Human biomonitoring initiative (HBM4EU): Human biomonitoring guidance values (HBM-GVs) derived for cadmium and its compounds

Farida Lamkarkach, Eva Ougier, Robert Garnier, Claude Viau, Marike Kolossa-Gehring, Rosa Lange, Petra Apel

Environment International 147 (2021) 106337

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Human biomonitoring initiative (HBM4EU): Human biomonitoring guidance values (HBM-GVs) derived for cadmium and its compounds

Farida Lamkarkach [a,*], Eva Ougier [a], Robert Garnier [b], Claude Viau [c], Marike Kolossa-Gehring [d], Rosa Lange [d], Petra Apel [d]

[a] ANSES, 14 rue Pierre et Marie Curie, 94701 Maisons-Alfort Cedex, France
[b] Paris Poison Centre, Toxicology Department (FeTox), APHP, Lariboisière-Fernand-Widal Hospital, Paris, France
[c] Department of Environmental and Occupational Health, School of Public Health, University of Montreal, Canada
[d] German Environment Agency (UBA), Corrensplatz 1, 14195 Berlin, Germany

ARTICLE INFO

Handling Editor: Lesa Aylward

Keywords:
Human biomonitoring
HBM4EU
Human biomonitoring guidance values
HBM-GV
Cadmium
Cd
Health effects
Kidney
Renal effect
Nephrotoxicity
Bone toxicity
Neurotoxicity
Reprotoxic effects
Exposure assessment
Biomarkers

ABSTRACT

Aims: The methodology agreed within the framework of the HBM4EU project is used in this work to derive HBM-GVs for the general population (HBM-GV_{GenPop}) and for workers (HBM-GV_{Worker}) exposed to cadmium (Cd) and its compounds.

Methods: For Cd, a significant number of epidemiological studies with dose–response relationships are available, in particular for kidney effects. These effects are described in terms of a relation between urinary Cd (U-Cd) or blood Cd (B-Cd) levels and low molecular weight proteinuria (LMWP) markers like beta-2-microglobulin (β2M) and retinol-binding protein (RBP). In order to derive HBM-GVs for the general population and workers, an assessment of data from evaluations conducted by national or international organisations was undertaken. In this work, it appeared relevant to select renal effects as the critical effect for the both groups, however, differences between general population (including sensitive people) and workers (considered as an homogenous population of adults who should not be exposed to Cd if they suffer from renal diseases) required the selection of different key studies (i.e. conducted in general population for HBM-GV_{GenPop} and at workplace for HBM-GV_{Worker}).

Results and conclusions: For U-Cd, a HBM-GV_{GenPop} of 1 μg/g creatinine (creat) is recommended for adults older than 50 years, based on a robust *meta*-analysis performed by EFSA (EFSA, 2009a). To take into account the accumulation of Cd in the human body throughout life, threshold or 'alert' values according to age were estimated for U-Cd. At workplace, a HBM-GV_{Worker} of 2 μg/g creat is derived from the study of Chaumont et al., (2011) for U-Cd, and in addition to this recommendation a HBM-GV_{worker} for B-Cd of 5 μg/L is also proposed. The HBM-GV_{Worker} for U-Cd is similar to the biological limit value (BLV) set by the new amendment of the European Carcinogens and Mutagens Directive in June 2019 (2 μg/g creat for U-Cd).

1. Introduction

Human biomonitoring (HBM) has been identified as the most appropriate method to determine the internal aggregated exposure to chemicals originating from all different sources and via all exposure routes. HBM has become an instrument of growing importance for chemical policy and risk communication to exposed populations. The European Joint Programm on Human Biomonitoring (HBM4EU) is a joint effort of 30 countries and the European Environment Agency, co-funded by the European Commission within the framework of Horizon 2020 (Ganzleben et al. 2017). With a project duration from 2017 until 2021, HBM4EU aims to harmonise and advance human biomonitoring in Europe by studying the internal exposure of European citizens to chemicals and its impact on health. The project generates scientific knowledge to answer concrete policy relevant questions in Europe and thus builds bridges between science and politicy, for the benefit of society by improving public health.

An important component of the HBM4EU project is the derivation of human biomonitoring guidance values (HBM-GVs) for priority substances identified in the HBM4EU prioritisation process at European level. HBM-GVs aim to improve chemical risk assessment or health impact assessment by comparing these benchmark values with

* Corresponding author.
E-mail address: farida.lamkarkach@anses.fr (F. Lamkarkach).

https://doi.org/10.1016/j.envint.2020.106337
Received 3 September 2020; Received in revised form 5 November 2020; Accepted 11 December 2020
Available online 30 December 2020

measured data in biomonitoring programmes. Where the database is sufficient, HBM-GVs are derived for the general population and for occupationally exposed adults with the contribution of national and EU expertise. In this paper the derivation of HBM-GVs both for the general population and for workers are presented for cadmium (Cd).

Cd is a hazardous metal found naturally in the environment at low levels and as a contaminant in food. Cd was, but is decreasingly used as industrial material. It is present in sewage sludge, in phosphates used as fertilizers or within industrial emissions. Cigarette smoke and food are considered important sources of exposure in non-occupationally exposed individuals. Indeed, food accounts for approximately 90% of Cd exposure in the non-smoking population (EFSA, 2009a). Workers can be exposed in industries using Cd compounds for plating of steel or iron, as plastic stabilizers, as pigments or in welding materials (IUPAC, 2018).

According to the Classification, Labelling and Packaging (CLP) regulation in Europe, Cd metal is classified as Carcinogenic Category 1B (Carc. 1B; may cause cancer), Mutagenic Category 2 (Mut. 2; suspected of causing genetic defects), and Reprotoxic Category 2 (Repr.2; suspected of damaging fertility and unborn child) (EC No 1272/2008). The Table 1 summarises the harmonised CLP classifications for the main Cd compounds (concerning carcinogenic, mutagenic and reprotoxic effects).

Due to the sufficient evidence that occupational exposure to Cd compounds is associated with an increased risk of lung cancer, Cd and its compounds are classified as carcinogenic to humans (Group 1) according to the International Agency for Research on Cancer (IARC). Inconsistent or limited evidence exist regarding the increased risks of prostate or kidney cancers (IARC 2012).

The use of Cd compounds is severely restricted in Europe and some compounds as Cd itself, Cd oxide, Cd sulfide, Cd sulfate, Cd dichloride, Cd fluoride, Cd carbonate, Cd hydroxide and Cd nitrate are identified as Substances of Very High Concern (SVHCs) and included in the REACH candidate list for authorisation (Annex XIV) according to REACH Regulation (EC No 1272/2008).

Moreover, since June 2019, Cd content in “CE marked” phosphate fertilisers has been limited to 60 mg/kg (EU 2019/1009).

In 2019, the European Parliament and the Council adopted a new limit value, at workplace, of 1 μg/m^3 for Cd inhalable fraction (Directive EU 2019-983) after a transitional period of 8 years. Within this transitional period a value of 4 μg Cd/m^3 is applied for the respirable fraction together with a biomonitoring system implemented with a biological limit value for urinary Cd (U-Cd) not exceeding 2 μg/g creat.

2. Material and methods

2.1. General methodology to derive HBM-GVs in the framework of the HBM4EU project

The definition as well as the methodology for deriving HBM-GVs for the general population (HBM-GV$_{GenPop}$) and for workers (HBM-GV$_{Worker}$) are detailed in the concept paper (Apel et al., 2020). The HBM-GVs derived for the general population (HBM-GV$_{GenPop}$) represent the concentration of a substance or its relevant metabolite(s) in human biological matrices (e.g. urine, blood, hair) at and below which, according to current knowledge, no risk of health impairments is to be expected, and consequently, no need for action is identified. The HBM-GVs derived for occupationally exposed adults (HBM-GV$_{Worker}$) represent a concentration of a substance or its relevant metabolite(s) in human biological media aiming to protect workers exposed to the respective substance, regularly (each work day) and over the course of a working life, from the adverse effects related to medium- and long-term exposure.

The methodological approach was developed on the basis of the procedure described in the German Human Biomonitoring Commission’s position paper (German Human Biomonitoring Commission, 2014; Apel et al., 2017), which in turn refers to previous work by the Commission but also by the working group around Hays *et al.*, (German Biomonitoring Commission 2007b; Hays et al., 2007 & 2009; Angerer et al., 2011), and in the guidance document elaborated by the French Agency for Food, Environmental and Occupational Health and Safety (ANSES) for the derivation of BLVs for chemicals used in the workplace (ANSES, 2014).

HBM-GV$_{GenPop}$ are similar to HBM-I values by the German Human Biomonitoring Commission (Apel et al., 2017; Schulz et al. 2012, Angerer et al., 2011) and partly to the Biomonitoring Equivalents by Hays et al. (2007), while HBM-GV$_{Worker}$ are similar to the BLVs decribed in ANSES methodologial report (ANSES, 2014).

For the derivation of HBM-GVs three options are available and briefly described below in order of preference: the first option consists in deriving the HBM-GVs on the basis of the relationship between the critical, i.e. the most sensitive health effect, and selected biomarkers’ levels. The second possible approach is based on the study of the correlation between external exposure and biomarkers’ concentrations (or available toxicokinetic models), this option requires external toxicity reference values (TRV) proposed by European or international bodies. The last option is to derive HBM-GVs from critical effects reported in animal toxicological studies (Apel et al. 2020).

2.2. Methodology used for deriving HBM-GVs for Cd and its compounds

In this paper, based on national and international recommendations, collected data on Cd were assessed to choose the relevant biomarkers, to identify the most sensitive critical effect and to select the key studies with the view of deriving HBM-GVs for the general population and workers. The consulted literature reveals, that effects of Cd exposure are mostly related to biomonitoring data, which provides a large database on a relationship between health effects and biomarkers levels of Cd.

2.2.1. Selection of biomarkers of exposure

The selection of the biomarkers is an important step for deriving HBM-GVs. The potential biomarkers of exposure are usually chosen according to their characteristics: specificity, half-life, sampling conditions, invasiveness of sampling, relations with the external exposure and/or the effects, analytical methods, etc. Analysis in blood, urine, faeces, liver, kidney, hair, and other matrices can be used as indicators of exposure to Cd, but in the general population or in workers, Cd exposure is commonly monitored through either analyzing blood or urine. Only these matrices are therefore considered here.

In order to justify the selection of biomarkers for the derivation of HBM-GVs, each relevant biomarker of Cd exposure is described with its

Table 1
Harmonised classification (Annex VI of CLP regulation).

Cd	Cd chloride	Cd oxide	Cd sulphate	Cd sulphide	Cd nitrate	Cd hydroxide
CAS No. 7440–43-9 Carc.1B (H350) Mut.2 (H341) Repr.2 (H361fd)	CAS No. 10108–64-2 Carc.1B (H350) Mut.1B (H340) Repr.1B (H360 FD)	CAS No. 1306–19-0 Carc.1B (H350) Mut.2 (H341) Repr.2 (H361fd)	CAS No. 10124–36-4 Carc.1B (H350) Mut.1B (H340) Repr.1B (H360FD)	CAS No. 1306–23-6 Carc.1B (H350) Mut.2 (H341) Repr.2 (H361fd)	CAS No. 10325–94-7 Carc.1B (H350) Mut.1B (H340)	CAS No. 21041–95-2 Carc.1B (H350) Mut.1B (H340)

advantages and disadvantages.

2.2.1.1. Cd in urine (U-Cd). Cd in urine is generally considered a good biomarker of long-term exposure to Cd (with a half-life of 10 to 20 years and even up to 40 years according to some authors (ANSES, 2018)) and is the most extensively studied biomarker of cumulative Cd body burden as urine is non-invasively accessible (though this view was criticised by Bernard (2016) for low levels of exposure). This biomarker is specific to Cd exposure. Therefore, it is the most reliable biomarker of Cd exposure and body burden, for the general population as well as for occupationally exposed adults. Moreover U-Cd is a good biomarker of exposure in terms of relation with health effects: U-Cd concentrations significantly increase when kidney is injured (Prozialeck and Edwards, 2010); several publications report correlations between U-Cd and concentrations of some urinary biomarkers, reflecting early stage of renal damage (ANSES, 2018).

However, U-Cd also depends on diuresis; misinterpretation of U-Cd results can occur depending on the urine dilution. Thus adjustment on creatinine excretion or urine specific gravity is recommended (IUPAC, 2018).

2.2.1.2. Cd in blood (B-Cd). B-Cd partially reflects the accumulated body burden over recent weeks and months. When exposure varies, it will better reflect these variations than U-Cd. Therefore, this biomarker can be used in association with U-Cd, as a biomarker of exposure for the biomonitoring at workplace to assess if exposure is controlled (especially for new employees) (ANSES, 2018). At steady state, a high correlation is observed between U-Cd and B-Cd (Akerstrom et al., 2013).

2.2.2. Review of national and international recommendations

Various EU/international bodies have already formulated recommendations for Cd in terms of internal but also external TRV. Indeed some of them derived internal critical values which are then converted into external TRV.

As a first step, a review of the reference values available from European or international agencies/institutes was conducted. For Cd, the data collection is based on assessments carried out by the European Food Safety Authority (EFSA, 2009a), the German Human Biomonitoring Commission (HBM Commission, 2011), the Agency for Toxic Substances and Disease Registry (ATSDR, 2012), the French Agency for Food, Environmental and Occupational Health and Safety (ANSES, 2018), the American Conference of Governmental Industrial Hygienists (ACGIH, 2018) and by the International Union on Pure and Applied Chemistry (IUPAC, 2018).

2.2.3. Identification of a critical effect and selection of key studies

A review of national and international derivations of internal TRV or internal critical values (used to calculate external TRV) was performed, as well as a bibliographic search on more recent or specific publications. Data collection was assessed to identify reliable information on possible critical effects and relevant studies (others than those described in the review of international or national recommendations for Cd exposure). The critical effect chosen from the adverse effects described in the literature (and based on national or EU organisation's evaluations) is the first adverse effect that occurs when the dose increases.

The bibliographical research was conducted in the following databases until 2019: Medline, Scopus. To do so, the following keywords were used: cadmium, guidance value, health effects, nephrotoxicity, bone toxicity, neurological toxicity, and reprotoxic effects.

Comments from experts of HBM4EU partner countries were taken into consideration for the final decision on HBM-GVs.

3. Results

3.1. Choice of biomarkers of exposure

For this project, with regard to the available data, both U-Cd and B-Cd were retained as biomarkers of exposure for the derivation of HBM-GVs. Advantages and disadvantages of each biomarker of exposure are summarised in Table 2.

3.2. Overview of already existing toxicity reference values

The epidemiological database on Cd allows for the derivation of HBM-GVs based on a relationship between human internal concentrations and health effects for both the general population and for workers.

An overview of these existing internal values for U-Cd and B-Cd is detailed in tables below for the general population and for workers. These tables describe the selected critical effect, the POD and assessment factors applied to calculate the corresponding internal TRV.

3.2.1. For the general population

For the general population, data lead to the identification of internal critical levels for U-Cd but not for B-Cd. The internal values (internal TRV or internal critical values) for the general population identified by European or international bodies are detailed in Table 3. Some of these values were converted to derive external reference values (e.g. tolerable weekly intake (TWI) by EFSA or Minimal Risk Levels (MRL) by ATSDR).

The approaches used by these organisations follow the first option described above, which is based on a relationship between health effects (mainly renal effects) and internal concentrations of U-Cd.

In 2009, a panel of experts of the European Food Safety Authority (EFSA) calculated a critical internal value of 1 μg/g creat for U-Cd concentration (on the basis of renal effects using a *meta*-analysis) to establish a TWI for Cd of 2.5 μg/kg bw (EFSA, 2009a).

The HBM Commission of the German Environment Agency (UBA) recommended in 2011 an HBM-I value of 1 μg/g creat (based on EFSA's appraisal) for U-Cd concentration in adults, and a specific value for children of 0.5 μg/g creat (HBM Commission, 2011).

In 2012, the Agency for Toxic Substances and Disease Registry published the evaluation of MRL for Cd. Indeed, ATSDR recommended a chronic MRL (oral route) of 0.1 μg/kg bw/d on the basis of an internal critical value of 0.5 μg/g creat for U-Cd concentration (derived from renal effects of Cd exposure).

More recently ANSES, in 2019, proposed a tolerable daily intake (TDI) of 0.35 μg/kg bw/d (or a TWI of 2.45 μg/kg bw). This value is derived through PBPK modelling from a threshold internal value of 0.5 μg/g creat for U-Cd concentration (based on Cd bone effects). Moreover, the French agency reported values depending on age not to be exceeded in order to respect the critical internal value of 0.5 μg/g creat in adults.

Table 2
Advantages and disadvantages of U-Cd and B-Cd as biomarkers of Cd exposure.

Biomarkers of exposure	Advantages	Disadvantages
U-Cd	Available data on relations both with health effects in general population and at workplace, and with cumulated exposure Biomarker of long-term exposure to Cd Non invasive	Depends on diuresis
B-Cd	Biomarker of long-term and recent exposure Available data on correlations with U-Cd	Invasive Less data available in general population on relation with health effects

U-Cd: Urinary Cadmium; B-Cd: Blood Cadmium.

Table 3
Overview of existing internal TRV for U-Cd for the general population.

Agency or committee (year)	Endpoint	Key study	Point of departure	Assessment factor	Critical value for U-Cd or internal TRV
EFSA (2009a)	Renal tubular dysfunction based on increased β2M concentration	Meta-analysis of 35 studies (EFSA 2009b)	BMD_5L_{95}: 4 μg/g creat	Chemical-specific "adjustment factor" of 3.9, to account for inter-individual variation	Internal critical value: 1 μg/g creat
UBA (2011)	Renal tubular dysfunction based on increased β2M concentration	Based on EFSA assessment (2009a)			HBM-I adults: 1 μg/g creat HBM-I children (3-14y): 0.5 μg/g creat
ATSDR, 2012	Renal tubular dysfunction (excess risk of LMW proteinuria - β2M or α1M)	Meta-analysis based on 7 studies (ATSDR, 2012)	$BMD_{10}L_{95}$: 0.5 μg/g creat	none	Internal critical value 0.5 μg/g creat
ANSES, 2019	Bone effects Osteoporosis and fractures	Engström et al., 2011, 2012)	NOAEL: 0.5 μg/g creat	none	Internal critical value 0.5 μg/g creat

BMD_5L_{95}: benchmark dose lower confidence limit (95%) for a 5% increase of the prevalence of elevated LMWP; β_2M: beta-2-microglobulin; α_1M: Alpha-1-microglobulin; HBM-I: Human Biomonitoring value below which, according to the current knowledge, there is no risk of adverse health effects; NOAEL: No Observed Adverse Effect Level.

3.2.2. For occupationally exposed adults

As for the general population, the approach used by national or international agencies to derive internal TRV for Cd is the first option according to the methodology developed in the framework of this project (i.e. relationships between health effects, renal effects and biomarker concentrations). For workers, in addition to those values recommended for U-Cd (Table 4), internal TRV can be found for B-Cd (Table 5).

In 2017, the European Scientific Committee on Occupational Exposure Limits (SCOEL), established a BLV for U-Cd of 2 μg/g creat based on renal effects observed in the general population.

ACGIH derived biological exposure indices (BEI) for U-Cd and B-Cd of 5 μg/g creat and 5 μg/L respectively, established from renal effects observed in occupational studies (ACGIH, 2016).

In 2018, based on occupational studies showing an association between U-Cd and renal effects, ANSES recommended a BLV for U-Cd of 5 μg/g creat associated with a threshold value for additional medical monitoring at 2 μg/g creat. The French agency also derived a BLV for B-Cd of 4 μg/L on the basis of occupational studies reporting a relationship between B-Cd and nephrotoxicity and a correlation between B-Cd and U-Cd (ANSES, 2018).

Up to now, no reference values (including internal TRV) have been derived for the known carcinogenicity of Cd exposure. Thus, whereas there is sufficient evidence that Cd and compounds are carcinogenic to humans (classification as carcinogenic to humans, group 1 by IARC), it does not seem possible to establish HBM-GVs based on this effect.

3.3. Choice of the critical effect

Based on assessments conducted by international organisations or national institutes (Tables 3–5), it appears that nephrotoxicity has often been identified as the most sensitive and robust endpoint for deriving internal TRV or internal critical values (for the general population and workers). Renal effects of Cd exposure have been well established and well documented since 1950. Moreover, quantitative relationships between concentrations of both U-Cd and B-Cd and renal dysfunction (tubular and glomerular toxicity) in workers and in occupationally unexposed persons are available and considered reliable (EFSA, 2009a; ANSES, 2018).

However, an assessment of the other possible effects of Cd exposure is required to conclude on the choice of the critical effect for deriving HBM-GVs in this work.

Bone effects have been reported in the general population at low levels of U-Cd (<1.0 μg/g creat) (Engström et al. 2011; 2012). Early biological signs of osteoclastic effects (such as increased urine deoxypyridinoline excretion or plasma osteocalcin concentration), but no decreased bone mineral density or increased risk of fractures have been demonstrated at low urine Cd levels (<5 μg/g creat) in younger subjects, including children (Malin-Igra et al. 2019). Concerning the clinical effects on both bone density and the risk of fractures observed at low U-Cd concentrations (<1 μg/g creat) in older people, one possible explanation is that they result from a direct effect of Cd, which would be intensified in older people. An alternative interpretation would be that bone demineralisation in old people could be responsible for a moderate increase of urine cadmium concentration, because: a) Cd release from the bone pool; b) calciuria and lowering of parathyroid hormone causing an

Table 4
Overview of existing internal TRV for U-Cd for workers.

Agency or committee (year)	Endpoint	Key study	Point of departure	Assessment factor	Internal TRV for U-Cd
ACGIH 2016 - USA	Renal tubular dysfunction (excess risk of LMW proteinuria - β2M, NAG or others)	Occupational studies (e.g. Chaumont et al. 2011)	**5** μg/g **creat**	**None**	BEI: **5 μg/g creat**
SCOEL 2017 **Europe**	Renal tubular dysfunction (excess risk of LMW proteinuria - β2M or α1M	Buchet et al., 1990;Hotz et al., 1999;Järup et al., 2000Noonan et al., 2002Jin et al., 2002) (general population)	LOAEL : 2 μg/g creat	None	BLV: **2** μg/g **creat**
ANSES 2018 France	Renal tubular dysfunction (excess risk of LMW proteinuria - β2M and RBP)	Chaumont *et al.* 2010 (Occupational studies)	$BMD_{10}L_{95}$: 5.5 μg/g creat	None	BLV: 5 μg/g creat
		Järup and Elinder 1994 (Occupational studies)	$BMD_{10}L_{95}$: 2 μg/g creat	None	Threshold value for initiating monitoring of renal function biomarkers 2 μg/g creat

BEI: Biological Exposure Indice; BLV: Biological limit value; β_2M: beta-2-microglobulin; α_1M: Alpha-1-microglobulin; RBP: Retinol-binding protein; NAG: N-acetyl-betaglucosaminidase; LOAEL: Lowest observed adverse effect level.

Table 5
Overview of existing internal TRV for B-Cd for workers.

Agency or committee - country	Endpoint	Key study	Point of departure	Internal TRV for B-Cd
ACGIH (2016) - USA	Renal dysfunction (with excess risk of LMW proteinuria - β2M)	Järup et al., 1988 (occupational study)	5%, 10% and 16% prevalence of tubular proteinuria appeared at B-Cd concentrations of 2.8, 5.6 and 10 µg/L The prevalence of tubular proteinuria may become significant even if B-Cd remain for many years below 5 µg/L	BEI: 5 µg/L
ANSES (2018) - **France**	Renal dysfunction (tubular toxicity with excess risk of LMW proteinuria - β2M , RBP, NAG and glomerular toxicity) And Correlation between U-Cd and B-Cd	Several occupational studies (e.g. Jakubowski et al., 1987; Roels et al., 1991; Bernard et al., 1990; Järup et al., 1988, 1995) ; And Zwennis and Franssen, 1992	B-Cd between 3.2 and 10 µg/L And [B-Cd] (µg/L) = 0,6 [U-Cd] (µg/g creat) + 0,8 (with U-Cd = 5 µg/g creat) B-Cd = 4 µg/L	BLV: 4 µg/L

upregulation of calcium and Cd intestinal absorption. Thus, within this project, it is not possible to establish a satisfactory point of departure (POD) for the bone effect.

The results of some studies published within the past ten years also support a causal association of Cd exposure in the general population with the risks of several cardiovascular diseases: coronary heart disease, myocardial infarction, atherosclerotic plaques, stroke, arterial hypertension, heart failure, peripheral arterial disease aortic aneurysm… (Tellez-Plaza et al., 2012 ; 2013a ; 2013b ; Borné et al., 2015 ; Oliver-Williams et al., 2018; …). However, for each of these diseases the available data are issued from a small number of prospective studies with in most cases a short follow-up and all the potential confounders are not appropriately taken into account (especially smoking and exposure to other metals or metalloids). Other limitations of the available data result from the biomonitoring choices: many studies use B-Cd when U-Cd can be regarded as a better measure of long-term exposure, especially in smokers and former smokers; several published prospective studies also used a unique measurement of U-Cd and/or B-Cd for the evaluation of cumulative exposure, which may be inappropriate. In the present state of knowledge, cardiovascular endpoints cannot be considered as critical effects of Cd.

Other Cd toxic effects such as neurological effects have also been reported by some authors. However, there is up to now still limited evidence of adverse Cd-related effects on the central nervous system (CNS) and peripheral nervous system (PNS) in humans or animals. Ciesielski et al. (2012) studied relationships between neurocognitive test scores and U-Cd in the U.S. general population; they report a statistically significant negative relationship among never-smokers after multivariable adjustment. A few studies have found that children's prenatal exposure, assessed by concentrations in the cord blood or in the mothers' urine, was associated with cognitive impairments. Several studies have also tested an association between children's post-natal Cd exposure and cognitive performances, with conflicting results (Kippler et al., 2012, Rodríguez-Barranco et al., 2014, Ciesielski et al., 2012, Cao et al., 2009; Gustin et al., 2018). Globally, in the present state of knowledge, data on the association of Cd exposure with neurotoxic effects are limited and neurological endpoints cannot be considered as critical effects of Cd.

In conclusion, based on the current data available and considering the level of evidence, it was decided to choose nephrotoxicity as the critical effect for establishing HBM-GVs for Cd. In terms of renal damage, tubular effects being more constant and better characterized than glomerular effects (at workplace and in the general population), they were retained as critical effects. Indeed, urinary excretion of some of low molecular weight proteins (LMWP), which are sensitive markers of tubular damage, increases with tubular dysfunction. Alpha-1-microglobulin and beta-2-microglobulin (α1M and β2M), and retinol-binding protein (RBP), despite their non-specificity to Cd exposure, are widely used as biomarkers of early effects of Cd exposure on kidney function (ANSES, 2018).

Cd exposure can also cause glomerular damage. A decrease of glomerular filtration rate (GFR) is reported after environmental and occupational exposure. Increased albuminuria has been used as a biomarker of increased glomerular permeability, a hallmark of early glomerular dysfunction.

Concerning β2M and RBP, Bernard (2004) proposed an interpretation of the clinical significance of urinary excretions, in terms of reversibility on tubular dysfuntion (Table 6).

These widely studied biomarkers of effect are selected to derive HBM-GVs for both populations. Several studies used the urinary level of 300 µg/g creat as the threshold for Cd nephrotoxicity. In this paper, and according to the assessments described above (e.g. EFSA 2009a), this value is also selected as threshold value for tubular dysfunction, which is the critical endpoint for the HBM-GVs derivation.

3.4. Derivation of a HBM-GV_{GenPop} for cadmium exposure

3.4.1. Choice of the key study and identification of a point of departure

Environmental studies showing relationships between U-Cd and renal effects are summarised in several reports e.g. EFSA (2009a), ASTDR (2012) and IUPAC (2018). Some authors showed that the threshold for the occurrence of nephrotoxic effects in the general population should be set lower than for industrial workers (German Human Biomonitoring Commission, Environment Agency 2011). In almost all studies (carried out for occupational or environmental exposure), the authors used a similar approach to identify a Benchmark Dose (BMD) as a point of departure (POD). Indeed, this POD corresponds to the level above which 5% (BMD_5) or 10% (BMD_{10}) of subjects have increased concentrations of biomarkers of tubular damage (β2M and RBP) or of glomerular toxicity. For β2M and RBP, the threshold concentrations can be identified using the values given in Table 6 (Bernard, 2004). EFSA, in 2009 reported U-Cd levels associated with renal dysfunction using the

Table 6
Significance of increased values of β2M and RBP (Bernard, 2004).

Urinary β2M or RBP (µg/g creat)	Clinical interpretation
< 300	Normal value
300–1000	Incipient Cd-induced tubular dysfunction (possibility of reversibility if Cd exposure is not too high)
1000–10000	Irreversible tubular proteinuria likely to accelerate the decline of GFR with age. At this stage GFR is normal or slightly impaired
>10000	Overt Cd nephropathy usually associated with a decreased GFR

β_2M: beta-2-microglobulin; RBP: Retinol-binding protein; GFR: glomerular filtration rate.

same approach and approximatively the same reference values for LMWPs threshold values. For the present work, more recent publications have been analysed. However a new *meta*-analysis including these new data was not performed.

Based on 35 studies including 30,000 subjects (Caucasians and Asians), the EFSA panel decided to perform a *meta*-analysis only with those studies using β2M as the biomarker for renal effects and measuring urinary Cd (in μg/g creat) as indicator of internal dose, though these criteria lead to the exclusion of well-conducted studies: CadmiBel (Buchet et al., 1990) and OSCAR (Järup et al., 2000). Association between U-Cd and β2M as an indicator of early nephrotoxic effects were examined. The experts then applied an adjustment to consider variability due to ethnicity; adjustment for urinary pH (due to the degradation of β2M in acidic urine) was also performed. In spite of the exclusion of some well-conducted studies and the absence of recent studies published on relationship between renal effects and U-Cd, this *meta*-analysis appears to be the most relevant study to derive HBM-GVs for general population (amount of studies, adjustments applied, quality of studies considered, comprehensiveness of evaluation…).

The EFSA *meta*-analysis derived a BMD corresponding to a 5% increase of the prevalence of elevated β2M excretion (statistical cut-off and biological cut-off value of 300 μg/g creat) and selected the 95% lower confidence limit for this value (BMD_5L_{95}) for the total population and for subjects above 50 years (adjusted to Caucasian ethnicity). The results ranging from 3.62 to 5.28 μg/g creat. As a result, the EFSA panel calculated a BMD_5L_{95} of **4 μg urinary Cd/g creat.**

3.4.2. Assessment factor and resulting HBM-GV_{GenPop}

To take into account intra-species variability, the EFSA panel applied a chemical-specific adjustment factor of 3.9 (equivalent to the 95th percentile (BMD) / Median (BMD)) on the point of departure (i.e. 4 μg urinary Cd/g creat).

As a result, a value of 1 μg/g creat was derived which can be regarded as HBM-GV_{GenPop} for adults over 50 years of age: **HBM-$GV_{GenPop\ (adults\ over\ 50\ years)}$ = 1 μg/g creat.** The PBPK model used by Anses (ANSES, 2019) to estimate threshold biological values of U-Cd in general population (ATSDR, 2012) was also used in the present evaluation to predict limits or so-called 'alert' values of U-Cd according to age (Table 7). This lead to HBM-GV_{GenPop} of 1 μg Cd/g creat at age 55–60 years (concentrations are predicted to reach a peak at age 55 years).

These reference values varying with age represent a further specification and advancement of the HBM-I values earlier proposed by the German Human Biomonitoring HBM Commission (2011) .

3.5. Derivation of HBM-GV_{worker} for cadmium exposure

3.5.1. For urinary Cd

Despite the strength of the EFSA *meta*-analysis described above, studies included in the *meta*-analysis are not representative of occupationnally exposed adults (EFSA 2009b). Among the available occupational studies, the study of Chaumont et al., (2011) was selected as the key study for deriving the HBM-GVs. This study was carried out in a large population of French, European and American workers (n = 599), the authors reported a BMDL (for smokers and non-smokers) using urinary β2M and RBP as biomarkers of effect.

The Chaumont et al. (2011) study, which was one of the key studies selected by ACGIH in 2016 and ANSES in 2018, reported urinary Cd levels corresponding to elevated urinary RBP and β2M concentrations for 5% of workers (BMD_5). The lowest BMD_5L_{95}, in the non-smoker subgroup (i.e. 5.5 μg/g creat) based on an increase in the prevalence of abnormal urinary concentrations of RBP (BMD_5L_{95}: 5.5 μg/g creat) or β2M (BMD_5L_{95}: 6.6 μg/g creat) is considered as the POD.

Although, the key study involves a large number of subjects and is carried out at the workplace (thus representative of the target population), and as the average age of workers in the study by Chaumont et al. (2011) was 45 years (±10 years), it seems more prudent to apply an assessment factor for intraspecies differences of 3 to take into account the following considerations:

- Cd cumulative behaviour, in order to ensure protection from health effects due to Cd exposure throughout the working period but also once retired,
- Inter-individual variability of the susceptibility to Cd effects in order to protect potentially vulnerable persons among workers.

Therefore, a HBM-GV_{Worker} for U-Cd of 1.83 (5 μg/g creat / 3) **μg/g creat rounded to 2 μg/g creat is recommended.**

3.5.2. For blood Cd

As described above, B-Cd can be recommended as a biomarker of exposure, in addition to U-Cd, for workers and especially for new employees or when the intensity of Cd exposure rapidly varies.

The derivations of internal TRV for B-Cd have been conducted by ACGIH and ANSES committees. ANSES recommendation is partly based on the French BLV for U-Cd (5 μg/g creat) which is higher than the HBM-GV_{worker}, for U-Cd, proposed above (i.e. 2 μg/g creat).

In 2016, ACGIH recommended a BEI of 5 μg/L. The committee maintained its previous recommendation., based on additional data (e.g. Järup et al., 1988 study) reporting a dose–effect relationship between B-Cd and the prevalence of tubular proteinuria (β_2M greater than 311 μg/g creat.) in 440 workers (326 men and 114 women). The ACGIH committee reported an increase of 5%, 10% and 16% in the prevalence of tubular dysfunction corresponding respectively to 2.8, 5.6 and 10 μg/L B-Cd. The experts concluded that it is prudent to maintain an average B-Cd level below 5 μg/L.

Therefore, on the basis nephrotoxicity and the evaluation conducted by the ACGIH committee, a **HBM-GV_{Worker} for B-Cd of 5 μg/L** can be recommended.

Table 7
U-Cd (median) alert levels for age ranges (with indicatory median body-weight considered for the age ranges).

Age (years)	Body weight (median) (kg)	U-Cd median (min–max) (ug/g creat)	U-Cd threshold values (μg/g creat)
=<10	23.8	0.1 (0.03–0.14)	0.1
11–20	52.8	0.18 (0.15–0.23)	0.2
21–30	67.3	0.29 (0.24–0.36)	0.3
31–40	72.4	0.5 (0.39–0.63)	0.5
41–50	72	0.8 (0.67–0.93)	0.8
>50	60	0.99 (0.95–1.00)	1

4. Discussion and conclusion

Within the framework of HBM4EU, we have conducted an up to date assessment to derive HBM-GVs for the general population and for workers. All the proposed values were identified using renal damages as critical effects. A comprehensive literature review on effects suspected to be related to Cd exposure showed also bone and cardiovascular effects for low cumulated exposure as indicated by U-Cd and/or B-Cd. However, for the time being, these effects were not selected as critical effects for the derivation of reference values, as the weigth of evidence was not considered sufficient within the HBM4EU project. **Moreover, since it was not possible to derive HBM-GV to protect the exposed population against the known carcinogenic effects of Cd, the values proposed in this assessment should be used with caution.**

For the present work, we selected key studies for renal damage, in each specific population. We considered that the general population constitutes a heterogenous population with people vulnerable to renal damage (*e.g.* people with diabetes, previous renal damage or arterial hypertension) even at a lower level of Cd exposure. Indeed, dose response effects observed in the general population at a low level of Cd exposure could be partially explained by pre-existing diseases. On the

contrary, workers that are occupationally exposed to Cd are considered as a healthy and homogeneous population. As a matter of fact, workers should not be exposed to Cd when suffering from diseases possibly worsened by this exposure.

However, in order to protect workers throughout their career and after retirement and also to protect vulnerable people who could be present at workplace, the assessment factor applied (3 for intra-species variability) provides a sufficient level of protection to the HBM-$GV_{workers}$. This value is consistent with the recommendations by SCOEL (2017) for which the European committee derived value to protect workers from renal diseases "during or, most often, after their occupational career".

The main limitation of the proposed HBM-GV_{GenPop} results from its derivation from the EFSA *meta*-analysis as this *meta*-analysis excluded high quality environmental studies because of methodological aspects (e.g. Cadmibel and OSCAR) and as it was performed more than 10 years ago, it does not include some recent well-conducted studies. However, the EFSA *meta*-analysis included more than 30 studies (with more than 30,000 individuals). A specificity of the present proposal of HBM-GV_{GenPop} is its association with a recommendation of 'alert values' according to age; these should be considered as thresholds for the prevention of toxic effects at older age, in long-term exposed individuals.

In 2008, Hays *et al.* calculated biomonitoring equivalent (BE) values for Cd in blood and urine (Hays et al., 2008). The authors based their derivation of BE both on the US Environmental Protection Agency chronic Reference Dose (RfD) (US EPA, 1994) and the Agency for Toxic Substances and Disease Registry chronic Minimal risk level (MRL) (ATSDR, 1999), both referring to kidney effects in humans. US EPA (1994) developed the RfD using a POD of 200 μg Cd/g renal cortex wet weight as NOAEL for proteinuria in humans. ATSDR derived its MRL from studies by Nogawa et al. (1989) and Nogawa & Kido (1993), giving a daily Cd dietary intake of 2.1 $\mu g.kg^{-1}.d^{-1}$ together with a U-Cd concentration of 5.4 μg Cd/g creat as NOAELs for proteinuria in humans.

- The urinary BE derivation based on the US EPA RfD used the relationship between Cd in the renal cortex and U-Cd concentrations (creatinine adjusted) as described by Orlowski et al. (1998), blood BE was then calculated using the relationships between U-Cd (creatinine adjusted) and B-Cd (Börjesson et al., 1997, Shimbo et al., 2000). The resulting BE points of departure (POD) were 6.3 μg/g creat and 5.3 μg/L, for U-Cd and B-Cd, respectively, and an intraspecies pharmacodynamic uncertainty factor of $10^{0.5}$ was applied to these POD, giving urine and blood Cd-BE of 2.0 μg/g creat and 1.7 μg/L, respectively
- The BE values derivation based on the ATSDR MRL used the U-Cd NOAEL (5.4 μg Cd/g creat) as POD for deriving a 4.4 μg/L B-Cd-POD, as described above (Börjesson et al., 1997, Shimbo et al., 2000). Finally, the intraspecies uncertainty factor used for the BE derivations from the US EPA RfD was also applied to these PODs giving BE values of 1.7 μg/g creat for U-Cd and 1.4 μg/L, for B-Cd.

BE values for U-Cd are higher than HBM-GV_{GenPop}. The reasons are that the underlying TRV used by Hays et al., 2008 for calculating BE are not valid anymore (see Table 3). The approach proposed by EFSA for the general population offers a more robust and reliable basis for U-Cd HBM-GV_{GenPop} determination.

In workers, the biomonitoring of B-Cd in addition to U-Cd can be useful to check if exposure to Cd is adequately controlled in the short term. The HBM-GV_{Worker} for U-Cd is in accordance with the recent value set by the European Parliament and the Council in the Carcinogens and Mutagens Directive.

A level of confidence or LoC is attributed to each proposed HBM-GV within the project to reflect the uncertainties; it can be either low, medium or high and constitutes a good incentive to later revise values with an estimated 'lower' level of confidence (Apel et al., 2020). The LoC is attributed regarding nature and quality of toxicological data; the critical effect and the mode of action; the selection of the key study; the selection of POD and the extrapolations across and within species.

The global level of confidence for U-Cd HBM-GV for the general population is set to "high", because of the robust available data, the confidence in the evidence of effects on the renal function and the strength of the *meta*-analysis (EFSA, 2009a, 2009b). The global level of confidence for U-Cd HBM-GV for the workers is set to "high/medium" because of the selection of a single key study of Chaumont et al. (2011), among workers with an average age of 45 years (+/− 10 years). The global level of confidence for B-Cd HBM-GV in the occupational field is set to "high/medium". The derivation of HBM-GV is based on the relationship between B-Cd and markers of renal toxicity identified in a single study (Järup et al., 1988).

Funding

The HBM4EU project has received funding from the European Union's Horizon 2020 research and innovation program under grant agreement No 733032 and received co-funding from the author's organizations.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

References

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

American Conference of Governmental Industrial Hygienists (ACGIH), 2016. Biological Exposure Index documentation for Cadmium and Inorganic Substances. Cincinnati, United States.

Angerer, J., Aylward, L.L., Hays, S.M., Heinzow, B., Wilhelm, M., 2011. Human biomonitoring assessment values: approaches and data requirements. Int. J. Hyg. Environ. Health 214 (5), 348–360.

Anses 2014. Reference Document for the derivation and the measurement of exposure limit values for chemical agents in the workplace (OELs). Request no 2009-SA-0339. Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail, France, 115 p. https://www.anses.fr/fr/system/files/VLEP2009sa0339RaEN.pdf, accessed 30 June 2019.

ANSES 2018. Collective expert appraisal: summary of discussion with conclusions, Evaluation of biomarkers and recommendations for biological limit values and biological reference values for cadmium and its compounds. French Agency for Food, Environmental and Occupational Health & Safety. Request no 2007-SA-0425 - VLB cadmium, https://www.anses.fr/en/system/files/VLEP2007SA0425RaEN.pdf, accessed 30 June 2019.

ANSES 2019. Rapport d'expertise collective: Exposition au cadmium Propositions de valeurs toxicologiques de référence par ingestion, de valeurs sanitaires repères dans les milieux biologiques (sang, urines, xxx). French Agency for Food, Environmental and Occupational Health & Safety. Request no 2015-SA-0140 – Cadmium. https://www.anses.fr/fr/system/files/VSR2015SA0140Ra-1.pdf, accessed 30 june 2019.

Apel, P., Angerer, J., Wilhelm, M., Kolossa-Gehring, M., 2017. New HBM values for emerging substances, inventory of reference and HBM values in force, and working principles of the German Human Biomonitoring Commission. Int J Hyg Environ Health (2 Pt A),152-166.

Apel, P., Rousselle, C., Lange, R., Sissoko, F., Kolossa-Gehring, M., Ougier, E., 2020. Human Biomonitoring Initiative (HBM4EU) - Strategy to derive Human Biomonitoring Guidance Values (HBM-GVs) for health risk assessment. Int. J. Hyg. Environ. Health 230.

ATSDR 1999. Toxicological Profile for Cadmium. Agency for toxic substances and disease registry: Atlanta, USA.

ATSDR 2012. Toxicological profile for Cadmium. Agency for toxic substances and disease registry: Atlanta, USA. http://www.atsdr. cdc.gov/toxprofiles/tp5.html https://www.atsdr.cdc.gov/toxprofiles/tp5.pdf, accessed 30 June 2019.

Bernard, A., 2016. Confusion about cadmium risks: the unrecognized limitations of an extrapolated paradigm. Environ. Health Perspect. 124, 1–5.

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

Bernard, A., Roels, H., Cardenas, A., Lauwerys, R., 1990. Assessment of urinary protein 1 and transferrin as early markers of cadmium nephrotoxicity. Br. J. Ind. Med 47 (8), 559–565.

Börjesson, J., Bellander, T., Järup, L., Elinder, C.G., Mattsson, S., 1997. In vivo analysis of cadmium in battery workers versus measurements of blood, urine, and workplace air. Occup. Environ. Med. 54, 424–431.

Borné, Y., Barregard, L., Persson, M., Hedblad, B., Fagerberg, B., Engström, G., 2015. Cadmium exposure and incidence of heart failure and atrial fibrillation: a population-based prospective cohort study. BMJ Open 5.

Buchet, J.P., Lauwerys, R., Roels, H., Bernard, A., Bruaux, P., Claeys, F., Ducoffre, G., de Plaen, P., Staessen, J., Amery, A., Lijnen, P., Thijs, L., Rondia, D., Sartor, F., Saint Remy, A., Nick, L., 1990. Renal effects of cadmium body burden of the general population. Lancet 336(8717), 699-702. Erratum in: Lancet (1991), 337(8756), 1554.

Cao, Y., Chen, A., Radcliffe, J., Dietrich, K.N., Jones, R.L., Caldwell, K., Rogan, W.J., 2009. Postnatal Cadmium Exposure, Neurodevelopment, and Blood Pressure in Children at 2, 5, and 7 years of age. Environ. Health Perspect. 117, 1580–1586.

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 beta2-microglobulin: a re-assessment in a large cohort of nickel-cadmium battery workers. Occup. Environ. Med. 68 (4), 257–264.

Ciesielski, T., Weuve, J., Bellinger, J.C., Schwartz, J., Lanphear, B., Wright, R.O., 2012. Cadmium Exposure and Neurodevelopmental Outcomes in U.S. Children. Environ. Health Perspect. 120, 758–763.

Directive EU 2019-983 of The European Parliament and the Council of 5 june 2019 amending Directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work.

EFSA 2009a. Scientific Opinion of the Panel on Contaminants in the Food Chain on a request from the European Commission on cadmium in food. The EFSA Journal (2009) 980:1–139 http://efsa. europa.eu/EFSA/efsa_locale-1178620753812_1211902396126.htm.

EFSA 2009b. Technical report of EFSA prepared by Assessment Methodology Unit on Meta-analysis of Dose-Effect Relationship of Cadmium for Benchmark Dose Evaluation. EFSA Scientific Report (2009) 254, 1-62.

Engström, A., Michaëlsson, K., Suwazono, Y., Wolk, A., Vahter, M., Akesson, 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 (3), 486–495.

Engström, A., Michaëlsson, K., Vahter, M., Julin, B., Wolk, A., Åkesson, A., 2012. Associations between dietary cadmium exposure and bone mineral density and risk of osteoporosis and fractures among women. Bones 50, 1372–1378.

Ganzleben, C., Antignac, J.P., Barouki, R., Castano, A., Fiddicke, U., Klánová, J., Lebret, E., Olea, N., Sarigiannis, D., Schoeters, G., Sepai, O., Tolonen, A., Kolossa-Gehrin, M., 2017. Human biomonitoring as a tool to support chemicals regulation in the European Union. Int. J. Hyg. Environ. Health 220, 94–97.

German Human Biomonitoring Commission - Kommission Human-Biomonitoring des Umweltbundesamtes 2007b. Ableitung von Human-Biomonitoring- (HBM-) Werten auf der Basis tolerabler Aufnahmemengen – Teil II: Grundlagen und Ableitungsweg. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 50 (2), 251–254. DOI 10.1007/s00103-007-0146-5.

German Human Biomonitoring Commission - Kommission Human-Biomonitoring des Umweltbundesamtes 2011. Aktualisierung der Stoffmonographie Cadmium – Referenz- und Human-Biomonitoring(HBM)-Werte. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 54, 981–996.

German Human Biomonitoring Commission - Kommission Human-Biomonitoring des Umweltbundesamtes 2014. Grundsatzpapier zur Ableitung von HBM-Werten. Bundesgesundheitsbl Gesundheitsforsch Gesundheitsschutz 57 (1), 138–147. http://link.springer.com/article/10.1007/s00103-013-1867-2.

Gustin, K., Tofail, F., Vahter, M., Kippler, M., 2018. Cadmium exposure and cognitive abilities and behavior at 10 years of age: A prospective cohort study. Environ. Int. 113, 259–268.

Hays, S.M., Becker, R.A., Leung, H.W., Aylward, L.L., Pyatt, D.W., 2007. Biomonitoring equivalents: a screening approach for interpreting biomonitoring results from a public health risk perspective. Regul. Toxicol. Pharm. 47 (1), 96–109.

Hays, S.M., Nordberg, M., Yager, J.W., Aylward, L.L., 2008. Biomonitoring Equivalents (BE) dossier for cadmium (Cd) (CAS No. 7440–43-9). Regul. Toxicol. Pharm. 51, S49–S56.

Hays, S.M., Aylward, L.L., 2009. Using Biomonitoring Equivalents to interpret human biomonitoring data in a public health risk context. J. Appl. Toxicol. 29, 275–288.

Hotz, P., Buchet, J.P., Bernard, A., Lison, D., Lauwerys, R., 1999. Renal effects of low-levelenvironmental cadmium exposure: 5-year follow-up of a subcohort from the Cadmibelstudy. Lancet 354 (9189), 1508–1513.

IARC 2012. Volume 100C: A Review of Human Carcinogens: Arsenic, Metals, Fibres, and Dusts. IARC monographs on the evaluation of carcinogens risks to human. International Agency for Research on Cancer: Lyon, France 501 p.

International Union on Pure and Applied Chemistry (IUPAC) 2018. Risk assessment of effects of cadmium on human health (IUPAC Technical Report). Pure Appl Chem:90 (4), 755-808.

Jakubowski, M., Trojanowska, B., Kowalska, G., Gendek, E., Starzyński, Z., Krajewska, B., Jajte, J., 1987. Occupational exposure to cadmium and kidney dysfunction. Int. Arch. Occup. Environ. Health 59 (6), 567–577.

Järup, L., Elinder, C.G., Spang, G., 1988. Cumulative blood-cadmium and tubular proteinuria: a dose-response relationship. Int. Arch. Occup. Environ. Health 60, 223–229.

Järup, L., Elinder, C.G., 1994. Dose-response relations between urinary cadmium and tubular proteinuria in cadmium-exposed workers. Am. J. Ind. Med. 26 (6), 759–769.

Järup, L., Persson, B., Elinder, C.G., 1995. Decreased glomerular filtration rate in solderers exposed to cadmium. Occup. Environ. Med. 52, 818–822.

Järup, L., Hellstrom, L., Alfven, T., Carlsson, M.D., Grubb, A., Persson, B., Pettersson, C., Spang, G., Schutz, A., Elinder, C.G., 2000. Low level exposure to cadmium and early kidney damage: the OSCAR study. Occup. Environ. Med. 57 (10), 668–672.

Jin, T., Nordberg, M., Frech, W., Dumont, X., Bernard, A., Ye, T.T., Kong, Q., Wang, Z., Li, P., Lundstrom, N.G., Li, Y., Nordberg, G.F., 2002. Cadmium biomonitoring and renal dysfunction among a population environmentally exposed to cadmium from smelting in China (ChinaCad). Biometals 15, 397–410.

Kippler, M., Tofail, F., Hamadani, J.D., Gardner, R., Grantham-McGregor, S.M., Bottai, M., Vahter, M., 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.

Malin-Igra, A., Vahter, M., Raqib, R., Kippler, M., 2019. Early-Life Cadmium Exposure and Bone-Related Biomarkers: A Longitudinal Study in Children. Environ. Health Perspect. 127 (3) https://doi.org/10.1289/EHP3655.

Nogawa, K., Honda, R., Kido, T., Tsuritani, I., Yamada, Y., Ishizaki, M., Yamaya, H., 1989. A dose–response analysis of cadmium in the general environment with special reference to total cadmium intake limit. Environ. Res. 48, 7–16.

Nogawa, K., Kido, T., 1993. Biological monitoring of cadmium exposure in itai–itai disease epidemiology. Int. Arch. Occup. Environ. Health 65, S43–S46.

Noonan, C., Sarasua, S.M., Campagna, D., Kathman, S.J., Lybarger, J.A., Mueller, P.W., 2002. Effects of Exposure to Low Levels of Environmental Cadmium on Renal Biomarkers. Environ. Health Perspect. 110 (2), 151–155.

Oliver-Williams, C., Green, Howard, A., Navas-Acien, A., Howard, B.V., Tellez-Plaza, M., Franceschini, N., 2018. Cadmium body burden, hypertension, and changes in blood pressure over time: results from a prospective cohort study in American Indians. Journal of the American Society of Hypertension Vol 12 (6), 426-437.

Orlowski, C., Piotrowski, J.K., Subdys, J.K., Gross, A., 1998. Urinary cadmium as indicator of renal cadmium in humans: an autopsy study. Human Exp. Toxicol. 17, 302–306.

Prozialeck, W.C., Edwards, J.R., 2010. Early biomarkers of cadmium exposure and nephrotoxicity. Biometals 23 (5), 793–809.

Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006 Commission regulation Reach.

Regulation (EU) 2019/1009 of the European Parliament and of the Council of 5 June 2019 laying down rules on the making available on the market of EU fertilising products and amending Regulations (EC) No 1069/2009 and (EC) No 1107/2009 and repealing Regulation (EC) No 2003/2003.

Rodríguez-Barranco, M., Lacasaña, M., Gil, F., Lorca, F., Alguacil, F., Rohlman, D., González-Alzaga, B., Molina-Villa, I., Mendoza, R., Aguilar-Garduño, C., 2014. Cadmium exposure and neuropsychological development in school children in southwestern Spain. Vol 134, October 2014, Pages 66-73.

Roels, H.A., Lauwerys, R.R., Bernard, A.M., Buchet, J.P., Vos, A., Oversteyns, M., 1991. Assessment of the filtration reserve capacity of the kidney in workers exposed to cadmium. Br. J. Ind. Med. 48 (6), 365–374.

Schulz, C., Wilhelm, M., Heudorf, U., Kolossa-Gehring, M., 2012. Reprint of "Update of the reference and HBM values derived by the German Human Biomonitoring Commission". Int. J. Hyg. Environ. Health 215 (2), 150–158.

SCOEL 2017. SCOEL/OPIN/336 Opinion from the Scientific Committee on Occupational Exposure Limits for cadmium and its inorganic compounds. European Commission. 52p.

Shimbo, S., Zhang, Z.W., Moon, C.S., Watanabe, T., Nakatsuka, H., Matsuda-Inoguchi, N., Higashikawa, K., Ikeda, M., 2000. Correlation between urine and blood concentrations, and dietary intake of cadmium and lead among women in the general population of Japan. Int. Arch. Occup. Environ. Health 73 (3), 163–170.

Tellez-Plaza, M., Navas-Acien, A., Menke, A., Crainiceanu, C., Pastor-Barriuso, R., Guallar, E., 2012. Cadmium Exposure and All-Cause and Cardiovascular Mortality in the U.S. General Population. Environ. Health Perspect. 120, 1017–1022.

Tellez-Plaza, M., Guallar, E., Howard, B.V., Navas-Acien, A., 2013. Cadmium and cardiovascular risk. Epidemiology 24 (5), 784–785.

Tellez-Plaza, M., Jones, M.J., Dominguez-Lucas, A., Guallar, E., Navas-Acien, A., 2013. Cadmium exposure and clinical cardiovascular disease: a systematic review. Curr Atheroscler Rep 15 (10), 356.

US Environmental Protection Agency (US EPA), 1994. Integrated Risk Information System (IRIS) assessment for cadmium.

Zwennis, W.C., Franssen, A.C., 1992. Assessment of occupational exposure to cadmium in the Netherlands, 1980–1989. Am. J. Ind. Med. 21 (6), 793–805.