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

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Abstract

Background: Cadmium (Cd) risk assessment currently relies on tubular proteinuria as 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.

Objectives: To examine whether the present confusion over Cd risks is not related to some conceptual or methodological problems.

Discussion: The cornerstone of the prevailing 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 is 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 the 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. Basically, 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 as essential elements for its intestinal absorption.

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

Introduction

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 (JECFA 2011; EFSA 2012). Tobacco plants also readily take up Cd, which makes of 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 has a human carcinogen, causing cancer of the lung by inhalation (IARC 2012). Studies conducted in the 1970-80s among populations heavily exposed to Cd in the industry or the environment have demonstrated that the earliest manifestation of Cd intoxication is a renal tubular dysfunction increasing the urinary excretion of low-molecular-weight (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 about 200 μg/g wet weight (200 ppm) (Kjellström et al. 1984; Roels et al. 1983). Interestingly, studies among 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 non-invasively by measuring U-Cd (Bernard et al. 1992; Roels et al. 1981a). 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 (Jin et al. 2002) and it is now well established that in populations highly exposed to the metal in the industry 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 of 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 the inter-individual variations in the renal toxicity of the metal (ACGIH 2012; Bernard 2004; Chaumont et al. 2011). The critical K-Cd of 200 ppm was also for many years the starting point for setting the tolerable intake of dietary Cd (JECFA 1972, 1989). In 1972 already, the FAO/WHO Joint Expert Committee on Food Additives (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 modelling that a 50-year exposure up to this PTWI should not entail a K-Cd higher than 50 ppm, which offered a safety margin of four against the risk of renal dysfunction. JECFA (1989) regularly confirmed this PTWI that was endorsed by the European Union in 1995 (SCF 1997).

Recently, however, the Scientific Committee of Occupational Exposure Limits (SCOEL) of the European Commission and the European Food Safety Authority (EFSA) revised the tolerable or acceptable exposure levels to Cd in the industry or from foods (SCOEL 2010; EFSA 2009, 2011). But instead of using the PoD as the critical K-Cd established in industrial workers, which

is probably the best estimate of the critical dose for renal dysfunction, these regulatory bodies based their assessment on the U-Cd threshold associated with LMW proteinuria in the general population. In 2010, SCOEL recommended to set the occupational exposure limit of U-Cd at 2 μg/g creatinine by selecting as PoD the U-Cd threshold associated with LMW proteinuria in the general population in Europe (SCOEL 2010). The reasoning of SCOEL is that this lower U-Cd threshold most probably reflects interactions with chronic renal diseases (mainly renal complications of diabetes) that SCOEL judged relevant for protecting workers after their occupational career. This decision appears now even more debatable 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 about the same time, EFSA lowered the tolerable weekly intake (TWI) of Cd from 7 to 2.5 μg/kg, a decision 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 by the meta-analysis of 54 epidemiological studies among environmentally exposed populations. 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 mean dietary exposure to Cd across European countries (range 1.9 to 3.0 μg/kg body weight per week) and of some groups (vegetarians, regular consumers of bivalve molluscs or wild mushrooms, around 4-5 μg/kg body weight per week) are close or exceed this new TWI, the EFSA concluded that measures should be taken to reduce Cd exposure at the population level (EFSA 2009). But surprisingly the following year, although using the same dataset and toxicokinetic model as EFSA, JECFA established a provisional tolerable monthly intake (PTMI) of Cd of 25 μg/kg,

which on a weekly basis (6 μg/kg) is more than double the TWI set by EFSA (JECFA 2011). This difference largely stems from the adjustment factor of 3.9 that EFSA used to account for the individual variability of U-Cd. Contrary to the TWI of EFSA, the PTMI established by JECFA is unlikely to be attained by all age groups of 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 May 12 2014, the European Commission adopted a regulation fixing 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 for reducing exposure to a cumulative toxicant like Cd the European Union amends the regulation by targeting only foods eaten during infancy and cocoa, a healthy food contributing only a few % of Cd dietary intake (EFSA 2012). The explanation is that the European Commission regulates food standards according to the ALARA (as low as reasonably achievable) principle (European Union 2014). With the current background levels of Cd in soils in Europe, it is indeed impossible to enforce Cd limits in cereals and vegetables that 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 on the basis that they did not consider the non-renal effects of Cd (Akesson et al. 2014; Satarug et al. 2010). A number of epidemiological studies suggest, indeed, 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 diseases, reproductive impairment, diabetes, hypertension, myocardial infarction, age-related macular degeneration, periodontal diseases, cancer at multiple sites and even mortality by all causes (Akesson et al.

2014; Gardner et al. 2013; Interdonato et al. 2014; 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 magnitude below the PoD of food standards. One Swedish study, for instance, reported a three- to four-fold increased risk of osteoporosis of the femoral neck, lumbar spine, and hip or spine among non-smoking women with a median U-Cd of 0.29 μg/g creatinine (Engström et al. 2011). These findings give the feeling that, in defiance of the basic principle of toxicology, Cd is more toxic at low than at high doses. All this is suggestive of non-monotonic responses, which might explain the associations of Cd with some endpoints (e.g. cancer) possibly linked to the oestrogen-mimicking properties of the metal (Byrne et al. 2009). It seems, however, very unlikely that the multiple outcomes associated with low U-Cd be the consequence of non-monotonic effects.

At current environmental levels, many years of exposure to cumulative toxicants may be required before clinically significant effects would occur. Therefore, quantifying the cumulative exposure over a long period of time is a major challenge, especially when dealing with variable and multiple sources of exposure. For Cd, most epidemiological studies have overcome this difficulty by using U-Cd as non-invasive measure of the 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) that postulates a monotonic increase of U-Cd from birth till the age of about 60. The significance of U-Cd as marker of Cd body burden was established in the 1980s on the basis of observations in industrial workers with high inhalation exposures (Lauwerys et al. 1979; Roels et al. 1981a). This unique property of urinary 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; Jarup et al. 2000; Roels et al. 1981b). This

extrapolation implicitly assumed that the relationship between U-Cd and K-Cd demonstrated in industrial workers held whatever the individuals' characteristics and the exposure conditions. The validity of this assumption is now 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 5 to 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 non-smoking subjects) (Chaumont et al 2013; Hoet et al. 2013; Kicinski et al. 2015). Also questioning 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 the metal (Chaumont et al. 2013; Ikeda et al. 2005; Paschal et al. 2000). More conclusively, recent observations show that in subjects who discontinued exposure to tobacco smoke U-Cd decreases at a rate that is much higher than that of the Cd body burden. Sánchez-Rodríguez et al. (2015) estimated that one year after the smoking ban in public spaces in Spain the median U-Cd of passive smokers had dropped by 40%. Similarly, using data from the National Health and Nutrition Examination Survey (NHANES 1999-2010), Adams and Newcomb (2014) estimated an average 23% decrease of U-Cd in active smokers (20 pack-year smoking history) one year after stopping smoking, while a 10 pack-year smoking history was associated with a 17% increase of U-Cd. According to these estimates, the U-Cd of most smokers should return to normal within 1-2 year 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). Altogether 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 also may 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 into a negative one (Chaumont et al. 2011; Haddam et al. 2011). Last, 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 Amazal et al. (2009) but also on the large adjustment factor EFSA applied to account for these physiological variations in U-Cd. Yet, the model of Amzal et al. (2009) has received some support from the recent study of Akerstrom et al. (2013a) describing a strong correlation between U-Cd and K-Cd. This study, however, did not really assess the ability of U-Cd to reflect the lifetime trend of the Cd body burden in the general population at large since it involved only adult kidney donors with a well-preserved renal function. Moreover, this study included a large proportion of current and past smokers who were not analyzed separately in order to specifically evaluate the contribution on U-Cd of the recent and cumulative exposure to 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 a recent exposure or proteinuria have a stronger impact on U-Cd excretion than 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 in the adult general population between U-Cd and urine LMW proteins, which have long been interpreted as evidence of the effects of Cd body burden on renal function (Buchet et al. 1990; Jarup et al. 2000), may simply be spurious associations driven by physiological variation 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 on repeated urine collections from the same individuals (Akerstrom et al. 2013b; Chaumont et al. 2013). This co-excretion mechanism between Cd and proteins, also observed with 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 an increased albuminuria or proteinuria such as diabetic nephropathy, cardiovascular and bone diseases (Barzilay et al. 2013; Ninomiya et al. 2009; Smink et al. 2012). In other terms, these associations between U-Cd and chronic diseases involving the kidney might simply reflect reverse causation as 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 in essential elements. The reason for this is that Cd opportunistically utilizes the same intestinal transporters as zinc, iron and calcium (Vesey 2010). Animal studies have demonstrated that requirements of these elements strongly up-regulate the expression of essential element

transporters, thereby increasing also the absorption of Cd. In humans, iron deficiency is known to increase the intestinal absorption of Cd and thereby the concentrations of the metal in blood or urine (Gallagher et al. 2011; Nordberg et al. 2015). Effects of calcium or zinc on the intestinal absorption of Cd are much less documented. Circumstantial evidence, however, strongly suggests that a deficiency or requirement in these elements increases the bioavailability of dietary Cd and thereby the susceptibility to Cd adverse effects. The Itai-Itai disease in Japan that affected mainly multiparous post-menopausal women is the 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 EFSA and JECFA used to derive the tolerable intakes of Cd. All studies showing an increased β_2-microglobulinuria caused by Cd were indeed conducted in Asia, i.e. among populations subsisting on rice, a staple food particularly poor in zinc and iron (JECFA 2011).

An important point, often overlooked, is that nutritional deficiencies or requirement 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 of Rentschler et al. (2014) Cd is absorbed by zinc-transporters, an up- or down-regulation of these 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 important needs in zinc have U-Cd values similar to those of adults, an explanation supported by the fact that Cd and zinc are strongly correlated in the urine of these children (Bernard and Chaumont 2013). Likewise, the decline or levelling of U-Cd after the age of 60 might result from the dysregulation of zinc transporters due

to ageing (Wong et al. 2013). There is thus a need to exercise great caution when interpreting associations of U-Cd with 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 Cd dietary intake (for review see, Akesson 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 have also high levels of zinc that can competitively inhibit the uptake and the toxicity of Cd (Brzóska et al. 2007). This mechanism has been proposed to explain the low absorption of Cd from oysters (Reeves and Chaney 2008; Vahter et al. 1996).

Conclusions

The present confusion about Cd risks illustrates the limitations of risk assessment paradigms that are not based on a sound understanding of factors governing 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 irrespectively of the intensity and route of exposure. This assumption is now challenged by studies showing that low-level U-Cd greatly varies within and between individuals depending mainly on recent exposure, essential element needs and renal parameters such as diuresis, proteinuria or glomerular filtration rate. The key issue to keep in mind when studying the effects of low exposures to Cd is that this heavy metal utilizes the same transport pathways as plasma proteins for its urinary excretion and 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 the renal function or the requirements in essential elements. The failure to consider these basic aspects of Cd toxicology may lead to interpretation fallacies such as the one that for more than two decades has confounded the metabolic associations between U-Cd and LMW proteinuria in the general population with early renal effects of chronic Cd poisoning.

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