by 28% at Cd concentrations as low as 5 μM . For example, the prostate of healthy unexposed humans accumulates Cd to concentrations of 12–28 μM and human lungs of nonsmokers accumulate Cd to concentrations of 0.9–6 μM (Jin et al. 2003). Further, *in vitro* studies provide evidence that Cd may act like an estrogen (Byrne et al. 2009), forming high-affinity complexes with estrogen receptors, suggesting a positive role in breast cancer carcinogenesis.

Along with this experimental evidence, recent epidemiological studies (Åkesson et al. 2008; Kellen et al. 2007; Kriegel et al. 2006; McElroy et al. 2006; Nawrot et al. 2006; van Wijngaarden et al. 2008; Vinceti et al. 2007), summarized in Table 2, gave important positive input into the discussion on the role of exposure to Cd in the development of cancer in humans. First, the results of a population-based case–control study noticed a significant 2-fold increased risk of breast cancer in women in the highest quartile of Cd exposure compared with those in the lowest quartile (McElroy et al. 2006). In a population based prospective cohort study with a median follow-up of 17.2 years in an area close to three zinc smelters, the association between incident lung cancer and urinary Cd was assessed (Nawrot et al. 2006). Cd concentration in soil ranged from 0.8 to 17.0 mg/kg. At baseline, geometric mean urinary Cd excretion was 12.3 nmol/day (1.78 $\mu\text{g/day}$) for people in the high-exposure area, compared with 7.7 nmol/day (0.87 $\mu\text{g/day}$) for those in the reference (low exposure) area. The risk of lung cancer was 3.58 higher in the high exposure area compared to the area with low exposure. As already mentioned above, 24-h urinary excretion is a biomarker of lifetime exposure to Cd. The risk for lung cancer was increased by 70% for a doubling of 24-h urinary Cd excretion. Confounding by co-exposure to arsenic was unlikely.

Epidemiological studies did not convincingly imply Cd as a cause of prostate cancer. Of 11 cohort studies, only three found a positive association (Verougstraete et al. 2003). However, a recent case–control study (Vinceti et al. 2007) with 40

Fig. 1 Standardized mortality rates and 95% CI for lung cancer for the five largest occupational cohort studies. Combined estimate denotes a meta-analysis of the five large cohort studies mentioned. Figure based on Verougstraete et al. (2003) (with permission)

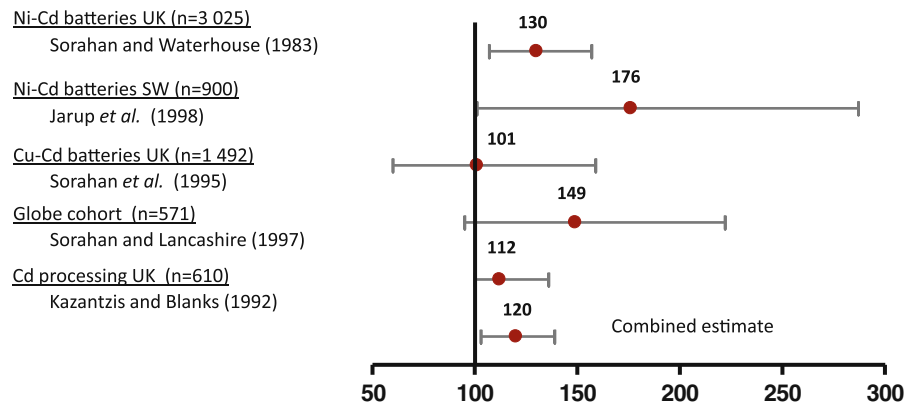


Table 2 Studies on cancer in association with environmental cadmium exposure

Site	Reference	Population	Effect size	Shape of the association
Breast	McElroy et al. (2006)	Case-control study: $n = 254$ cases, $n = 246$ controls, United States, based on NHANES sample	Odds ratio: 2.29 (95% CI 1.3–4.2) comparing the highest quartile of urinary Cd ($\geq 0.58 \mu\text{g/g crt}$) to the lowest ($< 0.26 \mu\text{g/g crt}$)	Continuous linear increase in risk
Endometrium	Åkesson et al. (2008)	Cohort study: 30,210 post menopausal women, 16 years follow-up, Sweden	Relative risk: 1.39 (95% CI 1.04–1.86) for highest tertile of intake of Cd $\geq 16 \mu\text{g Cd/day}$ versus $< 13.7 \mu\text{g Cd/day}$ (lowest tertile)	Third tertile significantly different from first. Shape linear
Lung cancer	Nawrot et al. (2006)	Cohort study: $n = 994$, 15 years follow-up, Belgium	Relative risk 1.31 (95% CI 1.03–1.65) for doubling in urinary Cd	Continuous linear increase in risk
Pancreas	Kriegel et al. (2006)	Case-control study: $n = 31$ cases, $n = 52$ controls, Egypt	Odds ratio 1.12 (95% CI 1.04–1.23) per $\mu\text{g/l}$ serum Cd.	Continuous increase risk
Prostate	Vinceti et al. (2007)	Case-control study: $n = 45$ cases, $n = 58$ controls, Italy	Odds ratio: 4.7 (95% CI 1.3–17.5) for highest quintile toenail Cd ($\geq 0.031 \mu\text{g/g}$) versus < 0.007	Threshold observed $\sim 0.015 \mu\text{g/g}$ toenail Cd
	Van Wijngaarden et al. (2008)	Cross-sectional: 320 men, NHANES population sample, United States	Significant Cd-zinc interaction: Men with zinc intake $< 12.7 \text{ mg/day}$ a urinary Cd increase of $1 \mu\text{g/g crt}$ is associated with a 35% increase in serum PSA	Effect size depends on zinc intake
Urinary bladder	Kellen et al. (2007)	Case-control study: $n = 172$ bladder cases, $n = 359$ controls, Belgium	Odds ratio: 5.7 (95% CI 5.0–13.8) comparing the highest ($\geq 1 \mu\text{g/l}$) to the lowest tertile ($< 0.2 \mu\text{g/l}$) of blood Cd	Continuous linear increase in risk

cases and 58 controls showed an excess cancer risk in subjects in the third and fourth (highest) quartiles (above $0.0145 \mu\text{g Cd/g}$) of toenail Cd concentration [OR = 1.3 (95% CI 0.3–4.9)] and 4.7 [(95% CI 1.3–17.5), respectively, P trend = 0.004] compared with subjects in the bottom quartile. A study (van Wijngaarden et al. 2008) reported an association between serum levels of Prostate Specific Antigen (PSA) and Cd exposure. They found effect-modification by zinc on the urinary Cd and PSA association in the NHANES population sample including 1,320

men. An increase in urinary Cd by $1 \mu\text{g/g}$ creatinine was associated with a 35% increase in PSA levels, in subjects with a zinc intake below the median (12.7 mg/day). In a case-control study, pancreatic cancer was associated with serum Cd levels (Kriegel et al. 2006). For each $1 \mu\text{g Cd per l}$ serum increase, the odds for pancreatic cancer increased with 12% (Table 3). Åkesson et al. (2008) reported an odds ratio of 2.9 for endometrial cancer among women with Cd intake above highest tertile. In a study of bladder cancer, Kellen et al. (2007) showed a 5.7-fold

Table 3 Selected studies on internal cadmium concentration in association with iron status

Author	Population	N	Iron indicator	Associations
Berglund et al. (1994)	Non-Smoking women, Sweden, 20–50 years	Women 57	Log S-Ferritin	Log BCd $r = -0.52$, $P < 0.01$
Olsson et al. (2002)	Men and women on farms in Sweden	Female Never-Smokers 38	S-Ferritin	BCd $r = -0.52$ exponential association
Muneko Nishijo et al. (2004)	Pregnant Japanese women 30–32 years	Women 50	Iron-Intake (mg)	BCd spearman $r = -0.35$, $P < 0.05$ UCd spearman $r = -0.28$, ns
Åkesson et al. (2002)	Early pregnant women gestational week 11 20–45 years, Sweden	Women: 210 Women 188	S-Ferritin	BCd spearman $r = -0.23$, $P \leq 0.01$ UCd spearman $r = -0.02$ ns
Nawrot et al. (2008)	Men and women in high and low exposure area, Belgium	Men and women 711	Log S-Ferritin	Log BCd regression coefficient = -0.110 ± 0.024 , $P \leq 0.001$
Kippler et al. (2009)	Pregnant Bangladeshi women in gestational week 14 14–44 years	Women 408	S-Ferritin	Ery Cd spearman $r = -0.17$, $P < 0.001$

BCd blood cadmium, UCd urinary cadmium, Ery erythrocytes

increase in risk between subjects with blood Cd at the lowest tertile ($<0.2 \mu\text{g/l}$) versus the highest tertile ($\geq 1 \mu\text{g/l}$).

Blood pressure and effects on arteries

Chronic exposure to Cd not only leads to its accumulation in the kidneys and liver but also in the endothelium and vascular smooth muscle cells (Messner and Bernhard 2010; Messner et al. 2009). Cd and Pb at exposure levels encountered at the workplace or in the environment are suspected to increase blood pressure and to cause hypertension (Nawrot et al. 2008). However, the influence of Cd on the cardiovascular system remains controversial. Cross-sectional and prospective studies by Staessen et al. (2000) showed that conventional or 24-h ambulatory blood pressure, or the risk of hypertension or cardiovascular diseases risk (Nawrot et al. 2008) in environmentally exposed populations were not associated with 24-h urinary Cd. Subjects with Itai-Itai disease also failed to develop hypertension (Nakagawa and Nishijo 1996). A recent report of NHANES showed a lower odds ratio for hypertension in the highest urinary Cd quartile compared with the lowest (Tellez-Plaza et al. 2008). Kurihara et al. (2004) studied urinary Cd normalised for creatinine as a biomarker of exposure and reported a significant odds ratio for hypertension less than unity in both

men [0.62 (95% CI 0.42–0.92)] and women [0.67 (95% CI 0.48–0.94)]. In contrast to these negative findings, Satarug et al. (2005) reported a positive association between blood pressure and urinary Cd in a population sample of 200 subjects that also showed tubular dysfunction. The association between blood pressure and cardiovascular risk is continuous without a threshold (Nawrot et al. 2003). Therefore, blood pressure should be treated as a continuous variable in epidemiological research rather than as arbitrary thresholds reflecting hypertension. Nevertheless, both at a continuous or a dichotomous (hypertension) scale there is no clear evidence for “pressor” effect due to environmentally Cd exposure.

Recently, NHANES data linked Cd with cardiovascular outcomes and peripheral arterial disease. Navas-Acien et al. (2004, 2005) reported that peripheral arterial disease might be associated with blood and urinary Cd, thus suggesting that Cd is involved in arterial dysfunction. The authors used the ankle-brachial index to reflect peripheral arterial disease. This non-invasive measure is useful in assessing the patency of the leg arteries and predicts cardiovascular morbidity and mortality (Resnick et al. 2004). After accounting for traditional cardiovascular risk factors, the odds ratio of peripheral arterial disease showed significant increase in the odds 2.82 (95% CI 1.36–5.85) for the highest blood Cd quartile ($>6.23 \text{ nmol/l}$ or $0.70 \mu\text{g/l}$) compared with the lowest quartile ($\leq 3.56 \text{ nmol/l}$ or $0.40 \mu\text{g/l}$) (Navas-Acien et al.

2004). This epidemiologic association is in line with data of the Atherosclerosis Risk Factors in Female Youngsters (ARFY) study, where blood Cd level was independently associated with early atherosclerotic vessel wall thickening [intima-media thickness exceeding the 90th percentile of the distribution; OR 1.6 (1.1–2.3)] (Messner et al. 2009). In contrast to these studies the Belgian populations did not show correlations between measures of arterial function and blood Cd and failed to confirm that increased Cd body burden (determined by 24-h urinary Cd excretion) was associated with decreased arterial function (Schutte et al. 2008a; Plusquin et al. 2005). Aortic pulse wave velocity, which is the gold standard of arterial stiffness, was significantly and inversely associated with 24-h urinary cadmium excretion (Schutte et al. 2008a).

Reproduction

No difference was found in fertility between men occupationally exposed to Cd and an appropriately matched control group ($n = 118$) by assessing birth experiences of their wives (Gennart et al. 1992). However, a hospital sample of the general population with infertility problems showed that blood and seminal Cd were significantly higher among infertility patients than controls (median seminal plasma Cd was 0.282 $\mu\text{g/l}$ in infertility patients vs. 0.092 $\mu\text{g/l}$ in controls). The percentage of motile sperm and sperm concentration correlated inversely with seminal plasma Cd among the infertility patients ($r = -0.20$, $P < 0.04$) (Benoff et al. 2009).

Prospective mortality studies

Recently, two population based cohort studies (Menke et al. 2009; Nawrot et al. 2008) showed higher risk for death in association with Cd exposure. The average urinary Cd concentration at baseline was about three times higher in the Belgian cohort ($\sim 1 \mu\text{g/g}$ creatinine) compared with the US cohort. The hazard ratios (95% CI) for all-cause mortality, associated with a 2-fold higher urinary Cd were 1.28 (95% CI 1.15–1.43) in men and 1.06 (95% CI 0.96–1.16) for women in the US cohort (NHANES III) and 1.20 (95% CI 1.04–1.39) in the men and women combined in the Belgian cohort. In the Belgian cohort the hazard rates were not different between men and women (no

urinary Cd by gender interaction in relation to mortality observed). Meta-regression of these three hazard ratios by a random effect model revealed a 17% (95% CI 4.1–33.2%; $P < 0.0001$) increase in the relative risk associated with a doubling of the urinary Cd concentration. The cause-related mortality pattern differed between the two cohorts. In the Belgian cohort deaths from non-cardiovascular but not cardiovascular causes increased with higher 24-h urinary Cd excretion (Nawrot et al. 2008). In the NHANES study, both non-cardiovascular and cardiovascular disease increased with higher urinary Cd concentrations in men whereas in women non-cardiovascular disease were borderline significantly associated but not cardiovascular mortality.

Previous studies in Japanese populations, showed associations between mortality and environmental exposure to Cd (Arisawa et al. 2007; Nishijo et al. 2006). However, there are important differences between the Japanese observations and the recent population based findings in the US and Belgium. First, the median urinary Cd level in the Japanese studies was 7.0 $\mu\text{g/g}$ creatinine (Arisawa et al. 2007), which probably explains the increased mortality from nephritis and nephrosis (Nishijo et al. 2006). By comparison, the median urinary Cd at baseline was $\sim 1 \mu\text{g/g}$ creatinine in Belgium and $\sim 0.34 \mu\text{g/g}$ creatinine (0.28 in men and 0.40 $\mu\text{g/g}$ creatinine in women) in the NHANESIII survey.

Prevention

Preventive measures that might diminish the Cd containing dust in our homes would be to replace carpets with floor coverings that can be cleaned with water. One may use a vacuum cleaner with a HEPA-filter combined with cyclone technology to remove particles as small as 0.3 μm to prevent small Cd-loaded particles from being remitted into the air (Yiin et al. 2002). For most of these preventive measures no hard scientific evidence based on intervention studies exists. Until now, only one intervention study has been reported (Kobayashi et al. 2008). A study in 50 persons, with urinary cadmium measured before and after soil replacement of a Cd-polluted rice basin, showed 10 years after soil replacement a decrease of 40% in urinary cadmium excretion, but the degree of renal tubular

injury (as reflected by $\beta 2$ -microglobulin, retinol binding protein (RBP), total protein, amino-N and glucose) did not improve.

Bioavailability of Cd in the soil and its transfer to plants

In the general nonsmoking population, not living in a Cd polluted area, the diet is the main source of Cd exposure. Most foods contain low concentrations of Cd, but high concentrations may be found in mushrooms, liver, kidney, and shellfish. Cereals, especially the non-refined wheat products, rice and vegetables, often contain elevated Cd concentrations. It seems likely that vegetarians have an increased intake of Cd.

Plant species and varieties differ extensively in their capacity to absorb and accumulate toxic metals. Lettuce, spinach, celery and cabbage (leaf vegetables) tend to accumulate relatively high concentrations of Cd, whereas beans (and other ‘fruit vegetables’) accumulate only low amounts of Cd. In two areas in the North of Belgium, home grown vegetables showed levels that exceeded the European limit (Fig. 2) with exception of beans and other ‘fruit vegetables’. Even in the reference area, with soil Cd levels that averaged 0.9 mg/kg soil, Cd content in about 50% of the celery were above the EU limit. Indeed, also in the non-polluted range (Cd levels below 1 mg Cd/kg soil) the transfer of Cd from the soil to plants is closely related with soil pH (Fig. 3). To know whether it is safe to grow vegetables in polluted areas, a representative soil sample should be taken to determine the soil Cd concentrations. Soil pH testing is necessary to establish the “lime requirement” of the soil. Natural forms of calcium carbonate are used to lime gardening and agricultural soils. Ground lime should be applied on a regular basis to maintain soil alkalinity, thereby reducing Cd uptake by plants. Table 4 lists the maximal allowable soil Cd level with respect to the grown vegetable. On the premise that the soil pH is high enough (pH-H₂O of 7.5; pH-KCl of 6.5) it is unlikely that vegetables grown on these specific soil Cd levels will exceed the EU limit value for Cd.

Bioavailability of Cd in the intestine and its transfer to blood

The amount of intestinally absorbed Cd is proportional to the Cd concentration in the food. However,

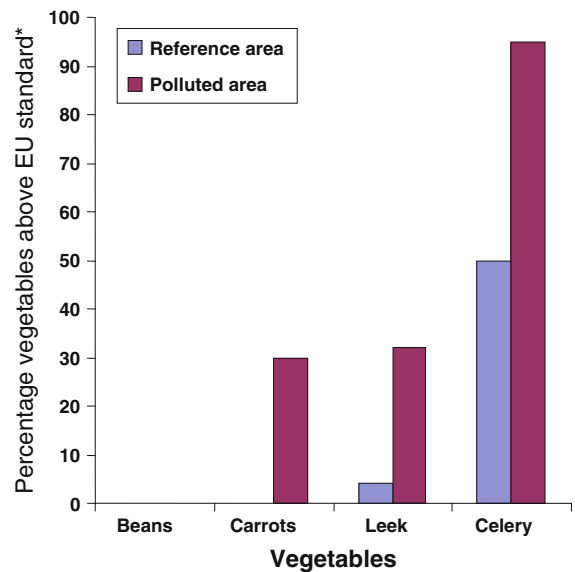


Fig. 2 Home grown vegetables from 127 households that grew vegetables and provided samples of beans, carrots, leek and celery. Vegetables were dried for 24 h at 60°C, incinerated at low temperature, digested with 3 mol/l hydrochloric acid and measured for cadmium by atomic absorption spectrometry. The geometric mean soil cadmium concentration was 5.8 times higher in the polluted area and averaged (5th–95th percentile interval) 0.9 mg/kg soil (0.4–1.6) in the low polluted area and 5.3 mg/kg (1.4–18.9) in the high polluted area ($P < 0.0001$). European limit values are 2 mg/kg (dry weight) for leafy vegetables and 0.9 mg/kg for all others

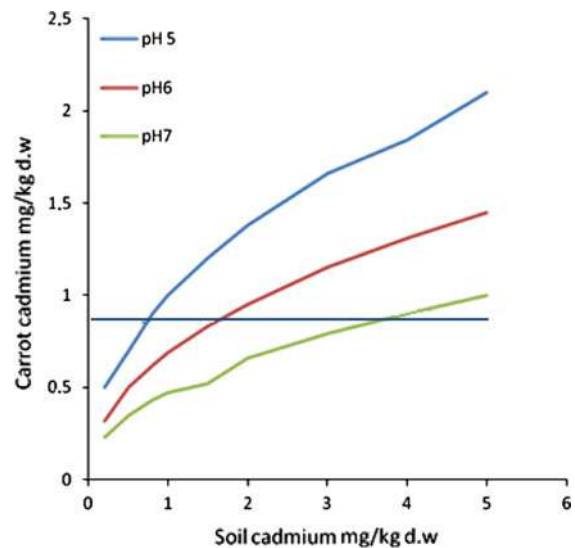


Fig. 3 Cadmium concentration in carrots in relation to the cadmium concentration and pH of the soil. Line denotes the EU limit value of 0.9 mg/kg d.w. (dry weight). pH based on pH-H₂O

Table 4 Maximal allowable soil cadmium levels depending on the grown vegetables

2 mg/kg*	5 mg/kg*	10 mg/kg*
Endives	Potatoes	Beans
Chervil	Strawberries	Peas
Parsley	Cauliflowers	Paprika
Rhubarb	Leeks	Tomato
Lettuce	Radishes	
Spinach	Salsify	
Watercress	Shallots	
Garden cress	Chicory	
Corn salad	Carrots	
Celery	Onion	

Maximal allowable soil concentrations for vegetable species that will not exceed

The EU guideline value for vegetables if the soil pH is high enough (pH-H₂O of 7.5; pH-KCL of 6.5)

there are factors that influence the rate of intestinal absorption of Cd. The rate of Cd absorption is increased if the nutritional status of calcium, iron or zinc is low. The duodenal iron transporter is up-regulated by iron deficiency, which leads to an increased intestinal absorption of dietary Cd. This is probably the main reason why the body burden of Cd is generally higher among women (Menke et al. 2009; Vahter et al. 2007) whose prevalence of iron depletion is higher than that of men. Urinary Cd increases longitudinally among pregnant women with exhausted iron stores (soluble transferrin receptor—serum ferritin ratio above 500) (Åkesson et al. 2002). The increase in urinary Cd with age is more pronounced in multiparous than in nullparous women (Åkesson et al. 2002). Table 3 lists recent studies linking iron status with blood and urine Cd. Most of the studies (Åkesson et al. 2002; Berglund et al. 1994; Kippler et al. 2009; Nawrot et al. 2008; Nishijo et al. 2004; Olsson et al. 2002) found a significant increase in body Cd stores in individuals with lower iron status. In Europe, iron deficiency is considered to be one of the main nutritional deficiency disorders affecting large fractions of the population, including, pre-postmenopausal and pregnant women. About 20% of young women have iron deficiency (serum ferritin <15 µg/l) (Grondin et al. 2008).

Conclusions

There has been substantial progress in the evaluation of the health effects of Cd and in the exploration of the shape of the concentration-response function at different organ systems. These results have important scientific, medical, and public health implications. To significantly reduce the adverse health effects of exposure to a toxic metal like Cd, the heart of the matter remains that further efforts must be made to reduce Cd pollution by appropriate legislation and its enforcement. However, in historically polluted areas, specific preventive strategies including covering of the polluted soil and restrictions to gardening and agriculture activities might be crucial depending on the concentrations and soil characteristics. The mean exposure for adults across Europe is close to the tolerable weekly intake of 2.5 µg/kg body weight. Subgroups such as vegetarians, children, smokers and people living in highly contaminated areas may exceed the tolerable weekly intake about 2-fold. To diminish the transfer of Cd from soil to plants, the soil Cd bioavailability should be reduced by maintaining agricultural and garden soil pH close to neutral. Balanced iron intake is effective in reducing the bioavailability of Cd present in the intestine, by reducing its absorption. Along with the recent knowledge concerning low dose Cd exposure, the current exposure to Cd at the population level should be kept as low as possible so that the urinary Cd concentration is kept below 0.66 µg/g creatinine (margin of safety = 3) as proposed by the EU (European Community report, EUR 23424 EN). The relations we discussed here between internal Cd dose and morbidity and mortality are based on individual data and satisfy Hill's criteria for causality (Hill 1965).

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