Confusion about Cadmium Risks: The Unrecognized Limitations of an Extrapolated Paradigm

Alfred Bernard

Louvain Centre for Toxicology and Applied Pharmacology, Institute of Experimental and Clinical Research (IREC), Catholic University of Louvain, Brussels, Belgium

BACKGROUND: Cadmium (Cd) risk assessment presently relies on tubular proteinuria as a critical effect and urinary Cd (U-Cd) as an index of the Cd body burden. Based on this paradigm, regulatory bodies have reached contradictory conclusions regarding the safety of Cd in food. Adding to the confusion, epidemiological studies implicate environmental Cd as a risk factor for bone, cardiovascular, and other degenerative diseases at exposure levels that are much lower than points of departure used for setting food standards.

OBJECTIVE: The objective was to examine whether the present confusion over Cd risks is not related to conceptual or methodological problems.

DISCUSSION: The cornerstone of Cd risk assessment is the assumption that U-Cd reflects the lifetime accumulation of the metal in the body. The validity of this assumption as applied to the general population has been questioned by recent studies revealing that low-level U-Cd varies widely within and between individuals depending on urinary flow, urine collection protocol, and recent exposure. There is also evidence that low-level U-Cd increases with proteinuria and essential element deficiencies, two potential confounders that might explain the multiple associations of U-Cd with common degenerative diseases. In essence, the present Cd confusion might arise from the fact that this heavy metal follows the same transport pathways as plasma proteins for its urinary excretion and the same transport pathways as essential elements for its intestinal absorption.

CONCLUSIONS: The Cd risk assessment paradigm needs to be rethought taking into consideration that low-level U-Cd is strongly influenced by renal physiology, recent exposure, and factors linked to studied outcomes.

CITATION: Bernard A. 2016. Confusion about cadmium risks: the unrecognized limitations of an extrapolated paradigm. Environ Health Perspect 124:1–5; http://dx.doi.org/10.1289/ehp.1509691

Introduction

Cadmium (Cd) has long been recognized as one of the most toxic elements. Decades of epidemiological research have provided a wealth of data on the cumulative and toxic properties of this heavy metal. Cd is easily taken up by plants so that most human foodstuffs contain trace amounts of Cd from natural or anthropogenic sources [Joint Expert Committee on Food Additives (JECFA 2011); European Food Safety Authority (EFSA 2012)]. Tobacco plants also readily take up Cd, which makes smoking an additional source of human exposure (Elinder et al. 1983). The danger of Cd is that it accumulates almost irreversibly (half-life > 15 years) in the body and particularly in the renal tubular cells, where it is transported by a low-molecular-weight (LMW) protein called metallothionein (Nordberg and Nordberg 1987). Prolonged exposure to Cd by inhalation or ingestion can cause kidney damage and bone demineralization and fractures (Nordberg et al. 2015). Cd and its compounds have also been classified as human carcinogens that can cause cancer of the lung by inhalation [International Agency for Research on Cancer (IARC) 2012]. Studies conducted in the 1970s and 1980s among populations heavily exposed to Cd in industrial settings or in the environment have demonstrated that the earliest manifestation of Cd intoxication is a renal tubular dysfunction that increases the urinary excretion of LMW proteins (molecular weight < 40 kD) such as β_2-microglobulin or retinol-binding protein (Bernard 2004). This LMW proteinuria is likely to occur with a 10% response rate when the concentration of Cd in kidney cortex (K-Cd) exceeds approximately 200 µg/g wet weight (200 ppm) (Kjellström et al. 1984; Roels et al. 1983). Interestingly, studies of industrial workers also showed that before the onset of tubular dysfunction, there is a curvilinear relationship between U-Cd and K-Cd, meaning that the Cd body burden of workers can be monitored noninvasively by measuring U-Cd (Bernard et al. 1992; Roels et al. 1981b). On the basis of that relationship, the U-Cd value corresponding to the critical K-Cd of 200 ppm was estimated at 10 µg/g creatinine, an estimate in concordance with that made from the relationships between U-Cd and LMW proteinuria (Bernard 2004; Chaumont et al. 2011; Nordberg et al. 2015). Similar observations were made in populations with high environmental exposure to Cd (Jin et al. 2002), and it is now well established that in populations highly exposed to the metal in either industrial settings or the environment, U-Cd rises in parallel with the Cd renal or body burden and remains elevated many years after cessation of exposure (Liang et al. 2012).

Discussion

For many years, health standards for Cd were derived from thresholds of Cd toxicity established in industrial workers. The critical U-Cd of 10 µg/g creatinine was the point of departure (PoD) of the occupational exposure limit of U-Cd, which was set at 4–5 µg/g creatinine after application of a safety margin accounting for inter-individual variations in the renal toxicity of the metal [American Conference of Governmental Industrial Hygienists (ACGIH) 2012; Bernard 2004; Chaumont et al. 2011]. For many years, the critical K-Cd of 200 ppm was the starting point for setting the tolerable intake of dietary Cd (JECFA 1972, 1989). In 1972, the Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) JECFA assigned a provisional tolerable weekly intake (PTWI) for Cd of 400–500 µg or of 7 µg/kg of body weight (JECFA 1972). JECFA predicted by toxicokinetic modeling that a 50-year exposure up to this PTWI would not entail a K-Cd higher than 50 ppm, which offered a safety margin of 4 against the risk of renal dysfunction. JECFA (1989) confirmed this PTWI, which was endorsed by the European Union in 1995 (European Commission, Directorate-General Industry 1997).

Recently, however, the Scientific Committee of Occupational Exposure Limits (SCOEL) of the European Commission and the EFSA revised the tolerable or acceptable exposure levels for Cd in industry or from food (EFSA 2009, 2011; SCOEL 2010). However, instead of using the critical K-Cd established in industrial workers, which is probably the best estimate of the critical dose for renal dysfunction, as the PoD, these regulatory bodies based their assessment on the U-Cd threshold associated with LMW proteinuria in the general population. In 2010, SCOEL recommended setting the occupational exposure limit of U-Cd at 2 µg/g creatinine by selecting the U-Cd

threshold associated with LMW proteinuria in the general population in Europe as the PoD (SCOEL 2010). SCOEL's reasoning was that this lower U-Cd threshold most likely reflected interactions with chronic renal diseases (mainly renal complications of diabetes) that SCOEL judged relevant for protecting workers after the end of their careers. At the present time, this decision appears even more debatable given that the U-Cd threshold selected by SCOEL derives from physiological associations merely reflecting the co-excretion of Cd with urinary proteins (see below). At approximately the same time, EFSA lowered the tolerable weekly intake (TWI) of Cd from 7 µg/kg to 2.5 µg/kg, a decision that was also reached by changing the PoD for the risk of LMW proteinuria (EFSA 2009). Rather than starting from the critical K-Cd, EFSA used the critical level of U-Cd (4 µg/g creatinine) derived from a meta-analysis of 54 epidemiological studies among environmentally exposed populations (EFSA 2009). To account for the large inter-individual variations in U-Cd, EFSA applied an adjustment factor of 3.9, leading to a value of 1.0 µg Cd/g creatinine. EFSA then estimated the TWI of Cd by using the toxicokinetic model of Amzal et al. (2009) linking the dietary intake of Cd to the U-Cd level. Because the mean dietary exposure to Cd across European countries (range 1.9–3.0 µg/kg body weight per week) and of some groups (vegetarians and regular consumers of bivalve mollusks or wild mushrooms; approximately 4–5 µg/kg body weight per week) was close to or exceeded this new TWI, EFSA concluded that measures should be taken to reduce Cd exposure at the population level (EFSA 2009). Surprisingly, the following year, despite using the same data set and toxicokinetic model as those used by EFSA, JECFA established a provisional tolerable monthly intake (PTMI) of 25 µg/kg for Cd, which on a weekly basis (6 µg/kg) was more than double the TWI set by EFSA (JECFA 2011). This difference largely stemmed from the adjustment factor of 3.9 that EFSA used to account for the individual variability of U-Cd. Unlike the TWI set by EFSA, the PTMI established by JECFA was unlikely to be attained by all age groups in the general population, even those with special dietary habits (vegetarians or regular consumers of chocolate). Despite these contradictory evaluations, EFSA maintained its conclusions, and on 12 May 2014, the European Commission adopted a regulation that set maximum limits for Cd in chocolate, cocoa-based products, and various foods for infants (EFSA 2011; European Union 2014). Amid this regulatory controversy, it may appear puzzling that in order to reduce exposure to a cumulative toxicant like Cd, the

European Union amended the regulation by selectively targeting only foods eaten during infancy and cocoa, a healthy food contributing only a few percent of dietary Cd intake (EFSA 2012). The explanation was that the European Commission regulates food standards according to the ALARA (as low as reasonably achievable) principle (European Union 2014). With the present background levels of Cd in soils in Europe, it is indeed impossible to enforce Cd limits in cereals and vegetables, which are the major contributors to dietary Cd.

Further adding to the confusion, leading experts in the field are now casting doubt on these scientific evaluations based on their lack of consideration of the nonrenal effects of Cd (Åkesson et al. 2014; Satarug et al. 2010). Indeed, a number of epidemiological studies suggest that at current background exposure levels (i.e., U-Cd < 1 µg/g creatinine), Cd causes a large burden of adverse health effects in the human population, including growth retardation, impaired child development, bone demineralization and fractures, kidney dysfunction and disease, reproductive impairment, diabetes, hypertension, myocardial infarction, age-related macular degeneration, periodontal disease, cancer at multiple sites, and even mortality by all causes (Åkesson et al. 2014; Gardner et al. 2013; Interdonato et al. 2015; Kippler et al. 2012; Satarug et al. 2010; Wu et al. 2014). Intriguingly, these outcomes, affecting all age groups and almost all vital organs, are seen at U-Cd levels < 0.5 µg/g creatinine, which is almost one order of magnitude below the PoD for food standards. One Swedish study, for instance, reported a 200–300% increased risk of osteoporosis of the femoral neck, lumbar spine, and hip or spine among nonsmoking women with a median U-Cd of 0.29 µg/g creatinine (Engström et al. 2011). These findings imply that, in defiance of the basic principle of toxicology, Cd is more toxic at low doses than at high doses. All of this evidence is suggestive of nonmonotonic responses, which might explain the associations of Cd with some endpoints (e.g., cancer) possibly linked to the estrogen-mimicking properties of the metal (Byrne et al. 2009). It seems, however, very unlikely that the multiple outcomes associated with low U-Cd are the consequences of nonmonotonic effects.

At the present environmental levels, many years of exposure to cumulative toxicants may be required before clinically significant effects occur. Therefore, quantifying cumulative exposure over a long period of time is a major challenge, especially when variable and multiple sources of exposure must be considered. For Cd, most epidemiological studies have overcome this difficulty by using U-Cd as a noninvasive measure of long-term

exposure to the metal. EFSA and JECFA also based their exposure assessment on U-Cd by adopting the model of Amzal et al. (2009), which postulates a monotonic increase of U-Cd from birth until the age of approximately 60. The significance of U-Cd as a marker of Cd body burden was established in the 1980s based on observations of industrial workers with high inhalation exposures (Lauwerys et al. 1979; Roels et al. 1981b). This unique property of U-Cd, not shared by any other element, was rapidly extrapolated to the general population largely under the influence of studies conducted in Belgium (Buchet et al. 1990; Hotz et al. 1999; Järup et al. 2000; Roels et al. 1981a). This extrapolation implicitly assumed that the relationship between U-Cd and K-Cd demonstrated in industrial workers held regardless of the individuals' characteristics and the exposure conditions. The validity of this assumption has now been called into question by studies showing that low-level U-Cd is strongly, if not mainly, influenced by factors unrelated to Cd body burden. One of the most challenging findings is that adolescents and young children have U-Cd values similar to, if not higher than, those of adults despite a Cd body burden that is 5–10 times lower (median values of U-Cd for most age groups of the general population are in the range of 0.2–0.4 µg/g creatinine in nonsmoking subjects) (Chaumont et al. 2013; Hoet et al. 2013; Kicinski et al. 2015). Further calling into question the reliability of U-Cd as a marker of cumulative exposure, some studies found no differences in U-Cd between never-smokers and past smokers, an unexpected observation for a biomarker supposedly reflecting the body burden of the metal (Chaumont et al. 2013; Ikeda et al. 2005; Paschal et al. 2000). More conclusively, recent observations showed that in subjects who discontinued exposure to tobacco smoke, U-Cd decreased at a much faster rate than did the Cd body burden. Sánchez-Rodríguez et al. (2015) estimated that 1 year after the smoking ban in public spaces in Spain took effect, the median U-Cd of passive smokers had dropped by 40%. Similarly, using data from the U.S. National Health and Nutrition Examination Survey (NHANES 1999–2010), Adams and Newcomb (2014) estimated an average 23% decrease of U-Cd in male smokers (20 pack-year smoking history) 1 year after stopping smoking, whereas a 10 pack-year smoking history was associated with a 17% increase of U-Cd in active male smokers. According to these estimates, the U-Cd of most smokers should return to normal within 1–2 years of smoking cessation, which may explain why some studies found no difference in U-Cd between never- and past smokers (Chaumont et al. 2013; Ikeda et al. 2005; Paschal et al. 2000). Taken together, these findings suggest

that in the general population, U-Cd may be influenced to a large extent by recent uptake of the metal. If so, this may also explain the large within-individual variability in U-Cd, which has been observed even when measured in 24-hour urine samples (Akerstrom et al. 2014; Gunier et al. 2013). Low-level U-Cd may be an even poorer proxy for the Cd body burden when it is expressed as a ratio to urinary creatinine. As observed recently, the adjustment for urinary creatinine does not abolish the relationship between Cd and creatinine in urine but changes its direction from a positive to a negative one (Chaumont et al. 2011; Haddam et al. 2011). Furthermore, several studies have reported positive associations between U-Cd and the glomerular filtration rate, which further illustrates the strong dependency of U-Cd on renal function (Hotz et al. 1999; Weaver et al. 2011, 2014). These findings cast doubt not only on the monotonic model of Amzal et al. (2009) but also on the large adjustment factor that EFSA applied to account for these physiological variations in U-Cd. Nevertheless, the model of Amzal et al. (2009) has received some support from the recent study by Akerstrom et al. (2013a), which described a strong correlation between U-Cd and K-Cd. This study, however, did not truly assess the ability of U-Cd to reflect the lifetime trend of the Cd body burden in the general population because it involved only adult kidney donors with well-preserved renal function. Moreover, Akerstrom et al. (2013a) included in their study a large proportion of active and past smokers who were not analyzed separately in order to specifically evaluate the contribution of recent and cumulative Cd exposure to U-Cd. Interestingly, Akerstrom et al. (2013a) found that subjects with low K-Cd (< 15 ppm) excreted proportionally more Cd (on average, a 60% higher U-Cd/K-Cd ratio) than those with higher K-Cd (≥ 15 ppm). The explanation proposed by the authors is that at low K-Cd, factors such as recent exposure or proteinuria have a greater impact on U-Cd excretion than does Cd body burden, which is in line with the views expressed in the present commentary.

Another matter of concern is the evidence that factors influencing low-level U-Cd may also influence markers of potential effects of Cd exposure, a situation that typically leads to confounding in epidemiology. For example, metallothionein, the main Cd-binding protein, follows the same glomerular filtration-tubular reabsorption pathway as other plasma proteins, including LMW proteins and albumin used as renal biomarkers (Bernard et al. 1987; Chaumont et al. 2012). Consequently, associations between U-Cd and urine LMW proteins in the adult general population, which have long been interpreted as evidence of the effects of Cd body burden on renal function (Buchet et al. 1990; Järup et al. 2000), may simply be spurious associations driven by physiological variations in the renal handling of proteins and Cd. Similar, and even stronger, associations between U-Cd and LMW proteinuria were indeed found in young children with a very low Cd body burden as well as in repeated urine collections from the same individuals (Akerstrom et al. 2013b; Chaumont et al. 2013). This co-excretion mechanism for Cd and LMW proteins, also observed for Cd and albumin (Akerstrom et al. 2013a, 2013b; Hotz et al. 1999; Paschal et al. 2000), might also explain the associations between U-Cd and degenerative diseases whose progression or severity is predicted by increased albuminuria or proteinuria, such as diabetic nephropathy and cardiovascular and bone diseases (Barzilay et al. 2013; Ninomiya et al. 2009; Smink et al. 2012). In other words, these associations between U-Cd and chronic diseases involving the kidney might simply reflect reverse causation because they might be driven by protein excretion and thus by the outcome itself.

It is well established that the bioavailability of Cd critically depends on the intake or requirement of essential elements because Cd opportunistically uses the same intestinal transporters as zinc, iron, and calcium (Vesey 2010). Animal studies have demonstrated that requirement of these elements strongly up-regulates the expression of essential element transporters, thereby also increasing the absorption of Cd. In humans, iron deficiency is known to increase the intestinal absorption of Cd, thereby increasing the concentration of the metal in blood or urine (Gallagher et al. 2011; Nordberg et al. 2015). The effects of calcium and zinc on the intestinal absorption of Cd are much less documented. Circumstantial evidence, however, strongly suggests that a deficiency in or requirement of these elements increases the bioavailability of dietary Cd and thereby susceptibility to its adverse effects. The occurrence of Itai-itai disease in Japan, which affected mainly multiparous postmenopausal women, is a dramatic illustration of this effect modification by calcium and other nutritional deficiencies. Regarding zinc, a recent study showed that the concentrations of Cd in blood and urine are associated with polymorphisms in zinc transporter genes (Rentschler et al. 2014). The importance of zinc and iron in Cd bioavailability and toxicity also emerges from the dose–response relationship used by EFSA and JECFA to derive the above-mentioned tolerable intakes of Cd. All of the studies showing increased β_2-microglobulinuria caused by Cd were conducted in Asia, that is, among populations subsisting on rice, a staple food that is particularly poor in zinc and iron (JECFA 2011).

An important point, often overlooked, is that nutritional deficiencies or requirements may also act as confounders, influencing both Cd exposure and outcomes involving essential elements. If, as suggested by animal studies (Vesey 2010) and the recent study by Rentschler et al. (2014), Cd is absorbed by zinc transporters, up- or down-regulation of zinc transporters should logically cause parallel variations in the intestinal absorption of Cd and zinc. This co-absorption mechanism might explain why growing children with a large requirement for zinc had U-Cd values similar to those of adults; this explanation is supported by the fact that Cd and zinc were strongly correlated in the urine of these children (Bernard and Chaumont 2013). Similarly, the decline or leveling of U-Cd after the age of 60 might result from the dysregulation of zinc transporters due to aging (Wong et al. 2013). Thus, there is a need to exercise great caution when interpreting associations between U-Cd and outcomes due to essential element deficiency such as retarded growth or bone demineralization. Associations of these endpoints with low-level U-Cd might simply reflect the enhanced intestinal co-absorption of Cd with essential elements. To avoid such confounding by nutritional deficiencies, some studies have used estimates of dietary Cd intake (for review, see Åkesson et al. 2014). At low background exposure levels, however, these estimates are largely driven by variations in dietary habits and thus in intakes of essential elements and other food constituents that may confound the analyses by influencing the studied outcomes or the absorption of Cd. In these studies, the issue is further complicated by the fact that foods with high levels of Cd, such as fungi, oysters, or chocolate, usually also have high levels of zinc that can competitively inhibit the uptake and toxicity of Cd (Brzóska et al. 2007). This mechanism has been proposed to explain the low absorption of Cd from oyster consumption (Reeves and Chaney 2008; Vahter et al. 1996).

Conclusions

The present confusion about the risks associated with Cd illustrates the limitations of risk assessment paradigms that are not based on a sound understanding of the factors that govern the metabolism and toxicity of chemicals. Cd risk assessment currently rests on the assumption that U-Cd reflects the lifetime accumulation of the metal in the body irrespective of the intensity and route of exposure. This assumption is now challenged by studies showing that low-level U-Cd varies greatly within and between individuals, depending mainly on recent exposure, essential element needs, and renal parameters such as diuresis, proteinuria, and glomerular filtration rate. The key issue to keep in mind when studying the effects of low

exposures to Cd is that this heavy metal uses the same transport pathways as plasma proteins for its urinary excretion and the same transport pathways as essential elements for its intestinal absorption. Variations in these transport mechanisms, whether related to physiology or disease, may generate secondary associations between biomarkers of Cd exposure and outcomes involving renal function or the requirement of essential elements. Failure to consider these basic aspects of Cd toxicology may lead to fallacious interpretations, such as the one that for more than two decades continues to confound the metabolic associations between U-Cd and LMW proteinuria in the general population with early renal effects of chronic Cd poisoning.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2012. 2012 TLVs® and BEIs®. Cincinnati, OH:ACGIH.

Adams SV, Newcomb PA. 2014. Cadmium blood and urine concentrations as measures of exposure: NHANES 1999–2010. J Expo Sci Environ Epidemiol 24:163–170.

Akerstrom M, Barregard L, Lundh T, Sallsten G. 2013a. The relationship between cadmium in kidney and cadmium in urine and blood in an environmentally exposed population. Toxicol Appl Pharmacol 268:286–293.

Akerstrom M, Barregard L, Lundh T, Sallsten G. 2014. Variability of urinary cadmium excretion in spot urine samples, first morning voids, and 24 h urine in a healthy non-smoking population: implications for study design. J Expo Sci Environ Epidemiol 24:171–179.

Akerstrom M, Sallsten G, Lundh T, Barregard L. 2013b. Associations between urinary excretion of cadmium and proteins in a nonsmoking population: renal toxicity or normal physiology? Environ Health Perspect 121:187–191; doi:10.1289/ehp.1205418.

Åkesson A, Barregard L, Bergdahl IA, Nordberg GF, Nordberg M, Skerfving S. 2014. Non-renal effects and the risk assessment of environmental cadmium exposure. Environ Health Perspect 122:431–438; doi:10.1289/ehp.1307110.

Amzal B, Julin B, Vahter M, Wolk A, Johanson G, Åkesson A. 2009. Population toxicokinetic modeling of cadmium for health risk assessment. Environ Health Perspect 117:1293–1301; doi:10.1289/ehp.0800317.

Barzilay JI, Gao P, Clase CM, Mente A, Mann JF, Sleight P, et al. 2013. Albuminuria and rapid loss of GFR and risk of new hip and pelvic fractures. Clin J Am Soc Nephrol 8:233–240.

Bernard A. 2004. Renal dysfunction induced by cadmium: biomarkers of critical effects. Biometals 17:519–523.

Bernard A, Chaumont A. 2013. Public health impact of low-environmental exposure to cadmium: the emerging risks of metabolic confounding [Abstract MS-1-1]. J Trace Elem Med Biol 27S1.

Bernard AM, Ouled Amor A, Lauwerys RR. 1987. The effects of low doses of cadmium–metallothionein on the renal uptake of beta 2-microglobulin in rats. Toxicol Appl Pharmacol 87:440–445.

Bernard A, Roels H, Buchet JP, Cardenas A, Lauwerys R. 1992. Cadmium and health: the Belgian experience. IARC Sci Publ 118:15-33.

Brzóska MM, Rogalska J, Galazyn-Sidorczuk M, Jurczuk M, Roszczenko A, Kulikowska-Karpińska E, et al. 2007. Effect of zinc supplementation on bone metabolism in male rats chronically exposed to cadmium. Toxicology 237:89–103.

Buchet JP, Lauwerys R, Roels H, Bernard A, Bruaux P, Claeys F, et al. 1990. Renal effects of cadmium body burden of the general population. Lancet 336:699–702.

Byrne C, Divekar SD, Storchan GB, Parodi DA, Martin MB. 2009. Cadmium—a metallohormone? Toxicol Appl Pharmacol 238:266–271.

Chaumont A, De Winter F, Dumont X, Haufroid V, Bernard A. 2011. The threshold level of urinary cadmium associated with increased urinary excretion of retinol-binding protein and β2-microglobulin: a re-assessment in a large cohort of nickel-cadmium battery workers. Occup Environ Med 68:257–264.

Chaumont A, Nickmilder M, Dumont X, Lundth T, Skerfving S, Bernard A. 2012. Associations between proteins and heavy metals in urine at low environmental exposures: evidence of reverse causality. Toxicol Lett 210:345–352.

Chaumont A, Voisin C, Deumer G, Haufroid V, Annesi-Maesano I, Roels H, et al. 2013. Associations of urinary cadmium with age and urinary proteins: further evidence of physiological variations unrelated to metal accumulation and toxicity. Environ Health Perspect 121:1047–1053; doi:10.1289/ehp.1306607.

EFSA (European Food Safety Authority). 2009. Cadmium in Food. Scientific Opinion of the Panel on Contaminants in the Food Chain (Question No EFSA-Q-2007-138). EFSA J 980:1–139. Available: http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/contam_op_ej980_cadmium_en_rev.1%2C2.pdf [accessed 22 May 2015].

EFSA. 2011. Statement on Tolerable Weekly Intake for Cadmium. EFSA Panel on Contaminants in the Food Chain (CONTAM). EFSA J 9:1975. Available: http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/1975.pdf [accessed 22 May 2015].

EFSA. 2012. Cadmium dietary exposure in the European population. European Food Safety Authority. EFSA J 10:2551. Available: http://www.efsa.europa.eu/sites/default/files/scientific_output/files/main_documents/2551.pdf [accessed 22 May 2015].

Elinder CG, Kjellström T, Lind B, Linnman L, Piscator M, Sundstedt K. 1983. Cadmium exposure from smoking cigarettes: variations with time and country where purchased. Environ Res 32:220–227.

Engström A, Michaëlsson K, Suwazono Y, Wolk A, Vahter M, Åkesson A. 2011. Long-term cadmium exposure and the association with bone mineral density and fractures in a population-based study among women. J Bone Miner Res 26:486–495.

European Commission, Directorate-General Industry. 1997. Opinion on cadmium. Expressed on 2 June 1995. In: Food Science and Techniques. Reports of the Scientific Committee for Food (Thirty-sixth Series), 67–70. Available: http://ec.europa.eu/food/fs/sc/scf/reports/scf_reports_36.pdf. [accessed 22 May 2015].

European Union. 2014. Commission Regulation No. 488/2014 Amending Regulation (EC) No. 1881/2006 as Regards Maximum Levels of Cadmium in Foodstuffs. Off J EU L 138:75–79.

Gallagher CM, Chen JJ, Kovach JS. 2011. The relationship between body iron stores and blood and urine cadmium concentrations in US never-smoking, non-pregnant women aged 20–49 years. Environ Res 111:702–707.

Gardner RM, Kippler M, Tofail F, Bottai M, Hamadani J, Grandér M, et al. 2013. Environmental exposure to metals and children's growth to age 5 years: a prospective cohort study. Am J Epidemiol 177:1356–1367.

Gunier RB, Horn-Ross PL, Canchola AJ, Duffy CN, Reynolds P, Hertz A, et al. 2013. Determinants and within-person variability of urinary cadmium concentrations among women in northern California. Environ Health Perspect 121:643–649; doi:10.1289/ehp.1205524.

Haddam N, Samira S, Dumont X, Taleb A, Lison D, Haufroid V, et al. 2011. Confounders in the assessment of the renal effects associated with low-level urinary cadmium: an analysis in industrial workers. Environ Health 10:37; doi:10.1186/1476-069X-10-37.

Hoet P, Jacquerye C, Deumer G, Lison D, Haufroid V. 2013. Reference values and upper reference limits for 26 trace elements in the urine of adults living in Belgium. Clin Chem Lab Med 51:839–849.

Hotz P, Buchet JP, Bernard A, Lison D, Lauwerys R. 1999. Renal effects of low-level environmental cadmium exposure: 5-year follow-up of a subcohort from the Cadmibel study. Lancet 354:1508–1513.

IARC (International Agency for Research on Cancer). 2012. Arsenic, metals, fibres and dusts. IARC Monogr Eval Carcinog Risk Hum 100C:121–145.

Ikeda M, Moriguchi J, Ezaki T, Fukui Y, Ukai H, Okamoto S, et al. 2005. Smoking-induced increase in urinary cadmium levels among Japanese women. Int Arch Occup Environ Health 78:533–540.

Interdonato M, Pizzino G, Bitto A, Galfo F, Irrera N, Mecchio A, et al. 2015. Cadmium delays puberty onset and testis growth in adolescents. Clin Endocrinol (Oxf) 83:357–362; doi:10.1111/cen.12704.

Järup L, Hellström L, Alfvén T, Carlsson MD, Grubb A, Persson B, et al. 2000. Low level exposure to cadmium and early kidney damage: the OSCAR study. Occup Environ Med 57:668–672.

JECFA (Joint Expert Committee on Food Additives). 1972. Evaluation of Certain Food Additives and the Contaminants Mercury, Lead, and Cadmium. Sixteenth Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, No. 505. Geneva:World Health Organization, 20–24. Available: http://apps.who.int/iris/bitstream/10665/40985/1/WHO_TRS_505.pdf [accessed 22 May 2015].

JECFA. 1989. Evaluation of Certain Food Additives and Contaminants. Thirty-third Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, No. 776. Geneva:World Health Organization, 28–31. Available: http://apps.who.int/iris/bitstream/10665/39252/1/WHO_TRS_776.pdf [accessed 22 May 2015].

JECFA. 2011. Evaluation of Certain Food Additives and Contaminants. Seventy-third Report of the Joint FAO/WHO Expert Committee on Food Additives. WHO Technical Report Series, No. 960. Geneva:World Health Organization, 149–162. Available: http://apps.who.int/iris/bitstream/10665/44515/1/WHO_TRS_960_eng.pdf [accessed 22 May 2015].

Jin T, Nordberg M, Frech W, Dumont X, Bernard A, Ye T, et al. 2002. Cadmium biomonitoring and renal dysfunction among a population environmentally exposed to cadmium from smelting in China (ChinaCad). Biometals 15:397–410.

Kicinski M, Vrijens J, Vermier G, Hond ED, Schoeters G, Nelen V, et al. 2015. Neurobehavioral function and low-level metal exposure in adolescents. Int J Hyg Environ Health 218:139–146.

Kippler M, Tofail F, Hamadani JD, Gardner RM, Grantham-McGregor SM, Bottai M, et al. 2012.

Early-life cadmium exposure and child development in 5-year-old girls and boys: a cohort study in rural Bangladesh. Environ Health Perspect 120:1462–1468; doi:10.1289/ehp.1104431.

Kjellström T, Elinder CG, Friberg L. 1984. Conceptual problems in establishing the critical concentration of cadmium in human kidney cortex. Environ Res 33:284–295.

Lauwerys R, Roels H, Regniers M, Buchet JP, Bernard A, Goret A. 1979. Significance of cadmium concentration in blood and in urine in workers exposed to cadmium. Environ Res 20:375–391.

Liang Y, Lei L, Nilsson J, Li H, Nordberg M, Bernard A, et al. 2012. Renal function after reduction of cadmium exposure: an 8-year follow-up of residents in cadmium-polluted areas. Environ Health Perspect 120:223–228; doi:10.1289/ehp.1103699.

Ninomiya T, Perkovic V, de Galan BE, Zoungas S, Pillai A, Jardine M, et al. 2009. Albuminuria and kidney function independently predict cardiovascular and renal outcomes in diabetes. J Am Soc Nephrol 20:1813–1821.

Nordberg GF, Nogawa K, Nordberg M. 2015. Cadmium. In: Handbook on the Toxicology of Metals. 4th ed. Vol. II. Specific Metals. Amsterdam, the Netherlands:Academic Press, 667–716.

Nordberg M, Nordberg GF. 1987. On the role of metallothionein in cadmium induced renal toxicity Experientia Suppl 52:669–675.

Paschal DC, Burt V, Caudill SP, Gunter EW, Pirkle JL, Sampson EJ, et al. 2000. Exposure of the U.S. population aged 6 years and older to cadmium: 1988–1994. Arch Environ Contamin Toxicol 38:377–383.

Reeves PG, Chaney RL. 2008. Bioavailability as an issue in risk assessment and management of food cadmium: a review. Sci Total Environ 398:13–19.

Rentschler G, Kippler M, Axmon A, Raqib R, Skerfving S, Vahter M, et al. 2014. Cadmium concentrations in human blood and urine are associated with polymorphisms in zinc transporter genes. Metallomics 6:885–891.

Roels HA, Lauwerys RR, Buchet JP, Bernard A. 1981a. Environmental exposure to cadmium and renal function of aged women in three areas of Belgium. Environ Res 24:117–130.

Roels HA, Lauwerys RR, Buchet JP, Bernard A, Chettle DR, Harvey TC, et al. 1981b. In vivo measurement of liver and kidney cadmium in workers exposed to this metal: its significance with respect to cadmium in blood and urine. Environ Res 26:217–240.

Roels H, Lauwerys R, Dardenne AN. 1983. The critical level of cadmium in human renal cortex: a reevaluation. Toxicol Lett 15:357–360.

Sánchez-Rodríguez JE, Bartolomé M, Cañas AI, Huetos O, Navarro C, Rodríguez AC, et al. 2015. Anti-smoking legislation and its effects on urinary cotinine and cadmium levels. Environ Res 136:227–233.

Satarug S, Garrett SH, Sens MA, Sens DA. 2010. Cadmium, environmental exposure, and health outcomes. Environ Health Perspect 118:182–190; doi:10.1289/ehp.0901234.

SCOEL (Scientific Committee on Occupational Exposure Limits). 2010. Recommendation from the Scientific Committee on Occupational Exposure Limits for Cadmium and its Inorganic Compounds: SCOEL/SUM/136. Available: http://ec.europa.eu/social/BlobServlet?docId=3803&langId=en [accessed 22 May 2015].

Smink PA, Lambers Heerspink HJ, Gansevoort RT, de Jong PE, Hillege HL, Bakker SJ, et al. 2012. Albuminuria, estimated GFR, traditional risk factors, and incident cardiovascular disease: the PREVEND (Prevention of Renal and Vascular Endstage Disease) study. Am J Kidney Dis 60:804–811.

Vahter M, Berglund M, Nermell B, Åkesson A. 1996. Bioavailability of cadmium from shellfish and mixed diet in women. Toxicol Appl Pharmacol 136:332–341.

Vesey DA. 2010. Transport pathways for cadmium in the intestine and kidney proximal tubule: focus on the interaction with essential metals. Toxicol Lett 198:13–19.

Weaver VM, Kim NS, Lee BK, Parsons PJ, Spector J, Fadrowski J, et al. 2011. Differences in urine cadmium associations with kidney outcomes based on serum creatinine and cystatin C. Environ Res 111:1236–1242.

Weaver VM, Vargas GG, Silbergeld EK, Rothenberg SJ, Fadrowski JJ, Rubio-Andrade M, et al. 2014. Impact of urine concentration adjustment method on associations between urine metals and estimated glomerular filtration rates (eGFR) in adolescents. Environ Res 132:226–232.

Wong CP, Magnusson KR, Ho E. 2013. Increased inflammatory response in aged mice is associated with age-related zinc deficiency and zinc transporter dysregulation. J Nutr Biochem 24:353–359.

Wu EW, Schaumberg DA, Park SK. 2014. Environmental cadmium and lead exposures and age-related macular degeneration in U.S. adults: the National Health and Nutrition Examination Survey 2005 to 2008. Environ Res 133:178–184.