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Biomonitoring Equivalents (BE) dossier for cadmium (Cd) (CAS No. 7440-43-9)

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ABSTRACT

Recent efforts by the US Centers for Disease Control and Prevention and other researchers have resulted in a growing database of measured concentrations of chemical substances in blood or urine samples taken from the general population. However, few tools exist to assist in the interpretation of the measured values in a health risk context. Biomonitoring Equivalents (BEs) are defined as the concentration or range of concentrations of a chemical or its metabolite in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guideline. This document reviews available pharmacokinetic data and models for cadmium and applies these data and models to existing health-based exposure guidance values from the US Environmental Protection Agency, the Agency for Toxic Substances and Disease Registry, Health Canada, and the World Health Organization, to estimate corresponding BE values for cadmium in blood and urine. These values can be used as screening tools for evaluation of biomonitoring data for cadmium in the context of existing risk assessments for cadmium and for prioritization of the potential need for additional risk assessment and risk management efforts for cadmium.

1. Introduction

Measurements of environmental chemicals in air, water, or other media can be compared to health-based exposure guidelines to screen which chemical exposures may be of concern, or to identify chemicals for which a wide margin of safety appears to be present. Interpretation of biomonitoring data for environmental compounds is hampered by a lack of similar screening criteria applicable to measurements of chemicals in biological media such as blood or urine. Such screening criteria would ideally be based upon data from robust epidemiological studies that evaluate a comprehensive set of health endpoints in relationship to measured levels of chemicals in biological media. However, development of such epidemiologically-based screening values is a resource- and time-intensive effort. As an interim effort, the development of Biomonitoring Equivalents (BEs) has been proposed (Hays et al. 2007).

A Biomonitoring Equivalent (BE) is defined as the concentration or range of concentrations of chemical in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guideline. Existing chemical-specific pharmacokinetic data are used to estimate biomarker concentrations associated with the Point of Departure (PODs; such as No Observed Effect Levels [NOELs], Lowest Observed Effect Levels [LOELs], or Benchmark Doses [BMDs]) and to estimate biomarker concentrations that are consistent with the guidance value. BEs can be estimated using available human or animal pharmacokinetic data. Guidelines for the derivation and communication of BEs are available in (Hays et al., 2008). BEs are designed to be screening tools to gauge which chemicals have large, small or no margin of safety compared to existing health-based exposure guidelines. BEs are only as robust as are the underlying health-based exposure guidelines that they are based upon and the underlying animal toxicology studies and pharmacokinetic data used to derive these health-based exposure guidelines. BEs are not designed to be diagnostic for potential health effects in humans, either individually or among a population.

This BE dossier is not designed to be a comprehensive compilation of the available hazard, dose–response or risk assessment information for cadmium. Rather, this dossier describes the scientific basis for and derivation of BE values for cadmium and discusses issues that are important for the interpretation of biomonitoring data using Biomonitoring Equivalents.

Cadmium (Cd; CAS No. 7440-43-9) is an element that occurs naturally in the earth's crust. Cadmium has an atomic weight of 112.4 g mol^{-1}, is silver-white malleable metal and has an oxidation state of +2. The naturally occurring isotopes are 106, 108, 110, 111, 112, 113, 114 and 116. Cd compounds consist of acetate, sulfide (yellow pigment), sulfoselenide, selenium sulfide (red pigment), stearate, oxide, carbonate, sulfate, and chloride. Of the many inorganic Cd compounds, several are quite soluble in water, e.g.,

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cadmium acetate, chloride, and sulfate; cadmium oxide and sulfide are almost insoluble. Cadmium oxide and cadmium carbonate might, however, be soluble at gastric pH. Cadmium is used in batteries, pigments, metal coatings, plastics, and some metal alloys (ATSDR, 1999). General population exposures to cadmium are estimated to be principally from food (highest levels are in leafy vegetables and potatoes) and tobacco smoke resulting from cadmium's presence in the earth's crust and uptake into plant materials (ATSDR, 1999; Nordberg et al. 2007).

1.1. Current health-based exposure guidance values

Ingestion of very high doses of cadmium can irritate the stomach, leading to vomiting and diarrhea and even death (ATSDR, 1999). The toxic endpoint of most relevance for chronic exposures to cadmium is an accumulation of cadmium levels in the kidney, leading to kidney damage. The International Agency for Research on Cancer (IARC) considers cadmium and cadmium compounds to be carcinogenic to humans (Group 1). The USEPA considers cadmium to be a probable human carcinogen by the inhalation route, with local carcinogenic effects on the lung. Reviews on cadmium toxicity are available (ATSDR, 1999; Nordberg et al., 2007).

Health-based exposure guidelines and toxicity values have been established for many chemicals for the general population by the USEPA (Reference Doses or Reference Concentrations [RfD or RfC]), the Agency for Toxic Substances and Disease Registry (ATSDR) (Minimal Risk Levels or MRLs), and various organizations outside the United States including Health Canada (HC) and the World Health Organization (WHO) (Tolerable Daily Intakes or TDIs). The chronic health-based exposure guideline values are designated with different names and have somewhat different definitions, but generally describe an estimate of daily intake rates (or air concentrations) for a chemical that are expected to be without adverse or deleterious effects in the general population, including sensitive subpopulations.[1] For chemicals considered to be carcinogenic, the USEPA also establishes estimates of the cancer potency of the chemicals by assigning a quantitative estimate of the upper bound of potential increased cancer risk associated with a unit of intake or air concentration (unit cancer risks, or UCRs). Finally, several US and international governmental bodies and independent organizations set chemical-specific air concentrations that workers can be repeatedly exposed to without experiencing adverse health effects (for example, Threshold Limit Values [TLVs], Permissible Exposure Limits [PELs], and Recommended Exposure Limits [RELs]. These values are generally not appropriate for application to the general population on a chronic basis, but can provide context for assessing estimated environmental exposure levels. That is, occupational exposure guidelines provide an estimate of exposure levels that are not expected to cause adverse effects in a healthy working population exposed on an occupational schedule.

Several health-based exposure guidance values and toxicity values are available for cadmium. Noncancer exposure guidelines from the USEPA, the WHO and ATSDR are described in Table 1, including information regarding the studies used as the basis for the derivation, the identified Point of Departure (POD) (No Observed Adverse Effect Level [NOAEL], Lowest Observed Adverse Effect Level [LOAEL], or Benchmark Dose) and the uncertainty factors applied to the POD to obtain the exposure guidance values. All non-cancer exposure guidance values have been established to protect against cadmium's effects on the kidney (deemed to be the most sensitive endpoint in humans). Cancer risk estimates have also been derived for cadmium by the USEPA and Health Canada to protect against respiratory system tumors resulting from inhalation exposures based on data from occupationally exposed workers. Since it is currently believed that these tumors only occur following inhalation of cadmium dusts, derivation of a BE is not appropriate because biomonitoring data cannot distinguish the route of exposure (Hays et al., 2008).

1.2. Pharmacokinetics

Absorption of cadmium from the gastrointestinal tract is estimated to be low, ranging from 0.5% to 12% (average 2%). Absorption following inhalation depends on the particle size and solubility of the cadmium compounds. It is estimated that 25–50% inhaled cadmium fumes are absorbed systemically. Some of an inhaled dose of cadmium will be cleared to the gastrointestinal tract. Factors that promote absorption of cadmium following oral ingestion are low intake of iron, calcium, zinc, copper, or protein. Dermal absorption of cadmium is considered negligible (Lauwerys and Hoet, 2001; Friberg et al., 1974; Nordberg et al., 1971). Transfer of cadmium to the fetus appears to be minor under relevant environmental exposure levels (Friberg et al., 1974); however, some studies have shown that the concentration of cadmium in cord blood is roughly 50% of the concentration in maternal blood (ATSDR, 1999).

In blood, cadmium is predominantly bound to the red blood cells and albumin (Lauwerys and Hoet, 2001; ATSDR, 1999). Cadmium enters the liver where it is then bound to metallothionein and redistributed to the bloodstream. Because of its small size, cadmium-metallothionein is efficiently transported to the kidney tubules via glomerular filtration (Nordberg et al., 2007). Besides kidney, liver is another principal site of storage for cadmium, with skin, bones and muscle being other tissue storage sites. Following chronic exposures, kidney has the highest concentrations of cadmium.

Cadmium is not biotransformed. The biological half-life of cadmium in humans is estimated to range from 6 to 38 years in the kidney and 4–19 years in the liver. Cadmium absorbed systemically is eliminated from the body via urinary and fecal excretion (Friberg et al., 1974; ATSDR, 1999). Cadmium can be excreted in human milk at concentrations 5–10% of maternal blood concentrations (ATSDR, 1999).

Several models of cadmium kinetics in humans have been developed. Most of the pharmacokinetic/toxicokinetic models developed for cadmium have been for the purpose of estimating an intake or exposure required to yield a target kidney cortex concentration. Models have ranged from simplistic one-compartment PK models (IPCS, 1992) to multi-compartment linear pharmacokinetic models (Kjellström and Nordberg, 1978; Nordberg and Kjellström, 1979). The more elaborate eight-compartment linear pharmacokinetic model of Kjellstrom and Nordberg takes into account the transfer of cadmium between the muscles, liver, and kidneys. The best-fit of the empirical data was achieved with shorter (8–14 years) half-lives for each compartment (Kjellström and Nordberg, 1978). The multi-compartment PBTK model as amended by Choudhury et al. (2001) provides a good agreement between estimated lifetime daily intakes of cadmium and urinary concentrations of cadmium measured in a sample of the U.S. population from NHANES III. The value of the multi-compartment model lies in the possibility of using it to calculate relationships between intake and Cd concentrations in several tissues, including blood and urine, after both short- and long-term exposure (Beckett et al. 2007; Nordberg et al. 2007).

[1] "An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. Generally used in EPA's noncancer health assessments." http://www.epa.gov/iris/gloss8.htm

Table 1
Exposure guidance values for cadmium from various agencies

Organization, Criterion, and Year of Evaluation	Study Description	Critical Endpoint and Dose	Uncertainty Factors	Value
Noncancer Endpoints				
USEPA RfD (USEPA IRIS record accessed 2007; evaluation conducted in 1994)	Numerous studies of chronically exposed human populations	NOAEL from human studies for proteinuria (as a sign of kidney effects preceding kidney damage): 200 μg g cadmium in renal cortex Estimated to correspond to absorbed dose of 0.00025 mg^{-1} kg^{-1} d Assuming 5% absorption from water and 2.5% absorption from food, corresponds to following intake rates: 0.005 mg kg^{-1} d^{-1} in water 0.01 mg kg^{-1} d^{-1} in food	10 10 – interindividual	0.0005 mg kg^{-1} d^{-1}(in water) 0.001 mg kg^{-1} d^{-1} (in food)
ATSDR MRL (ATSDR 1999)	Study of Japanese residents with well-characterized long-term cadmium intakes	NOAEL for kidney proteinuria 0.0021 mg kg^{-1} d^{-1} in food	10 10 – interindividual	0.0002 mg kg^{-1} d^{-1}
Joint FAO/WHO PTWI (JECFA 2001; evaluation conducted in 2000)	Numerous studies	NOAEL for kidney proteinuria 2.5 μg Cd g^{-1} creatinine in urine	Various assumptions	0.007 mg kg^{-1} wk^{-1} (equivalent to 0.001 mg kg^{-1} d^{-1})
Cancer Endpoints				
USEPA (USEPA IRIS record accessed 2007; evaluation conducted in 1994)	Cancer mortality in cadmium smelter workers (specific to inhalation route)	Lung, bronchus, and trachea cancer mortality	Not applicable	Inhalation cancer slope factor: 1.8 × E-3 per $\mu g/m^3$ Risk-specific doses: 1E-06 risk: 6E-04 $\mu g/m^3$ 1E-05 risk: 6E-03 $\mu g/m^3$ 1E-04 risk: 6E-02 $\mu g/m^3$
Health Canada, (1994; evaluation conducted in 1994)	Rat bioassay data for cadmium chloride aerosols	Lung tumors	Not applicable	1E-05 risk: 5.1E-04 $\mu g/m^3$

Cadmium pharmacokinetics are reviewed in more detail by Friberg et al. (1974, 1985) and by ATSDR (1999).

1.3. Biomarkers

Table 2 summarizes the advantages and disadvantages of available biomarkers for cadmium. The advantages of using biomonitoring to assess cumulative exposures to cadmium have been known for decades (Lauwerys and Hoet, 2001). While blood, urine, feces, and hair have all been suggested, blood and urine have generally been the biomarkers of choice for assessing cadmium exposures. Generally, urinary cadmium concentrations (U-Cd) are believed to be an indicator of chronic exposures and steady-state renal cadmium concentrations, while blood cadmium concentrations (B-Cd) are believed to reflect both recent exposure and cadmium in the body accumulated over time (Lauwerys and Hoet, 2001; Alessio et al., 1993; Nordberg et al., 2007).

The concentration of cadmium in the renal cortex is believed to be the critical dose metric associated with cadmium-induced proteinuria, and urinary cadmium levels are believed to be directly correlated with renal cortex cadmium concentrations (Orlowski et al., 1998; Satarug et al., 2002; Nordberg et al., 2007). Therefore, urinary cadmium concentration is likely to be a close surrogate for the critical dose metric and thus cadmium-induced proteinuria (JECFA 2001; ACGIH 2001). Given that cadmium concentrations in blood are likely to be more transient in nature than renal cortex levels, blood cadmium concentrations, while still useful, may not be as directly correlated with the critical dose metric associated with the critical toxic response.

Table 2
Available biomarkers for cadmium

Analyte	Medium	Advantages	Disadvantages
Cadmium	Blood	Indicator of historical and recent exposures	More invasive
	Urine	Relevant to critical dose metric (renal concentrations); less invasive; indicator of historical exposures	
	Hair	Least invasive	Susceptible to external contamination (not indicative of absorbed dose)

2. BE derivation

The approach used for derivation of BE values is dictated by consideration of several factors:

- Whether the exposure guidance value was derived based on animal toxicology data or human epidemiology studies. For cadmium, human studies form the basis for all relevant exposure guidance values.
- How directly related the biomarker is to the mechanism of action and thus critical dose metric for the compound. For cadmium, urinary cadmium concentrations are directly relevant to the critical internal dose metric for the most sensitive human toxic response, renal cortex cadmium concentration.
- The availability of PK data or models for humans, the animal species of interest (when the guidance value is derived from animal toxicity data, or both. For cadmium, substantial human data are available relating urinary cadmium to the critical dose metric and relating blood cadmium concentrations to urinary concentrations.

All available non-cancer exposure guidance values (Table 1) are based on protecting against kidney toxicity as evidenced by

proteinuria (of some form) in humans. These exposure guidance values have relied on estimates of internal dose (either renal cortex concentration or urinary concentration) from human populations as the POD. Thus, derivation of BE values associated with these exposure guidance values begins with consideration of these POD values. Fig. 1 presents a schematic of the approach used to derive the BE values. Briefly, the approach is as follows:

- Identify the critical dose metric associated with the POD.
- Estimate the urinary cadmium concentration (creatinine-adjusted) associated with the POD (BE_{POD}).
- Convert the urinary creatinine-adjusted BE_{POD} to a volume-adjusted urinary concentration and to a blood concentration using available pharmacokinetic data to obtain the BE_{POD} values for these biomarkers.
- Divide the BE_{POD} by appropriate intraspecies uncertainty factors used in the derivation of each respective exposure guidance value to derive the BE values.

These steps are described in detail below, and are also presented and summarized in Table 3.

Identification of the critical dose metric at the POD. All three of the available non-cancer exposure guidance values were developed using human data on kidney effects as the basis for derivation. USEPA (1994) developed an RfD using a Point of Departure (POD) of 200 μg Cd g^{-1} renal cortex wet weight as a No-Observed-Effect-Level (NOEL) for proteinuria in humans. The joint FAO/WHO PTWI for cadmium was derived by choosing a urinary cadmium concentration associated with an absence of proteinuria. Finally, ATSDR relied on a study of a Japanese population (Nogawa et al., 1989) that estimated daily cadmium dietary dose (estimated from cadmium concentration in rice used for food in the region) that resulted in rates of β_2-microglubulinuria equivalent to those in a control population (approximately 5%). In addition, Nogawa and Kido (1993) also evaluated the creatinine-adjusted urinary cadmium concentrations in the same study population. The dietary intake of 0.0021 mg kg^{-1} d^{-1} identified by ATSDR as a point of departure was associated with a urinary concentration of 5.4 μg g^{-1} cr, (3.8 μg L^{-1}).

BE values are derived here only for exposure guidance values derived for non-cancer endpoints. As discussed above, the cancer slope factors established for cadmium are based on a

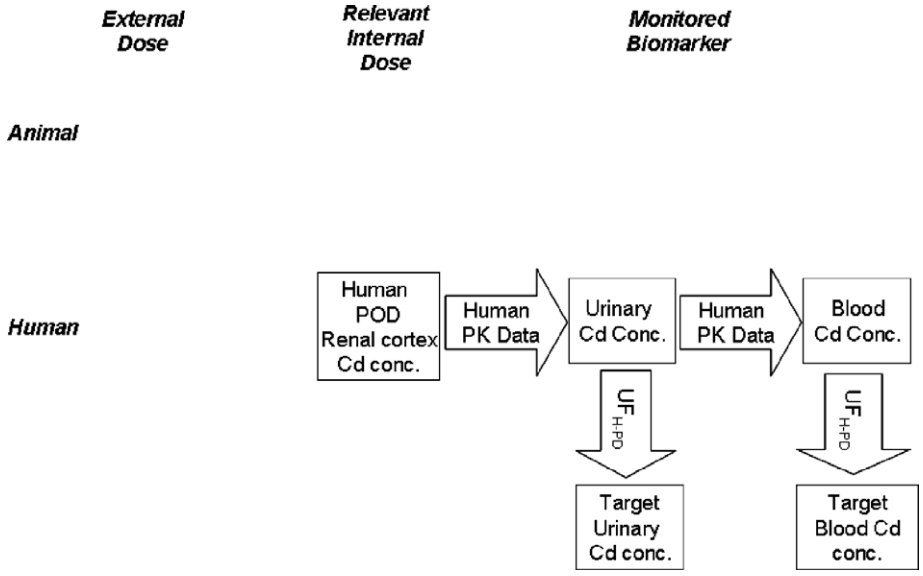

Fig. 1. Schematic of approach used to estimate BE values for cadmium in humans corresponding to oral exposure guidance values. Current exposure guidance values are based upon estimates of human internal doses (renal cortex Cd concentration or urinary Cd concentration). POD: Point of departure; $UF_{H\text{-}PD}$: component of intraspecies uncertainty factor for pharmacodynamic sensitivity. See text for discussion of approach.

Table 3
Biomonitoring Equivalents (BEs) for exposure guidance values and underlying PODs

BE derivation step	USEPA chronic RfD			ATSDR chronic MRL			WHO JECFA PTWI		
Target organ	Kidney			Kidney			Kidney		
POD	200 μg g^{-1} Renal cortex Cd concentration			0.0021 mg kg^{-1} d^{-1} Dietary Cd intake			2.5 μg g^{-1} cr Urinary Cd concentration		
Matrix	*Urine*		*Blood*	*Urine*		*Blood*	*Urine*		*Blood*
BE_{POD}	6.3 μg g^{-1} cr[a]	4.6 μg L^{-1}[b]	5.3 μg L^{-1}[c]	5.4 μg g^{-1} cr[d]	3.8 μg L^{-1}[b]	4.4 μg L^{-1}[c]	2.5 μg g^{-1}	1.8 μg L^{-1} [b]	
Intraspecies uncertainty factors[e]							Not specified		
Pharmacodynamic	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$	$10^{0.5}$			
Pharmacokinetic	1	1	1	1	1	1			
BE value	2.0 μg g^{-1} cr	1.5 μg L^{-1}	1.7 μg L^{-1}	1.7 μg g^{-1} cr	1.2 μg L^{-1}	1.4 μg L^{-1}	Not calculated		
Confidence rating[e]	High	High	Medium	High	High	Medium	Not evaluated		

[a] Calculated using Eq. (1) discussed in text.
[b] Calculated assuming a ratio of 0.73 g crL^{-1} urine. See text for discussion.
[c] Calculated using the average of Eqs. (4) and (5) in text.
[d] Calculated as the average of values for men and women reported in Table 1 from Nogawa and Kido (1993).
[e] See discussion in text.

carcinogenic response observed in the respiratory tract of exposed workers, which is believed to be a local, rather than systemic, response to inhalation exposure to cadmium-containing dusts. Because biomonitoring data cannot provide information on the route of exposure, and exposure to cadmium in the general population occurs via mixed routes, derivation of a BE for the cancer endpoint for cadmium is inappropriate. The following sections describe the derivation of BE values for the available non-cancer exposure guidance values for cadmium.

2.1. Methods

The advantages of relying on biomonitoring for assessing cadmium exposures have been known for decades (Nordberg et al., 2007). As a result, there have been several studies that have attempted to correlate biomonitoring levels of cadmium with internal dose metrics (such as renal cortex cadmium levels). The following section reviews the approaches available for calculating BEs by relating renal cortex cadmium levels with both urinary and blood cadmium concentrations and relating urinary and blood cadmium concentrations.

2.1.1. Urinary BE derivation

2.1.1.1. Creatinine-adjusted basis. There have been two major approaches to developing an understanding of the relationship between cadmium concentrations in the renal cortex and in urine. One approach has measured the concentrations of cadmium post-mortem (in cadavers) in the renal cortex and in urine. The other approach has utilized X-ray fluorescence to determine the concentration of cadmium in vivo in the kidney and in urinary voids. The former has the advantage of being able to more accurately quantify cadmium concentrations in the renal cortex (as opposed to using X-ray fluorescence). The latter approach has the advantage of quantifying cadmium concentrations in urine voids (as opposed to the former which relies on collecting a urine sample post-mortem from the bladder). Since the US EPA RfD is based on a renal cortex critical concentration of 200 $\mu g\,g^{-1}$ as determined from cadavers (personal communications; Drs. Monica Nordberg [Karolinska Institute] and Bruce Fowler [ATSDR]), the relationship between renal cortex and urine cadmium concentrations developed from cadavers is considered more relevant for the calculation of BEs based on the 200 $\mu g\,g^{-1}$ critical renal cortex cadmium concentration.

Two studies have correlated cadmium concentrations in renal cortex and urine in human cadavers (Orlowski et al., 1998; Satarug et al., 2002). Orlowski et al. conducted a careful analysis and found that the concentration of protein in urine samples from the cadavers increased with time post-death and were elevated compared to urine samples from a control (living) population, even for urine samples collected within one day of death. The authors attributed this to autolysis of the bladder wall and concluded that this was falsely elevating urinary cadmium concentrations measured in autopsy specimens through release of cadmium from bladder wall tissue that occurred during autolysis (Orlowski et al., 1998). The authors used two approaches for correcting for this additional urinary cadmium contribution, providing consistent results for the correlation between renal cortex and urinary cadmium concentrations. Satarug et al. (2002) did not correct for this phenomenon. The Orlwoski et al. study also included individuals with renal cadmium concentrations that covered a broader range than those found by Satarug et al. (2002) (see Fig. 2). The relationship between renal cortex and U-Cd (creatinine-adjusted) reported by Orlowski ($r = 0.85$) is:

$$\mathrm{U-Cd}(\mu g\,g^{-1}cr) = 0.12 + 0.031 * \mathrm{K-Cd}(\mu g\,g^{-1}\mathrm{w.w.}), \quad (1)$$

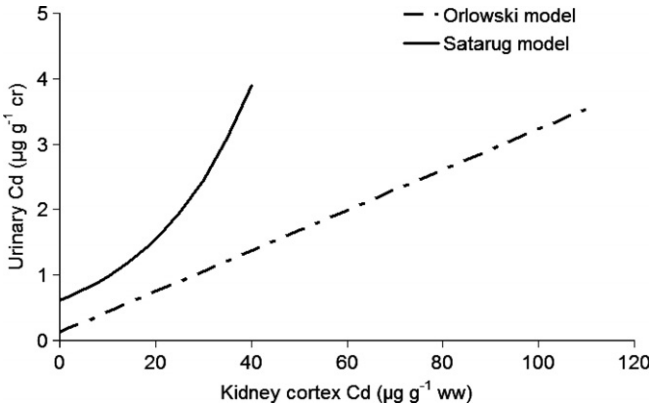

Fig. 2. Comparison of modeled relationship between renal cortex cadmium and urinary cadmium concentrations from Orlowski et al. (1998) and Satarug et al. (2002). The Satarug et al. model predicts very high urinary cadmium concentrations for a range of renal cortex cadmium concentrations considered typical for the non-occupationally exposed population. Use of the Satarug model would yield higher BE estimates for cadmium in urine for a given critical renal cortex cadmium concentration.

where K-Cd is the concentration of cadmium (Cd) in the kidney in units of µg Cd per gram kidney wet weight (w.w.).

The study authors report lower correlation coefficients between renal cortex cadmium concentrations and U-Cd reported on a volume basis, but did not report the equation for this relationship. Eq. (1) will be used to relate renal cortex cadmium concentrations with urinary cadmium concentrations (creatinine-adjusted).

2.1.1.2. Conversion to a urinary volume basis. The concentration of cadmium in spot urine samples (expressed as either $\mu g\,g^{-1}$ cr or $\mu g\,L^{-1}$) have been found to correlate with 24-h urine composites (Alessio et al., 1993). No studies could be found that provide either data or evaluations of correlations between renal cortex cadmium concentrations and urinary cadmium concentrations reported on a volume basis. Instead, a relationship between rates of daily creatinine excretion and daily urine volume among humans can be used to extrapolate from the relationship above relating renal cortex and creatinine-adjusted U-Cd.

Mage et al. (2004) derived predictive equations specific for men and women to estimate daily creatinine excretion as a function of height, weight, and age based on established formulas scaled to body surface area (Eqs. 3a and b in Mage et al. 2004):

$$Male\ \ Cn = 1.93(140 - A) * BW^{1.5} * h^{0.5} \quad (2)$$

And

$$Female\ Cn = 1.64(140 - A) * BW^{1.5} * h^{0.5} \quad (3)$$

where Cn is creatinine excretion in $\mu g\,d^{-1}$, A is age in years, BW is bodyweight in kg, and h is height in cm.

These formulas for adults were applied to standard bodyweights (70 kg for men, 55 kg for women) and average US heights for men and women (175 and 160 cm for men and women, respectively) to estimate average creatinine production per day. Using these standard heights and body weights, average daily creatinine excretion is predicted to be 1.5 and 0.9 $g\,d^{-1}$ for men and women, respectively. The average between men and women (1.2 $g\,d^{-1}$) will be used in these calculations.

For adults, 24-h urinary volume estimates from the literature for healthy adult men and women are summarized by Perucca et al. (2007, Table 2 in that publication). A weighted average for the four studies of healthy individuals tabulated there yields estimates of average urinary volumes for men and women of 1.7 and 1.6 L per 24 h, respectively, with coefficients of variation of approx-

imately 30%. The average between men and women (1.65 L d^{-1}) will be used in these calculations.

Taking the ratio of these two estimates provides a scaling factor of 0.73 g cr L^{-1} urine. The U-Cd concentrations reported in units of μg g^{-1} cr can be converted to units of μg L^{-1} using this ratio.

2.1.2. Blood cadmium concentrations

No studies were found that related renal cortex cadmium with blood cadmium concentration in cadavers. Only one study, Börjesson et al. (1997), attempted to correlate kidney and blood cadmium concentrations in living individuals using X-ray fluorescence. However, this study found a poor correlation between renal cortex and blood cadmium concentrations and since the critical renal cortex dose metric was determined using cadavers, this study does not provide a reliable means of relating cadmium concentrations in renal cortex and blood.

Several investigators have attempted to correlate urinary and blood cadmium concentrations. Shimbo et al. (2000) obtained matched urine and blood samples from 607 non-smoking women from the general population in 30 different survey sites, representing seven different administrative regions in Japan. Equations representing the relationship between B-Cd (μg L^{-1}) and U-Cd (μg g^{-1} cr) were reported for an analysis of all individual volunteers and also as averaged for the 30 different survey sites and for the seven different regions. In the full dataset, the relationship between urinary and blood Cd ($r = 0.64$) was

$$\mathrm{Log}[\mathrm{U-Cd}(\mu g\ g^{-1}\ cr)] = 0.42 + 0.7 * \log[\mathrm{B-Cd}(\mu g\ L^{-1})] \quad (4)$$

In a study of thirty occupationally exposed workers, Börjesson et al. (1997) also found a good correlation between B-Cd (μg L^{-1}) and U-Cd (μg g^{-1} cr). A linear relationship between the two was derived independently using data reported in Börjesson et al. (1997):

$$\mathrm{B-Cd}(\mu g\ L^{-1}) = 0.9 + 0.7 * \mathrm{U-Cd}(\mu g\ g^{-1}\ cr), (R^2 = 0.6) \quad (5)$$

Alessio et al. (1993) collected blood and urine samples from 105 occupationally exposed volunteers. A good correlation between B-Cd (μg L^{-1}) and U-Cd (μg L^{-1}) was found, with a linear relationship ($r = 0.69$):

$$\mathrm{B-Cd}(\mu g\ L^{-1}) = 1.29 + 0.30 * \mathrm{U-Cd}(\mu g\ L^{-1}) \quad (6)$$

Since an extra step in extrapolation is needed to relate urinary cadmium concentration in units of μg L^{-1} to renal cortex cadmium concentration (adjustment for urinary creatinine excretion), the relationship established by Alessio et al. (1993) relating B-Cd and U-Cd in units of μg L^{-1} will not be utilized in calculating BEs.

A plot of the modeled relationships obtained by Shimbo et al. (2000) and Börjesson et al. (1997) provide somewhat different results over the U-Cd concentration range of interest, (see Fig. 3). Possible reasons for this difference are gender or smoking status (Shimbo et al. studied exclusively female non-smokers while Börjesson et al. (1997) included almost exclusively male participants and the smoking status was not reported) or differences in exposure levels (Shimbo et al. conducted their study among the general population, while the Börjesson et al. data were derived from occupational exposures with generally higher concentrations of urinary and blood cadmium than observed by Shimbo et al.). Without more information, the estimated blood cadmium BE values are based on an average of the estimates obtained from Eqs. (4) and (5).

2.2. Results of modeling and identification of BE values

The BE_{POD} values for urine and blood based on the exposure guidance values from Table 1 are presented in Table 3.

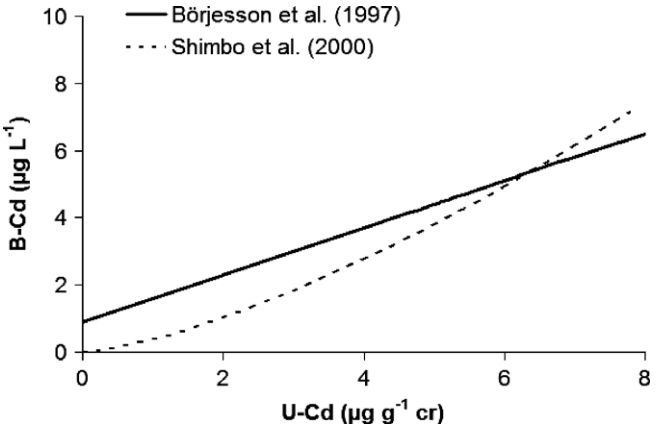

Fig. 3. Comparison of the modeled relationships between urinary cadmium (U-Cd; μg g^{-1} cr) and blood cadmium (B-Cd; μg L^{-1}) concentrations from two studies (Eqs. (4) and (5) in the text). In the derivation of the BE values, these models are applied to the urinary BE_{POD} values to estimate corresponding blood concentrations. The urinary BE_{POD} values for the USEPA RfD and ATSDR MRL are 6.3 and 5.4 μg g^{-1} cr, respectively; in this range the two models illustrated here agree well.

The BE_{POD} for the USEPA RfD was estimated using the relationships between renal cortex and urinary concentrations and between urinary and blood concentrations as described above.

The BE_{POD} for the ATSDR MRL was established based on data from Nogawa and Kido (1993) identifying the urinary concentration corresponding to the dietary NOAEL in their research population identified by the ATSDR as the NOAEL for the MRL derivation. This urinary cadmium concentration is the BE_{POD} for the ATSDR MRL (Table 3). The estimated blood concentration associated with the urinary BE_{POD} was estimated using Eqs. (4) and (5) above.

The Joint FAO/WHO PTWI (WHO JECFA 2001) was established by determining an exposure that would protect against a critical urinary cadmium concentration (2.5 μg g^{-1} cr) associated with a NOAEL for proteinuria, and this value can be regarded as the BE_{POD}. However, none of the documentation describing the establishment of the PTWI provides a clear description of uncertainty factors applied to this value or other methods used to establish the PTWI. Therefore, a BE is not calculated for the WHO PTWI for cadmium.

The BE_{POD} values are extrapolated to BE values through application of appropriate intraspecies uncertainty factors. Guidance for evaluation of such uncertainty factors is provided in the BE Derivation Guidelines (Hays et al., 2008). Because the biomarkers used here relate directly to the critical internal dose metric, the biomarker concentrations measured in individuals will directly reflect pharmacokinetic uncertainties that typically are accounted for through application of the default pharmacokinetic uncertainty factors for relating external to internal doses. That is, biomarker concentrations in individuals who absorb cadmium more efficiently or eliminate cadmium less efficiently than average will reflect these pharmacokinetic sensitivities directly in elevated biomarker concentrations. Because the biomarkers are directly related to the critical dose metric, no additional pharmacokinetic uncertainty factor components are required in the BE derivation; only the default pharmacodynamic uncertainty factor component (one half an order of magnitude) is explicitly retained (Hays et al., 2008).

Table 3 presents and summarizes the BE_{POD} values and extrapolation of these values to the BE values associated with the exposure guidance values in Table 1. The BEs based on EPA's RfD and ATSDR's MRL are very similar, reflecting the high degree of consensus among agencies regarding the point of departure and tolerable exposures to cadmium. Because the full derivation of the WHO JECFA PTWI was not available, only the BE_{POD} value could be derived

for this exposure guidance value. This value is lower than the BE_{POD} values identified by the other agencies.

2.3. Discussion of sources of variability and uncertainty

This section presents a brief overview of sources of variability in the BE values derived and presented in Table 3.

2.3.1. Uncertainty in methods used to calculate BEs

Biomonitoring has long been recognized as a valuable and important means of quantifying exposure to cadmium and as a tool in helping to understand the dose–response relationship between cadmium exposure and effects (Lauwerys and Hoet 2001). As a result, there have been sufficient studies conducted over the past two decades exploring the relationship between cadmium levels in the renal cortex and levels measured in matrices easily biomonitored and exploring the relationships among cadmium levels in the various matrices. As a result, there is high confidence in the empirical relationships used to calculate the BEs. Additional research into the correlation between cadmium in blood and urine among individuals exposed to cadmium at environmentally relevant levels could improve this confidence.

2.3.2. Interindividual variability

While relationships between biomarker concentrations and the critical renal cortex concentrations are well established, there remains individual variability in the relationships between biomarkers. For example, Shimbo et al. (2000), in their study relating urinary and blood concentrations of cadmium, demonstrate up to 3-fold variation (above or below the mean) among individuals in the measured urinary concentration of cadmium associated with a blood cadmium concentration. Similarly, the relationship reported here relating urinary concentrations on a creatinine-adjusted basis to a volume-adjusted basis represents an average relationship, and individuals may excrete more or less than the average amount of creatinine in a 24-h period, or excrete more or less than the average amount of urine, particularly when samples are taken on a spot basis (rather than 24-h collection). These factors can also result in a total of approximately a 2- to 3-fold variation in measured concentrations in an individual at any given time (Scher et al. 2007).

2.3.3. Exposure patterns

Given the long half-life of cadmium in blood and urine, intraday, daily, weekly and even monthly variations in cadmium exposures will have a minimal impact on biomonitoring levels. Historically elevated exposures (either because of temporal trends in background exposures or as a result of past occupational exposures) will likely persist as elevated biomarker concentrations for many years and even decades. Regardless, the direct relationship between cadmium in urine (and blood) and renal cortex still provides a direct measure of potential health risks.

2.3.4. Analytical issues

The analytical methods for quantifying cadmium in urine and blood are well established (ACGIH, 2001; CDC, 2005). The CDC notes molybdenum oxide interferes with the quantification of cadmium at low levels in urine using ICP-MS (CDC, 2005).

2.3.5. Gender and age

Because of cadmium's long half-life in humans, the concentration of cadmium in blood and urine increases with age. Women tend to have higher concentrations of cadmium in blood and urine, presumably because of a higher percent absorption following oral exposures (ATSDR, 1999).

2.3.6. Smoking, drugs, alcohol or other co-exposures

Cigarette smoke is a significant source of cadmium exposure. Smokers are consistently found to have higher concentrations of cadmium in their blood and urine. Alcohol does not appear to impact the pharmacokinetics or levels of exposure to cadmium.

2.4. Confidence assessment

Guidelines for derivation of BE values (Hays et al., 2008) specify consideration of two main elements in the assessment of confidence in the derived BE values: robustness of the available pharmacokinetic models and data, and understanding of the relationship between the measured biomarker and the critical or relevant target tissue dose metric.

2.4.1. Summary of confidence ratings for BE values

Urinary cadmium is either directly used to establish the exposure guidance value (e.g., ATSDR's MRL) or is directly related to the internal critical dose metric of renal cortex cadmium concentrations (e.g., EPA's RfD). The concentration of cadmium in blood is thought to be also related to renal cortex cadmium concentrations, although there may be more variability in this relationship because cadmium in blood may reflect recent exposure more directly than it reflects renal cortex concentration (which is influenced primarily by long-term exposures). B-Cd has been found to be fairly well correlated with U-Cd, therefore, B-Cd is likely to be directly related to the critical dose metrics. The empirical data used to calculate the BE are robust and have been replicated in multiple studies. Additional confidence could be gained by analyzing large biomonitoring databases (such as CDC's NHANES) that include paired urinary and blood samples to further evaluate the correlation between U-Cd and B-Cd and the factors that influence that relationship

- Relevance of biomarker to relevant dose metrics: HIGH for urinary BE values; MEDIUM for blood BE values.
- Robustness of pharmacokinetic data/models: HIGH for urinary BE values; MEDIUM for blood BE values.

The summary confidence ratings are presented in Table 3.

3. Discussion and interpretation of BE values

Ideally, screening levels for biomonitoring data would be based on a robust set of studies of health effects in humans related directly to measured levels of the compound in urine or blood. Such screening values exist for a limited number of environmental chemicals (e.g., lead and mercury). The database for such an evaluation seems to exist for cadmium. However, in the absence of such a concerted effort to develop such a relationship, estimates of chemical concentrations consistent with existing health-based exposure guidelines can serve as screening values for initial interpretation of measured concentrations in biological media (e.g., blood and urine).

The BE values presented here represent the concentrations of cadmium in blood and urine that are consistent with the derivation of exposure guideline values that have been established (Table 1), based on the current understanding of the pharmacokinetic properties of this compound. These BE values should be regarded as interim screening values that can be updated or replaced if the scientific and regulatory communities update the underlying exposure guidance values based on new assessments of acceptable or tolerable concentrations in human biological media.

The BE values presented here are screening values and can be used to provide a screening level assessment of measured blood

and urine concentrations of cadmium in population- or cohort-based studies. Comparison of measured values to the values presented here can provide an initial evaluation of whether the measured values in a given study are of low, medium, or high priority for risk assessment follow-up. Measured biomarker values in excess of the BE_{POD} indicate a high priority for risk assessment follow-up. Values below the BE_{POD} but above the BE suggest a medium priority for risk assessment follow-up, while those below the BE values suggest low priority. Based on the results of such comparisons, an evaluation can be made of the need for additional studies on exposure pathways, potential health effects, other aspects affecting exposure or risk, or other risk management activities.

BE values do not represent diagnostic criteria and cannot be used to evaluate the likelihood of an adverse health effect in an individual or even among a population. Further discussion of interpretation and communications aspects of the BE values is presented in LaKind et al. (2008).

Conflict of interest disclosure statement

The authors declare that they have no conflicts of interest.

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